Neurology of COVID-19

editor
Alberto Priori

Milano University Press

NEUROLOGY OF COVID-19

editor
Alberto Priori

Milano University Press

Neurology of COVID-19 / Alberto Priori. Milano: Milano University Press, 2021.

ISBN 979-12-80325-33-4 (print)

ISBN 979-12-80325-35-8 (PDF)

ISBN 979-12-80325 37-2 (EPUB)

DOI 10.54103/milanoup.57

This volume, and Milano University Press publications in general, unless otherwise specified, are submitted to an external refereeing process under the responsibility of the Milano University Press Editorial Board. The works published are evaluated and approved by the Editorial Board of the publishing house, and must be compliant with the Peer review policy, the Open Access, Copyright and Licensing policy and the Publication Ethics and Complaint policy as reflected in MilanoUP publishing guidelines (Linee Guida per pubblicare su MilanoUP).

The present work is released under Creative Commons Attribution 4.0 - CC-BY-ND, the full text of which is available at the URL: https://creativecommons.org/licenses/by-nd/4.0/deed.it.

This and other volumes of Milano University Press are available in open access at: https://libri.unimi.it/index.php/milanoup

© Alberto Priori
© Milano University Press

Published by:
Milano University Press
Via Festa del Perdono 7 – 20122 Milano
Sito web: https://milanoup.unimi.it
e-mail: redazione.milanoup@unimi.it

The print edition of this volume can be ordered from all physical and online bookstores, and is distributed by Ledizioni (www.ledizioni.it)

With the patronage of the Società Italiana di Neurologia

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

The book has been partly supported by "Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Italy.

Aldo Ravelli Center
for Neurotechnology
and Experimental
Brain therapeutics

UNIVERSITÀ DEGLI STUDI
DI MILANO

Table of contents

General note on figures and tables

Unless otherwise indicated, figures and tables have been prepared by the author(s) of the chapter in question.

The Editor is committed to striving to satisfy all copyright requirements concerning graphics, images and tables for which it has not been possible to identify the type of licence used.

Editors

Chief Editor

Alberto Priori

Professor of Neurology

Director of "Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy;

Director of Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, Milan, Italy.

Deputy Editor

Michelangelo Dini

Research fellow

"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy.

List of Contributors

Elio Agostoni

Director of Neuroscience Department and Niguarda Neuro Center, Milan, Italy;
Director of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.
Email: elioclemente.agostoni@ospedaleniguarda.it

Paola Alberti

School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy.
Email: paola.alberti@unimib.it

Francesca Bai

Clinic of Infectious Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
Email: francesca.bai@unimi.it

Beatrice Benatti

Luigi Sacco University Hospital, Psychiatry 2 Unit, University of Milan, Milan, Italy;
"Aldo Ravelli" Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy.
Email: beatrice.benatti@unimi.it

Maria Donata Benedetti

Neurology Unit, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy.
Email: mariadonata.benedetti@univr.it

Alberto Benussi

Neurology Unit, Department of Clinical and Experimental Sciences, ASST Spedali Civili of Brescia and University of Brescia, Brescia, Italy.
email: alberto.benussi@unibs.it

Simone Beretta

School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy.
Email: beretta.simone@gmail.com

Elisabetta Bernardi

Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
Email: elisabetta.bernardi@unimi.it

Laura Bertolasi

Neurology Unit, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy.
Email: laura.bertolasi@aovr.veneto.it

Tommaso Bocci

"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy;
Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, Milan, Italy.
Email: tommaso.bocci@unimi.it

Matteo Bonifazi

Department of Anesthesia and Intensive Care, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: matteo.bonifazi@unimi.it

Laura Brighina

NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy.
Email: brighina.laura@asst-monza.it

Silvio Brusaferro

President of the Italian National Institute of Health, Rome, Italy;
Full Professor of Hygiene and Public Health, University of Udine, Udine, Italy.
Email: presidenza@iss.it

Gaetano Pietro Bulfamante

Professor of Pathological Anatomy
Pathological Anatomy Unit, Department of Health Sciences, University of Milan, Milan, Italy;
Human Pathology Unit, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: gaetano.bulfamante@unimi.it

Laura Campiglio

Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, Milan, Italy.
Email: laura.campiglio@asst-santipaolocarlo.it

Maria Paola Canevini

Professor of Child Neurology
Epilepsy Center – Sleep Medicine Center, Childhood and Adolescence Neuropsychiatry Unit, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy;
Department of Health Sciences, University of Milan, Milan, Italy.
Email: mariapaola.canevini@unimi.it

Laura Carpenito

School of Pathology, University of Milan, Milan, Italy.
Email: laura.carpenito@unimi.it

Angelo Cascio Rizzo

Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.
Email: angelo.casciorizzo@ospedaleniguarda.it

Stefano Centanni

Professor of Respiratory Medicine
Respiratory Unit, ASST Santi Paolo e Carlo, San Paolo University Hospital, Department of Health Sciences, University of Milan, Milan, Italy.
Email: stefano.centanni@unimi.it

Valentina Chiesa

Epilepsy Center, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: valentina.chiesa@asst-santipaolocarlo.it

Davide Chiumello

Associate Professor of Anesthesiology
Department of Anesthesia and Intensive Care, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: davide.chiumello@unimi.it

Giacomo Pietro Comi

Professor of Neurology
Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Milan, Italy;
Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Email: giacomo.comi@unimi.it

Gianluca Costamagna

Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Milan, Italy.
Email: gianluca.costamagna@unimi.it

Antonella D'Arminio Monforte

Professor of Infectious Diseases
Clinic of Infectious Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
Email: antonella.darminio@unimi.it

Bernardo Dell'Osso

Associate Professor of Psychiatry
Luigi Sacco University Hospital, Psychiatry 2 Unit, University of Milan, Milan, Italy;
"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy;
Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA;
Centro per lo studio dei meccanismi molecolari alla base delle patologie neuro-psicogeriatriche", University of Milan, Milan, Italy.
Email: bernardo.dellosso@unimi.it

Benedetta Demartini

"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy;
Psychiatry 52 Unit, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: benedetta.demartini@unimi.it

Michelangelo Dini

"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy.
Email: michelangelo.dini@unimi.it

Carlo Ferrarese

Professor of Neurology
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy.
Email: carlo.ferrarese@unimib.it

Roberta Ferrucci

Associate Professor of Psychology.
"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy;
Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, Milan, Italy.
Email: roberta.ferrucci@unimi.it

Orsola Gambini

Professor of Psychiatry
"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy;
Psychiatry 52 Unit, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: orsola.gambini@unimi.it

Nicolaja Girone

Luigi Sacco University Hospital, Psychiatry 2 Unit, University of Milan, Milan, Italy.
Email: girone.nicolaja@asst-fbf-sacco.it

Giuditta Giussani

Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.
Email: giuditta.giussani@ospedaleniguarda.it

Alessandro Innocenti

Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.
Email: alessandro.innocenti@ospedaleniguarda.it

Valeria Isella

School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy.
Email: valeria.isella@unimib.it

Francesca Lanzani

Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.
Email: francesca.lanzani@ospedaleniguarda.it

Fabrizio Luiso

Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
Email: fabrizio.luiso@unimi.it

Chiara Manfredi

Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, Milan, Italy.
Email: chiara.manfredi@asst-santipaolocarlo.it

Giulia Marchetti

Associate Professor of Infectious Diseases
Clinic of Infectious Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
Email: giulia.marchetti@unimi.it

Sara Meoni

Université Grenoble Alpes, Inserm, CHU Grenoble Alpes, Grenoble Institut Neurosciences, Grenoble, France;
Movement Disorders Unit, Division of Neurology, CHU Grenoble Alpes, Grenoble, France;
"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy.
Email: smeoni@chu-grenoble.fr

Elena Moro

Professor of Neurology
Université Grenoble Alpes, Inserm, CHU Grenoble Alpes, Grenoble Institut Neurosciences, Grenoble, France;
Movement Disorders Unit, Division of Neurology, CHU Grenoble Alpes, Grenoble, France;
"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy.
Email: emoro@chu-grenoble.fr

Veronica Nisticò

"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy.
Email: veronica.nistico@unimi.it

Alessandro Padovani

Professor of Neurology
Neurology Unit, Department of Clinical and Experimental Sciences, ASST Spedali Civili of Brescia and University of Brescia, Brescia, Italy.
Email: alessandro.padovani@unibs.it

Giulia Michela Pellegrino

Department of Health Sciences, University of Milan, Milan, Italy;
Casa di Cura del Policlinico, Department of Neurorehabilitation Sciences, Milan, Italy.
Email: g.pellegrino@ccppdezza.it

Alessandro Pezzini

Neurology Unit, Department of Clinical and Experimental Sciences, ASST Spedali Civili of Brescia and University of Brescia, Brescia, Italy.
email: alessandro.pezzini@unibs.it

Andrea Pilotto

Neurology Unit, Department of Clinical and Experimental Sciences, ASST Spedali Civili of Brescia and University of Brescia, Brescia, Italy.
Email: andrea.pilotto@unibs.it

Alberto Priori

Professor of Neurology
Director of "Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy;
Director of Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, Milan, Italy.
Email: alberto.priori@unimi.it

Roberta Rovito

Clinic of Infectious Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
Email: roberta.rovito@unimi.it

Marco Scarabello

Diagnostic and Interventional Neuroradiology Department, ASST Santi Paolo e Carlo, San Carlo Borromeo Hospital, Milan, Italy.
Email: marco.scarabello101782@asst-santipaolocarlo.it

Emma Scelzo

Neurology Unit I, San Paolo University Hospital, ASST Santi Paolo e Carlo, Milan, Italy.
Email: emma.scelzo@asst-santipaolocarlo.it

Giuseppe Francesco Sferrazza Papa

Department of Health Sciences, University of Milan, Milan, Italy;
Casa di Cura del Policlinico, Department of Neurorehabilitation Sciences, Milan, Italy.
Email: giuseppe.sferrazza@unimi.it

Vincenzo Silani

Professor of Neurology
Department of Neurology and Laboratory of Neuroscience, Istituto Auxologico Italiano, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy;
"Aldo Ravelli" Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy.
Email: vincenzo.silani@unimi.it

Gioacchino Tedeschi

President of the Italian Society of Neurology; Professor of Neurology, Campania University "L. Vanvitelli", Naples, Italy.
Email: gioacchino.tedeschi@unicampania.it

Delfina Tosi

Pathological Anatomy Unit, Department of Health Sciences, University of Milan, Milan, Italy.
Email: delfina.tosi@unimi.it

Valentina Toto

Human Pathology Unit, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.

Gemma Tumminelli

Epilepsy Center, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: gemma.tumminelli@asst-santipaolocarlo.it

Carla Uggetti

Diagnostic and Interventional Neuroradiology Department, ASST Santi Paolo e Carlo, San Carlo Borromeo Hospital, Milan, Italy.
Email: carla.uggetti@asst-santipaolocarlo.it

Luca Valvassori

Diagnostic and Interventional Neuroradiology Department, ASST Santi Paolo e Carlo, San Carlo Borromeo Hospital, Milan, Italy.
Email: luca.valvassori@asst-santipaolocarlo.it

Chiara Vannicola

Child Neuropsychiatry and Epilepsy Center, ASST Santi Paolo e Carlo, Milan, Italy.
Email: chiara.vannicola@asst-santipaolocarlo.it

Daniele Velardo

Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Email: daniele.velardo@policlinico.mi.it

Ilaria Viganò

Child Neuropsychiatry and Epilepsy Center, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy.
Email: ilaria.vigano@asst-santipaolocarlo.it

Preface

In December 2019, a novel coronavirus, designated as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), was identified as the cause of a disease that was named COVID-19 (coronavirus disease 2019). The virus rapidly spread worldwide and it was declared a pandemic by the World Health Organization on March 11, 2020.

At the very early stages of the pandemic, it became increasingly evident that COVID-19 is not limited to the respiratory system, and that other organs can be affected. In particular, virus-related neurological manifestations were frequently reported in COVID-19 patients all over the world.

Neurological complications are common in patients during acute infection as well as in the long term. They are particularly frequent in hospitalized patients, among whom more than 80% may develop neurological symptoms at some point during their disease course, and in patients with severe COVID-19. There is also increasing recognition that psychiatric manifestations represent possible complications of infection.

Over the last year, the scientific literature on nervous system-related manifestation of COVID-19 has continued to grow, producing over 4,500 publications, including over 700 reviews and close to 40 systematic reviews (available from: www. https://pubmed.ncbi.nlm.nih.gov/).

Despite this rapidly expanding scientific literature, the mechanisms contributing to neurological and psychiatric symptoms of COVID-19 are still not fully understood and more pathogenetic studies are needed to shed light on this topic. An understanding of the mechanisms underlying such manifestations will be essential to promote optimal use of targeted therapeutic strategies.

The book edited by Alberto Priori and Michelangelo Dini brings together the contributions of a group of internationally renowned experts who have gained extensive clinical experience in major hospitals in the northern Italian region of Lombardy, the first European region to face the COVID-19 emergency in 2020. It offers a comprehensive and updated account of the neurological aspects of SARS-CoV-2 infection. The aim of the authors is to provide practical clinical insights for clinicians of all specialties involved in the management of COVID-19 patients. Each chapter presents a critical review of the existing literature, followed by practical clinical considerations based on the lessons learnt by each author during the course of the COVID-19 pandemic.

The urgent need for solid and timely scientific information has been evident since the early phases of this unprecedented health emergency. The Italian Istituto Superiore di Sanità (ISS), in its dual capacity of research institution and technical-scientific body of the Italian National Health System, has put in place

several strategies to meet this need. Among them, the ISS COVID-19 reports ("Rapporti ISS COVID-19"), written by over 400 ISS and external experts organized into 22 Working Groups, have covered a broad spectrum of operational indications: from the management of SARS-CoV-2 cases to the reopening of commercial and tourist activities, to the outbreaks in schools and other education institutes, to mention only a few. These reports, freely available from the official ISS website, have also been translated into English and Spanish at the request of several foreign organizations; a testimony to the Italian leadership demonstrated during the pandemic.

The first three chapters of the book define the landscape of SARS-CoV-2 infection and the nervous system. Chapter 1 reviews the pathogenesis of SARS-CoV-2-related brain damage, while Chapter 2, after a brief overview of the lung-brain axis, offers a detailed account of dyspnea and respiratory failure in COVID-19, and of post-COVID-19 sequelae. The neurogenic component of COVID-19-related respiratory failure is then explored in Chapter 3.

The book then deals more specifically with the "neurology of COVID-19", starting with an overview of the neurological manifestations and two methodological chapters on neuroimaging and neuropathology.

The following chapters illustrate specific neurological manifestations, including encephalomyelitis, stroke, seizures, delirium, as well as psychiatric conditions, such as mood disorders, psychotic disorders, anxiety disorders, obsessive-compulsive disorders, eating disorders, autism spectrum disorders, somatic symptoms and related disorders. Cognitive dysfunction in COVID-19 as a key factor in determining the functional outcome for a large number of patients is also discussed, highlighting the importance of including cognitive rehabilitation in multidisciplinary rehabilitation programs. Similarly, the authors highlight the need for observational, multicenter studies to better understand the impact of COVID-19 on patients with pre-existing neurological diseases, such as neuroinflammatory and neuro-oncological diseases, who represent a particularly vulnerable and frail population. The related chapter addresses some topics of high potential interest and provides some considerations on COVID-19 vaccination in these frail neurological categories.

Further issues presented in specific chapters are the COVID-19-related disorders of the peripheral nervous system and the muscular system, and the neurological manifestations in children. Although relatively rare, there is an increasing number of reports of cases of neurological symptoms, such as seizures, encephalitis, stroke or neuropathies, in a small proportion of children affected by SARS-CoV-2 suggesting a possibly greater neurological involvement in the pediatric population affected by SARS-CoV-2 than in those affected by other human coronaviruses.

Finally, the book covers two major areas of interest for the management of the COVID-19 pandemic: vaccines and telemedicine. In particular, the

advantages and limitations, clinical implications, and future challenges of "teleneurology" (a word used to indicate the application of telemedicine to neurology) are comprehensively discussed. Telemedicine is the delivery of medical care by electronic communication between a health care professional and a patient at different locations. It is no surprise that the pandemic has greatly pushed telemedicine and teleneurology forward, with the double aim of reducing exposure to SARS-CoV-2 infection while ensuring patients receive all the assistance they need. In addition, during the pandemic, the use of virtual communication for seminars, webinars, educational training and teaching courses has greatly helped health operators and scientific communities. To give an example, in 2020, the ISS hosted weekly scientific meetings on "COVID-19 - the state of the art" by teleconference, with insights and comparisons by leading epidemiological and clinical experts and provided courses in distance learning methods aimed at all health professionals and socio workers, and school and support staff. These events were followed by over 500,000 registered users.

All the changes imposed by the pandemic have happened very fast, in days or weeks, requiring the availability of adequate equipment and the rapid development of a technology infrastructure to support them. Telemedicine and teleneurology expand access and availability from outpatient to acute care and rehabilitation. While, still in their infancy, there are, as pointed out by the authors, considerable possibilities for improvement.

In conclusion, "Neurology of COVID-19" is an innovative reference book for clinicians of all specialties involved in the management of patients with SARS-CoV-2 infection, presenting "the state of the art" in the field, but also offering food for thought about present limitations and future challenges.

Public health policies at international, national and regional levels will certainly benefit from this book and we should be grateful to the authors for their efforts. I also hope that, starting from this experience, other similar contributions covering all clinical aspects of COVID-19 can be made available to public health bodies and to the scientific community at large.

Silvio Brusaferro
President of Istituto Superiore di Sanità
Rome, Italy

Foreword

Neurology of COVID-19 deals with a recent disease that has deeply changed the practice of neurologists worldwide, and as such it represents an important novelty in the scenario of neurological textbooks. COVID-19 had a double impact on neurologists. First, at the onset of the pandemic, neurologists were required to help colleagues of other medical specialties (respiratory medicine, infectious diseases, intensive care, emergency departments) thus going back to being medical doctors. Many neurologists had to update their knowledge of using ventilators and of internal medicine. A further important issue was the description and discovery of the effect of SARS-CoV-2 infection on the nervous system. *Neurology of COVID-19* deals with the pathophysiology, neuropathology, neuroimaging, neurological, and psychopathological and cognitive manifestations of SARS-CoV-2 in adults and children. Italy was the first European country to face the pandemic, and Italian neurologists immediately began to study their patients and to report their observations. This, in several cases, opened up new avenues towards improving the understanding and management of COVID-19 that were then replicated and expanded by colleagues in other countries. As President of the Italian Neurological Society, I am, therefore, proud and honored to introduce *Neurology of COVID-19*. I believe it will become a reference book in its field. The efforts of Professor Alberto Priori who edited the book and of all the contributors will certainly draw the attention of other specialists to the neurological aspects of this novel condition. Notably, all the contributors and the editors were dealing with COVID-19 on the front-line and had a direct experience with the many faces of the neurological aspects of SARS-Cov-2 infection.

Gioacchino Tedeschi
President of the Italian Neurological Society

Introduction

Our neurological department came face to face with COVID-19 suddenly in February 2020 when a 63-year-old colleague was admitted for focal motor seizures. Brain neuroimaging showed only a mild leukoaraiosis without focal lesions. Two days later, fever, cough, and interstitial pneumonia developed, his general medical condition rapidly worsened, and he later died. Just one month later, in March 2020, northern Italy became the second country most affected by COVID-19 in the world, and the national death toll overtook that in China. Hospital staff soon realized that COVID-19 was far more severe than they had expected from the few data available at that time (mostly from the daily newspapers and media channels, which in January 2020 represented the only source of information).

Restoring the balance

The COVID-19 pandemic has forced hospitals to adjust to rapidly changing circumstances. Since March 8, 2020, health authorities have transformed the regional public health system. Within days, the number of patients accessing emergency departments (ED) for COVID-19 dramatically increased, requiring hospital managements to reorganize all their wards. Within a week, most hospital beds were dedicated to COVID patients and, COVID aside, most other routine clinical activities were gradually reduced and eventually stopped. Events escalated so suddenly that even departments not usually in the first line of defense against COVID-19 had to deal with the prevailing circumstances. The decision to transform most operating theaters into intensive care units (ICU) meant redefining surgical guidelines. Surgeons generally accepted this 'revolution' in their daily activity without any complaints. The number of people, contacts, friends and relatives who fell ill, many of whom later died, of COVID, had "cooled down the sacred fire of surgery". And everybody learnt to do nasopharyngeal swabs (NPS).

COVID teams

To address the urgent need for physicians and to reallocate unemployed health specialists, the hospital assigned all physicians to "COVID teams". Each team was made up of a specialist in infectious diseases (ID), respiratory medicine, internal medicine, and other specialties (including ophthalmology, pathology, maxillofacial surgery, ear-nose-and throat [ENT], neurology, general surgery, orthopedic surgery, urology). With this approach, teams were created in which

non-COVID-related specialists could train others to treat patients on their own in case the epidemiologic situation worsened or any doctors fell ill. Because most COVID-19 patients are elderly, and have comorbidities, a further advantage was that the multidisciplinary teams worked well together and were relatively autonomous. This meant that external consultations were not required, thus reducing the number of contacts and, therefore, the risk of infection.

Hubs & Spokes

On March 8, 2020, the Lombardy region instituted a regional healthcare system to assist patients with acute illnesses including cardiovascular disease, stroke, oncology, and surgery during the COVID-19 epidemic (Deliberation of the Lombardy Region n. XI/2906). To manage these diseases, the territorial emergency medical system (EMS) in Lombardy identified and linked together 13 central hospitals (Hubs) and 42 peripheral hospitals (Spokes). The main aim of this was to enable hospitals to create a well-organized territorial network, with well-trained operators and shared protocols that would guarantee appropriate and timely medical assistance, and ensure patients' safety.

Personal protective equipment (PPE)

The Covid-19 outbreak meant that hospital managements suddenly had to to devise new specific procedures. One of these was that the use of personal protective equipment (PPE) was required on all the wards. The fear of infection and the need to respect the new rules generated tensions that proved difficult to de-escalate. Watching doctors tying up the lab coat on support workers and vice versa may, at times, have been amusing, but keeping the department up and running meant implementing strong preventive measures also for patients and instructing them on the importance of self-care (e.g., wearing surgical masks at all times, frequent hand washing, etc.).

From mid-February 2020, the authorities limited hospital access only to patients. Everyone had to have their temperature measured and undergo careful questioning about any fever or respiratory symptoms at home. Since then, patients have had to use gloves and face masks. In a delicate setting such as psychiatry, where patients are often in a confusional state and experiencing delirium, compulsory face masks interfered with the therapeutic relationship. In addition, for patients without cognitive and psychiatric disturbances, the mask became an emotional obstacle to smiling, a potent 'drug'. No relatives could enter the wards, causing many patients to experience significant psychological distress, which, in turn, also affected doctors and all other healthcare workers.

Teaching: students and residents

During the Covid-19 outbreak, academic staff made a great effort to continue teaching by rapidly activating online lessons, seminars, webinars and examinations for medical students and in-house consultants. Those involved needed to have an open mind about these new modalities in order to adapt to these individual teaching methods. Some of us will always remember the video medical graduation examination sessions we attended as members of the exam commission. A medical degree is arguably the most important event in any student's career, and one which they look forward to. We had to watch our students on a computer screen as they defended the results of their thesis, sitting alone in their bedrooms without the comfort of cheering relatives and friends, but still wearing their best clothes, as if participating in the real ceremony.

Residents no longer worked a rotating shift system but were integrated into the COVID units, working on the internal medicine and respiratory medicine wards. They were re-located around the hospital according to their expertise. Final year ID, respiratory medicine, internal medicine and anesthesiology students were recruited as part of the medical team and allowed to treat patients. Others (from pathologists to ENT and many other specialties) worked in COVID teams, volunteered to work in the emergency network, and some worked in the occupational health service.

Work overload

The upheaval caused by the pandemic has also led to an increased the work load; many operators had to prolong their working hours and skip their day off to allow the hospitals to adjust to the new organizational model that had been designed. To mitigate the daily stress and emotional burden, our hospital provided a 'decompression room' and psychological support group sessions. The decompression room is a physical and mental space where staff can go to relax to help them relieve work pressures. The small group sessions help the doctors and nurses to develop inter-professional group thinking. A theme which was addressed right at the start was moral distress, while the focus later switched to a more closely related intervention to prevent post-traumatic stress disorder. The rehabilitation team has also created a 'muscle reconditioning' space intended for workers who complain of muscle tension.

Tele(phone)medicine

A powerful tool that is easily accessible to the whole population (from children to the elderly) ensures assistance at home for many patients, and reduces the danger of infection, is an internet video meeting or a telephone call. On

most wards, the hospital set up a call center, often managed by residents or medical students, to answer patients' phone calls and e-mails and reschedule medical appointments. Outpatient activities were limited to urgent cases for all specialties and were mainly telephone consultations. Patients who could not go to the hospital because of the lockdown restrictions could reach the rehabilitation team by phone or videocalls. The rehabilitation team also created video tutorials that allowed patients to continue their exercises at home.

A lesson on empathy

Apart from the purely medical response, a major issue in dealing with COVID-19 is the human aspect. All the physicians and nurses involved are facing difficult moment in their professional lives, especially when they represent the only link between COVID patients, who cannot receive visits, and their families. Our hearts and minds will forever remember some extraordinary and extremely difficult medical conversations with patients passing away. Solidarity, empathy and compassion are cardinal points in the work that we do. We feel helpless, and at times in despair, when facing the silent yet deafening plea for oxygen that patients about to die convey through their terrified eyes. Nonetheless, a smile and a caress can transmit incredible power and strength to our patients. Each of us, at least once over the past months, has felt humankind's vulnerability in this massive global crisis.

Nurses, close to the patients

Nurses are on the frontline. Since the COVID-19 outbreak began, day after day they have been facing difficult and stressful situations. For example, patients complaining of mild respiratory difficulties enter the emergency department unaided, then rapidly evolve into severely distressed persons needing mechanical ventilation (either invasive or non-invasive), and several later die. Nurses are put under extreme psychological pressure. What is more, seeing the eyes of a patient in sudden need for oxygen, clenching the nurse's hand in the desperate effort to breathe, reminds us that such patients are facing this situation alone. As infection prevention policies forbid relatives to enter the wards, nurses fully realize that, as the patient's situation worsens and their fears increase, they have no support from their loved ones. Given that nurses are often the last people a dying patient sees, patients tend to share with them their most intimate feelings and life stories. When their shift ends, nurses find it tremendously difficult to leave all of this behind. Moreover, upon returning home, nurses cannot even embrace their own loved ones because of the risk of transmitting the disease. Hence, they face a high risk of experiencing psychological scars that will be

hard to heal. Research already shows that both patients who survived and hospital workers are at an increased risk of long-term psychological distress, and possibly even trauma.

Neurology

Within a week of Lombardy's COVID-19 catastrophic outbreak erupting, the hospital directors transformed the neurology unit into a COVID ward. All the neurological subspecialty outpatient clinics provided phone or internet consultations for patients or their general practitioner. Surprisingly, for the first two weeks, no patients with acute neurological problems presented to the emergency department. Three weeks later, neurological non-COVID patients progressively began attending the emergency department again. During the second and third wave of pandemic (after the summer of 2020) several hospitals created a Neuro-Covid ward for patients either with pre-existing neurological disorders who were infected by SARS-CoV-2, or COVID-19 cases with neurological complications. By the autumn of 2020, we had realized that COVID-19 patients infected during the winter or spring of 2020 often had neurological sequelae.

This book reports how several neurological departments located in large hospitals in the most affected area in Italy experienced the COVID-19 outbreak and its neurological manifestations. We believe that a pandemic event of this magnitude implies a multidisciplinary response, so we include chapters from all the main neurological subspecialties, along with those from infectivologists, pneumologists, pathologists and several other colleagues, in a single reference book. Despite the tragedy, we feel that the COVID-19 pandemic has offered a unique opportunity to develop a new healthcare management model as a trigger for future innovation in medical and neurological practice. This book witnesses the tremendous vitality of Italian neurology in response to a novel disease that is likely to add a new chapter to the neurology textbooks. Lastly, the issue of how some COVID-19 complications (e.g., the development of long-term cognitive impairment) will evolve in the future is still unknown and this will require close neurological follow-up for which this book will represent both a starting point and a guide.

Alberto Priori
Professor of Neurology
University of Milan
San Paolo University Hospital
Italy

Chapter 1. SARS-CoV-2 and the nervous system: review on pathogenesis of nervous system SARS-CoV-2 damage

Francesca Bai, Roberta Rovito, Giulia Marchetti,
Antonella d'Arminio Monforte

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a newly emerged enveloped virus, positive-sense single-stranded RNA, of the *Coronaviridae* family, belonging to the genus of all highly pathogenic coronaviruses, i.e., Betacoronavirus[1]. After SARS-CoV and the Middle Eastern respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is the third coronavirus to have caused a large outbreak in humans. SARS-CoV emerged in South China in 2002[2], MERS-CoV in Saudi Arabi in 2012[3], and SARS-CoV-2 in the Hubei province of China in 2019 most likely due to species barrier spillover, making the One Health approach a worldwide priority.

SARS-CoV-2 genome is more closely related to the genome of SARS-CoV than to MERS-CoV (80% and 50% identity, respectively)[4-6]. Overall, SARS-CoV-2 appears to be less lethal than SARS-CoV and MERS-CoV but is more highly transmissible. The main cellular target of SARS-CoV-2 is the angiotensin converting enzyme 2 (ACE2), a cell surface carboxypeptidase that is part of the renin-angiotensin system (RAS)[7]. SARS-CoV-2 has a strong affinity for ACE2[7,8]. Two-thirds of the SARS-CoV-2 genome encodes for non-structural proteins necessary for the replicase complex, whereas the remaining genome encodes for accessory and structural proteins[4,5,9]; the latter include spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The S protein is composed of two domains, one containing the receptor binding domain (RBD) and the other the membrane fusion domain, i.e., S1 and S2, respectively. The RBD of the S protein mediates viral entry by binding to the human ACE2. The binding is followed by proteolytic activation between S1/S2 at the plasma membrane by the transmembrane protease serine 2 (TMPRSS2) or at the endosomal membrane by cathepsin L[10]. The genome is then released in the cytosol where it is translated in viral proteins that form the RNA-dependent RNA polymerase. The genomic and sub-genomic RNAs are replicated, with the latter translated in accessory and structural proteins used for virion assembly. Finally, the viral RNA genomes are incorporated into the virions which are released from the

plasma membrane[9,11,12]. ACE2 is expressed by the respiratory tract, and, after having entered the host via epithelial cells, the vascular endothelial cells and macrophages may be the first targets[13-15].

SARS-CoV-2 is the etiologic agent of coronavirus disease 2019 (Covid-19) which is characterized by severe 'flu'-like symptoms that can progress to life-threatening systemic inflammation and multiorgan dysfunction[16]. Severe COVID-19 is observed in about 20% of patients infected with SARS-CoV-2, and the factors that dictate whether or not a patient develops the severe form are not yet known, although older age is one of the main known risk factors associated with severity together with obesity, cardiovascular diseases and male gender. One of the hallmarks of COVID-19 severity is the 'cytokine storm'[17-19], i.e., an uncontrolled increase in pro-inflammatory mediators following innate immune activation. The increased cytokine and chemokine concentration further amplifies the tissue damage by means of endothelial dysfunction and vasodilatation, eventually creating a hypoxic environment and organ failure[20]. Clinical aggravation occurs approximately one week after the onset of symptoms[17,21,22], which roughly corresponds to the temporal bridging of the innate and adaptive immune response. Once the disease becomes systemic, the disease will involve other organs and systems.

SARS-CoV-2 and the nervous system: pathogenetic aspects

Central nervous system and peripheral nervous system manifestations in COVID-19 disease

Central nervous system (CNS) and peripheral nervous system (PNS) involvement were described following SARS and MERS, even if these involved only a small proportion of cases: in fact, the prevalence of CNS and PNS complications ranged from 0.04% for SARS to 0.20% for MERS, and from 0.05% for SARS to 0.16% for MERS, respectively[23]. As the COVID-19 pandemic progressed, neurological manifestations increased. These included neurological symptoms that are present at the time of COVID-19 diagnosis in a considerable number of patients, and neurological complications that could appear later[24-26].

The neurological manifestations in COVID-19 disease have been categorized in three groups: (i) CNS involvement, characterized by dizziness, headache, impaired consciousness, acute cerebrovascular disease and epilepsy; (ii) PNS involvement, including anosmia, hypogeusia, visual impairment and neuralgia; and (iii) skeletal muscle impairment[27]. Neurological symptoms, such as loss of the sense of smell and taste, headache, fatigue, nausea and vomiting, dizziness, are reported in more than one-third of COVID-19 patients[17,28]; but more severe manifestations, as well as encephalopathy, stroke, Guillain-Barré syndrome, acute hemorrhagic necrotizing encephalitis, and acute disseminated

encephalomyelitis seem to be less common[23,29]. However, the prevalence of neurological manifestations associated with COVID-19 varies widely among the different studies, ranging from 7% to over 84%[27,30].

Given the high prevalence of COVID-19 disease worldwide, and the non-specificity of neurological symptoms associated with SARS-CoV-2 infection, that are, in fact, described also in the course of other viral infections, experts advise caution in attributing any specific causal links between SARS-CoV-2 and neurological symptoms[27]. The pathogenesis of CNS infection by SARS-CoV-2 and the neurological complications are still poorly understood and more pathogenetic studies are needed to shed light on this topic.

ACE2 receptors are expressed in different brain regions

ACE2 receptors are widely expressed in human organs, including in multiple CNS structures, such as brainstem, cortex, striatum and hypothalamus, and in several cell types, such as neurons and glia[26,31,32]; recently, ACE2 has also been found in the human cerebral vasculature in postmortem brain samples and appears to be upregulated in brain tissues by oxidative stress, apoptosis and neuroinflammation that characterize several neurological diseases or hypertension[31,32]. ACE2 in brain was also found in the neurons of the subfornical organ, where the virus could more easily find a means of entering the CNS, thanks to the lack of a blood brain barrier (BBB)[7]. Additional receptors may play a role in SARS-CoV-2 invasion of the brain: CD147 (or basigin, BSG) and Neuropilin1 (NRP1), to which the spike protein is capable of binding. Recently, a furin-like cleavage site on the spike protein of SARS-CoV-2 was demonstrated to be specific for this virus; the association between the furin-like cleavage site and its protease in host has been demonstrated to be critical for the neurotropism of the *Coronaviridae* family and thus the presence of this site could explain the ability of SARS-CoV-2 to invade the CNS[33].

Possible mechanisms of neurotropism and neurovirulence of SARS-CoV-2

Neurological manifestations could be caused by SARS-CoV-2 through a direct or indirect mechanism. The possible mechanisms of neurological impairment that have been identified so far are: (i) a direct effect of the virus entry into the CNS; (ii) para-infectious or post-infectious immune-mediated disease; (iii) a secondary involvement of the CNS following the systemic effects of COVID-19, such as systemic inflammatory response syndrome, sepsis and multiorgan failure[23,24]. The different mechanisms are not mutually exclusive and might co-exist. Similarly, Neuro-COVID has also been described as a process in three phases: (i) neuroinvasion; (ii) CNS clearance; and (iii) immune response. In the first phase, the virus reaches the CNS through the systemic circulation and/or through the trans-cribriform route along the olfactory nerve; it seems that the viral load in the CSF gradually increases until the second phase. In the

second phase, the interaction between the subunit S1 of the spike protein and the ACE2 receptor allows viral entry into the neuronal cells with subsequent neuronal damage; early after the infection, neuronal damage leads to the onset of anosmia and/or dysgeusia, while later the involvement of the nucleus of the solitary tract may cause severe respiratory impairment. During the second phase, the viral load starts to decrease until SARS-CoV-2 indirectly affects the CNS. In the third and last phases, the viral infection causes immune-mediated CNS impairment. The virus could stimulate the production of antibodies against glial cells, as a para- or post-infective mechanism, similar to that observed after other viral infections. In this phase, the respiratory symptoms may become even more severe, leading to neurotoxic hypoxia and brain damage[34].

CNS impairment as a consequence of a direct viral effect

Different experimental models were used to study the presence and the consequences of SARS-CoV-2 in the CNS: neural cell lines, animal models and brain organoids[35,36]. Published studies have shown that SARS-CoV-2 can infect and replicate in induced pluripotent stem cell (iPSCs)-derived human neural progenitor cells (hNPCs) and in neurospheres or brain organoids produced from these cells[25,32]. Animal experiments have provided information as to the neuroinvasive potential of SARS-CoV-2: the presence of the virus was found in neurons of different brain areas, and this was later compared with the pulmonary involvement. Interestingly, not all infected animals showed neurological symptoms or signs of CNS infection[24]. The neurotropism and neurovirulence of SARS-CoV-2 have also been demonstrated by the finding of viral acid nucleic in the cerebrospinal fluid (CSF) and in brain tissue samples[26], even if with a low frequency.

Detection of SARS-CoV-2 in cerebrospinal fluid

Neurotropism is a common characteristic of human coronaviruses (HCoVs) and several studies have demonstrated that SARS-CoV-2 is able to invade the CNS[33,37]. The detection of the viral RNA in the cerebrospinal fluid (CSF) by Real-Time Reverse Transcription PCR (RT-PCR) has been described by different authors in some cases of encephalopathy with a prevalence of 6.4%[38-43]. However, in the majority of patients diagnosed with encephalopathy, SARS-CoV-2 RNA was not detected in the CSF[41,42,44,45]. A possible explanation for this could be that the virus is cell-bound and spreads from cell to cell and does not transit freely in the CSF. Alternatively, the viral concentrations in the CSF could be below the level of detection of the test or the PCR reaction is inhibited by the presence of hemoglobin products for the breakdown of erythrocytes. The detection rate is also highly dependent on the type of neurological disease and the time of sample collection[41]. Finally, the absence of the virus in the CSF despite inflammation (confirmed by high levels of CSF white blood cells and

protein levels described in some patients with encephalitis) suggests that the encephalitis could be the result of systemic immune-mediated inflammation and is not driven only by a direct neuroinvasion of SARS-CoV-2[27,42,46].

The detection rate of SARS-CoV-2 RNA in the CSF was generally higher in patients diagnosed with encephalitis and much lower in patients with encephalopathy, cerebrovascular accidents or Guillain-Barré syndrome. Interestingly, patients without neurological manifestations were all negative for CSF SARS-CoV-2 RNA[41]. Moreover, almost half the patients with a negative test for SARS-CoV-2 in the CSF showed the presence in the CSF of antibodies specific for SARS-CoV-2, and, according to available data, 23.3% of tested patients present intrathecal antibody synthesis[41] that could suggest the invasion of the virus into the CNS[47].

Detection of SARS-CoV-2 in brain tissue samples

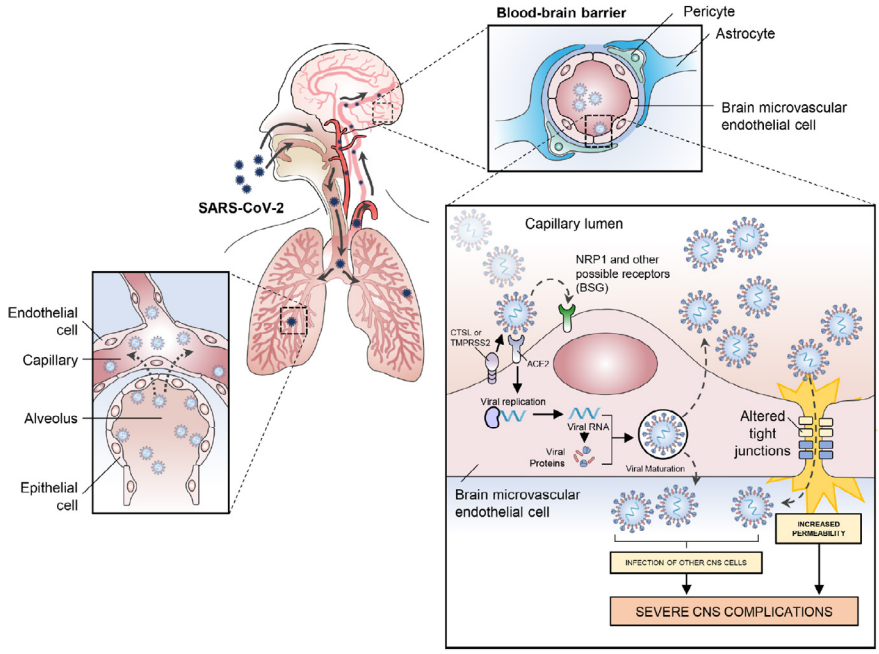
Postmortem examination is the definitive means of assessing viral neuroinvasion, in addition to that of the CSF, and previous studies have investigated the detection of SARS-CoV-2 in postmortem human brain samples, but so far with contrasting results. Some authors, in fact, reported the detection of the virus in brain autopsies (even though the viral load was low), by PCR and quantitative PCR (qPCR), or of viral nucleocapsid and/or spike proteins by immunohistochemistry[1,46,48]. Conversely, in other studies, the virus was not detected in brain cells. Thus, the hypothesis that the virus is intrinsically neuroinvasive and is able to create a persistent infection in the CNS requires clarification[27,49,50]. SARS-CoV-2 was detected in different cell types as well as frontal lobe neurons, glial cells, endothelial cells, pericytes of brain capillaries and vagus nerve fibers[45,51-53], and viral proteins were found in a smaller proportion of patients in different brain regions, as well as brainstem, cerebellum, cerebrum and the olfactory system[41]. The highest detection rate of SARS-CoV-2 RNA was found in brainstem, as well as the most severe microgliosis and lymphocytic infiltration, suggesting that the brainstem could be a major target of SARS-CoV-2 in the CNS[41].

The most common findings in the CNS of patients who died from COVID-19 are hypoxic injury and vascular accidents[41] and microglial activation was found in the compromised brain areas in more than half the patients. The detection rate of SARS-CoV-2 was higher in regions with microgliosis and lymphocytic infiltration than in areas with hypoxic injury and vascular impairment[41].

Routes of neuroinvasion

Coronaviruses may reach the CNS through any of three different pathways: (i) hematogenous dissemination; (ii) the "Trojan horse" mechanism; and (iii) neuronal retrograde propagation[27,28,54,55]. In the first case, after a phase of viremia, the virus can cross the BBB and enter the CNS.

Figure 1.1: Possible SARS-CoV-2 entry to the central nervous system (CNS) via blood circulation



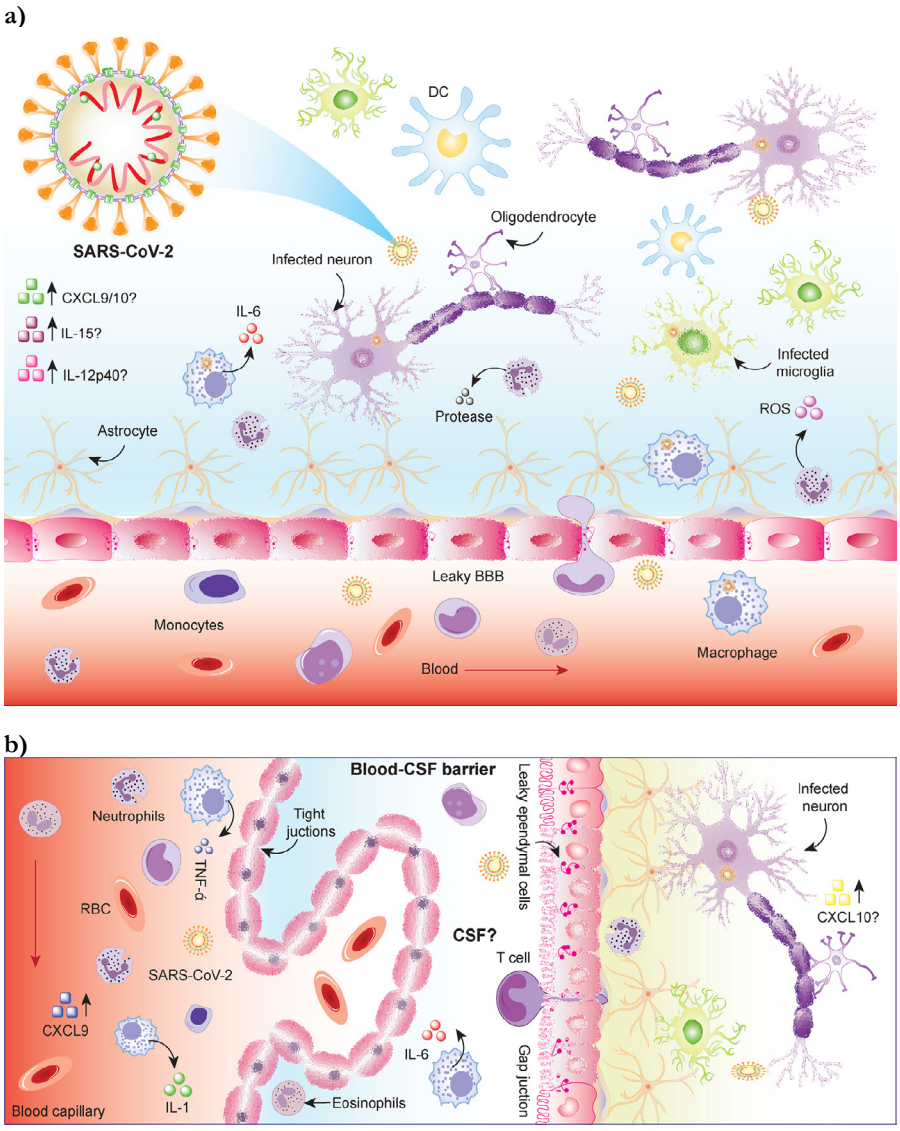
Passage of SARS-CoV-2 from the upper respiratory tract and the alveolar epithelial cells to the blood circulation; crossing of the Blood Brain Barrier (BBB) and invasion of the CNS. Reproduced from [25] with permission.

The passage of the virus to the blood circulation may follow the infection of type II alveolar epithelial cells, which highly express ACE2, and the epithelial cells of the gastrointestinal tract, which also express ACE2 receptors and can be infected by SARS-CoV-2[53]. The most plausible scenario is that of access through the respiratory tract: the damage to lung blood vessels following SARS-CoV-2 infection, including endothelial necrosis and capillary injury, has been demonstrated in postmortem analyses, and suggests that the virus can translocate from the lungs to the pulmonary microcirculation and then spread to other organs[25,56].

The "Trojan horse" mechanism is the process by which the virus infects lymphocytes and monocytes, and the latter, activated by the infection, can disseminate and cross the BBB; infected macrophages have been described in COVID-19, suggesting that latent SARS-CoV-2 infection can establish in immune cells[25,56]. Finally, the trans-synaptic dissemination can be retrograde or antegrade and use an exocytosis/endocytosis mechanism or the rapid axonal transport; it could be facilitated by proteins called dinein and kinesin, both possible targets of the virus[57,58].

The virus can either infect endothelial cells of the BBB or epithelial cells of the blood-CSF barrier in the choroid plexus to enter the CNS.

Figure 1.2: Passage of SARS-CoV-2 through the Blood Brain Barrier triggering a neuroinflammation process



SARS-CoV-2 infection of microglia and neurons triggers an inflammatory cascade with release of pro-inflammatory cytokines and chemokines in the Central Nervous System (CNS). b) These pro-inflammatory cytokines and chemokines, in turn, reduce the integrity of the Blood Brain Barrier (BBB) and allow the entry of other viruses and mediators of inflammation into the CNS. This neuroinflammation process eventually causes neurotoxicity and neuronal death. Reproduced from [65] with permission.

During transcellular migration, the virus invades host endothelial cells to cross the BBB, while during paracellular migration, the virus invades the tight junctions formed by the endothelial cells[59]. ACE2 and NRP1 have been found in human brain microvascular endothelial cells (BMVECs) and may allow viral entry to the CNS; the examination of postmortem brain samples by transmission electron microscopy has found the presence of viral-like proteins inside BMVECs in the frontal lobe[45]. Human choroid plexus expresses ACE2 and, thanks to its greater permeability compared to BBB, it could provide a second entry route to the CNS[25,60]; on the other hand, the low viral load in the blood makes this an unlikely means of entry to the CSN[25].

BBB is negatively affected by viral infections, not only thanks to the productive or non-productive infection of endothelial cells, but also by the host immune response that stimulate the release of pro-inflammatory cytokines, chemokines and cell adhesion molecules, finally leading to changes in the structural and functional integrity of the BBB[31]. The inflammatory mediators could break down the BBB by reducing the integrity of the tight junction proteins[61]. In turn, BBB dysfunction creates a vicious circle, allowing the passage of other free viral particles and infected immune cells to the CNS.

The increase in BBB permeability has been described in COVID-19 patients with neurological symptoms[62] and, recently, a possible direct role for SARS-CoV-2 in modifying BBB properties has been reported. In a BBB-on-a-chip *in vitro* model of the human BBB, the subunits S1, S2 and RBD of the spike protein are able to promote a loss of barrier integrity, triggering a proinflammatory response on brain endothelial cells that includes upregulation of Matrix Metalloproteinases (MMP), cell adhesion molecules (ICAM-1 and VCAM-1), leukocyte chemotaxis factors (CXCL10 and RANTES) and cytokines (IL-1β and IL-6), and may finally contribute to a destabilization of BBB function[31].

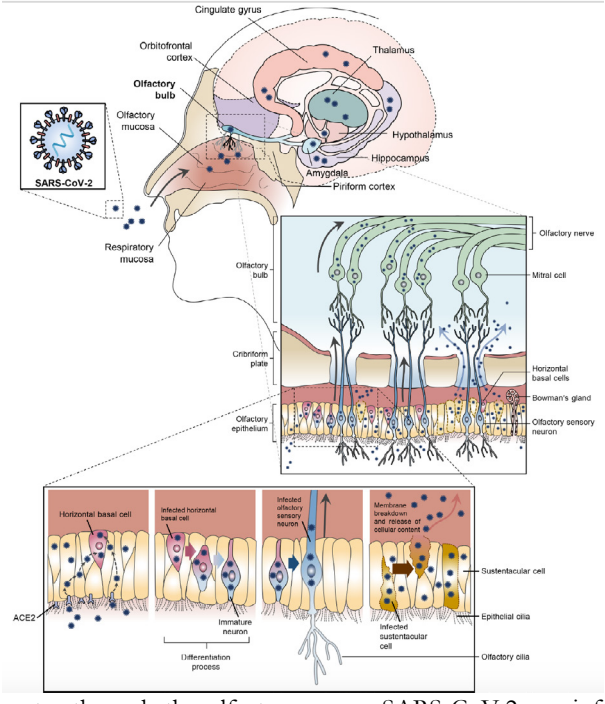
On entry into the CNS, SARS-CoV-2 may cause active infection of resident cells, thanks to the presence of its receptors, such as ACE2, NRP1 and BSG)[45]. Furthermore, the virus or infected lymphocytes could stimulate the production of pro-inflammatory cytokines, such as TNF-α and IL-6, and chemokines, such as CCL5, CXCL10 and CXCL11, that can induce chemoattraction of other activated T cells in the CNS. Activated astrocytes can, in turn, produce chemokines and participate in the recruitment of leukocytes. This process, for which the viral infection is the first trigger, finally causes neuroinflammation and neurotoxicity, damaging oligodendrocytes and neurons[63].

The presence of SARS-CoV-2 in the brain was not always associated with the severity of neuroinflammation and immune-activation, probably underlining the fact that the virus can hide in neurons and elude the surveillance of the immune system, or that the immune response is not effectively activated in the infected areas unless the neurons that were infected first have been significantly impaired[41].

As regards peripheral nerve dissemination, coronaviruses are known to invade peripheral nerve terminals and spread retrogradely across nerve synapses, reaching the CNS. Several viruses may spread to the peripheral nerves by binding to specific receptors on the axons or dendrites of the neurons[64]. Once the neurons are infected, the viruses reside in endosomal vesicles, resulting from the cytomembrane during viral entry, and use dinein to transport the vesicles along the microtubule to the centrosome beside the nucleus. Gradually, the viral capsid disassembles, according to the change in pH in the endosomal vesicle, and the viral nucleic acids are then released to the cytoplasm, allowing viral replication. Finally, viral nucleic acids and viral proteins are transported to synaptic membrane for further assembly and transmission to the next neuron and to the CNS[7].

Recently, a rapid accumulation of SARS-CoV-2 in the brain was reported after intranasal injection using a new humanized ACE knock-in-mouse model[56]. The most likely way of entering the CNS following intranasal infection is through the olfactory receptor neurons, also known as olfactory sensory neurons[27,29].

Figure 1.3: Possible SARS-CoV-2 entry to the central nervous system (CNS) via the olfactory nerve



SARS-CoV-2 entry through the olfactory nerve. SARS-CoV-2 can infect the olfactory epithelium thanks to the ACE2 receptor expressed by the horizontal basal cells. Horizontal basal cells can mature in infected olfactory neurons that are connected with neurons in the olfactory bulb; these neurons allow the viral spread to other areas in the CNS. Furthermore, the infected olfactory epithelial cells can release the virus at the cribriform plate. Reproduced from [25] with permission.

The virus can pass the neuroepithelium of the olfactory mucosa and reach the olfactory bulb, the olfactory nerve, and, from there, eventually spread to the hippocampus or other brain structures[27,32]. The ability to enter the olfactory bulb was reported for SARS and another coronavirus, OC43, using murine models of human coronavirus infection[65], and several studies have recently proposed this process in the context of SARS-CoV-2[25,33,56,59,66,67]. Figure 1.3 shows the proposed mechanism for SARS-CoV-2 entry into the CNS through the olfactory receptor neurons[25]. Given that SARS-CoV-2 spreads through the respiratory tracts, the olfactory nerve may serve as a major retrograde route for the spread of the virus to the CNS[7,68]. Furthermore, the proximity of the cribriform plate to the infected nasal epithelium, possible traumas due to sneezing, and the detection of the highest SARS-CoV-2 viral load in nasal swabs compared to bronchoalveolar lavage or pharyngeal swabs, all seem to confirm the different means of entry into the CNS through this route[25,32].

SARS-CoV-2 could infect the olfactory neurons thanks to its binding to NRP1 and BSG. In fact, both these proteins are expressed in the olfactory bulb at higher levels than ACE2 or TMPRSS2; NRP1 is also expressed in the olfactory epithelium[69-73]. In contrast, in another model, the first target of the virus could be the sustentacular cells (SUSs) thanks to their expression of ACE2 and TMPRSS2; the infection of these cells triggers a cascade of events leading to anosmia and eventually allows access of the virus to the CNS.

The possible entry through olfactory receptor neurons has also been hypothesized after the detection of SARS-CoV-2 RNA and viral proteins, with associated microgliosis and/or lymphocytic infiltrations, in the olfactory mucosa of most of the autopsies that have been carried out[41]. In animal models, immunostaining for SARS-CoV-2 revealed extensive staining in secondary and tertiary brain regions connected with the olfactory bulb, and the possibility of invasion of the brain in a retrograde manner along gustatory and trigeminal pathways at the early stage of infection was shown[24].

Other potential routes of brain infection through nerve dissemination could be possible, as well as via vagus, trigeminal and nasopharyngeal nerves; in fact, ACE2 and NRP1 are expressed in the vagus nerve in animal models, and trigeminal and nasopharyngeal nerves are easily exposed to SARS-CoV-2[25,53]. SARS-CoV-2 fragments have been found in a patient's conjunctiva, where the sensory nerve endings of the trigeminal nerve are found. In addition, local peripheral nerves of the gastrointestinal tract may play a role in the retrograde penetration of SARS-CoV-2 to the CNS[53].

However, additional data on humans are needed to understand if these mechanisms are likely to produce CNS infection[25].

Indirect CNS damage in the course of SARS-CoV-2 infection: non-specific complications of systemic disease

The CNS could also be damaged by hyperinflammation syndrome and the "cytokine storm" that is triggered outside the brain by SARS-CoV-2, or by the severe effects of systemic disorders, such as sepsis, hyperpyrexia, hypoxia, hypercoagulability and critical illness with multiorgan failure[25,32,74,75].

The excessive levels of proinflammatory cytokines and chemokines in the systemic circulation, caused by a maladaptive innate immunity, may increase the permeability of the BBB; the passive flow of cytokines/chemokines to the CNS, together with infected immune cells, could damage the brain[58,61]. Furthermore, IL-6, IL-1 and TNF-α are all upregulated in the brain of infected animal models and are produced in the human CNS following brain injuries[37]. In fact, sepsis and the subsequent inflammatory "cytokine storm" has been implicated in cases of an altered state of consciousness[37]. Increased levels of pro-inflammatory cytokines in the CNS could also persist for a lengthy period of time, leading to a post-infectious proinflammatory state that may contribute to possible long-term neuroinflammation[61].

Metabolic imbalances, including disorders of blood calcium, sodium and glucose, and renal and/or liver dysfunction, may have secondary negative effects on CSN function[56].

Systemic factors could also be responsible for the increased risk of cerebrovascular disease in COVID-19 patients. The SARS-CoV-2 binding to the ACE2 receptor on endothelial cells may result in increased blood pressure. Arterial hypertension can also complicate severe or critical COVID-19 as consequence of the viral infection or kidney damage, and can result in ischemic or cerebral bleeding[74]. Together with an increase in blood pressure, thrombocytopenia and thrombus formation due to hypercoagulability in the brain or in peripheral veins could finally lead to stroke. Indeed, the marked systemic inflammation and hypercoagulability that characterize severely affected patients are associated with increased risk of thrombotic events and stroke. Cases of myocarditis associated with SARS-CoV-2 have also been described and can lead to ischemic stroke through heart failure, with a reduction in the cerebral blood supply, or supra- and ventricular arrhythmias causing intra-ventricular thrombus formation. Finally, systemic and CNS inflammatory vasculitis have been reported from autopsies of COVID-19 patients[56].

Severe COVID-19 with acute respiratory failure, severe acute respiratory distress syndrome (ARDS), or even cardiac arrest can be associated with cerebral hypoxia[32,74]. Hypoxia may cause indirect neuronal damage[56]. There is, however, some evidence that the possible hypoxic injury is not an underlining mechanism of CNS impairment in COVID-19. In fact, hypoxia causes specific features on cerebral imaging: (i) the localization of lesions in grey matter; (ii) the edema, loss

of grey/white matter differentiation, reversal sign, white cerebellum sign, linear hyperdensity outlining the cortex and pseudo-subarachnoid bleeding on a CT scan; or (iii) cytotoxic edema within the first 24 hours with T2-hyperintensity of the lesions, subsequent pseudo-normalization of the lesions after 1 week and T1-hyperintensity after 1-2 weeks suggesting cortical laminar necrosis on MRI[76]. The evolution of these lesions has not been described in COVID-19 patients. Moreover, most patients are intubated and on mechanical ventilation before they develop cerebral hypoxia[74].

It has been hypothesized that the gut-brain axis could also be responsible for the CNS impairment during the clinical course of SARS-CoV-2 infection; however, the actual impact of SARS-CoV-2 on gut microbiota has yet to be established. The possible relationships between gut and brain could be due to a direct viral invasion of the CNS through systemic circulation or the vagal nerve after entry from the gut, or the disruption of the homeostasis of mucosal immunity and gut microbiota with repercussions on the CNS. In fact, a gut dysbiosis induced by the virus could make the CNS even more susceptible to harmful agents including pathogens and SARS-CoV-2 itself[77].

One last mechanism of possible CNS damage is the effect of empiric treatments for COVID-19; rhabdomyolisis was sometimes described after treatment with antivirals, such as remdesivir and lopinavir/ritonavir, while toxic myopathy can be caused by chloroquine or some antibiotics[74]. Finally, a myasthenic syndrome was reported after treatment with chloroquine. However, we must consider that most of these therapies are no longer recommended in the guidelines for COVID-19 treatment, and this mechanism could explain only a small part of the neurological complications associated with COVID-19[78,79]. A possible alteration of the adaptive cellular immune response to viruses could be caused by the use of steroids, even if their role in switching off the inflammatory response seems to be more important than any possible negative effects[46].

Indirect CNS damage during SARS-CoV-2 infection: para-infectious and post-infectious immune-mediated disease

SARS-CoV-2 could cause indirect damage to the CNS because of an infection-triggered excessive and detrimental immune activation[47]. Autoimmune responses to the virus have also been proposed as para- or post-infectious mechanism of CNS damage and could explain some neurological manifestations, such as Guillain-Barré syndrome, acute necrotizing encephalopathy, and acute disseminated encephalomyelitis, that have been described in COVID-19 patients[26,37,43].

As regards immune-mediated process, SARS-CoV-2 infection may be associated with a process of neuroinflammation, similar to that described in other

viral infections and in neurological diseases, such as Alzheimer's and Parkinson's disease. SARS-CoV-2 could escape from the immune system and spread to all CNS tissue, causing increased viral replication or over-reactive innate immune responses[61]. The activation of glial cells by SARS-CoV-2 could result in further production of cytokines/chemokines that ultimately damage neurons[61].

The neuroinflammation could also be associated with cellular senescence and a state of cell proliferative arrest, as an adaptive response to the viral infection, eventually resulting in neurodegenerative processes. The possibility that neurodegenerative diseases could follow the viral infection in certain patients as long-term consequences is still under investigation[32,58]. The possible causes could be the establishment of a latent reservoir of SARS-CoV-2 in the CNS and long-term neuroinflammation[26,61]. Following latent viral infection, vascular endothelium dysfunction and oxidative stress could persist, and both these processes have been well described as determinants of neurodegeneration[61,80].

Immune-mediated demyelinating diseases have been described for other coronaviruses, following the virus-induced inflammation and activation of glial cells; the same mechanism could lead do demyelinating diseases also after SARS-CoV-2 infection[67].

Brain regions affected by SARS-CoV-2 infection

Brainstem could be one of the major areas affected by SARS-CoV-2 infection in the CNS; one hypothesis is that the infection of respiratory centers in the medulla oblongata and the pons could contribute partially to the respiratory breakdown of COVID-19 patients. The spread via synapse-connected route into the brainstem cardiorespiratory centers of the medulla oblongata has been demonstrated for other coronaviruses and is thus likely also for SARS-CoV-2[8]. Grey matter could be directly impacted by the infection as demonstrated by edema and partial neuronal degeneration observed in autopsies. Finally, demyelinating lesions have been described in the white matter and the spine[8].

Neuropathological findings of COVID-19 patients

Histological findings described in COVID-19 patients are heterogeneous[81]. The most frequent are: (i) microglial activation, mostly confined to the brainstem, the cerebellum, the frontal lobe and meninges; (ii) lymphoid inflammation including perivascular lymphocytosis, parenchymal lymphocytic infiltration and leptomeningeal lymphocytic inflammation with a prevalence of infiltration of CD8+ cytotoxic T lymphocytes; (iii) hypoxic-ischemic changes; (iv) variable degrees of astrogliosis in all brain regions; (v) myelin loss; (vi) acute/subacute brain infarcts; and (vii) primary hemorrhage and microthrombi[48,81,82].

Conclusions

SARS-CoV-2 may be neurotropic and it has been demonstrated that it can reach the CNS. The exact mechanisms of neuropathogenesis of SARS-CoV-2 infection are still unknown and are likely to be multifactorial. It is likely that the virus could harm the CNS both directly, entering the CNS and triggering a process of neuroinflammation, and indirectly, thanks to systemic inflammation and immune-mediated processes. Viral entry to the CNS is under investigation: similar to other viruses and coronaviruses, SARS-CoV-2 could enter the CNS through the systemic circulation crossing the BBB, through the infection of immune cells, such as lymphocytes and monocytes (the "Trojan horse" mechanism) or through a neuronal retrograde dissemination, via olfactory mucosa or gastrointestinal tract. Future studies will promote a better understanding of the real neurovirulence of SARS-CoV-2.

Take-home message

- SARS-CoV-2 infection can involve the Central Nervous System (CNS) causing neurological symptoms at the time of the diagnosis or neurological complications that could appear later, defined as "Neuro-COVID".
- SARS-CoV-2 could determine neurological impairment directly invading the CNS or indirectly by para/post-infectious immune-mediated disease or by a secondary involvement of the CNS in the course of systemic COVID-19 disease.
- The virus reaches the CNS through the blood circulation crossing the Blood Brain Barrier (BBB) and/or through the olfactory nerve. The exact mechanisms of viral entry into the CNS are still not completely understood.
- SARS-CoV-2 can infect the microglia and neuronal cells and the viral presence in the CNS triggers an inflammatory cascade; pro-inflammatory cytokines and chemokines increase the permeability of the BBB, allowing the arrival of new viral particles, as well as immune system cells and inflammatory mediators, in the CNS. A process of neuroinflammation is then established which ultimately causes neurotoxicity.
- The long-term consequences of "Neuro-COVID" and the possibility of establishing a latent viral reservoir in the CNS or developing neurodegenerative diseases following the acute viral infection is still under investigation.

References

1. Coronaviridae Study Group of International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5(4):536-544.
2. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med.* 2004;10(12 Suppl):S88-97.
3. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012;367(19):1814-1820.
4. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020;395(10224):565-574.
5. Zhang YZ, Holmes EC. A Genomic Perspective on the Origin and Emergence of SARS-CoV-2. *Cell.* 2020;181(2):223-227.
6. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579(7798):270-273.
7. Huang J, Zheng M, Tang X, et al. Potential of SARS-CoV-2 to Cause CNS Infection: Biologic Fundamental and Clinical Experience. *Front Neurol.* 2020;11:659.
8. Bougakov D, Podell K, Goldberg E. Multiple Neuroinvasive Pathways in COVID-19. *Mol Neurobiol.* 2021;58(2):564-575.
9. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat Rev Microbiol.* 2009;7(6):439-450.
10. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280.e8.
11. Snijder EJ, van der Meer Y, Zevenhoven-Dobbe J, et al. Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. *J Virol.* 2006;80(12):5927-5940.
12. Wu HY, Brian DA. Subgenomic messenger RNA amplification in coronaviruses. *Proc Natl Acad Sci U S A.* 2010;107(27):12257-12262.
13. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. *Cell.* 2020;181(5):1016-1035.e19.
14. Hui KPY, Cheung MC, Perera RAPM, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. *Lancet Respir Med.* 2020;8(7):687-695.
15. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci.* 2020;12(1):8.
16. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720.

17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
18. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis*. 2020;71(15):762-768.
19. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-2629.
20. Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. *Trends Immunol*. 2020;41(12):1100-1115.
21. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
22. COVID-19 Investigation Team. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nat Med*. 2020;26(6):861-868.
23. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol*. 2020;19(9):767-783.
24. Liu JM, Tan BH, Wu S, et al. Evidence of central nervous system infection and neuroinvasive routes, as well as neurological involvement, in the lethality of SARS-CoV-2 infection. *J Med Virol*. 2021;93(3):1304-1313.
25. Burks SM, Rosas-Hernandez H, Alejandro Ramirez-Lee M, et al. Can SARS-CoV-2 infect the central nervous system via the olfactory bulb or the blood-brain barrier? *Brain Behav Immun*. 2021;95:7-14.
26. Jha NK, Ojha S, Jha SK, et al. Evidence of Coronavirus (CoV) Pathogenesis and Emerging Pathogen SARS-CoV-2 in the Nervous System: A Review on Neurological Impairments and Manifestations. *J Mol Neurosci*. 2021;19:1-18.
27. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. *Nat Rev Neurol*. 2020;16(11):636-644.
28. Conde Cardona G, Quintana Pájaro LD, Quintero Marzola ID, et al. Neurotropism of SARS-CoV 2: Mechanisms and manifestations. *J Neurol Sci*. 2020;412:116824.
29. Wang SC, Su KP, Pariante CM. The three frontlines against COVID-19: Brain, Behavior, and Immunity. *Brain Behav Immun*. 2021;93:409-414.
30. Helbok R, Chou SH, Beghi E, et al. NeuroCOVID: it's time to join forces globally. *Lancet Neurol*. 2020;19(10):805-806.
31. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood-brain barrier. *Neurobiol Dis*. 2020;146:105131.
32. DeKosky ST, Kochanek PM, Valadka AB, et al. Blood Biomarkers for Detection of Brain Injury in COVID-19 Patients. *J Neurotrauma*. 2021;38(1):1-43.
33. Singal CMS, Jaiswal P, Seth P. SARS-CoV-2, More than a Respiratory Virus: Its Potential Role in Neuropathogenesis. *ACS Chem Neurosci*. 2020;11(13):1887-1899.

34. Panciani PP, Saraceno G, Zanin L, et al. SARS-CoV-2: "Three-steps" infection model and CSF diagnostic implication. *Brain Behav Immun*. 2020;87:128-129.
35. Sanclemente-Alaman I, Moreno-Jiménez L, Benito-Martín MS, et al. Experimental Models for the Study of Central Nervous System Infection by SARS-CoV-2. *Front Immunol*. 2020;11:2163.
36. Song E, Zhang C, Israelow B, et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain. *J Exp Med* 2021; 218(3):e20202135.
37. Armocida D, Palmieri M, Frati A, et al. How SARS-Cov-2 can involve the central nervous system. A systematic analysis of literature of the department of human neurosciences of Sapienza University, Italy. *J Clin Neurosci*. 2020;79:231-236.
38. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55-58.
39. Huang YH, Jiang D, Huang JT. SARS-CoV-2 Detected in Cerebrospinal Fluid by PCR in a Case of COVID-19 Encephalitis. *Brain Behav Immun*. 2020;87:149.
40. Virhammar J, Kumlien E, Fällmar D, et al. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. *Neurology*. 2020;95(10):445-449.
41. Li YC, Zhang Y, Tan BH. What can cerebrospinal fluid testing and brain autopsies tell us about viral neuroinvasion of SARS-CoV-2. *J Med Virol*. 2021;93(7):4247-4257.
42. Edén A, Kanberg N, Gostner J, et al. CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series. *Neurology*. 2021;96(2):e294-e300.
43. Espíndola OM, Brandão CO, Gomes YCP, et al. Cerebrospinal fluid findings in neurological diseases associated with COVID-19 and insights into mechanisms of disease development. *Int J Infect Dis*. 2021;102:155-162.
44. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(23):2268-2270.
45. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol*. 2020;92(7):699-702.
46. Koralnik IJ, Tyler KL. COVID-19: A Global Threat to the Nervous System. *Ann Neurol*. 2020;88(1):1-11.
47. Heming M, Li X, Räuber S, et al. Neurological Manifestations of COVID-19 Feature T Cell Exhaustion and Dedifferentiated Monocytes in Cerebrospinal Fluid. *Immunity*. 2021;54(1):164-175.e6.
48. Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol*. 2020;19(11):919-929.
49. Schaller T, Hirschbühl K, Burkhardt K, et al. Postmortem Examination of Patients With COVID-19. *JAMA*. 2020;323(24):2518-2520.
50. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological Features of Covid-19. *N Engl J Med*. 2020;383(10):989-992.

51. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med.* 2020;383(6):590-592.
52. Bulfamante G, Bocci T, Falleni M, et al. Brainstem neuropathology in two cases of COVID-19: SARS-CoV-2 trafficking between brain and lung. *J Neurol.* 2021;18:1-6.
53. Lima M, Siokas V, Aloizou AM, et al. Unraveling the Possible Routes of SARS-COV-2 Invasion into the Central Nervous System. *Curr Treat Options Neurol.* 2020;22(11):37.
54. Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. *J Neurol.* 2020;267(8):2179-2184.
55. Saleki K, Banazadeh M, Saghazadeh A, Rezaei N. The involvement of the central nervous system in patients with COVID-19. *Rev Neurosci.* 2020;31(4):453-456.
56. Pennisi M, Lanza G, Falzone L, et al. SARS-CoV-2 and the Nervous System: From Clinical Features to Molecular Mechanisms. *Int J Mol Sci.* 2020;21(15):5475.
57. Desforges M, Le Coupanec A, Dubeau P, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? *Viruses.* 2019;12(1):14.
58. Pacheco-Herrero M, Soto-Rojas LO, Harrington CR, et al. Elucidating the Neuropathologic Mechanisms of SARS-CoV-2 Infection. *Front Neurol.* 2021;12:660087.
59. Achar A, Ghosh C. COVID-19-Associated Neurological Disorders: The Potential Route of CNS Invasion and Blood-Brain Relevance. *Cells.* 2020;9(11):2360.
60. Deffner F, Scharr M, Klingenstein S, et al. Histological Evidence for the Enteric Nervous System and the Choroid Plexus as Alternative Routes of Neuroinvasion by SARS-CoV2. *Front Neuroanat.* 2020;14:596439.
61. ElBini Dhouib I. Does coronaviruses induce neurodegenerative diseases? A systematic review on the neurotropism and neuroinvasion of SARS-CoV-2. *Drug Discov Ther.* 2021;14(6):262-272.
62. Bellon M, Schweblin C, Lambeng N, et al. Cerebrospinal fluid features in SARS-CoV-2 RT-PCR positive patients. *Clin Infect Dis.* 2020; ciaa1165.
63. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci.* 2020;11(7):995-998.
64. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheimers Dis.* 2020;76(1):3-19.
65. Acharya A, Kevadiya BD, Gendelman HE, Byrareddy SN. SARS-CoV-2 Infection Leads to Neurological Dysfunction. *J Neuroimmune Pharmacol.* 2020;15(2):167-173.
66. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci.* 2021;24(2):168-175.
67. Mahalakshmi AM, Ray B, Tuladhar S, et al. Does COVID-19 contribute to development of neurological disease? *Immun Inflamm Dis.* 2021;9(1):48-58.

68. DosSantos MF, Devalle S, Aran V, et al. Neuromechanisms of SARS-CoV-2: A Review. *Front Neuroanat*. 2020;14:37.

69. Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science*. 2020;370(6518):856-860.

70. Wang K, Chen W, Zhang Z, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduct Target Ther*. 2020;5(1):283.

71. Daly JL, Simonetti B, Klein K, et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. *Science*. 2020;370(6518):861-865.

72. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. *Cell*. 2020;183(1):16-27.e1.

73. Chekol Abebe E, Mengie Ayele T, Tilahun Muche Z, et al. Neuropilin 1: A Novel Entry Factor for SARS-CoV-2 Infection and a Potential Therapeutic Target. *Biologics*. 2021;15:143-152.

74. Finsterer J. Putative mechanisms explaining neuro-COVID. *J Neuroimmunol*. 2020;350:577453.

75. Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: a review and a call for action. *J Neurol*. 2020;267(6):1573-1576.

76. Huang BY, Castillo M. Hypoxic-ischemic brain injury: imaging findings from birth to adulthood. *Radiographics*. 2008;28(2):417-39; quiz 617.

77. Chaves Andrade M, Souza de Faria R, Avelino Mota Nobre S. COVID-19: Can the symptomatic SARS-CoV-2 infection affect the homeostasis of the gut-brain-microbiota axis? *Med Hypotheses*. 2020;144:110206.

78. Update to living WHO guideline on drugs for covid-19. *BMJ*. 2021;372:n860.

79. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis*. 2020; ciaa478.

80. Yachou Y, El Idrissi A, Belapasov V, Ait Benali S. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. *Neurol Sci*. 2020;41(10):2657-2669.

81. Lou JJ, Movassaghi M, Gordy D, et al. Neuropathology of COVID-19 (neuro-COVID): clinicopathological update. *Free Neuropathol*. 2021;2:2.

82. von Weyhern CH, Kaufmann I, Neff F, Kremer M. Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *Lancet*. 2020;395(10241):e109.

Chapter 2. The lung-brain axis

Giuseppe Francesco Sferrazza Papa, Giulia Michela Pellegrino, Stefano Centanni

Introduction

There is an intrinsic connection between neurological and respiratory functions both in conditions of health and of disease. Over the past decades, it has become increasingly acknowledged that lung and brain represent an integrated physiological *ensemble* such that insults involving one organ will necessarily affect the other. For instance, it has been shown that neurological conditions such as brain death[1], traumatic brain injury[2], or status epilepticus[3] may cause pulmonary edema and lung injury, thus further worsening clinical outcomes[4,5]. On the other hand, severe respiratory disorders such as acute respiratory distress syndrome (ARDS) may be responsible for poor neurocognitive outcomes[6].

After a brief overview of neurobiology and physiology, this chapter will introduce the concepts of dyspnea and respiratory failure in COVID-19, and then focus on post-COVID sequelae with a special focus on the respiratory and neurological aspects. Finally, we will provide some practical recommendations for the clinician caring for patients post COVID. Further insights into the neurogenic component of COVID-19-related respiratory failure are discussed elsewhere in the book.

Neurobiology and pathophysiology

Breathing is a key homeostatic function that regulates gas exchanges of oxygen (O_2) and carbon dioxide (CO_2) in the lung in order to stabilize pH and support metabolism. Ventilation is the result of the integrated actions between the mechanical properties of the airways, lungs, respiratory muscles, and the chest wall, while gas exchanges are due to the capacity of the lung to exchange gases across the alveolar–capillary membrane.

Respiratory movements occur automatically and continuously, and are driven by the rhythmic motor activity generated within neural circuits in the brainstem and spinal cord[7]. The underlying neural machinery is not a simple trigger, but rather a complex flexible system that provides physiological and behavioral

integration. Recent research showed that the brainstem respiratory network works at multiple hierarchical levels, which allows flexible expression of different rhythmogenic mechanisms under different physiological conditions and enables a wide repertoire of respiratory patterns[8]. The core circuit components of the neural machinery that generates the rhythm and shapes the inspiratory and expiratory motor patterns are located within three adjacent structural compartments in the ventrolateral medulla: the Bötzinger complex (BötC), pre-Bötzinger complex (pre-BötC), and rostral ventral respiratory group (rVRG)[8]. Recent experiments showed that, in adult mammals, the rhythm is dominated by the pre-BötC[9] which seems to work as a self-organized group-pacemaker[10].

The respiratory rhythm should then be modulated to satisfy the body's metabolic demand and transformed into an efficient pattern of movement. To regulate this task, the brain links sensory information to the motor output, the respiratory muscles. To provide this regulation, carotid bodies and brainstem chemosensory organs monitor blood O_2 and CO_2 levels. The carotid bodies are located at the bifurcation of the carotid arteries and produce signals that relate mostly to O_2 levels in arterial blood[10,11]. Although lung and cardiac diseases are the main causes of breathing disorders, dysfunctions of the neural control of breathing may play a role in some diseases such as sudden infant death syndrome (SIDS)[12,13]. Several genetic disorders cause abnormal respiration, including Rett syndrome[14] and congenital central hypoventilation syndrome (also known as Ondine's curse)[15]. Death due to progressive respiratory failure occurs in neurodegenerative diseases such as amyotrophic lateral sclerosis, and may play a role in some cases of Parkinson's disease[16] and multiple system atrophy (MSA).

Respiratory dysfunction and brainstem viral infections

The relationship between respiratory alterations and brainstem viral infections has long been studied and appears to stem from both primary respiratory and brainstem affections.

A) *Primary respiratory affections* - changes in primary afferent neurosensors subsequent to respiratory viral infections may alter the synaptic integration of peripheral inputs at the brainstem level. The most frequent consequence is cough hypersensitivity following an acute respiratory viral infection. Studies employing capsaicin inhalation challenge to measure cough reflex sensitivity have documented a transient tussive hyper-responsiveness induced by upper respiratory infections (URI) that reverts to normal values by 4-8 weeks post infection. An underlying hypersensitivity of the cough reflex potentiates the effect of the exogenous stimulus, resulting in refractory, chronic cough in a particular subgroup of individuals[17].

Numerous mechanisms have been proposed to explain the transient cough and enhancement of cough reflex sensitivity associated with acute viral URI. Direct effects of the viral infection on airway epithelium include inflammation and cytokine release which stimulate sensory afferent nerves. Other airway effects of URI include increase in neurotransmitter levels, such as Substance P, reduced activity of neutral endopeptidases, increased neural receptor levels (NK-1), and transient modulation of airway neural activity. Increased leukotriene production and mucus hypersecretion are likely additional contributors to cough induction. Many patients experience cough during acute COVID-19 pneumonia, and less frequently report cough as a symptom of long COVID. The latter might result from the invasion of vagal sensory neurons by SARS-CoV-2 or a neuroinflammatory response, or both, leading to peripheral and central hypersensitivity of cough pathways similar to that of the cough hypersensitivity syndrome.

B) *Brainstem affections* - brainstem viral infections can cause respiratory complications, both by direct pulmonary involvement and respiratory muscle failure.

Most tumoral and infectious causes of brainstem encephalitis (BE) determine ventilatory failure by compromising the central ventilatory control, as is the case of Listeria Monocitogenes, herpes simplex virus (HSV) 1 and 2, and human herpes virus 6 (HHV6); some may affect respiratory muscles as well, such as the Epstein-Barr virus (EBV)-related overlapping of BE and Guillain-Barré syndrome, while others primarily determine bulbar muscle impairment and subsequent respiratory failure, such as the progressive multifocal leukoencephalopathy (PML) caused by the JC polyomavirus[18].

Brain stem encephalitis caused by enterovirus 71 determines a release of cytokines and chemokines which may induce secondary pulmonary edema (PE). The disease is a hyperinflammatory syndrome resulting from hypercytokinemia and central nervous system inflammation of various inflammatory mediators. Some studies have shown that proinflammatory cytokines (interleukin [IL]-6, tumor necrosis factor [TNF]-α, and IL-1β) are associated with brainstem encephalitis that is complicated by PE[19].

Recent reports have provided some evidence of the occurrence of acute respiratory failure in COVID-19 due to neurotropism of the brainstem by SARS-CoV-2, which may contribute to the pulmonary damage. SARS-CoV-2 probably invades the brain via axonal transport and transneuronal spread from the olfactory nerves on to the rhinencephalon, finally reaching the brainstem and causing the irreversible respiratory failure seen in severe COVID-19, typically characterized by lack of dyspnea[20].

Patients with COVID-19 often develop respiratory failure 8-14 days after symptom onset, with "silent hypoxemia" and a high respiratory rate, resulting in hypocapnia. The hypoxia in COVID-19 leading to stimulation of the pre-BÖTC via the chemoreceptor area is expected to cause an increased respiratory

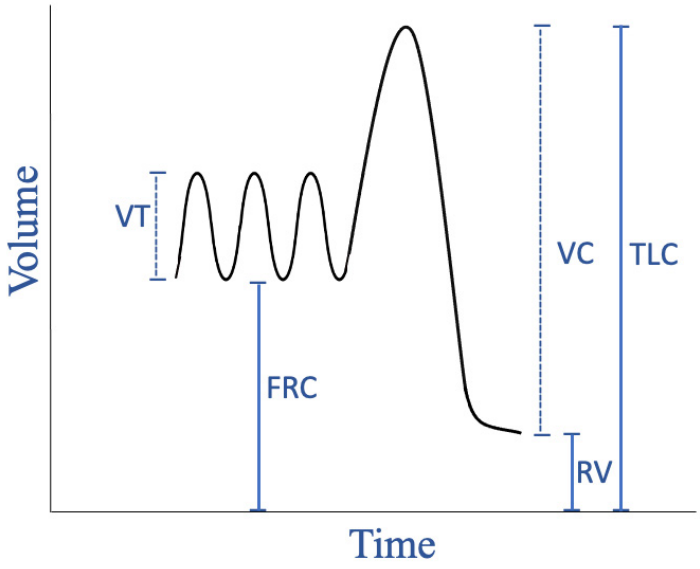
rate and depth that has often been reported in COVID-19 patients. On the contrary, the patients with profound hypoxia seemingly appear to be asymptomatic, though respiratory failure is expected to occur quite soon. Damage to vagal receptors of the lungs, and perhaps mechanoreceptors of the respiratory muscles, might explain the lack of dyspnea, along with a possible defective central neural system processing of the respiratory signals[21].

Respiratory clinical physiology

Patients with persistent respiratory symptoms after COVID-19 need to be thoroughly examined to assess the presence of disease sequelae. Outside the emergency setting, pulmonary function testing (PFTs) is part of the key investigations, and this must be performed before any invasive or second-line imaging tests such as computed tomography.

As the COVID-19 infection quite often affects lung parenchyma, spirometry and lung volume measurements may be of help to detect the lung disease. This is strongly suggested by a decrease in total lung capacity (TLC), forced vital capacity (FVC), and the forced expiratory volume in 1 s (FEV1) below the threshold of natural variability[22] (Figure 2.1).

Figure 2.1: Lung volumes



VT: tidal volume; RV: residual volume; FRC: functional residual capacity; VC: expiratory vital capacity; TLC: total lung capacity.

Measurement of lung gas exchange is also part of the clinical evaluation of the patients affected by COVID-19 infection. For instance, a decrease in diffusing capacity for carbon monoxide is an index of alveolar inflammation or pulmonary fibrosis. Similarly, a decrease in arterial oxygen tension will indicate an important gas exchange impairment[22]. In contrast, an increase in arterial CO_2 tension is consistent with an impairment in ventilation as a result of the inability of the inspiratory muscles to maintain the minute ventilation required to satisfy metabolic requirements. Under these conditions, measuring the inspiratory muscle force and diaphragm activity with ultrasound will help estimate the severity of the respiratory muscle defect.

Dyspnea: a complex symptom

The American Thoracic Society defines dyspnea as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses"[23]. There are numerous sensory receptors located throughout the respiratory system that send afferent information to the central nervous system. It is widely accepted that there are at least three main dyspnea components, depending on quality of the symptom, the generating stimuli, and the pathways involved: 1) air hunger; 2) work/effort; and 3) chest tightness.

1) Air hunger is a primordial sensation that signals the urgency to breathe and correlates with the failure of pulmonary ventilation in maintaining gas exchanges. It is strongly linked to the development of hypercapnia, and, to a lesser extent, of hypoxia. To the best of our practical daily experience, this is the principal component of the dyspnea experienced during COVID-19.

2) Respiratory effort arises when the work of breathing or the required motor command is increased by high minute ventilation, by impedance to inspiration, by weakness of respiratory muscles, or by placing inspiratory muscles at a disadvantageous length.

3) Chest tightness appears to be specific to bronchoconstriction and is the earliest symptom of asthma. It arises from the activation of rapidly adapting stretch receptors (RARs) and C-fiber receptors in the lungs.

Given the different mechanisms underlying dyspnea, it is of practical help to assess not only the presence and intensity, but also the different qualitative components. The widely used one-dimensional scales (such as the BORG scale[24], the Visual Analog Scale [VAS][25], or the Medical Research Council [MRC] scale[26]) adequately measure the intensity of the perceived dyspnea but cannot characterize its different components. In the past years, there has been great interest in the development of novel tools that capture the different, multidimensional

qualities of dyspnea such as the Multidimensional Dyspnea Profile (MDP) and the Dyspnea-12 Questionnaire (D12)[27].

Respiratory failure in COVID-19

The clinical spectrum of COVID-19 is quite heterogeneous. In a recent study, severity of the respiratory infection, older age, and renal impairment, and absence of any comorbidities were predictors of 28-day mortality in patients affected by COVID-19[28]. Respiratory failure due to interstitial pneumonia, decreased lung compliance, and hypoxemia are the most critical features of the disease[28,29]. Examining a series of ventilatory features such as lung elastance, ventilation-to-perfusion ratio, lung weight and lung volume recruitability, Gattinoni et al. were able to identify patterns with different combinations of the lung function/imaging parameters possibly explaining the changes in the severity of the disease over time and its susceptibility to different treatments[30].

In addition, disproportionate endothelial damage may disrupt pulmonary vasoregulation, thus promoting ventilation-perfusion mismatch and fostering thrombogenesis. Finally, remarkably increased respiratory drive could potentially increase tidal strain and energy loads to highly vulnerable tissue, thus adding patient self-inflicted lung injury[31] to the mix of the lung's inflammatory assault[32].

Mechanical ventilation support keeps patients alive until their own biological mechanisms are able to outwit the coronavirus[33]. The best way to minimize ventilator-associated complications is to avoid intubation unless it is absolutely necessary[34,35]. In a cohort of 64 patients, Brusasco et al.[36] reported successful treatment of severe COVID-19 pneumonia by CPAP ventilation in 83% of the cases, with only four deaths and seven patients requiring subsequent intubation. In a multicenter study performed on 175 patients, Aliberti et al.[37] reported only a 55% efficacy of helmet CPAP in treating severe COVID-19 pneumonia, with higher rates of CPAP failure occurring in patients with more severe pneumonia upon admission and higher IL6 levels.

Even though there is no consensus as to the best length of time for mechanical ventilation, most of the studies agree on the concept of stopping the treatment as soon as possible to avoid risks of infection and death[38].

It has been documented that, whereas the most severe and critical COVID-19 patients have no significant long-term sequelae, a substantial proportion suffers from long-lasting symptoms and respiratory impairment. In a study performed on severe and critical COVID-19 patients, about 25% of patients complained of persistent fatigue at the 3-month follow-up. Twenty percent of the patients exhibited signs of fibrosis on lung HRCT, and this was somewhat correlated with length of stay in the intensive care unit (ICU) and mechanical ventilation.

Post-COVID clinical *sequelae*

COVID-19 infection has been shown to frequently cause complications that last weeks to months after recovery. This has been named Long COVID and defined as a post-viral illness that can affect survivors of COVID-19 regardless of the initial disease severity or patient age, with a prevalence in the female sex and in those patients exhibiting more than five early COVID-19 symptoms or early dyspnea[39].

Clinical manifestations are quite heterogenous and fluctuate over time, with the most common symptoms being fatigue and dyspnea that can last for months after acute COVID-19. Other persistent symptoms may include cognitive and mental impairment, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and heart problems. Possible pathophysiologic mechanisms are persisting tissue damage within the lung, brain, and heart, and/or exaggerated inflammatory processes as a result of viral persistence, immune dysregulation, or autoimmunity.

Interestingly, many of the above mentioned respiratory, cardiovascular, gastrointestinal, and neurological problems that follow the COVID-19 infection have also been reported in other chronic diseases involving the neural system, such as chronic pain, migraine and myalgic encephalomyelitis or chronic fatigue syndrome. Whether this could be explained by neural mechanisms activated independently of the underlying diseases is an interesting hypothesis that, however, still has to be demonstrated.

Practical recommendations for the clinician

Patients recovering from COVID-19 pneumonia frequently report symptoms such as dyspnea, cough, asthenia, and general malaise even some time after the initial infection.

In view of possible further pharmacological or physical treatments, the patient should be carefully evaluated according to different criteria (Table 2.1). In chronological order, there has been a tentative suggestion to first review the clinical history of the patient along with the time course and duration of the COVID-19 disease and consider any other associated diseases that could potentially interfere with recovery. Measuring dyspnea with the VAS scale should be performed with current scales such as the MRC or multidimensional tools. Measuring oxygen saturation at rest and during walking is another simple and effective way of evaluating the patient's clinical condition and excluding severe diseases such as persistence of pulmonary thromboembolism. Routine blood tests are then recommended along with pulmonary function testing inclusive of spirometry, measurement of lung volumes, DLCO, assessment of the respiratory muscle force, and blood gas analysis. Based on these findings, CT scans

will then be recommended to provide support to steroid therapy in case of persistence of interstitial lung disease.

Finally, a cardiopulmonary exercise test could be indicated in case the dyspnea cannot be explained on the grounds of the above mentioned clinical, functional, and radiological tests. This can identify the presence of anomalous respiratory or cardiovascular adaptations to exercise and/or locomotor muscle deconditioning. In the opposite case, the hypothesis of psychogenic dyspnea could find substantial support[40].

Table 2.1: Practical issues in managing patients after COVID-19 pneumonia or post-COVID syndrome

Assessment	Treatment
SYMPTOMS AND LUNG FUNCTION	
• Assess dyspnea (exertional), cough and fatigue *(consider referral to neurologist)* • Spirometry and DLCO • Consider ABG if SpO2<92% in room air or suspected chronic respiratory failure *In selected patients*:* • full PFTs with body plethysmography • respiratory muscle testing *(e.g., MIP/MEP, SNIP)* • Perform CPET	• Check adherence to therapy and other coexisting medical conditions • Avoid empiric use of bronchodilators (*indicated only for obstructive pulmonary diseases*) • Vaccines (SARS-CoV-2, pneumococcal, flu) • Rehabilitation for selected patients • Consider enrolling in clinical trials
IMAGING	
• Follow up ground glass areas/lung nodules *(e.g., high-risk patients such as smokers)* • Avoid unjustified use of CT scan • Consider use of lung and diaphragm ultrasound	

ABG: arterial blood gas; COPD: chronic obstructive pulmonary disease; CT: computed tomography; PFT: pulmonary function tests; CPET: cardiopulmonary exercise testing; DLCO: diffusing capacity of the carbon monoxide; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; SNIP: sniff nasal inspiratory pressure. * Particularly for patients who underwent long term invasive ventilation.

Take-home message

- SARS-CoV-2 induces a wide spectrum of neurological and respiratory manifestations that may co-exist with and complicate the clinical course of the disease.
- Respiratory failure due to interstitial pneumonia is the dominant clinical issue and the main determinant for the prognosis in the acute care setting; assessing and monitoring its severity and minimizing invasive support may help to improve treatment efficacy.
- Post-COVID syndrome is an intriguing clinical entity that is currently the subject of much debate. Many survivors have been affected, with heterogenous clinical presentation often requiring a multidisciplinary diagnostic approach.
- Given the complex interactions between lung, muscles, and brain after acute respiratory failure, not only due to SARS-CoV-2, clinical physiology should guide the physician in detecting respiratory alterations and provide appropriate treatment.

Acknowledgments
The authors are grateful to Fabiano Di Marco for reviewing the practical recommendations section, to Federica Bonazza for technical support, and to Riccardo Pellegrino for reviewing and editing this chapter.

Funds
SC and GFSP are the recipients of a clinical research grant on COVID-19 funded by DG Welfare of Regione Lombardia for the RECOVER project (*recovernet.org*).

References

1. Avlonitis VS, Wigfield CH, Kirby JA, Dark JH. The hemodynamic mechanisms of lung injury and systemic inflammatory response following brain death in the transplant donor. *Am J Transplant.* 2005;5(4 Pt 1):684-693.
2. Holland MC, Mackersie RC, Morabito D, et al. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma.* 2003;55(1):106-111.
3. Johnston SC, Darragh TM, Simon RP. Postictal pulmonary edema requires pulmonary vascular pressure increases. *Epilepsia.* 1996;37(5):428-432.
4. Baumann A, Audibert G, McDonnell J, Mertes PM. Neurogenic pulmonary edema. *Acta Anaesthesiol Scand.* 2007;51(4):447-455.
5. Stevens RD, Puybasset L. The brain-lung-brain axis. *Intensive Care Med.* 2011;37(7):1054-1056.
6. Hopkins RO, Weaver LK, Pope D, et al. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;160(1):50-56.
7. Smith JC, Abdala APL, Borgmann A, et al. Brainstem respiratory networks: Building blocks and microcircuits. *Trends Neurosci.* 2013;36(3):152-162.
8. Smith JC, Abdala APL, Rybak IA, Paton JFR. Structural and functional architecture of respiratory networks in the mammalian brainstem. *Philos Trans R Soc B Biol Sci.* 2009;364:2577-2587.
9. Janczewski WA, Feldman JL. Distinct rhythm generators for inspiration and expiration in the juvenile rat. *J Physiol.* 2006;570(2):407-420.
10. Feldman JL, Del Negro CA. Looking for inspiration: new perspectives on respiratory rhythm. *Nature.* 2006;7:232-242.
11. Feldman JL, Mitchell GS, Nattie EE. Breathing: Rhythmicity, plasticity, chemosensitivity. *Annu Rev Neurosci.* 2003;26:239-266.
12. Kinney HC, Richerson GB, Dymecki SM, et al. The brainstem and serotonin in the sudden infant death syndrome. *Annu Rev Pathol Mech Dis.* 2009;4:517-550.
13. Paterson DS, Trachtenberg FL, Thompson EG, et al. Sudden Infant Death Syndrome. *JAMA.* 2006;296(17):2124-2132.
14. Chahrour M, Zoghbi HY. Review The Story of Rett Syndrome: From Clinic to Neurobiology. *Neuron.* 2007;56:422-437.
15. Weese-Mayer DE, Berry-Kravis EM, Marazita ML. In pursuit (and discovery) of a genetic basis for congenital central hypoventilation syndrome. *Respir Physiol Neurobiol.* 2005;149:73-82.
16. D'Arrigo A, Floro S, Bartesaghi F, et al. Respiratory dysfunction in Parkinson's disease: a narrative review. *ERJ Open Res.* 2020;6(4):1-12.
17. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. *Lancet.* 2008;371(9621):1364-1374.

18. Harypursat V, Zhou Y, Tang S, Chen Y. JC Polyomavirus, progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome: A review. *AIDS Res Ther.* 2020;17(1):1-11.
19. Solomon T, Lewthwaite P, Perera D, et al. Virology, epidemiology, pathogenesis, and control of enterovirus 71. *Lancet Infect Dis.* 2010;10(11):778-790.
20. Rodarte JR, Rehder K. Dynamics of respiration. In: Macklem PT, Mead J. (eds.) *Handbook of Physiology*. Section 3, Vol. III, Part 1. The Respiratory System. Mechanics of Breathing. Bethesda, American Physiological Society. 1986. p.130-144.
21. Ottestad W, Seim M, Maehlen JO. COVID-19 with silent hypoxemia. *Tidsskr Nor Laegeforen*. 2020;140(7):19-21.
22. Xiaoneng M, Wenhua J, Zhuquan S, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J.* 2020;55(6):2-5.
23. American Thoracic Society. Dyspnea. Mechanisms, Assessment, and Management: A Consensus Statementt. *Am J Respir Crit Care Med.* 1999;19(3):173-177.
24. Borg GAV. Psychophysical bases of perceived exertion. *Med Sci Sport Exerc.* 1982;14:377-381.
25. Lansing RW, Moosavi SH, Banzett RB. Measurement of dyspnea: Word labeled visual analog scale vs. verbal ordinal scale. *Respir Physiol Neurobiol.* 2003;134(2):77-83.
26. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* 1988;93(3):580-586.
27. Banzett RB, O'Donnell CR, Guilfoyle TE, et al. Multidimensional dyspnea profile: An instrument for clinical and laboratory research. *Eur Respir J.* 2015;45(6):1681-1691.
28. Novelli L, Raimondi F, Ghirardi A, et al. At the peak of covid-19 age and disease severity but not comorbidities are predictors of mortality: Covid-19 burden in Bergamo, Italy. *Panminerva Med.* 2021;63(1):51-61.
29. Grasselli G, Greco M, Zanella A, et al. Risk Factors Associated with Mortality among Patients with COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med.* 2020;180(10):1345-1355.
30. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes?. *Intensive Care Med.* 2020;46(6):1099-1102.
31. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med.* 2017;195(4):438-442.
32. Marini JJ, Hotchkiss JR, Broccard AF. Bench-to-bedside review: Microvascular and airspace linkage in ventilator-induced lung injury. *Crit Care.* 2003;7(6):435-444.
33. Tobin MJ. Basing Respiratory Management of Coronavirus on Physiological principles. *Am J Respir Crit Care Med.* 2020;201(11):1319-1328.
34. Tobin MJ. Mechanical ventilation. *N Engl J Med.* 1994;330(15):1056-1061.

35. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med.* 2001;344(26):1986-1996.
36. Brusasco C, Corradi F, Di Domenico A, et al. Continuous positive airway pressure in COVID-19 patients with moderate-to severe respiratory failure. *Eur Respir J.* 2021;57(2):1-4.
37. Aliberti S, Radovanovic D, Billi F, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study. *Eur Respir J.* 2020;56(4):1-5.
38. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. *Ann Intensive Care.* 2020;10(1):4-6.
39. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med.* 2021;27(4):626-631.
40. Rinaldo RF, Mondoni M, Parazzini EM, et al. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur Respir J.* 2021;1-11.

Chapter 3. Does the COVID-19 related respiratory failure have a neurogenic component?

Davide Chiumello, Matteo Bonifazi

Pathological pathways

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has pushed the response of health systems to maximum capacity. Worldwide the surge of cases has overwhelmed the facilities and human resources available[1-4]. Intensive care units have found themselves with no available beds due to the huge influx of severe cases over just a few weeks, with acute respiratory distress syndrome (ARDS) as the main reason for admission[1-4]. Indeed, its structure and mechanism of transmission and replication make SARS-CoV-2 highly infectious[5-9].

One widely reported phenomenon is the presence of a profoundly hypoxemic patient with the slightest, or no, dyspnea, out of proportion to the extent of radiographic abnormalities and changes in lung compliance. This clinical manifestation has been called "happy hypoxemia or hypoxia" but has been better described as "silent hypoxemia". This has led to speculation that there are underlying pathophysiologic differences between lung injury due to COVID-19 and ARDS from other causes[10-14].

Histological SARS-CoV-2 has been established as a cause of severe alveolar damage and pneumonia. The consolidation of lung parenchyma precipitates the alterations in blood gases in COVID-19 patients that are known to complicate and cause hypoxemic respiratory failure[15,16]. Indeed, the damage caused by SARS-CoV-2 at the level of gaseous exchange in the lungs causes exudative and organized diffuse alveolar damage. It has been reported that severely hypoxemic COVID-19 patients may present quite different characteristics: 1) normal breathing ("silent" hypoxemia) or remarkably dyspneic; 2) quite responsive to nitric oxide or unresponsive; 3) deeply hypocapnic or normo/hypercapnic; and 4) responsive to a prone position or not responsive. Therefore, the same disease presents itself with notable heterogeneity. The ongoing exudation and fibrosis in the terminal bronchioles and alveolar walls thicken the gaseous barrier leading

to profound hypoxia and the risk of hypoxemic-respiratory failure. Many patients with a severe drop in partial alveolar (pa)O_2 remain asymptomatic, initially due to possible compensation by an increase in the rate of breathing that comes into play through the neurogenic mechanism against hypoxia resulting from a poor diffusion of O_2 across the alveolar barrier[15-17]. A possible explanation for such severe hypoxemia occurring in a compliant lung is the possible loss of lung perfusion and hypoxic vasoconstriction[10-13].

However, the alteration of paO_2 and $paCO_2$ in COVID-19 is complex and difficult to understand when compared to conventional viral cases of pneumonia. The reason for this added complexity is the concurrent renal, gastrointestinal, and adrenal damage, coagulation abnormalities, and metabolic derangements like lactate production from cellular damage that are known contributors to the maintenance of blood pH and blood gases, and act as buffers to combat any alteration that may occur in these parameters.

An alarming but yet unexplored component in COVID-19 is the damage to the neurons in the central nervous system (CNS) that has been reported to start during the disease course in some patients. Emerging data on COVID-19 cases from hospitals and autopsies in the last few months have helped in understanding the pathogenesis of respiratory failures in COVID-19[18-21]. Recent reports have provided overwhelming evidence of the occurrence of acute respiratory failure in COVID-19 due to neurotropism of the brainstem by SARS-CoV-2[22-26]. It is easy to compute the complexity that ongoing damage to respiratory regulating neurons in CNS would add to the pulmonary damage in COVID-19. Knowledge of the circuit of neural projections and synapses that regulate the breathing process is essential to understanding respiratory failure in general and that seen in COVID-19.

The breathing process carried forward by the CNS under physiological conditions is an involuntary (autonomous) process enforced by pacemaker cells in the pre-Bötzinger complex (pre-BÖTC) on either side of the medulla oblongata in the brainstem. These neurons produce rhythmic discharges that reach the phrenic nerve motor neurons. In addition, dorsal (DRG) and ventral (VRG) groups of respiratory neurons are present in the medulla, and they are known to project to the pre-BÖTC pacemaker neurons. The rhythmic discharges of the pre-BÖTC pacemaker neurons are modified by a pneumotaxic center (nucleus parabrachialis), which may play a role in switching between inspiration and expiration in the pons and afferents in the vagus nerve from receptors in the airways and lungs.

A rise in the $paCO_2$ or H+ ion concentration of arterial blood or a drop in its paO_2 increases the rhythmic discharge in the medulla oblongata and vice versa[22-28].

The effects of variations in serum chemistry on the rhythmic discharge of pre-BÖTC are mediated via respiratory chemoreceptors: the carotid and aortic

bodies and the central chemoreceptor area in the medulla[29]. Each carotid and aortic body contains isles of two types of cells, glomus type I and glomus type II cells (supporting cells), surrounded by fenestrated sinusoidal capillaries. The glomus type I is closely associated with glossopharyngeal nerve afferent nerve (CN-IX) endings and is stimulated by hypoxia-induced inhibition of O_2-sensitive potassium K+ channels. The transmitter involved appears to be dopamine, which stimulates the nerve endings by way of D2 dopaminergic receptors. The glomus type I receptors in the carotid/aortic bodies are stimulated, with increased afferent nerve discharges, by a rise in the $paCO_2$ or H+ concentration of arterial blood or a decline in its paO_2 below 55-60 mmHg. Therefore, the stimulatory effects of hypoxia on ventilation are not manifested until they become strong enough. In addition, even though spontaneous breathing is not usually a conscious phenomenon, both inspiration and expiration are under voluntary control. The pathways for voluntary control pass from the neocortex (Brodman's area 4 neurons) to the motor neurons innervating the respiratory muscles, without influencing the medullary neurons[20-30].

Invasion of the CNS by SARS-CoV-2 has recently been shown in areas such as the brainstem that control the normal breathing process with nuclei like the pre-BÖTC. This may explain why some of the patients with COVID-19 who have been reported to have recovered from pneumonia could not be weaned off invasive mechanical ventilation, and the occurrence of acute respiratory arrests seen in COVID-19. This debate is important for many reasons, one of which is the fact that permanent damage to the medullary respiratory centers by SARS-CoV-2 would not benefit from mechanical ventilators, something which could be happening during the management of COVID-19 patients[20-31]. Moreover, there have been reports of acute respiratory failure in 45-65% of cases of COVID-19 in which the patients lost spontaneous breathing, required mechanical ventilation, and then later died. Some of the patients with COVID-19 that have been reported to recover from pneumonia but could not be weaned off invasive mechanical ventilation need to be investigated for deteriorating SARS-CoV-2 neurotropism that can prove fatal. The occurrence of these spontaneous (autonomic) breathing control failures early in COVID-19 is alarming and possibly reflects the damaging effect of SARS-CoV-2 on the CNS nuclei that control normal involuntary breathing mechanics[18-30].

SARS-CoV-2 probably invades the brain via axonal transport and transneuronal spread from the olfactory nerves on to the rhinencephalon, ultimately reaching the brainstem and causing the irreversible respiratory failure seen in severe COVID-19, typically characterized by lack of dyspnea. Additionally, SARS-CoV-2 has been isolated from the cerebrospinal fluid (CSF) of COVID-19 patients and the hematogenous or lymphatic routes have been proposed as ways through which the virus may gain entry to the CNS[20-30].

It is more likely that the virus invades the brainstem in the early phases of COVID-19. Therefore, respiratory failure due to damage in respiratory regulating centers can occur long before the hypoxemic influence comes into effect, as has been reported recently, since severe respiratory distress is observed 8-14 days after symptoms develop. In fact, even partial damage to the pacemaker neurons in the pre-BÖTC area can lead to intervals of loss of autonomic breathing and lead to the neurological manifestations reported in COVID-19. Moreover, the spinal motor neurons that act as a nuclear group for phrenic nerve, emerging as nerve roots, are located at cervical nerves 3, 4, and 5 (C3, C4, and C5) and could be involved, as has recently been reported, in affecting the diaphragm and thoracic muscles, completely interrupting respiratory function[21-31].

Clinical features and possible treatments

Correlating the pulmonary sign and symptoms of patients with COVID-19 and the ongoing neurological deficits can help identify the possible regions of the CNS where SARS-CoV-2 impacts the breathing process. The ability of COVID-19 patients to retain control over voluntary breathing suggests that the neocortical projections of the brain to the spinal motor neurons are spared. Moreover, the damage to both the pneumotaxic center and vagus nerves is also expected to result in inspiratory spasms as if the patient was holding their breath in the inspiratory phase of breathing (apneusis), as has been reported. Damage to the central chemoreceptor can strongly affect breathing rate and depth. Partial neurotoxicity of the neurons in the pre-BÖTC region which normally generates pacemaker impulses for autonomic breathing appears to be the most likely explanation for the patient having a sensation of losing the ability to breathe spontaneously, while a complete or substantial loss of the neurons in this region would induce neurogenic acute respiratory arrest despite the presence of moderate hypoxia and hypocapnia.

The question of survival in COVID-19 patients could also be best explained by the degree of the quantitative loss of neurons in the pre-BÖTC region and the ability of the neurons to compensate for a partial loss in those patients who survive the episode of medullary neurotoxicity in COVID-19. Paralysis of the diaphragm and damage to spinal motor neurons below C5 segments, or a combination of these, can contribute to syndromic respiratory failure[21-33].

All these signs could, therefore, be explained by the concept of central neurogenic respiratory failure. Given this, it is important to mention that, in a severe case of COVID-19, distinguishing hypoxemic respiratory failure from exclusive respiratory arrest due to damage to the brainstem pre-BÖTC and phrenic nerve nuclear group at C3-C5 is difficult if not impossible. A respiratory arrest that cannot be explained by the extent of lung damage in early onset COVID-19

and abnormal breathing patterns should undergo thorough clinical investigation, since, as previously mentioned, neuro-invasiveness by SARS-CoV-2 can occur early during COVID-19 and could be missed.

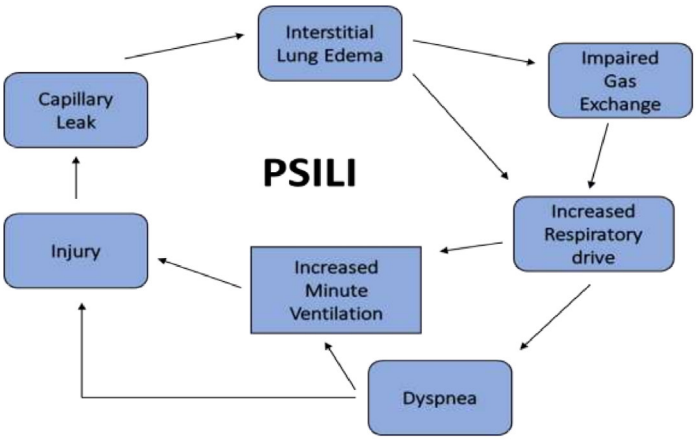
Moreover, the decline in arterial O_2 tension is normally detected by O_2-sensing cells in the carotid body (CB), the main arterial chemoreceptor, which rapidly activates sensory fibers impinging on neurons in the brainstem to induce compensatory hyperventilation and increase the heart rate. In this way, both O_2 uptake and its distribution to the tissues are enhanced. Indeed, bilateral removal of the CB in humans leaves individuals unaware of hypoxemia, with complete abolition of the hypoxic ventilatory response. Therefore, inhibition of CB responsiveness to hypoxia could be a plausible explanation for the impaired respiratory drive and reduced dyspnea that characterizes the "silent hypoxemia" observed in COVID-19 patients. The CB parenchyma is organized into clusters of cells called glomeruli. Each glomerulus is composed of 4-8 neuron-like glomus or Type I cells, which are in close contact with a network of fenestrated capillaries and are richly innervated by afferent sensory fibers of the petrosal ganglion. Glomus cells, the O_2-sensing elements in the CB, contain abundant synaptic vesicles with neurotransmitters that are rapidly released in response to hypoxia to activate the sensory fibers that connect the brainstem respiratory and autonomic centers. In addition, the CB glomeruli also contain a smaller number of glial-like, Type II or sustentacular cells with interdigitating processes that envelop the glomus cells. Type II cells are multipotent stem cells that can differentiate into O_2 sensitive glomus cells to support CB growth under sustained hypoxia. Although acute O_2-sensing is an intrinsic property of CB glomus cells, the functional responses of these cells are modulated by numerous auto- and paracrine signals generated within the organ. In this regard, a local renin-angiotensin system (RAS) and its principal components (angiotensinogen, angiotensin-converting enzyme, and angiotensin receptors) have been described in the CB. Indeed angiotensin-converting enzyme 2 (ACE2) has an important regulatory role in the RAS and it has been identified as the functional receptor by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters human cells.

Based on the high ACE2 expression found in human CB, it is plausible that infection of chemosensory glomus cells by SARS-CoV-2 could alter their ability to detect changes in arterial O_2 tension. This could mask the hypoxemia, as occurs in cases of "silent hypoxemia" in COVID-19 patients. Several studies show a highly individual variability of ACE2 expression in human CB tissue, which could explain why there appears to be no explanation as to why any particular COVID-19 patient should experience "silent hypoxemia".

Therefore, ventilation dysregulation and dyspnea add to an already injured lung, exacerbating the damage. In fact, breathing produces a phenomenon of continuous cyclic strain deformation, where the applied pressure is inspiratory

pressure. The overall strain for the whole lung can be defined as the ratio between the tidal volume (Vt) and a reference volume, usually the volume of air at the end of passive expiration, and the functional residual capacity (FRC). Stress, the force acting on a surface unit, produces its deformation. Transpulmonary pressure corresponds to the stress in the lung. Strain and stress in the lung tissue are closely related to each other through a constitutive relation (stress = tissue elastance*strain)[34-44]. Both play an important role in the onset and development of ventilator-induced lung injury (VILI) and patient self-inflicted lung injury (P-SILI).

Figure 3.1: Patient self-inflicted lung injury cycle (PSILI)



High values of strain are known to be harmful to the lung and to increase mortality[34-42].

Assisting ventilation both with non-invasive support and invasive mechanical ventilation can be used to minimize stress and strain when impending respiratory failure is recognized.

Continuous positive airway pressure (CPAP) helmets and non-invasive ventilation (NIV) can prevent excessive respiratory effort. The latter can be assessed through monitoring esophageal pressure swings, a surrogate of the transpulmonary pressure in spontaneously breathing patients[43-46].

CPAP potentially modulates drive by improving oxygenation by means of positive airway pressure, optimized oxygen delivery, and improvement of lung mechanics, while NIV may reduce respiratory drive by several mechanisms: 1) unloading respiratory muscles from inspiratory effort, which also reduces CO_2 production; and 2) improving oxygenation and lung mechanics through increases in positive end-expiratory pressure (PEEP)[43-46].

Despite respiratory support, the neurological involvement of SARS-COV-2 requires an additional strategy to control dyspnea in these patients. In fact,

respiratory drive and respiratory rate could be controlled through sedation to prevent and treat high respiratory frequencies along with respiratory support. Sedation also plays an important role in making patients comfortable and helping them to cope with what could be several days of non-invasive ventilation as compliance to treatment is fundamental given the lengthy course of the disease. Indeed, measuring respiratory drive in patients with COVID-19 acute distress syndrome (CARDS) could be important when selecting the initial ventilatory support and in deciding when to wean the patient off mechanical ventilation. Indeed, vigorous breathing efforts can amplify the severity of lung injury, which in turn can influence the duration of mechanical ventilation and impact patient outcome.

The prone position has been widely adopted in COVID-19 patients to treat hypoxemia[45]. However, its role has been fundamental not only to restore gas exchange in both awake and sedated patients, but in particular to homogenize the lung and reduce unprotective lung ventilation, thus reducing lung injury[48-50].

Despite this, some patients will remain dyspneic, breathing spontaneously, with or without respiratory support. Vigorous and dysregulated respiratory effort, even if under control in terms of respiratory rate, may promote P-SILI, with generation of high stress and strain, as shown by a high swing in esophageal, thus transpulmonary, pressure.

Ultimately, this phenomenon worsens the respiratory failure; the patient must be intubated and mechanical ventilation is required in up to 20-30% of cases. When invasive mechanical ventilation is instituted, there is often an initial phase of deep sedation, which may decrease the respiratory drive and, occasionally, a period of neuromuscular blockade, which eliminates breathing effort. Once assisted breathing is restored, uncontrolled high respiratory drive may also resume.

SARS-CoV-2 neurological involvement could also be seen during mechanical ventilation; an alteration of the central nervous system with dyspnea and delirium can promote the development of asynchronies and VILI[51,52].

Ventilator asynchronies have been associated with longer duration of mechanical ventilation and increased mortality. In particular, reverse trigger is defined as a dyssynchrony in which the patient starts to activate the inspiratory muscle during a passive insufflation of the lung (i.e., in non-triggered breaths). The inspiratory muscle causes an increase in the inspiratory effort with larger Vt and double cycling (breath stacking) with increased stress and strain, leading to unprotective ventilation[52-53].

Thus, in these patients, early detection of the possible presence of asynchrony and reverse trigger is fundamental. Moreover, impaired respiratory drive and excessive inspiratory efforts represent a challenge during the weaning process from mechanical ventilation, leading to increased mortality and fewer days off mechanical ventilation.

As has been said, pharmacological intervention with opioids, drugs modulating agitation and anxiety like dexmedetomidine, as suggested in a recent study, and partial muscular paralysis by low-dose neuromuscular blocking agents could achieve protective Vts and inspiratory pressures in CARDS patients exhibiting uncontrolled high respiratory drive during assisted ventilation[54,55]. Non-pharmacological techniques, such as extracorporeal carbon dioxide removal ($ECCO_2R$) or venous-venous extracorporeal membrane oxygenation (ECMO), could also be applied in selected severe cases of CARDS and refractory hypercapnia[56-58].

Conclusions

With a rapid rise in mortality in patients with COVID-19 exhibiting extrapulmonary manifestations, there is an urgent need to understand and diagnose the neurological symptoms early in the course of this disease. Future research is needed to understand the route of virus entry (neural or through the bloodstream), the neuronal damage and the affected areas in the brain, including pathological assessment of the respiratory center in the brainstem.

Take-home message

- COVID-19 is a systemic disease with multiple organ involvement, especially the lung.
- Respiratory failure is not only due to direct damage to the lung but is a consequence of neurological involvement.
- Respiratory effort and its neurological control play an important role in causing acure respiratory distress and lung damage.
- Sedation together with lung ventilatory strategies to prevent VILI should be tailored based on pathophysiology assessment.
- Understanding neural patterns can help identify phenotypes of respiratory efforts in COVID-19 patients.

References

1. Umakanthan S, Sahu P, Ranade AV, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). *Postgrad Med J*. 2020;96(1142):753-758.
2. Liu J, Liu S. The management of coronavirus disease 2019 (COVID-19). *J Med Virol*. 2020;92(9):1484-1490.
3. Adil MT, Rahman R, Whitelaw D, et al. SARS-CoV-2 and the pandemic of COVID-19. *Postgrad Med J*. 2021;97(1144):110-116.
4. Atzrodt CL, Maknojia I, McCarthy RDP, et al. A Guide to COVID-19: a global pandemic caused by the novel coronavirus SARS-CoV-2. *FEBS J*. 2020;287(17):3633-3650.
5. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci U S A*. 2020;117(21):11727-11734.
6. Scialo F, Daniele A, Amato F, et al. ACE2: The Major Cell Entry Receptor for SARS-CoV-2. *Lung*. 2020;198(6):867-877.
7. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26(7):1017-1032.
8. Mittal A, Manjunath K, Ranjan RK, et al. COVID-19 pandemic: Insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. *PLoS Pathog*. 2020. doi: 10.1371/journal.ppat.1008762. [Preprint]
9. Costa LB, Perez LG, Palmeira VA, et al. Insights on SARS-CoV-2 Molecular Interactions With the Renin-Angiotensin System. *Front Cell Dev Biol*. 2020. doi: 10.3389/fcell.2020.559841. [Preprint]
10. Dhont S, Derom E, Van Braeckel E, et al. The pathophysiology of 'happy' hypoxemia in COVID-19. *Respir Res*. 2020;21(1):198.
11. Tobin MJ, Jubran A, Laghi F. Misconceptions of pathophysiology of happy hypoxemia and implications for management of COVID-19. *Respir Res*. 2020;21(1):249.
12. Simonson TS, Baker TL, Banzett RB, et al. Silent hypoxaemia in COVID-19 patients. *J Physiol*. 2021;599(4):1057-1065.
13. Breville G, Accorroni A, Allali G, Adler D. [Physiopathologie de l'hypoxémie silencieuse dans le Covid-19]. *Rev Med Suisse*. 2021;17(736):831-834.
14. Losonczy G, Lukácsovits J, Süttő Z, et al. [Súlyos hypoxaemia légszomj nélkül COVID-19-pneumoniában] *Orv Hetil*. 2021;162(10):362-365.
15. Tabary M, Khanmohammadi S, Araghi F, et al. Pathologic features of COVID-19: A concise review. *Pathol Res Pract*. 2020;216(9):153097.
16. Calabrese F, Pezzuto F, Fortarezza F, et al. Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists. *Virchows Arch*. 2020;477(3):359-372.
17. Batah SS, Fabro AT. Pulmonary pathology of ARDS in COVID-19: A pathological review for clinicians. *Respir Med*. 2021. doi: 10.1016/j.rmed.2020.106239. [Preprint]

18. Kumar A, Pareek V, Prasoon P, et al. Possible routes of SARS-CoV-2 invasion in brain: In context of neurological symptoms in COVID-19 patients. *J Neurosci Res.* 2020;98(12):2376-2383.
19. Montalvan V, Lee J, Bueso T, et al. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. *Clin Neurol Neurosurg.* 2020. doi: 10.1016/j.clineuro.2020.105921. [Preprint]
20. Chigr F, Merzouki M, Najimi M. Autonomic Brain Centers and Pathophysiology of COVID-19. *ACS Chem Neurosci.* 2020;11(11):1520-1522.
21. Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. *J Neurol.* 2020;267(8):2179-2184.
22. Baig AM, Sanders EC. Potential neuroinvasive pathways of SARS-CoV-2: Deciphering the spectrum of neurological deficit seen in coronavirus disease-2019 (COVID-19). *J Med Virol.* 2020;92(10):1845-1857.
23. Bocci T, Bulfamante G, Campiglio L, et al. Brainstem clinical and neurophysiological involvement in COVID-19. *J Neurol.* 2021. doi: 10.1007/s00415-021-10474-0. [Preprint]
24. Baig AM. Computing the Effects of SARS-CoV-2 on Respiration Regulatory Mechanisms in COVID-19. *ACS Chem Neurosci.* 2020;11(16):2416-2421.
25. Machado C, DeFina PA, Chinchilla M, et al. Brainstem Dysfunction in SARS-COV-2 Infection can be a Potential Cause of Respiratory Distress. *Neurol India.* 2020;68(5):989-993.
26. Gandhi S, Srivastava AK, Ray U, Tripathi PP. Is the Collapse of the Respiratory Center in the Brain Responsible for Respiratory Breakdown in COVID-19 Patients? *ACS Chem Neurosci.* 2020;11(10):1379-1381.
27. Dey J, Alam MT, Chandra S, et al. Neuroinvasion of SARS-CoV-2 may play a role in the breakdown of the respiratory center of the brain. *J Med Virol.* 2021;93(3):1296-1303.
28. Guerrero JI, Barragán LA, Martínez JD, et al. Central and peripheral nervous system involvement by COVID-19: a systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings. *BMC Infect Dis.* 2021;21(1):515.
29. Porzionato A, Emmi A, Stocco E, et al. The potential role of the carotid body in COVID-19. *Am J Physiol Lung Cell Mol Physiol.* 2020;319(4):L620-L626.
30. Lambermont B, Davenne E, Maclot F, Delvenne P. SARS-CoV-2 in carotid body. *Intensive Care Med.* 2021;47(3):342-343.
31. Anoop UR, Verma K. Pulmonary Edema in COVID19-A Neural Hypothesis. *ACS Chem Neurosci.* 2020;11(14):2048-2050.
32. González-Duarte A, Norcliffe-Kaufmann L. Is 'happy hypoxia' in COVID-19 a disorder of autonomic interoception? A hypothesis. *Clin Auton Res.* 2020;30(4):331-333.
33. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play

a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552-555.

34. Cruces P, Retamal J, Hurtado DE, et al. A physiological approach to understand the role of respiratory effort in the progression of lung injury in SARS-CoV-2 infection. *Crit Care*. 2020;24(1):494.
35. Neetz B, Herth FJF, Müller MM. [Behandlungsempfehlungen zur Beatmung von COVID19-Patienten]. *Gefasschirurgie*. 2020:1-9.
36. Yoshida T, Grieco DL, Brochard L, Fujino Y. Patient self-inflicted lung injury and positive end-expiratory pressure for safe spontaneous breathing. *Curr Opin Crit Care*. 2020;26(1):59-65.
37. Gattinoni L, Tonetti T, Quintel M. Regional physiology of ARDS. *Crit Care*. 2017;21(Suppl 3):312.
38. Chiumello D, Carlesso E, Brioni M, Cressoni M. Airway driving pressure and lung stress in ARDS patients. *Crit Care*. 2016;20:276.
39. Pan C, Chen L, Zhang YH, et al. Physiological Correlation of Airway Pressure and Transpulmonary Pressure Stress Index on Respiratory Mechanics in Acute Respiratory Failure. *Chin Med J*. 2016;129(14):1652-1657.
40. Yoshida T, Amato MBP, Kavanagh BP, Fujino Y. Impact of spontaneous breathing during mechanical ventilation in acute respiratory distress syndrome. *Curr Opin Crit Care*. 2019;25(2):192-198.
41. Gama de Abreu M, Güldner A, Pelosi P. Spontaneous breathing activity in acute lung injury and acute respiratory distress syndrome. *Curr Opin Anaesthesiol*. 2012;25(2):148-155.
42. Nieman GF, Satalin J, Andrews P, et al. Personalizing mechanical ventilation according to physiologic parameters to stabilize alveoli and minimize ventilator induced lung injury (VILI). *Intensive Care Med Exp*. 2017;5(1):8.
43. Spinelli E, Mauri T, Beitler JR, et al. Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions. *Intensive Care Med*. 2020;46(4):606-618.
44. Mauri T, Yoshida T, Bellani G, et al; PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med*. 2016;42(9):1360-1373.
45. Groff P, Ferrari R. Non-invasive respiratory support in the treatment of acute hypoxemic respiratory failure secondary to CoViD-19 related pneumonia. *Eur J Intern Med*. 2021;86:17-21.
46. Coppola S, Pozzi T, Busana M, et al. Oesophageal manometry and gas exchange in patients with COVID-19 acute respiratory distress syndrome. *Br J Anaesth*. 2020;125(5):e437-e438.
47. Grasselli G, Greco M, Zanella A, et al; COVID-19 Lombardy ICU Network. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med*. 2020;180(10):1345-1355.

48. Gattinoni L, Busana M, Giosa L, et al. Prone Positioning in Acute Respiratory Distress Syndrome. *Semin Respir Crit Care Med.* 2019;40(1):94-100.

49. Pelosi P, Caironi P, Taccone P, Brazzi L. Pathophysiology of prone positioning in the healthy lung and in ALI/ARDS. *Minerva Anestesiol.* 2001;67(4):238-247.

50. Coppo A, Bellani G, Winterton D, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. *Lancet Respir Med.* 2020;8(8):765-774.

51. Solverson K, Weatherald J, Parhar KKS. Tolerability and safety of awake prone positioning COVID-19 patients with severe hypoxemic respiratory failure. *Can J Anaesth.* 2021;68(1):64-70.

52. Ge H, Pan Q, Zhou Y, et al. Lung Mechanics of Mechanically Ventilated Patients With COVID-19: Analytics With High-Granularity Ventilator Waveform Data. *Front Med* (Lausanne). 2020. doi: 10.3389/fmed.2020.00541. [Preprint]

53. Coppola S, Pozzi T, Chiumello D. Reverse trigger in COVID-19 ARDS. *Minerva Anestesiol.* 2021. doi: 10.23736/S0375-9393.21.15798-0. [Preprint]

54. Adams CD, Altshuler J, Barlow BL, et al. Analgesia and Sedation Strategies in Mechanically Ventilated Adults with COVID-19. *Pharmacotherapy.* 2020;40(12):1180-1191.

55. Kotfis K, Williams Roberson S, Wilson JE, et al. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care.* 202028;24(1):176.

56. Chen Y, Wang S, Huang J, et al. Application of extracorporeal carbon dioxide removal combined with continuous blood purification therapy in ARDS with hypercapnia in patients with critical COVID-19. *Clin Hemorheol Microcirc.* 2021. doi: 10.3233/CH-201080. [Preprint]

57. Husain-Syed F, Birk HW, Wilhelm J, et al. Extracorporeal Carbon Dioxide Removal Using a Renal Replacement Therapy Platform to Enhance Lung-Protective Ventilation in Hypercapnic Patients With Coronavirus Disease 2019-Associated Acute Respiratory Distress Syndrome. *Front Med* (Lausanne). 2020;12;7:598379.

58. Ma X, Liang M, Ding M, et al. Extracorporeal Membrane Oxygenation (ECMO) in Critically Ill Patients with Coronavirus Disease 2019 (COVID-19) Pneumonia and Acute Respiratory Distress Syndrome (ARDS). *Med Sci Monit.* 2020;6;26:e925364.

Chapter 4. Neurological manifestations: an overview

Chiara Manfredi, Emma Scelzo, Vincenzo Silani, Carlo Ferrarese, Alberto Priori

Introduction

Coronaviruses are enveloped, positive stranded RNA viruses which represent important human and animal pathogens, predominantly causing respiratory and gastrointestinal tract infections[1]. However, neurological symptoms have been reported in COVID-19 patients from all over the world (Table 4.1)[2-4].

Mao et al.[5], in the first retrospective study on neurological manifestations, estimated that more than one-third (36.4%) of patients with COVID-19 develop neuropsychiatric symptoms, out of which the most common were central nervous system (CNS) manifestations followed by peripheral nervous system (PNS) involvement[5].

Table 4.1: Summary of the neurological manifestations of COVID-19

Non-specific	CNS manifestations	PNS manifestations
Headache	Encephalitis	Smell and taste disturbances
Dizziness	Encephalopathy	GBS
Myalgia	Ischemic stroke/TIA	MFS
Lightheadness	Hemorragic stroke	Cranial neuropathy
Syncope	Subaracnoid Hemorrage	Optic neuritis
	Cerebral venous thrombosis	Posterior ischemic optic neuropathy
	Seizures	Myositis
	Myelitis	Rhabdomyolysis
	ADEM	
	CNS vasculitis	
	Movement disorders	

CNS: Central Nervous System; PNS: Peripheral Nervous System; TIA: Transient Ischemic Aattack; ADEM: Acute Disseminated Encephalomyelitis; GBS: Guillain-Barré Syndrome; MFS: Miller-Fisher Syndrome.

Neurological complications appear to be even more common in hospitalized patients. It has been reported that over 80% of COVID-19 patients who require hospitalization may develop neurological symptoms at some point during

their disease course[6]. Moreover, it seems that patients with a severe course of COVID-19 are more likely to develop neurological complications[5].

Rates of symptoms vary by geographical location and patient characteristics. Overall, the most common neurological manifestations reported in Asia, Europe and the US were smell and taste disturbances, myalgia, headache, encephalopathy, and dizziness. Cerebrovascular events, movement disorders, motor and sensory deficits, ataxia, and seizures are not common[2,5,6-8].

The EAN survey and the Global Consortium Study of Neurological Dysfunction in COVID-19

In April 2020, the European Academy of Neurology (EAN) core COVID-19 Task Force conducted a survey on neurological symptoms observed in patients with SARS-CoV-2 infection to assess their incidence and characteristics. They distributed a 17-question online survey to EAN members and other physicians worldwide, collecting data from a total of 2,343 responders (82% neurologists), mostly from Europe. According to the survey, the most frequent neurological symptoms were headache (61.9%), myalgia (50.4%), smell and taste disturbances (particularly anosmia, 49.2%, and ageusia, 39.8%), impaired consciousness (29.3%), and psychomotor agitation (26.7%). Other reported neurological symptoms were encephalopathy and acute cerebrovascular disorders (21%).

The results of the survey, in agreement with the data available in the literature, showed that neurological symptoms occurred predominantly in hospitalized patients and appeared at various times during the infection course. As expected, the most severe neurological features were reported by physicians in the Intensive Care Units (ICUs). Moreover, despite some observed differences, which could be attributable to the setting and the degree of involvement of the responders during the outbreak, there was no great difference in neurological manifestations between countries or continents[9].

From March to October 2020, the Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID) and the EAN Neuro-COVID Registry (ENERGY) performed a multicohort study including COVID-19 patients from 13 countries and 4 continents. The study aimed to determine neurological phenotypes, incidence, and outcomes among hospitalized patients. This study showed that approximately 80% of the patients had neurological manifestations (both self-reported symptoms and/or neurological signs or syndrome). In particular, the most common self-reported symptoms included headache (37%) and smell or taste disturbances (26%), while the most prevalent neurological signs and/or syndromes were acute encephalopathy (49%), coma (17%), and stroke (6%). Moreover, the presence of any neurological sign was associated with higher in-hospital mortality, even after adjusting for age, sex, race, and ethnicity[10].

Neurological manifestations of COVID-19

Non-specific symptoms

SARS-CoV-2 can potentially present with several non-specific neurological symptoms. In the case series of Mao et al., the most common neurological symptoms were dizziness (16.8%), headache (13.1%), myalgia (10.7%), and altered mental status (14.8%)[5].

These data appear also to be in line with the results of the EAN survey. Interestingly, Favas et al. found that, in health care workers, the incidence of non-specific symptoms was higher compared with the general population[4].

Smell and taste disturbances

Smell and taste disturbances have been reported as common early symptoms in patients with COVID-19, and were rarely the only manifestation. Interestingly, they can be a sign of a milder form of infection and can occur both during and after presentation of general symptoms[11]. Early data suggested that smell and taste disturbances are due to the direct effects of the virus on the olfactory system and gustatory receptors[12], since the SARS-CoV-2 could enter the brain through the olfactory epithelium and the neural-mucosal interface[13]. Magnetic resonance imaging (MRI) signal abnormalities in one or both olfactory bulbs have been described in patients with COVID-19, sometimes resolved on follow-up imaging[14,15]. In an autoptic study, pathologic findings demonstrated severe and widespread tissue damage involving the olfactory nerve, the gyrus rectus, and the brainstem, along with numerous particles referable to virions of SARS-CoV-2[16]. According to a systematic review of 212 studies conducted by Favas et al., the most common smell disturbance was anosmia; other symptoms reported were hyposmia, phantosmia and parosmia. Among taste disturbances, the most commonly reported were dysgeusia and ageusia. Overall, the incidence of smell disturbances ranged from 4.9% to 85.6%, while incidence of taste disturbances varied from 0.3% to 88.8%[2]. Nevertheless, further data on long-term prognosis are needed. In one series, 72.6% of affected patients recovered their olfactory function within the first week after resolution of the disease[11], while in a survey of non-hospitalized patients with olfactory or gustatory dysfunction from Northern Italy, resolution rates after nearly a month from symptom onset were 87% and 82%, respectively[17].

CNS manifestations

Cerebrovascular diseases (CVD) were reported in 0.5-5.9% of COVID-19 patients and, of these, the most common type was acute ischemic stroke (0.4-4.9%) followed by hemorrhagic stroke (0.2-0.9%) and cerebral venous thrombosis[4].

These rates of cerebrovascular events associated with COVID-19 are mostly based on observational cohort studies on hospitalized COVID-19 patients from different epicenters around the world, mainly in China, Europe, and the US[5,18-21]. These reports reflect a wide variety of populations in terms of disease severity, comorbidities, and follow-up, all of which are likely to contribute to the rate of cerebrovascular events. Overall, the mean age of patients with COVID-19 and stroke appears to be similar to those without COVID-19. But the relative risk of CVD may vary according to the severity of the disease. In particular, early case series suggest that patients with a more severe illness could have a higher risk of developing an acute CVD[22]. These data are also supported by evidence that the incidence of acute CVD was higher in ICU patients (0.8-9.8%)[4].

Several cases of meningoencephalitis (both viral and apparently autoimmune) were reported in COVID-19 patients[4]. Moriguchi et al. described the first case of viral encephalitis with COVID-19, confirmed by cerebrospinal fluid (CSF) analysis[23]. Other cases of meningoencephalitis have been reported in patients in whom CSF was either negative for SARS-CoV-2 or not tested. Isolated meningoencephalitis without any respiratory involvement has also been reported[24,25].

Incidence of disturbances of consciousness and delirium ranged from 3.3% to 19.6% in retrospective studies[4]. Early studies indicate that 20-30% of COVID-19 patients will present with/or develop delirium or mental status changes during their hospitalization, with rates of 60-70% in cases of severe illness at all ages[26]. Encephalopathy is more common in critically ill patients with COVID-19. In a cohort study of 2,088 patients with COVID-19 admitted to an ICU, 55% presented delirium[27] .

A few retrospective studies have reported seizures, with an incidence ranging from 0.5% to 1.4%[4].

Posterior reversible encephalopathy syndrome (PRES) has also been reported and may be due to hypertension and renal failure in some patients[28-30]. In one case series, neuroradiological findings consistent with PRES were seen in over 1%[31].

A few case reports have described patients with clinical and neuroimaging findings consistent with acute disseminated encephalomyelitis (ADEM)[4]. Some patients had myelitis with or without brain involvement. An additional case report describes a case of acute necrotizing encephalopathy in a patient with COVID-19[32].

Three cases of generalized myoclonus were reported from Spain, with normal CSF and imaging findings. In all these patients, myoclonus could not be explained by hypoxia, metabolic cause, or drug effect, and the EEG showed mild diffuse slowing without any epileptic activity. Patients were treated symptomatically with antiepileptic drugs (AEDs) and/or propofol sedation and appeared to recover gradually with immunotherapy[33].

PNS manifestations

All variants of Guillain-Barré syndrome (GBS) such as AIDP, AMAN, AMSAN have been reported in COVID-19 patients[4]. Cases of Miller Fisher syndrome (MFS) were also described, one of these being associated with serum GD1b-IgG antibodies[34]. Both para- and post-infectious patterns are described. GBS was a presenting feature in one case report by Zhao et al.[35]. However, while Toscano et al. reported a series of five patients with GBS, with an interval between COVID-19 onset and symptoms of GBS ranging from 5 to 10 days[36], a cohort study from the UK failed to show any specific association between GBS and COVID-19 infection[37]. Therefore, it is still not certain if there is a potential causal association of COVID-19 with the risk of GBS.

Several peripheral nerve and plexus syndromes have been reported in patients with COVID-19 including cranial neuropathies (facial nerve palsy, ocular motor neuropathies, Tapia syndrome), peripheral motor neuropathy, and neuralgic amyotrophy[38-40].

Since myalgia and fatigue are common symptoms in COVID-19, some speculate that COVID-19 may be associated with a viral myositis, although there is still no conclusive evidence for this[41]. Different studies have reported the incidence of rhabdomyolysis to be 0.2-2.6%[4].

Long-term effects

The issue of the long-term effects of the SARS-CoV-2 infection is much more complex. These have been described in various ways, including "Long COVID" and "post-COVID syndrome". In particular, there is some evidence to suggest that both patients recovering from a severe illness and patients with milder symptoms who never required hospitalization may report prolonged neurological symptoms that persist for weeks to months after the acute infection[42-44].

In a survey of 180 non-hospitalized COVID-19 patients, over 50% reported having at least one persistent symptom (most frequently fatigue and anosmia) approximately 4 months after the onset of symptoms[45]. Moreover, preliminary data related to extrapyramidal disorders[46] and cognitive disturbances[47] are still coming in, but the whole picture of the consequences of the pandemic will only be clarified after longitudinal studies are completed.

Take-home message

- Over one-third of patients with COVID-19 develop neuropsychiatric symptoms.
- Central nervous system manifestations are more common than peripheral nervous system symptoms.
- The most common neurological manifestations are smell and taste disturbances, myalgia, headache, encephalopathy, and dizziness.
- Patients may report long-lasting neurological symptoms that persist for weeks to months after the acute infection.

References

1. Chen X, Yu B. First two months of the 2019 coronavirus disease (COVID-19) epidemic in China: real-time surveillance and evaluation with a second derivative model. *Glob Health Res Policy*. 2020. doi: 10.1186/s41256-020-00137-4. [Preprint]
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020:395(10223):507-513.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
4. Favas TT, Dev P, Chaurasia RN, et al. Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. *Neurol Sci*. 2020;41(12):3437-3470.
5. Mao L, Jin H, Wang M, Hu Y, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
6. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol*. 2020;7(11):2221-2230.
7. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. *Nat Rev Neurol*. 2020;16(11):636-644.
8. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*; 2020;95(8):e1060-e1070.
9. Moro E, Priori A, Beghi E, et al. EAN core COVID-19 Task Force. The international European Academy of Neurology survey on neurological symptoms in patients with COVID-19 infection. *Eur J Neurol*. 2020;27(9):1727-1737.
10. Chou SH, Beghi E, Helbok R, et al. Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19-A Report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. *JAMA Netw Open*. 2021. doi: 10.1001/jamanetworkopen.2021.12131. [Preprint]
11. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. 2020;277(8):2251-2261.
12. Vaira LA, Salzano G, Fois AG, et al. Potential pathogenesis of ageusia and anosmia in COVID-19 patients. *Int Forum Allergy Rhinol*. 2020;10(9):1103-1104.
13. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci*. 2021;24(2):168-175.
14. Aragão MFVV, Leal MC, Cartaxo Filho OQ, et al. Anosmia in COVID-19 Associated with Injury to the Olfactory Bulbs Evident on MRI. *AJNR Am J Neuroradiol*.

2020;41(9):1703-1706.

15. Laurendon T, Radulesco T, Mugnier J, et al. Bilateral transient olfactory bulb edema during COVID-19-related anosmia. *Neurology*. 2020;95(5):224-225.
16. Bulfamante G, Chiumello D, Canevini MP, et al. First ultrastructural autoptic findings of SARS-Cov-2 in olfactory pathways and brainstem. *Minerva Anestesiol*. 2020;86(6):678-679.
17. Paderno A, Mattavelli D, Rampinelli V, et al. Olfactory and Gustatory Outcomes in COVID-19: A Prospective Evaluation in Nonhospitalized Subjects. *Otolaryngol Head Neck Surg*. 2020;163(6):1144-1149.
18. Klok FA, Kruip MJHA, Van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res*. 2020;191:148-150.
19. Lodigiani C, Iapichino G, Carenzo L, et al. Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14.
20. Requena M, Olivé-Gadea M, Muchada M, et al. COVID-19 and Stroke: Incidence and Etiological Description in a High-Volume Center. *J Stroke Cerebrovasc Dis*. 2020. doi: 10.1016/j.jstrokecerebrovasdis.2020.105225. [Preprint]
21. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. *J Stroke*. 2020;51(7):2002-2011.
22. Li Y, Man L, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. 2020;5(3):279-284.
23. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55-58.
24. Huang YH, Jiang D, Huang JT. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav Immun*. 2020. doi: 10.1016/j.bbi.2020.05.012. [Preprint]
25. Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain Behav Immun*. 2020. doi: 10.1016/j.bbi.2020.04.024. [Preprint]
26. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020.382(23):2268-2270.
27. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. 2021;9:239-250.
28. Franceschi AM, Ahmed O, Giliberto L, et al. Hemorrhagic Posterior Reversible Encephalopathy Syndrome as a Manifestation of COVID-19 Infection. *AJNR Am J Neuroradiol*. 2020;41(7):1173-1176.
29. Kishfy L, Casasola M, Banankhah P, et al. Posterior reversible encephalopathy syndrome (PRES) as a neurological association in severe Covid-19. *J Neurol Sci*. 2020. doi: 10.1016/j.jns.2020.116943. [Preprint]

30. Princiotta Cariddi L, Tabaee Damavandi P, Carimati F, et al. Reversible Encephalopathy Syndrome (PRES) in a COVID-19 patient. *J Neurol.* 2020;267(11):3157-3160.
31. Lin E, Lantos JE, Strauss SB, et al. Brain Imaging of Patients with COVID-19: Findings at an Academic Institution during the Height of the Outbreak in New York City. *AJNR Am J Neuroradiol.* 2020;41(11):2001-2008.
32. Delamarre L, Gollion C, Grouteau G, et al. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. *J Neurol Neurosurg Psychiatry.* 2020;91(9):1004-1006.
33. Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, et al. Generalized myoclonus in COVID-19. *Neurology.* 2020;95(6):e767-e772.
34. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *J Neurology.* 2020;95(5):e601-e605.
35. Zhao H, Shen D, Zhou H, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* 2020;19(5):383-384.
36. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barré Syndrome Associated with SARS-CoV-2. *N Engl J Med.* 2020;382(26):2574-2576.
37. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain.* 2021;144(2):682-693.
38. Dinkin M, Gao V, Kahan J, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology.* 2020;95(5):221-223.
39. Decavel P, Petit C, Tatu L. Tapia syndrome at the time of the COVID-19 pandemic: Lower cranial neuropathy following prolonged intubation. *Neurology.* 2020;95(7):312-313.
40. Siepmann T, Kitzler HH, Lueck C, et al. Neuralgic amyotrophy following infection with SARS-CoV-2. *Muscle Nerve.* 2020;62(4):E68-E70.
41. 42. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology.* 2020;94(22):959-969.
42. Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res.* 2020;6(4):00542-2020.
43. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;397(10270):220-232.
44. Graham EL, Clark JR, Orban ZS, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". *Ann Clin Transl Neurol.* 2021;8(5):1073-1085.
45. Petersen MS, Kristiansen MF, Hanusson KD, et al. Long COVID in the Faroe Islands - a longitudinal study among non-hospitalized patients. *Clin Infect Dis.* 2020. doi: 10.1093/cid/ciaa1792. [Preprint]
46. Sulzer D, Antonini A, Leta V, et al. COVID-19 and possible links with Parkinson's

disease and parkinsonism: from bench to bedside. *NPJ Parkinsons Dis*. 2020. doi: 10.1038/s41531-020-00123-0. [Preprint]

47. Ferrucci R, Dini M, Groppo E, et al. Long-Lasting Cognitive Abnormalities after COVID-19. *Brain Sci*. 2021;11(2):235.

Chapter 5. Neuroimaging in COVID-19

Marco Scarabello, Carla Uggetti, Luca Valvassori

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Human coronaviruses have neuroinvasive capacities and may be neurovirulent by two main mechanisms[1–3]: viral replication into glial or neuronal cells of the brain or autoimmune reaction with a misdirected host immune response[4]. Prior to the current pandemic there were reports of encephalitis-like syndromes caused by human coronaviruses[5]. Reports on central nervous system involvement during COVID-19 started early during the first wave[6] and large multicenter studies were subsequently carried out[7-17]. These studies showed a number of neuroradiological patterns, some of them similar to known disease entities or pathological conditions, with various frequencies and associated risk factors. The objective of this section is to highlight the different imaging features that must be recognized, the techniques to depict them and how to best interpret them with the current available knowledge.

Prevalence of abnormal neuroimaging findings

One of the earliest studies on neurological symptoms in patients with COVID-19[14] showed an estimated overall prevalence of 36.4% in hospitalized patients. Twenty-four percent of them had symptoms referred to the central nervous system. In another large retrospective cohort[8] 2,611 adults, 269 examinations were performed in 185 patients. MRI and CT examinations were performed and were available on 1.6% and 6.6% of patients, showing a low prevalence of neuroimaging studies in patients with COVID-19. Consecutive patients with neurological manifestations and brain magnetic resonance imaging (MRI) were selected among 16 French hospitals during 2020[7], excluding ischemic infarcts, cerebral venous thrombosis and previous chronic lesions. Among these 37 highly selected patients there were various patterns that can be strictly related to neuroradiological findings during COVID-19. Interestingly, there were 16/37 patients (43%) with unilateral fluid attenuation inversion recovery (FLAIR) and/

or diffusion hyperintensities in mesial temporal lobe; 11 (30%) showed non-confluent multifocal white matter hyperintense lesions on FLAIR/diffusion, with variable enhancement, associated with hemorrhagic lesions; 9 (24%) showed extensive and isolated white matter microhemorrhages; 4 (11%) showed extensive and confluent supratentorial white matter FLAIR hyperintensities; 2 (5%) showed FLAIR and diffusion ovoid hyperintense lesion located in the central part of the splenium of the corpus callosum; 2 (5%) showed non-confluent multifocal white matter hyperintense lesions on FLAIR/diffusion with variable enhancement; 2 (5%) showed acute necrotizing encephalopathy; 2 (5%) FLAIR or diffusion hyperintense lesions involving both middle cerebellar peduncles. The majority of the patients had one neuroimaging pattern (76%), with the rest multiple coexisting patterns. These patients underwent neuroimaging mainly because of alteration of consciousness (73%), pathologic wakefulness after sedation (41%), confusion (32%), and agitation (19%). From the available evidence it appears that neurological manifestations severe enough to warrant advanced neuroimaging are relatively uncommon and have a plethora of imaging patterns, some of them are more frequent than others and the majority are fairly unspecific, similar to other neuroradiological patterns related to various inflammatory, microvascular, and immune-mediated disorders.[18] Specific imaging patterns will be further discussed below.

Anosmia, usually associated to ageusia, is a frequent symptom in patients affected by COVID-19. MRI abnormalities of the olfactory bulb of these patients have been reported in several studies, with discordant results, also due to different technical approaches. A thinning and T2-hyperintensity of the olfactory bulbs can be sometimes detected with focused MRI studies.

Macrovascular pathology

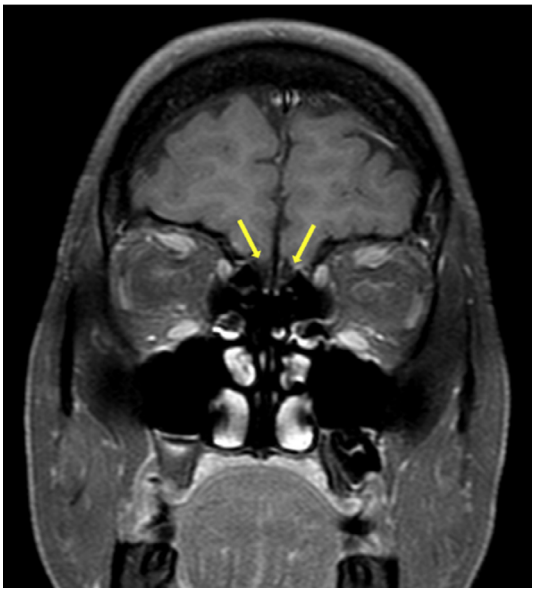
There have been various reports of ischemic and hemorragic stroke in patients with COVID-19. Klironomos et al.[8] reported 8.6% of patients having acute ischemic stroke and 6.3% having non-traumatic brain hemorrhage. One of the early studies[15] reported 4.6% incidence of acute ischemic stroke among patients hospitalized for COVID-19. Later studies[19,20] reported rates of acute ischemic stroke between 0.9% to 3.3%. It has been shown that COVID-19 increases stroke-related mortality[19]. Neuroimaging in acute stroke is fairly established[21] and presents no particular issue specific to COVID-19, except for the fact that a continuous flux of potentially COVID-19 positive patients through the CT scanner located in the emergency department may contribute to the delay of the first diagnostic step[22]. Brain hemorrhages have been reported, both as a presenting illness and as complications of anticoagulant therapy.

Table 5.1: Neuroimaging findings in COVID-19

	Description	Prevalence	Location	Imaging technique	Association
Macrovascular pathology	Ischemic stroke, lacunar stroke, cerebral venous thrombosis, brain parenchymal hemorrhage	0.9% to 8.6%	Brain hemisphere, basal ganglia, deep white matter	Noncontrast CT, CT angiography, MRI (DWI, FLAIR)	COVID-19 worsens the prognosis of ischemic stroke. Potential delay of diagnostic imaging due to patient isolation
White matter abnormalities	Nonconfluent white matter FLAIR hyperintensities	30% (selected patients)	Supratentorial WM, deep periventricular WM, splenium of corpus callosum, deep cerebellar WM, middle cerebellar peduncles	CT, MRI (FLAIR, DWI, T2-weighted)	Similar to an inflammatory demyelinating disease, such as acute disseminated enceph- alomyelitis or acute hemorrhagic leukoencephalitis
	Confluent white matter FLAIR hyperintensities	11% (selected patients)	Supratentorial WM	CT, MRI (FLAIR, DWI, T2-weighted)	Unclear pathogenesis. Severely ill patients, maybe post-hypoxic leukoencephalopathy or toxic-metabolic.
DWI abnormalities	b=1000 hyperintensities with low ADC values	Variable, low if ischemic stroke is excluded	Discrete foci in hemispheric WM, splenium of corpus callosum, globus pallidus	DWI, with ADC map	Hypoxic, toxic-metabolic, immune mediated injury patterns
SWI abnormalities	Round or ovoid foci of signal drop in GRE or SWI images, from punctate to a few millimiters	Variable, up to 74%	Splenium of the corpus callosum, juxtacortical U-fibers, and main white matter tracts	SWI, GRE	Found in more severe cases, and patients with worse prognosis
Pathological contrast-enhancement	Parenchymal or leptomeningeal contrast enhancement	Variable	Hemispheric WM, leptomeninges, cranial nerves, lumbar nerve roots	Post contrast T1-weighted, FLAIR images	Breakdown of the blood-brain barrier from various insults
Encephalitis-like abnormalities	FLAIR hyperintese lesions in gray and white matter, with variable diffusion restriction and contrast enhancement	Few case reports	Mesial temporal lobe, diffuse subcortical and deep WM	FLAIR, DWI, Post contrast T1-weighted, FLAIR	Similar to limbic enhcephalitis or ADEM

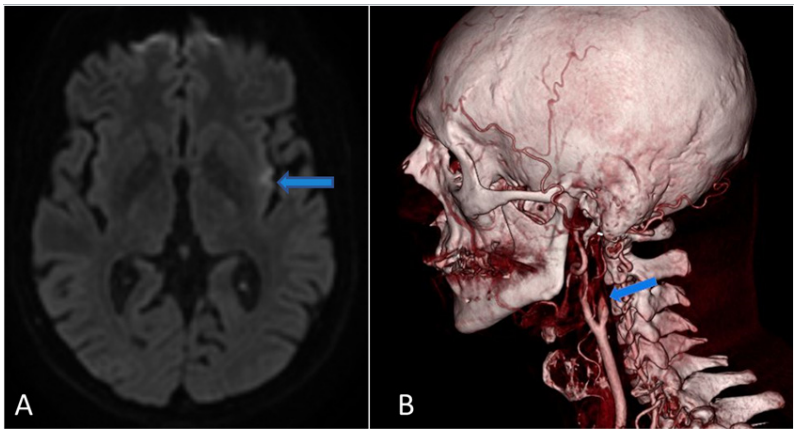
CT: computed tomography, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging, FLAIR: fluid-attenuated inversion recovery, SWI: susceptibility-weighted imaging, WM: white matter, ADEM : acute disseminated encephalomyelitis.

Figure 5.1: 52 yo female COVID-19 patient with anosmia



FLAIR coronal scan shows thinning and T2-hyperintensity in the bilateral olfactory bulbs (arrows)

Figure 5.2



A: FLAIR axial scan shows a small acute ischemic lesion (blue arrow) in the left insular cortex in a previously healthy 33 yo man. B: Sagittal contrast-enhanced CT of the epiaortic vessels shows dissection (blue arrow) of the cervical segment of the ipsilateral internal carotid.

White matter abnormalities

Kremer et al.[7] reported a prevalence of 30% (CI 15-45%) of non-confluent multifocal white matter hyperintense lesions on FLAIR and diffusion-weighted images with variable enhancement associated with hemorrhagic lesions among patients with severe COVID-19, and 11% of extensive and confluent supratentorial white matter FLAIR hyperintensities, making white matter one of the main structures to be analyzed in severe COVID-19 with brain lesions. White matter changes can be in the form of symmetrical, periventricular lesions[8] located posteriorly in the occipital and parietal lobes[15] or even affect middle cerebellar peduncles. Ventricle size changes and dynamic evolution of white matter lesions has also been reported, with improvement in a small percentage of cases (14%)[23]. White matter can also been affected by COVID-19-related diffuse posthypoxic leukoencephalopathy[24]. Isolated lesions of the corpus callosum have been reported[7] as well as lesions located on the midline in the splenium of the corpus callosum, which is a typical locations for toxic-metabolic damage[25-27].

Diffusion abnormalities

Klironomos et al.[8] reported 5/41 patients with acute ischemic infarcts and 5/41 with acute lacunar infarcts. One patient from their series presented with restricted diffusion in the splenium of corpus callosum. One patient had restricted diffusion in the globus pallidus. Kremer et al.[7], who decided to exclude patients with macrovascular pathology, reported diffusion weighted imaging (DWI) abnormalities in the form of non-confluent white matter abnormalities (with corresponding FLAIR hyperintensities) both supra- and infratentorially, along with restricted diffusion in the middle cerebellar peduncles. If we exclude DWI changes due to acute ischemic/cytotoxic damage from macrovascular or lacunar infarcts which are common in adult and elderly patients and not strictly related to COVID-19 effects, there are patterns resembling acute disseminated encephalomyelitis (ADEM)[28], hypoxic damage (bilateral globus pallidus), toxic-metabolic damage (splenium of corpus callosum), which could be a consequence of microvascular damage, hypoxic ischemia during severe COVID-19 pneumonia, and immune-mediated white matter lesions.

Susceptibility weighted imaging abnormalities

Susceptibility weighted imaging (SWI) abnormalities were reported as the most frequent finding in patient with central nervous system involvement by Klironomos et al.[8] being found in 74% of them (29/39). Interestingly, the shape of susceptibility foci were reported as round or ovoid, the latter probably due to microscopic thrombi along small medullary veins with subsequent

microbleeds[29]. They were more frequently located in the splenium of the corpus callosum, juxtacortical U-fibers, and main white matter tracts. Fifty-nine percent of patients had SWI abnormalities in the corpus callosum. Low signal intensity foci were also reported in subarachnoid and intraventricular location, as well as cortical superficial siderosis. There were reports of susceptibility changes in patients with severe COVID-19 on mechanical ventilation/oxygenation[30-32], the pathophysiology of which is the subject of ongoing research, with some advocating possible COVID-19-mediated microvascular damage and thrombosis and others focusing on secondary effects induced by the severe illness and hypoxic-ischemic environment[29,33]. Generally, patients whose neuroimaging findings included susceptibility changes had worse clinical conditions, worse prognosis, longer duration of mechanical ventilation and worse laboratory profiles (high peak D-dimer, lower nadir platelet count, higher international normalized ratio)[29].

Perfusion abnormalities

Among the largest cohort of patients with abnormal neuroimaging findings there were reports describing no significant perfusion abnormalities[8] using dynamic susceptibility contrast (DSC) technique (19/39 patients), with relative cerebral blood flow (rCBF) within normal range, but also studies highliting a significant proportion of patients with perfusion-weighted abnormalities[34-38]. Chougar et al.[34] performed three-dimensional pseudocontinuous arterial spin labeling (pCASL) on 46/73 patients in their neuroimaging cohort, with roughly half of them belonging to the intensive care unit (ICU) subgroup. Twenty-two patients out of 46 had perfusion abnormalities, 9 were seizure related, 4 secondary to ischemic lesions and 10 were isolated. The proportion of patients with pCASL abnormal values were higher in the ICU group and more of the latter had isolated perfusion abnormalities. Lambrecq et al. analyzed clinical, biological, brain MRI and electroencephalographic findings in patients with neurological symptoms during COVID-19. Half of the foty patients who underwent perfusion weighted imaging showed abnormal results: 19/20 of them had hypoperfusion, especially in frontal and temporal lobes and a minority of them showed hyperperfusion (4/20). Hypoperfusion seemed to represent an important feature in the radar chart of what they described as COVID-19–related encephalopathy. Other studies reported a similar proportion of perfusion abnormalities, with the temporal lobes often affected[36-38].

Pathological contrast-enhancement

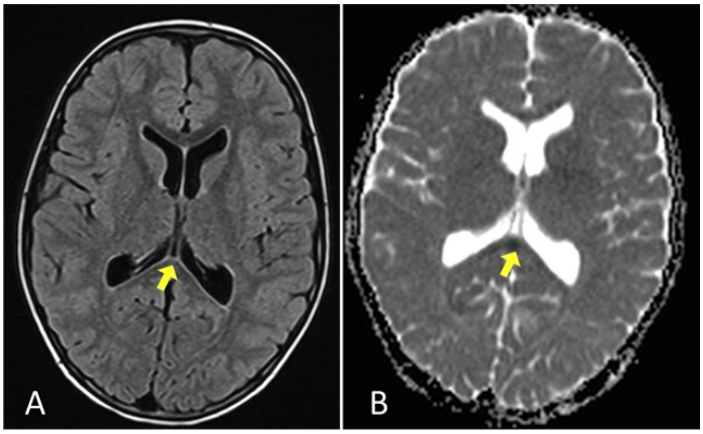
Enhancement in brain MRI after administration of gadolinium-based contrast agents reflects disruption or abnormal permeability of the blood-brain barrier. Several different mechanisms can lead to such effects and therefore there were different reports of contrast-enhancing (CE) lesions associated with pathological CE. Kremer et al.[7] reported variable CE in non-confluent white matter lesions, with superimposed hemorrhagic changes. Klironomos et al.[8] reported pathological CE after ischemic, hemorrhagic and hypoxic insults in three patients, which are expected from the breakdown of the blood brain barrier. Interestingly, they reported subtle leptomeningeal enhancement, most visible on contrast-enhanced T2-weighted FLAIR and they demonstrated progression of the enhancement in one patient at follow-up although there was clinical improvement. Two patients in their series exhibited cranial nerve enhancement (bilateral facial nerve CE and vestibular nerve respectively) and two others showed pathological CE along the roots of the cauda equina. The studies by Kandemirli[10] and Chougar[34] also showed variable leptomeningeal and perivascular white matter pathological CE in a small proportion of patients.

Encephalitis and encephalitis-like abnormalities

There were several reports of encephalitis and encephalitis-like syndromes in patients with COVID-19. Moriguchi et al.[39] reported a case of a 24-years old man who was found unconscious and had generalized seizures and neck stiffness at admission to the hospital. Cerebrospinal fluid analysis found SARS-CoV-2 RNA. Brain MRI showed signs of ventriculitis along the right temporal horn, restricted diffusion and high FLAIR signal in the right hippocampus. Hayashi et al.[27] reported a case of mild encephalitis/encephalopathy with a reversible splenial lesion.

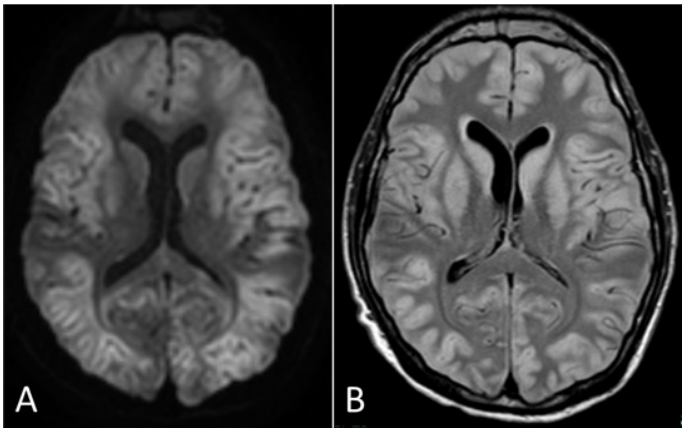
Grimaldi et al.[40] showed a peculiar case of a man presented with subacute cerebellar syndrome and myoclonus several days after general infectious symptoms began. Of note, brain MRI findings were normal and brain ^{18}F-FDG PET showed diffuse cortical hypometabolism associated with putaminal and cerebellum hypermetabolism. Autoimmune limbic encephalitis was also described and reviewed by the group led by Pizzanelli[41], with the usual brain MRI signature. Acute disseminated encephalomyelitis has also been reported, with the pattern of abnormal neuroimaging findings, in adults and children[42,43]. Finally, in critically ill COVID-19 patients severe hypoxic, toxic and metabolic encephalopathies may be found.

Figure 5.3



FLAIR scan (A) and Diffusion weighted image (DWI) show an alteration in the central aspect of the splenium of corpus callosum, consistent with the diagnosis of mild encephalopathy with a reversible splenial lesion (MERS).

Figure 5.4



Diffusion weighted (A) and FLAIR (B) images show widespread gyral T2 hyperintensity, swelling and restricted diffusion, consistent with extensive anoxic suffering in a 40 yo male patient with severe respiratory failure due to COVID-19.

Practical implications in neuroimaging of COVID-19 neuropathology

Many retrospective studies and case reports have been published on neuroimaging during COVID-19. Some patterns have emerged and there is evidence that more severe disease and the need for mechanical ventilation are risk factors for a positive brain MRI. Most of the findings are not specific to COVID-19 and are in fact common to other disease entities and etiologies. The majority of the findings are still being analyzed form the pathophysiological point of view to ascertain the cause, mechanism and possible treatment. From the neuroradiological perspective, since COVID-19 can have epidemic waves and variable disease course, it is important to note that SARS-CoV-2 positive patients can present with acute neurological emergencies unrelated to the viral illness and time-dependent imaging needs to be performed accordingly. This review can provide the necessary references to guide in the differential diagnosis of central nervous system pathology in patients with COVID-19.

Take-home message

- The majority of patients with COVID-19 showed abnormal findings at CT and MRI caused by concurrent macrovascular pathology, mainly ischemic stroke.
- Highly selective studies have shown a few neuroimaging patterns directly or indirectly related to the viral illness itself.
- The most prevalent abnormalities were non-confluent and confluent white matter FLAIR hyperintensities with variable enhancement, leptomeningeal enhancement, small SWI susceptibility foci.
- The neuroimaging patterns resemble known immune-mediated, toxic, hypoxic or severe illness-related abnormalities.
- The prevalence of abnormal CT and MRI findings increases with the severity of COVID-19.

References

1. Bohmwald K, Gálvez NMS, Ríos M, et al. Neurologic Alterations Due to Respiratory Virus Infections. 2018. Available from: www.frontiersin.org https://doi.org/10.3389/fncel.2018.00386
2. Desforges M, Le Coupanec A, Stodola JK, et al. Human coronaviruses: Viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res*. 2014;194:145-158.
3. Desforges M, Le Coupanec A, Dubeau P, et al. Human coronaviruses and other respiratory viruses: Underestimated opportunistic pathogens of the central nervous system? *Viruses*. 2019;12(1).
4. Li Y, Li H, Fan R, et al. Coronavirus Infections in the Central Nervous System and Respiratory Tract Show Distinct Features in Hospitalized Children. *Intervirology*. 2017;59(3):163-169.
5. Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection*. 2015;43(4):495-501.
6. Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: Imaging features. *Radiology*. 2020;296(2):E119-120.
7. Kremer S, Lersy F, De Sèze J, et al. Brain MRI findings in severe COVID-19: A retrospective observational study. *Radiology*. 2020;297(2):E242-251.
8. Klironomos S, Tzortzakakis A, Kits A, et al. Nervous system involvement in coronavirus disease 2019: Results from a retrospective consecutive neuroimaging cohort. *Radiology*. 2020;297(3):E324-334.
9. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*. 2020;95(8):e1060-1070.
10. Kandemirli SG, Dogan L, Sarikaya ZT, et al. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. *Radiology*. 2020;297(1):E232-235.
11. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55-58.
12. Radmanesh A, Derman A, Lui YW, et al. COVID-19–associated diffuse leukoencephalopathy and microhemorrhages. *Radiology*. 2020;297(1):E223-227.
13. Franceschi AM, Ahmed O, Giliberto L, Castillo M. ADULT BRAIN Hemorrhagic Posterior Reversible Encephalopathy Syndrome as a Manifestation of COVID-19 Infection. *AJNR Am J Neuroradiol*. 2020;41(7):1173-1176.
14. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
15. Mahammedi A, Saba L, Vagal A, et al. Imaging of Neurologic Disease in Hospitalized Patients with COVID-19: An Italian Multicenter Retrospective Observational Study. *Radiology*. 2020;297(2):E270-273.

16. Kremer S, Lersy F, Anheim M, et al. Neurologic and neuroimaging findings in patients with COVID-19: A retrospective multicenter study. . 2020;95(13):e1868-1882.
17. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(23):2268-2270.
18. Gulko E, Oleksk ML, Gomes W, et al. MRI brain findings in 126 patients with COVID-19: Initial observations from a descriptive literature review. *Am J Neuroradiol*. 2020;41(12):2199-2203.
19. Requena M, Olivé-Gadea M, Muchada M, et al. COVID-19 and Stroke: Incidence and Etiological Description in a High-Volume Center. *J Stroke Cerebrovasc Dis*. 2020;29(11):105225.
20. Elfasi A, Echevarria FD, Rodriguez R, et al. Impact of COVID-19 on Future Ischemic Stroke Incidence. *eNeurologicalSci*. 2021;22:100325.
21. Menon BK, d'Esterre CD, Qazi EM, et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. *Radiology*. 2015;275(2):510-520.
22. Siegler JE, Zha AM, Czap AL, et al. Influence of the COVID-19 Pandemic on Treatment Times for Acute Ischemic Stroke: The Society of Vascular and Interventional Neurology Multicenter Collaboration. *Stroke*. 2021;52(1):40-47.
23. Agarwal S, Melmed K, Dogra S, et al. Increase in Ventricle Size and the Evolution of White Matter Changes on Serial Imaging in Critically Ill Patients with COVID-19. *Neurocrit Care*. 2021. doi: 10.1007/s12028-01207-2. [Preprint]
24. Tristán-Samaniego DP, Chiquete E, Treviño-Frenk I, et al. COVID-19-related diffuse posthypoxic leukoencephalopathy and microbleeds masquerades as acute necrotizing encephalopathy. *Int J Neurosci*. 2020;1-6. doi:10.1080/00207454.2020.1865346. [Preprint]
25. Elkhaled W, Abid F Ben, Akhtar N, et al. A 23-year-old man with SARS-CoV-2 infection who presented with auditory hallucinations and imaging findings of cytotoxic lesions of the corpus callosum (CLOCC). *Am J Case Rep*. 2020;21:1-6.
26. Kakadia B, Ahmed J, Siegal T, et al. Mild encephalopathy with reversible splenium lesion (MERS) in a patient with COVID-19. *J Clin Neurosci*. 2020;79:272-274.
27. Hayashi M, Sahashi Y, Baba Y, et al. COVID-19-associated mild encephalitis/encephalopathy with a reversible splenial lesion. *J Neurol Sci*. 2020;415:116941.
28. Toledano-Massiah S, Badat N, Leberre A, et al. Unusual brain MRI pattern in 2 patients with COVID-19 acute respiratory distress syndrome. *Am J Neuroradio*l. 2020;41(12):2204-2205.
29. Agarwal S, Jain R, Dogra S, et al. Cerebral Microbleeds and Leukoencephalopathy in Critically Ill Patients with COVID-19. *Stroke*. 2020;2649-2655.
30. Thurnher MM, Boban J, Röggla M, Staudinger T. Distinct pattern of microsusceptibility changes on brain magnetic resonance imaging (MRI) in critically ill patients on mechanical ventilation/oxygenation. *Neuroradiology*. 2021. doi: 10.1007/s00234-021-02663-5. [Preprint]

31. Conklin J, Frosch MP, Mukerji SS, et al. Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19. *J Neurol Sci*. 2021;421:117308.
32. Conklin J, Frosch MP, Mukerji S, et al. Cerebral Microvascular Injury in Severe COVID-19. *medRxiv Prepr Serv Heal Sci*. 2020. doi: 10.1101/2020.07.21.20159376. [Preprint]
33. Dixon L, Mcnamara C, Gaur P, et al. Cerebral microhaemorrhage in COVID-19: A critical illness related phenomenon? *Stroke Vasc Neurol*. 2020;5(4):315-322.
34. Chougar L, Shor N, Weiss N, et al. Retrospective observational study of brain MRI findings in patients with acute SARS-CoV-2 infection and neurologic manifestations. *Radiology*. 2020;297(3):E313-323.
35. Lambrecq V, Hanin A, Munoz-Musat E, et al. Association of Clinical, Biological, and Brain Magnetic Resonance Imaging Findings with Electroencephalographic Findings for Patients with COVID-19. *JAMA Netw Open*. 2021;4(3).
36. Helms J, Kremer S, Merdji H, et al. Delirium and encephalopathy in severe COVID-19: A cohort analysis of ICU patients. *Crit Care*. 2020;24(1).
37. Larvie M, Sarikaya B, Lev MH, Hess CP. More on Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(26):e110.
38. Zhan M, Qin Y, Xue X, Zhu S. Death from Covid-19 of 23 Health Care Workers in China. *N Engl J Med*. 2020;382(23):2267-2268.
39. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55-58.
40. Grimaldi S, Lagarde S, Harlé JR, et al. Autoimmune Encephalitis Concomitant with SARS-CoV-2 Infection: Insight from 18F-FDG PET Imaging and Neuronal Autoantibodies. *J Nucl Med*. 2020;61(12):1726-1729.
41. Pizzanelli C, Milano C, Canovetti S, et al. Autoimmune limbic encephalitis related to SARS-CoV-2 infection: Case-report and review of the literature. *Brain, Behav Immun - Heal*. 2021;12:100210.
42. Langley L, Zeicu C, Whitton L, Pauls M. Acute disseminated encephalomyelitis (ADEM) associated with COVID-19. *BMJ Case Rep*. 2020;13(12).
43. McLendon LA, Rao CK, Da Hora CC, et al. Post-COVID-19 Acute Disseminated Encephalomyelitis in a 17-month-old. *Pediatrics*. 2021;e2020049678.

Chapter 6. Neuropathology

Gaetano Pietro Bulfamante, Valentina Toto, Laura Carpenito, Delfina Tosi

The state of the art

Up to 1st of June 2021 only 150 articles appeared in PubMed's database using the search queries "SARS-CoV-2 Neuropathology" and "COVID-19", an extremely low number compared with the 85,519 articles using a "SARS-CoV-19" entry and the 140,077 with the keyword "COVID-19". Furthermore, the cases studied were extremely limited[1]. There are several reasons for this low number of publications, and the difficulty in performing brain biopsies or autopsy on subjects infected with SARS-CoV-2 or affected by COVID-19 plays an important role. To date, this explains how our knowledge of the neuropathology of this infection is limited and sometimes contradictory. The poor understanding of the neuropathology of this infection and of this disease is of considerable concern considering that neurological complications of COVID-19[2] have frequently been observed, both in the acute and in the long-term phases of the disease. Complications such as autoimmune encephalitis, memory loss, sleep disorders, severe mood disorders, and persistent headache can last for months and significantly affect the rehabilitation period that nowadays potentially involves the millions of COVID-19 patients and are expressed by the more than 120 million subjects infected with SARS-CoV-2[1]. Still today, in the scientific literature the prevailing thoughts are based on the following points: 1) SARS-CoV-2 does not infect the central nervous system (CNS) directly; 2) theoretically, the virus can infect the endothelial cells of the CNS vessels since they express the ACE2 receptor; 3) the detectable damage to the CNS in people with COVID-19 is the result of thrombotic microangiopathies[3] and of the local activation of an inflammatory response supported by cytokines, including IL-2 and IL-12[4-6]. Despite this, recent observations suggest the presence of SARS-CoV-2 in the parenchymal tissue of the brain[7,8] and that suggests how the virus can enter the CNS in different pathways other than through the circulatory system[9,10]. It is possible that the incongruity of the immunohistochemical findings related to the presence of the virus in the CNS depends on different factors such as the viral load at the time of the biopsy / autopsy, the type and clone of

the antibody used for its recognition, and the time elapsed between death and carrying out the autopsy itself[10-12].

Autopsy, biopsy, fixation and gross pathology

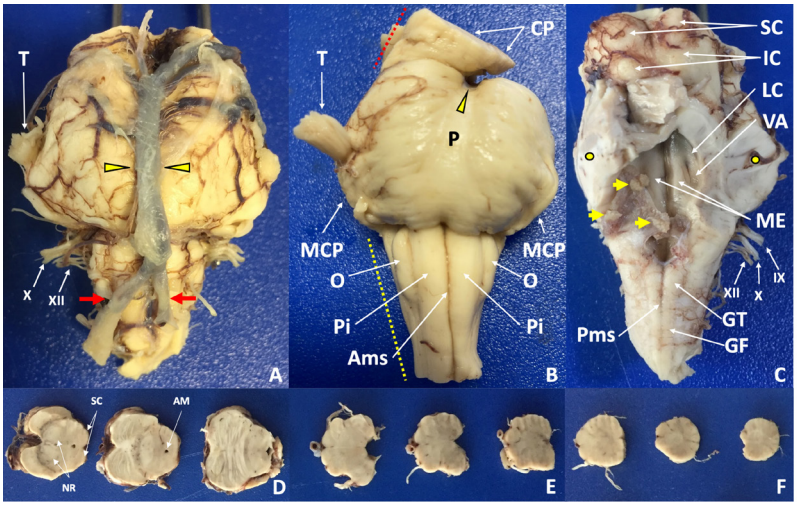
An adequate autopsy evaluation of the CNS must be based both on its rapid evisceration from the body and on its adequate fixation. CNS biopsies also need an appropriate fixation procedure, although they have a simpler protocol of execution. The autopsy must be performed as soon as possible after the patient's death due to the immediate onset of the postmortal involutionary phenomena, which produces tissue alterations that can lead to misinterpretation of the histopathological findings, i.e., by reducing tissue immunoreactivity. In our practice, the evisceration of the brain-brainstem-cerebellum block (B-BS-C block) was performed within three hours after death, through instrumental determination of death by continuous electrocardiographic monitoring showing a flat trace for at least 20 minutes. Autopsy must be performed in a Biosafety Level 3 (BSL 3) autopsy room according to the rules of the Centers for Disease Control and Prevention (CDC) and the staff must be adequately protected[1]. The removal of the skull cap must be carried out with an electric oscillating saw equipped with an aspiration system for the bone dust and for the blood and tissue microparticles that are produced during the cutting procedure. The epidural space, the dura mater, the dural venous sinuses opened *in situ*, the subdural space, the leptomeninges must be examined and their characteristics must be recorded. The brainstem should be at best dissected at the level of the junction with the spinal cord, given the importance of its examination in patients with COVID-19 disease or infected with SARS-CoV-2. This procedure can be easily performed using a thin double-edged scalpel and a gouge. Once the B-BS-C block has been eviscerated, it must be quickly examined also on the lower surface, ensuring that the olfactory and optic nerves have also been removed. Then, it must be weighed. The entire visceral block must be suspended in abundant 10% buffered formalin: that of an adult must be completely immersed in at least 5 liters of formalin, suspending it at the edges of the vessel with a thin cord passing under the basilar artery of the Circle of Willis; the eyelet below the artery where the cord passes must be obtained with a thin scalpel blade while the artery is placed in traction with a small anatomical forceps, ensuring no damage to the underlying Varolius pons[11] (Figure 6.1A). The fixation of the brain suspended in formalin is crucial to avoid any anatomical artifacts to the B-BS-C block structures produced by the pressure against the walls of the container. The macroscopic examination of the inner part of the B-BS-C block performed with parallel serial cuts immediately after its evisceration should be avoided as it irreparably damages the histological details. However, following evisceration, it

is recommended to quickly collect small tissue samples for electron microscopy and for molecular or microbiological /virological investigations. These samples must not compromise the visceral integrity of the block. Moreover, it is important to note the areas from which the samples are taken. It is also important to collect samples of the corresponding contralateral areas in order to correlate the histopathological patterns to the molecular, ultrastructural or microbiological / virological findings when the final sampling for histological examination is carried out. The complete or partial removal of the spinal cord should be performed by removing the vertebral bodies that need to be examined, using an oscillating saw, a Brunetti's chisel and a gouge. The spinal cord is removed inside the dural sac and, once eviscerated, it is stretched and fixed at the margins on a cork dissecting board, with pins set in the dura mater, before immersing it in abundant formalin. The B-BS-C block fixation lasts from 21 to 27 days, depending on its size. The fixation protocol requires the following essential steps: 1) a complete change of formalin on the 2nd, 4th, 6th, 13th and 20th days; 2) a dissection of the block into two parts on the 4th day through a full-thickness cut of the brain. This procedure is performed to facilitate the entry of the formalin into the ventricular cavities and to facilitate the fixation of the deep structures; 3) immersion without suspension of the two parts of the block back in formalin. The first cut must be made according to the chosen section plane (coronal, sagittal or transverse). The subsequent cuts must be performed at the end of the fixation on seriated planes approximately 1 cm apart. On the 21st or 27th day, the B-BS-C block (according to the macroscopic assessment of adequate fixation also of the deepest parenchymal areas) should be macroscopically examined and sampled for histological examination. The serial sections are to be performed with a long Virchow brain sectioning knife. The blade must be wet with water after each cut to ensure it slides continuously in one direction to avoid sawing movements. For convenience, it may be useful to perform a macroscopic examination of the parenchyma on serial macrosections after having separated the brain from the brainstem and the latter from the cerebellum, first dissecting the midbrain at the level of the cerebral peduncles and then the cerebellar peduncles (Figure 6.1B-F).

The fixation procedure of the spinal cord should last from 8 to 10 days, depending on its thickness and length, changing the formalin on the 2nd, 4th, 6th days. Biopsies performed *in vivo* on patients infected with or suspected of infection with the SARS-CoV-2, including those of the CNS, should be fixed for at least 24 hours in formalin before processing them for paraffin embedding[13,14]. It is a good practice to process autopsy samples under vacuum, with three steps in Xylene or equivalent for at least 1 hour each. The procedures we performed have sometimes produced unexpected results when compared with the data published by other research groups. This suggests that, regardless of the other variables already listed

in the previous paragraph, the SARS-CoV-2 virus is very labile after the patient's death, most of all in its identification with immunohistochemical methods.

Figure 6.1: Macroscopic examination of the midbrain and brainstem

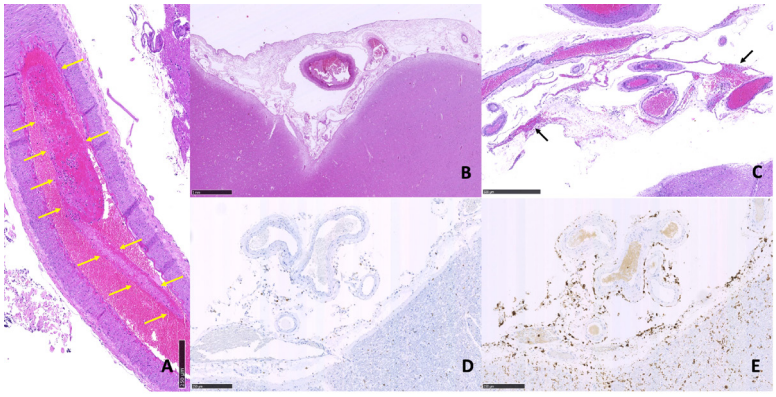


A. Anterior surface with some vessels of the Circle of Willis and the leptomeninges in place. The yellow arrowheads indicate the basilar artery, under which the string must be passed to suspend the brain in formalin after its evisceration, to allow a correct fixation. Red arrows: vertebral arteries. T = trigeminal nerve root (V cranial nerve). X: vagus nerve. XII: hypoglossal nerve. **B.** Midbrain and brainstem (pons and medulla oblongata) after the removal of the vessels of the Circle of Willis and the leptomeninges. Red dotted line = midbrain. CP = cerebral peduncle (lateral rotated in the picture). P = pons; Yellow arrowhead = interpeduncular fossa; MCP = middle cerebellar peduncle; T = trigeminal nerve root (V cranial nerve). Yellow dotted line = medulla oblongata; O = olives; Pi = pyramid; Ams = anterior median sulcus. **C.** Posterior surface of the midbrain and brainstem, after the removal of the cerebellum. The image highlights the anterior wall of the IV ventricle where the medial eminence (ME), the locus coeroules (LC), the underlying vestibular area (VA) and several choroid plexus (yellow arrows) are observed. SC: superior colliculus. IC: inferior colliculus. Yellow dot: inferior cerebellar peduncle. IX: glossopharyngeal nerve. X: vagus nerve. XII: hypoglossal nerve. GT: gracile tubercle. GF: gracile fasciculus. Pms: posterior median sulcus. **D-F.** Multiple midbrain and brainstem sections after section on transverse planes at a distance of approximately 0.5 cm. In D in the leftmost section performed at the level of the midbrain, the substantia nigra is clearly observed. NR: nucleus ruber. SC: superior colliculus. AM: aqueductus mesencephali (Silvius aqueductus).

Damage to the meninges and choroid plexus

The presence of the spike glycoprotein of SARS-CoV-2 has been detected both in the leptomeninges and in the stroma of the choroid plexus in patients affected by COVID-19[15,16]. The lesions described in association with the detection of the virus or in COVID-19 disease are inflammatory or thrombotic. The meningitis sustained by T lymphocytes with increased macrophages and, less frequently, with the detection of vascular thrombosis has been observed in many patients, involving also the vessels of the Circle of Willis[17,18]. Subarachnoid hemorrhages are only occasionally described in the literature, mostly as small or punctate[19,20].

Figure 6.2: Leptomeninges and large intracranial vessels in patients with COVID-19 disease



A. Large arterial vessel of the Circle of Willis subocluded by a thrombus in an acute phase of evolution. The yellow arrows delimit the edges of the thrombus which in the image appears attached to the highest part of the vessel**. B.** Leptomeninges with moderate edema. The arachnoid vessels are not thrombosed. **C.** Leptomeninges with small subarachnoid hemorrhagic extravasations (arrows). Also in this image the arachnoid vessels are not thrombosed. **D.** Leptomeninges characterized by a few positive macrophages (dark brown cells) with the immunohistochemical staining for CD68 PGM1. Macrophages are mostly located perivascularly. Some isolated CD68 PGM1 positive cells can also be observed in the underlying nervous parenchyma (cells most likely referable to microglia). **E**. Same area as the previous image, stained with immunohistochemical reaction for CD163. It can be seen that the number of CD163 + inflammatory cells are significantly higher than CD68 PGM1 + cells, although they largely maintain the same arrangement. CD163 marks the activated macrophages (M2) indicating the presence of a local reactive / inflammatory state.

We have observed recent thrombosis of a vessel of the Circle of Willis in only one patient (Figure 6.2A); leptomeninges mostly showed mild focal edema. We have only occasionally detected small subarachnoid hemorrhagic suffusions

(Figure 6.2C); on the contrary, we have almost always observed an increase in macrophages in the meninges (CD68 PGM1 + cells) and a very large population of M2 macrophages (CD163 + cells). This demonstrates the presence of a leptomeningeal inflammatory state (Figure 6.2D and E).

Macroscopic parenchymal lesions

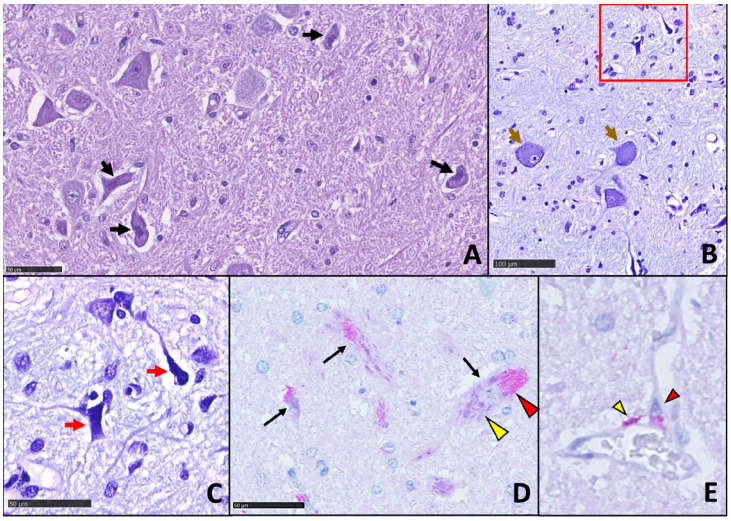
The frequency of macroscopic lesions in the CNS changes significantly in the different case series that have been studied. In almost all cases, these lesions are ischemic or hemorrhagic, and involve also widespread cortical areas. They can affect either the brain, the cerebellum or the brainstem[18]. Cerebral edema is one of the most reported alterations[19,21] but its direct relationship with the viral infection appears difficult to define, given that this disease can be traced back to many other pathogenic causes during an autopsy. There were occasional macroscopic cerebral lesions (a small cerebral infarction occurring a few days before death in a single intubated and mechanically ventilated patient) and non-specific even in our autopsy experience, while diffuse cerebral edema was almost always detected, with from mild to moderate weight gain of the B-BS-C block.

Neuronal, glial and vascular histological damages

Several autopsy or biopsy studies have described alterations in single neurons or glial activation, as well as vascular thrombosis involving both major and minor intracranial vessels. However, the question as to whether the neuronal damage is directly caused by the virus or is the result of hypoxic / ischemic mechanisms or immune-mediated processes remains unanswered[1,22]. The most frequent histological damage described is: 1) sparse neuropil infiltration of inflammatory cells (depending on the case: T lymphocytes, B lymphocytes, microglia, neutrophil granulocytes. T lymphocytes are often arranged in a cap around small vessels, while B lymphocytes prevail within the parenchyma with more frequent distribution in single cells. Neutrophil granulocytes mostly characterize micro-areas of ischemic necrosis); 2) acute hypoxic-ischemic neuronal changes, including perikaryal cytoplasmic eosinophilia and nuclear pyknosis (so-called "red neurons"); 3) microglial activation with microglial nodules, with or without neuronophagia features; 4) focal demyelination[18,23]; 5) localized axonal swellings, demonstrated with amyloid precursor protein (APP) immunostain, indicative of subacute and acute axonal damage[24-26]. In our experience, we have observed neuronal histological alterations, particularly at the level of the brainstem[10]. The altered neurons are distributed quantitatively in different ways at the different sites of the B-BS-C block, resulting very high at the level of the Varolius pons, the medulla oblongata and the basal fronto-temporal areas of the brain, while they progressively decrease proceeding

from basal ganglia / thalamus to the cortex of the latero-superior areas of the brain (GP Bulfamante, unpublished data, 2021).

Figure 6.3: Brainstem neurons in patients with COVID-19 disease; many of them show evident structural alterations



A. The neurons indicated by the arrows show marked regressive morphological alterations both nuclear and cytoplasmic. The nuclei are shrunken with heavily thickened chromatin and often have an angled profile. The cytoplasms are not red (as in the "red cells") but equally have reduced volumes, asymmetric profiles and a hyperchromatic halo at the outer membrane. These structural changes make these neurons clearly different from morphologically normal ones. **B-C.** Neuronal alterations referable to different evolutionary stages, with Nissl staining. In the red box "B" and "C" two neurons are observed with marked compaction of the pyrenephorus, which appears completely dark blue. In image "B" the two brown arrows indicate two neurons with swollen pyrenephorus and peripheral dispersion of Nissl substance. **D.** Neurons positive with immunohistochemical staining for SARS-CoV-2 Nuclear Protein: staining was developed with red color. The arrows identify three neurons infected with the virus; the rightmost cell presents regressive alterations. Immunohistochemical positivity shows itself as small red droplets (red arrowheads) in the cytoplasm; these droplets should not be confused with the irregular granules of intracytoplasmic Nissl substance (yellow arrowhead). Since in damaged neurons the substance of Nissl can undergo modifications (compaction, loss of volume of the single granules) it is not advisable to develop immunohistochemical reactions for the detection of SARS-CoV-2 on the central nervous system with brown tracer. **E.** Immunohistochemical stain for the SARS-CoV-2 Nuclear Protein: the stain was developed with red color. In this image there are two cells with cytoplasmic positivity. The one indicated by the red arrowhead clearly appears to be an endothelial cell. The other (yellow arrowhead) is difficult to attribute: it could be a perivascular cell in the Virchow-Robin space.

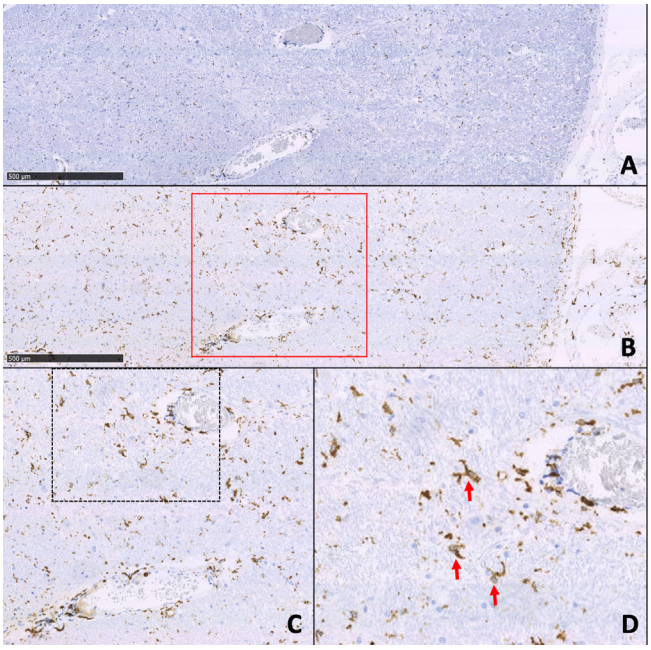
Neuronal alterations may be similar to those described in shrunken cells caused by hypoxia / ischemia, but with no evidence of red staining of the cytoplasm (Figure 6.3A-C). Another type of neuronal damage is represented by the presence of cells with swollen pyrenephorus and peripheral dispersion of Nissl substance (Figure 6.3B). Neurons were found to be infected by SARS-CoV-2 in several areas[10] (Figure 6.3D) and the number of infected neurons changes within the brain following the neuronal alterations listed above (GP Bulfamante, unpublished data, 2021). The virus has also been observed in some endothelial and perivascular cells of the Virchow-Robin space of intraparenchymal vessels (Figure 6.3E).

Our experience of the autopsy histopathological characteristics of the CNS in COVID-19 patients also involved the glia. The most frequent finding that cannot be correlated with any pre-COVID-19 diseases regarded the activation state of this cellular compartment. Immunohistochemical staining for CD68 PGM1 highlighted the constant increase of intraparenchymal cells, identifiable as microglia cells: these cells are almost always distributed as single cells, small, with no enlarged and vacuolated cytoplasm, a feature that makes them easily identifiable when they intervene in an area of infarction. Some of these cells are observed on the contour of the intraparenchymal blood vessels (Figure 6.4A). Microglia represents the main innate immune system within the central nervous system and plays a fundamental role during inflammatory processes, traumatic events, and in the pathogenesis of neurodegenerative disorders or in case of neoplasms[27]. This glial population has different embryological origins compared to monocytes / macrophages, which originate from the hematopoietic system, even if it shares with them some surface antigens and some functions, such as phagocytosis and modulation of the inflammatory process[27,28]. These cells do not only respond to a noxious stimulus or a pathological condition; they are also involved in the regulation of neuronal development during the embryonic and fetal period, and in the regulation of its homeostasis in adult life[29,30]. CD163 immunohistochemical staining also demonstrates the presence of a much larger cell population than CD68 PGM1 positive cells and most CD163 positive cells do not co-express CD68 PGM1 (GP Bulfamante, unpublished data, 2021). (Figure 6.4B-D).

Similarly to monocytes/macrophages, two activation states have also been recognized for microglia: the "classic" state, M1-like or pro-inflammatory, and the "alternative" state, M2-like or anti-inflammatory / protective marked by immunohistochemical positivity for CD163 protein. These two different microglial activation states are expressed in different pathophysiological conditions. They are characterized by cytokine secretion that arranges the complex immune response in the tissue microenvironment. The ability of the microglia to regulate and modulate its phagocytic capacities in response to an external stimulus is of particular importance in this context; the precise regulation of the microglial

activation state, therefore, ensures the control of adverse events that would lead to irreversible and sometimes fatal tissue damage[28].

Figure 6.4: Glial population of the brainstem

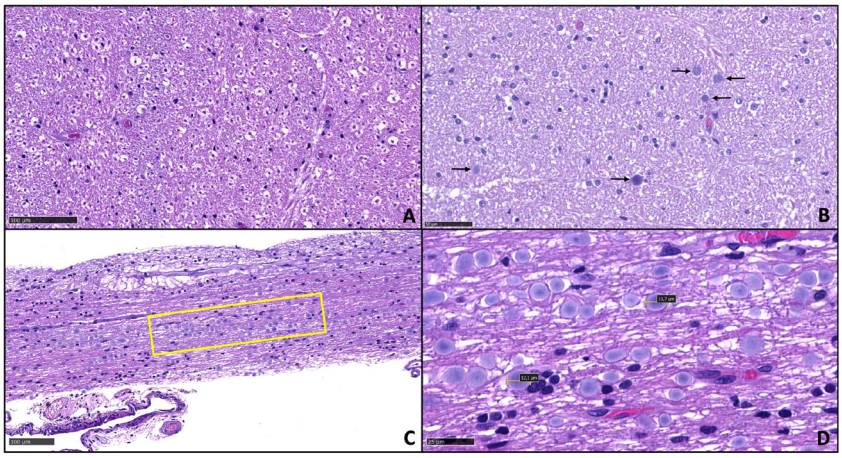


A. Immunohistochemical staining for CD68 PGM1, developed in brown, shows the presence of a sparse but widespread population of positive cells. These are identifiable as microglia due to their morphology. **B.** Immunohistochemical staining for CD163 shows that the population of CD163 + cells is clearly superior to CD68 PGM1 + ones. The red box is enlarged in the next image. **C.** At higher enlargement it is appreciated how many of the CD163 + cells are arranged in close contact with the intraparenchymal blood vessels. The black dotted box highlights the enlarged area in image "D". The image does not have the scale bar because it is a digital enlargement of the previous image. **D.** The high magnification shows how many CD163 + cells have a glial dendritic appearance. The image does not have the scale bar because it is a digital magnification of the image "B".

Its ability to remove sialic acid residues from the neuronal cell surface, thus activating the complement cascade and its own phagocytic activity, appears to be particularly important to help understand its role during SARS-CoV-2 infection[31]: complement factors C1q and C3 can stimulate microglia in the phagocytosis of synapses and neurons through the complement receptor 3 (CR3), consisting of CD11b and CD18 subunits. It is also known that microglia can play a role as a viral "reservoir" in the course of HIV1 infection, through mechanisms not yet fully understood, probably depending on specific immunophenotypic characteristics of the cells themselves[32]. Sialic acid bound to glycoproteins and

gangliosides is used by several viruses as an entry receptor within human cells; SARS-CoV-2 itself penetrates inside the cells through the spike glycoproteins. Our working group has recently used an immunohistochemical approach to demonstrate the presence of this virus in the glial cells of the brainstem[10]. This suggests a more important role of microglia both in the acute phase and in the post-COVID-19 conditions. Our findings regarding the histopathology of the neuropil and white matter of the CNS were also found to be only partially comparable to those of the previous studies[18,23-26]. The rapid evisceration and fixation of the B-BS-C block allowed us to recognize and adequately grade the distribution of tissue edema as it avoided the well-known and frequent post-mortal alterations of the parenchymal tissue of the brain, which can make recognition of tissue edema extremely confusing (Figure 6.5A and B). We found the damage to the myelin sheaths and subacute and acute axonal damage[7,10]. We also observed the widespread presence of structures similar to the more recently formed (non-stratified) amylaceous corpora or to the Lewy bodies present in some neurodegenerative diseases[10] (Figure 6.5B-D) in middle-aged patients not suffering from neurodegenerative diseases.

Figure 6.5: White matter of the brain



A-B. Brain. The white matter appears edematous with the presence of numerous small hollow halos on the contour of the glial cells. Hollow halos are also observed between the myelin sheaths and their respective axons. In "B" the arrows identify some corpora amylacea. **C-D.** Olfactory nerve. This structure also appears markedly damaged and it is characterized by the presence of numerous corpora amylacea in a middle-aged patient not suffering from neurological degenerative diseases, such as Alzheimer's disease. In "C" the yellow box indicates the enlarged area in image "D". In the latter, it is observed that the corpora amylacea can also be large reaching a diameter of about 12 microns.

These structures are particularly abundant both in the brainstem and in the basal areas of the brain, particularly at the level of the frontal and temporal lobes. It is not yet clear whether these findings are a consequence of the involution of single pyrenophores or axonal spheroids at points of axonal distruption. However, in patients who died from COVID-19, the close quantitative correlation between the areas of the greatest tissue damage and these amorphous structures suggests that the latter can be a prompt indicator in the routine histopathological examination of tissue damage, which requires in-depth studies with histochemical and immunohistochemical methods for its identification.

Viral entry pathways into the CNS

To date, this topic is still one of the most discussed, and several studies have not showed the presence of SARS-CoV-2 in the brain of patients with COVID-19[23,33-37]. It is reasonable to assume that this discrepancy is the result of different factors, including the time elapsed between death and the evisceration of the brain, the different viral load at the time of death, and the viral detection methods (type and clone of the antibody; *in situ* hybridization; qRT-PCR). Theoretically speaking, the virus could infect the parenchymal tissue of the brain either through the circulatory system (in this case, the role of endothelial and perivascular cells would be crucial)[38], or by tracing back to the CNS via nerves connecting it to other organs typically infected by the virus, i.e., the lung[10], or airborne, coming into contact with the nervous olfactory epithelium. The latter, through the cribriform plate of the ethmoid, projects into the mucosa that covers some parts of the nasal cavities[39]. The current state of knowledge considers all these pathways to be potentially possible. It is not to be excluded that the virus could reach the CNS by several routes in single patients, and that, in different autopsy cases, the different geography of the observed damage in the CNS may be an expression of the type of route of infection followed by the virus. Our impression and our current topic of investigation is that there is quantitatively less damage resulting from the bloodstream infection, at least at the level of cortical neurons, and that it occurs particularly in the areas of the brain that are further from the basal cortex of the frontal and temporal lobes.

Conclusions

It is undeniable that, still today, after over 4 million deaths from COVID-19 and over 180 million people infected with SARS-CoV-2 worldwide, our knowledge of the neuropathological characteristics of this infection and

disease is limited. From a histopathological point of view, it is difficult to define whether the observable neuronal or glial damage is a direct effect of the viral infection or a secondary effect of the disease rather than an expression or co-expression[40-43] of other previous diseases. Many patients are elderly and, therefore, their CNS is characterized by alterations due to aging, degenerative neurological diseases, or vascular diseases. It is, therefore, extremely difficult to decide which and how many of the macroscopic or histological alterations highlighted are the expression of previous diseases or, instead, the direct effect of the viral infection in single cases[8]. Secondly, many patients affected by COVID-19 were hospitalized in intensive care units, sometimes for many days, and were mechanically ventilated before they died. These conditions could be the cause of the hypoxic changes or of the inflammatory state detected during autopsy. Thirdly, it has been argued that the viral load in the brain can be reduced in the case of prolonged illness[39,44]: this makes it difficult to detect the presence of the virus in the CNS and removes an important correlative element with the pathological alterations eventually detected, even in patients without other previous diseases. Fourthly, the number of patients dying from COVID-19 who underwent autopsy is unacceptably low, even in countries adequately equipped with autopsy rooms with a BLS 3. All this is of particular concern if we consider that, with the prolongation of the pandemic, the weight of the poor neurological outcomes of this disease in survivors is becoming increasingly clear, with evident consequences on the health costs of rehabilitation, on the social costs (also in terms of work) and personal costs. Neuropathology studies on COVID-19 should address a large cohort of patients and case-control series, and explore both the damage to the CNS that can lead to a patient's death, such as those involving the primary respiratory and cardiovascular control center in the medulla oblongata[9,10,17,39], and the damage to the brain or cerebellar areas capable of worsening the quality of life of disease survivors. The SARS-CoV-2 pandemic, even after the number of cases worldwide has significantly decreased, will continue to represent a health emergency for many years, and medical research must continue to address this.

Take-home message

- The autopsy study of the CNS is still fundamental to better understand the SARS-CoV-2 infection, its way of transmission and spreading, and many clinical aspects of the disease.
- It is important to remove and fix the brain as soon as possible after the patient's death.
- In our experience, SARS-CoV-2 can directly damage neurons, glia and myelin contributing to the overall cerebral damage, potentially caused also by alterations in oxygenation from lung disease and/or mechanical ventilation during COVID-19.
- The current state of knowledge suggests that the virus can migrate via nerves, probably with a mechanism similar to the Herpesviruses.

References

1. Farhadian SF, Seilhean D, Spudich S. Neuropathogenesis of acute coronavirus disease 2019. *Curr Opin Neurol.* 2021;34(3):417-422.
2. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* 2020;26:1017-1032.
3. Venter C, Bezuidenhout JA, Laubscher GJ, et al. Erythrocyte, platelet, serum ferritin, and P-selectin pathophysiology implicated in severe hypercoagulation and vascular complications in COVID-19. *Int J Mol Sci.* 2020;21:8234.
4. Song E, Bartley CM, Chow RD, et al. Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms. *Cell Rep Med.* 2021;2(5):100288.
5. Farhadian S, Glick LR, Vogels CBF, et al. Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19. *BMC Neurol.* 2020;20:248.
6. Benameur K, Agarwal A, Auld SC, et al. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. *Emerg Infect Dis.* 2020;26:2016-2021.
7. Bulfamante G, Chiumello D, Canevini MP, et al. First ultrastructural autoptic findings of SARS-Cov-2 in olfactory pathways and brainstem. *Minerva Anestesiol.* 2020;86(6):678-679.
8. Champion SN, Williams IM, Lage MM, Stagner AM. The pathology of the brain and the eye in SARS-Co-V2 infected patients: A review. *J Neuroophthalmol.* 2021. doi: 10.1097/WNO.0000000000001275. [Preprint]
9. Bocci T, Bulfamante G, Campiglio L, et al. Brainstem clinical and neurophysiological involvement in COVID-19. *J Neurol.* 2021. doi: 10.1007/s00415-021-10474-0. [Preprint]
10. Bulfamante G, Bocci T, Falleni M, et al. Brainstem neuropathology in two cases of COVID-19: SARS-CoV-2 trafficking between brain and lung. *J Neurol.* 2021. doi: 10.1007/s00415-021-10604-8. [Preprint]
11. Carpenito L, D'Ercole M, Porta F, et al. The autopsy at the time of SARS-CoV-2: Protocol and lessons. *Ann Diagn Pathol.* 2020;48:151562.
12. Bulfamante G, Perrucci GL, Falleni M, et al. Evidence of SARS-CoV-2 Transcriptional Activity in Cardiomyocytes of COVID-19 Patients without Clinical Signs of Cardiac Involvement. *Biomedicines.* 2020;8(12):626.
13. Henwood AF. Coronavirus disinfection in histopathology. *J Histotechnol.* 2020;43(2):102-104.
14. Darnell ME, Taylo DR. Evaluation of inactivation methods for severe acute respiratory syndrome coronavirus in noncellular blood products. *Transfusion.* 2006;46(19):1770-1777.
15. Ritschel N, Radbruch H, Herden C, et al; DGNN-Taskforce, "CNS-COVID19"; "DEFEAT PANDEMIcs – Neuropathologische Referenzdiagnostik bei COVID-19". [COVID-19: Auswirkungen auf das zentrale und periphere Nerven-

system] *Pathologe*. 2021;42(2):172-182.

16. Fuchs V, Kutza M, Wischnewski S, et al. Presence of SARS-CoV-2 Transcripts in the Choroid Plexus of MS and Non-MS Patients With COVID-19. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(2):e957.
17. Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol*. 2020;19(11):919-929.
18. Serrano GE, Walker JE, Arce R, et al. Mapping of SARS-CoV-2 Brain Invasion and Histopathology in COVID-19 Disease. *medRxiv* 2021. doi: 10.1101/2021.02.15.21251511. [Preprint]
19. Pajo AT, Espiritu AI, Apor ADAO, Jamora RDG. Neuropathologic findings of patients with COVID-19: a systematic review. *Neurol Sci*. 2021;42(4):1255-1266.
20. Mukerji SS, Solomon IH. What can we learn from brain autopsies in COVID-19? *Neurosci Lett*. 2021;742:135528.
21. Conklin J, Frosch MP, Mukerji SS, et al. Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19. *J Neurol Sci*. 2021;421:117308.
22. Thakur KT, Miller EH, Glendinning MD, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain*. 2021. doi: 10.1093/brain/awab148. [Preprint]
23. Fisicaro F, Di Napoli M, Liberto A, et al. Neurological Sequelae in Patients with COVID-19: A Histopathological Perspective. *Int J Environ Res Public Health*. 2021;18(4):1415.
24. Reichard RR, Kashani KB, Boire NA, et al. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol*. 2020;140(1):1-6.
25. Jaunmuktane Z , Mahadeva U, Green A, et al. Microvascular injury and hypoxic damage: emerging neuropathological signatures in COVID-19. *Acta Neuropathol*. 2020;140(3):397-400.
26. Baba Y, Ghetti B, Baker MC, et al. Hereditary diffuse leukoencephalopathy with spheroids: clinical, pathologic and genetic studies of a new kindred. *Acta Neuropathol*. 2006;111(4):300-311.
27. Lenz KM, Nelson LH. Microglia and Beyond: Innate Immune Cells As Regulators of Brain Development and Behavioral Function. *Front Immunol*. 2018;13;9:698.
28. Kanazawa M, Ninomiya I, Hatakeyama M, et al. Microglia and Monocytes/Macrophages Polarization Reveal Novel Therapeutic Mechanism against Stroke. *Int J Mol Sci*. 2017;18(10):2135.
29. Rabinowicz T, de Courten-Myers GM, Petetot JM, et al. Human cortex development: estimates of neuronal numbers indicate major loss late during gestation. *J Neuropathol Exp Neurol*. 1996;55(3):320-328.
30. Vilalta A, Brown GC. Neurophagy, the phagocytosis of live neurons and synapses by glia, contributes to brain development and disease. *FEBS J*. 2018;285(19):3566-3575.

31. Schmidt S, Linnartz B, Mendritzki S, et al. Genetic mouse models for Parkinson's disease display severe pathology in glial cell mitochondria. *Hum Mol Genet*. 2011;20(6):1197-1211.

32. Siew JJ, Chern Y. Microglial Lectins in Health and Neurological Diseases. *Front Mol Neurosci*. 201814;11:158.

33. Al-Sarraj S, Troakes C, Hanley B, et al. Invited Review: The spectrum of neuropathology in COVID-19. *Neuropathol Appl Neurobiol*. 2021;47(1):3-16.

34. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell*. 2020;183:16-27.e1.

35. Kantonen J, Mahzabin S, Mäyränpää MI, et al. Neuropathologic features of four autopsied COVID-19 patients. *Brain Pathol*. 2020;30(6):1012-1016.

36. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological Features of Covid-19. *N Engl J Med*. 2020;383(10):989-992.

37. Schaller T, Hirschbühl K, Burkhardt K, et al. Postmortem Examination of Patients With COVID-19. *JAMA*. 2020;323(24):2518-2520.

38. Boldrini M, Canoll PD, Klein RS. How COVID-19 Affects the Brain. *JAMA Psychiatry*. 2021. doi: 10.1001/jamapsychiatry.2021.0500. [Preprint]

39. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci*. 2021;24(2):168-175.

40. Estrada E. Cascading from SARS-CoV-2 to Parkinson's Disease through Protein-Protein Interactions. *Viruses*. 2021;13(5):897.

41. Rosen B, Kurtishi A, Vazquez-Jimenez GR, Møller SG. The Intersection of Parkinson's Disease, Viral Infections, and COVID-19. *Mol Neurobiol*. 2021. doi: 10.1007/s12035-021-02408-8. [Preprint]

42. Kamel WA, Ismail II, Ibrahim M, Al-Hashel JY. Unexplained worsening of Parkinsonian symptoms in a patient with advanced Parkinson's disease as the sole initial presentation of COVID-19 infection: a case report. *Egypt J Neurol Psychiatr Neurosurg*. 2021;57(1):60.

43. Rethinavel HS, Ravichandran S, Radhakrishnan RK, Kandasamy M. COVID-19 and Parkinson's disease: Defects in neurogenesis as the potential cause of olfactory system impairments and anosmia. *J Chem Neuroanat*. 2021;115:101965.

44. Aschman T, Schneider J, Greuel S, et al. Association Between SARS-CoV-2 Infection and Immune-Mediated Myopathy in Patients Who Have Died. *JAMA Neurol*. 2021. doi: 10.1001/jamaneurol.2021.2004. [Preprint]

Chapter 7. Encephalomyelitis in COVID-19

Alessandro Padovani, Andrea Pilotto, Alessandro Pezzini,
Alberto Benussi

Introduction

After the first cases of the novel coronavirus disease 2019 (COVID-19) were reported in Wuhan, China, in December 2019, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly became a pandemic, forcing health-care systems and governments across the world to take measures to contain the infection, and simultaneously engaging the health community in a race against time to develop effective treatments[1,2]. The SARS-CoV-2 is a positive-sense, enveloped, single-stranded RNA virus that primarily affects the lungs, and the recent disease has been designated as COVID-19. As with many other flu-like syndromes, the most common symptoms of COVID-19 are fever and dry cough, whereas other manifestations, including rhinorrhea and gastrointestinal symptoms, are much less frequent[3]. Reports from China at the beginning of the outbreak, and from other countries afterwards, have clearly demonstrated that most patients (80%) have mild symptoms with no or mild pneumonia; among those patients with more significant symptoms, 15% have severe respiratory distress and 5% have respiratory failure, septic shock, and/or multi- organ failure[4,5]. Although the scientific community is still trying to understand the syndromic complexity of COVID-19, growing evidence indicates that the disease is not limited to the respiratory system and that SARS-CoV-2 has an organotropism beyond the respiratory tract, including the kidneys, liver, heart, skin, and brain. COVID-19-associated neurological manifestations range from mild symptoms such as dizziness, headache, dysgeusia, or anosmia to severe disorders such as stroke, Guillain-Barré syndrome (GBS), acute hemorrhagic necrotizing encephalopathy, meningoencephalitis, and cerebral venous thrombosis. The frequency of reported neurological signs and symptoms is variable but, in spite of this, substantial. In an early Chinese retrospective study, 36.4% of 214 COVID-19 patients had neurological symptoms which included dizziness (16.8%), headache (13.1%), impaired consciousness (7.5%), dysgeusia (5.6%), and anosmia (5.1%)[5]. In Western studies, dysgeusia and anosmia are reported in many patients[6,7]. A French study reports that 49 out of 58 (84%)

COVID-19 intensive care unit (ICU) patients had neurological signs which included agitation (69%), confusion (65%), corticospinal tract signs (67%), and dysexecutive syndrome (33%)[8]. A study from a British referral center described cases of septic or para-infectious encephalopathy, autoimmune encephalitis including acute disseminated encephalomyelitis (ADEM), and GBS[9]. An Italian study also reported a wide range of encephalopathies during the first wave, including ADEM, limbic encephalitis, necrotizing hemorrhagic encephalopathies and meningoencephalitis[10]. In general, neurological complications have been reported to be more common in older age groups and patients with pre-existing comorbidities, including diabetes mellitus, hypertension, malignancies, immunological disorders, obesity, chronic respiratory disease, coronary artery disease, and liver failure[11]. Neurological abnormalities and manifestations have been described as the presenting symptom of SARS-CoV-2 in some patients, while in most cases the neurological onset followed the classical respiratory onset. More recently, there has been growing evidence favoring a relatively high neurological involvement in the so-called Long COVID. In fact, viral infections can damage the structure and function of the nervous system, manifesting as encephalitis, toxic encephalopathy, and post-infectious demyelinating disease[11,12]. Coronaviruses can invade the nervous tissues involving immune-functioning macrophages, microglia, or astrocytes[13] and cause nerve damage through direct infection pathways (circulatory and neuronal), hypoxia, immune injury, attacking ACE2 enzymes, and other mechanisms[14]. The involvement of the nervous system can be due to a direct action of these viruses on the nervous tissue and/or to an indirect action through the activation of immune-mediated mechanisms. While the first can be verified during the acute phase of the disease, the second is mostly apparent only days, weeks, or even months after the acute phase.

Encephalitis and myelitis as a possible manifestation of the disease

Different cases and reviews have consistently shown that patients with COVID-19 are at higher risk for developing CNS involvement, including meningitis, encephalitis and myelitis. In most cases, case reports or limited series of patients, it was not clear whether CNS involvement was secondary to direct infection or para-infectious immune-mediated disease. The description of encephalitis and myelitis syndromes seen with COVID-19 were, in fact, generally highly heterogenous in their presentation[9,10,15] suggesting varied underlying neuropathogenesis, and, in some instances, were not directly correlated with COVID-19. Acute presentations were potentially a consequence of systemic pro-inflammatory cytokines transcending the blood-brain barrier (BBB) or,

more rarely, due to direct viral invasion of the central nervous system (CNS)[9,15]. Later, post-infectious presentations were likely to be due to immune-mediated processes operating through cellular or antibody pathways[9,10].

The wide spectrum of clinical presentation of encephalomyelitis in patients with SARS-CoV-2 respiratory infection, however, closely resembles those phenotypes already associated with influenza and other corona-viruses[15-18], indicating that SARS-CoV-2 behaves like other viruses.

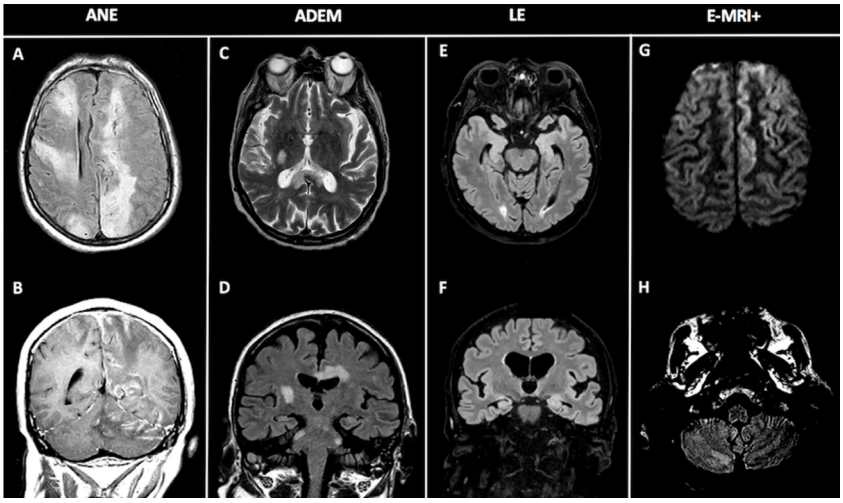
Nevertheless, the neurological complications of influenza have an estimated incidence of between 0.21 and 12 cases per million and particularly affect children[18], whereas the incidence of encephalomyelitis in COVID-19 is estimated to be at least 50 per 100,000 cases[10,20]. The trends in CNS complications in SARS-CoV and MERS-CoV proposed by Ellul and co-authors[15] had an estimated incidence of between 37 and 224 cases per 100,000 symptomatic patients. Several risk factors for encephalomyelitis as a complication of COVID-19 have been elucidated. Demographic risk factors such as old age and underlying comorbidities increased risk of complications from COVID-19 infection, including the development of encephalitis. Additionally, patients who are severely ill with COVID-19 are at a much higher risk of suffering from complications such as encephalitis and myelitis. This incidence as a complication of COVID-19 was less than 1% in the general population of COVID-19 patients but there is a notable rise to 6.7% in those who are severely ill. Although there are case reports of several patients developing encephalomyelitis weeks after initial infection with COVID-19[22], most patients develop both COVID-19 symptoms and CNS symptoms during the same period. Most often, patients present with respiratory symptoms and develop encephalomyelitis an average 14.5 days later, during their hospital stay[21,22].

Encephalitis

SARS-CoV-2 infection has been associated with a wide clinical spectrum of encephalitis, characterized by heterogeneous clinical presentation and outcomes. As far as encephalitis-related symptoms are concerned, the most common included loss or decreased level of consciousness and altered mental state or delirium, while seizures, headaches, and limb weakness were reported in 15-37% of cases[21,22]; other less common symptoms were aphasia, ataxia, and myoclonus. Patients who suffer from encephalitis as a complication of COVID-19 had much poorer outcomes compared to the general population of COVID-19 patients, including admission to intensive care facilities, use of ventilators, and a high rate of mortality. Common magnetic resonance imaging (MRI) brain findings include diffuse white matter hyperintensities and hemorrhagic lesions on fluid-attenuated inversion recovery and T2 sequences (see Figure 7.1) whereas other less common MRI findings include cerebral edema and venous thrombosis. Several cases with encephalitis as a complication of COVID-19 showed

normal brain imaging results likely due to milder encephalitis or imaging conducted before brain changes developed[22].

Figure 7.1: Brain Magnetic Resonance Imaging findings according to encephalitis phenotypes



A and **B** Case of acute necrotizing encephalitis (ANE) characterized by FLAIR diffuse bilateral hyperintensities. **B** with linear Gadolinium-enhancement on coronal T1. **C** and **D** A case of ADEM with T2 and FLAIR hyperintensities (involving corpus callosum, bilateral cerebellar peduncles and right thalamus) on axial (C) and coronal (D) plane. **E** and **F** A case of limbic encephalitis (LE) characterized by increased T2-FLAIR signal within bilateral mesial temporal lobes and (E) and coronal (F) planes. **G** and **H** A case of unspecific alterations defining the group of E-MRI+: DWI hyperintensities on frontal superior and medium gyrus and FLAIR hyperintensity on right cerebellar tonsil. ADEM: acute disseminated encephalomyelitis; ANE: acute necrotizing encephalitis; E-MRI+: encephalitis with MRI alterations; LE: limbic encephalitis.

Electroencephalography (EEG) in some patients showed patterns of general slowing while sharp waves and epileptiform activity were uncommon findings. Analyses of cerebrospinal fluid (CSF) showed mild pleocytosis and/or hyperproteinorrachia in almost all cases, whereas most COVID-19 studies failed to detect SARS-CoV-2 in the CSF samples of the COVID-19 patients with neurological manifestations[21]. To date, few cases of encephalitis have showed the presence of SARS-CoV-2 in CSF, despite negative peripheral and respiratory findings[23]. There may be various reasons for this. The virus may be cell-bound without entering the CSF or have concentrations below the level of detection of the testing method.

In addition, the presence of heme products owing to the breakdown of erythrocytes in the CSF can interfere with the PCR tests used for detecting SARS-CoV-2. Viruses can be associated with limited viremia in blood and CSF. SARS-CoV-2 RNA can only be detected from blood in 1% of the actively infected cases. It is interesting to note that the absence of the virus in the CSF could not definitely exclude a direct viral invasion, as demonstrated for other infectious diseases such as West Nile virus or enterovirus infections[24]. However, the clinical courses and CSF alterations in most patients argue against any direct CNS damage and conversely make a claim for neuroinflammatory and, in rarer cases, autoimmune responses as major players in COVID-19 encephalitis.

For these reasons, several authors have suggested the use of high-dose steroid treatment (such as methylprednisolone 1 g for 5 days) that has been demonstrated to be effective in reducing the CSF markers of inflammatory response[22]. Immunoglobulin administration or plasmapheresis are indicated, according to the current guidelines, in patients fulfilling criteria for autoimmune encephalitis, particularly in those rare cases presenting an antibody-mediated form of disease[24]. This particular approach in COVID-19 disease is still much debated, as most cases did not present CSF alterations suggestive of an immune-mediated inflammatory CNS response.

Acute transverse myelitis

Acute transverse myelitis is clinically characterized by sensorimotor disturbances, bladder/bowel dysfunction, and/or autonomic dysfunction attributable to the spinal cord. It typically manifests as a rapid disease progression from within a few hours to up to 21 days, with a sensory level, bilateral pyramidal signs, and bladder/bowel dysfunction. Acute demyelinating diseases of the CNS, such as multiple sclerosis, neuromyelitis optica spectrum disorder, and acute disseminated encephalomyelitis are other frequently encountered causes of acute myelitis. There is evidence that inflammatory reactions to infectious disease might exacerbate autoimmune diseases, making diagnostic differentiation difficult[25,26]. Many viruses can be directly implicated in the etiopathogenesis of acute transverse myelitis, including varicella-zoster, herpes simplex, Epstein-Barr, West Nile, Dengue, Japanese encephalitis, Zika, influenza, echovirus and hepatitis B, mumps, measles, and rubella viruses[5]. However, it is usually difficult to differentiate between a viral-induced and an immune-mediated transverse myelitis. Not surprisingly, several reports have linked the SARS-CoV-2 virus to the pathogenesis of acute transverse myelitis (ATM)[27,31]. Most patients had typical features of ATM with acute onset of paralysis, sensory level, and sphincter deficits due to spinal cord lesions demonstrated by imaging. Male and females were similarly affected, and mean age was 49 years, with two peaks at 29 and 58 years, but pediatric cases were also described. The main clinical manifestations were quadriplegia and paraplegia. MRI showed localized ATM lesions affected

≤3 cord segments in one-third of cases, whereas most patients had longitudinally-extensive ATM (LEATM) involving ≥4 spinal cord segments[31]. Most cases had a latency of 10 days to 6 weeks that may indicate post-infectious neurological complications mediated by the host's response to the virus, but in one-third a brief latency (15 hours to 5 days) suggested a direct neurotropic effect of SARS-CoV-2.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) has also been described after SARS-CoV-2 as well as other coronavirus infections, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses[32]. ADEM affected predominantly women (2 out of 3) ranging in age from 27 to 64 years (mean age 43 years). The onset of ADEM cases was delayed after the onset of COVID-19 symptoms, which were more severe in terms of respiratory function compared to other encephalitis. Lesions revealed by MRI included cervicothoracic spinal cord lesions down to the conus medullaris, lesions in pons and medulla-cord junction, multiple T1 post-Gd enhancing white matter lesions plus bilateral edema of the optic nerves, hyperintense FLAIR lesions in the medial temporal lobe, bilateral lesions involving cerebral white matter, corpus callosum and brainstem. Indeed, immunomodulatory treatment showed high efficacy in the typical ADEM[22].

Acute necrotizing hemorrhagic encephalopathy

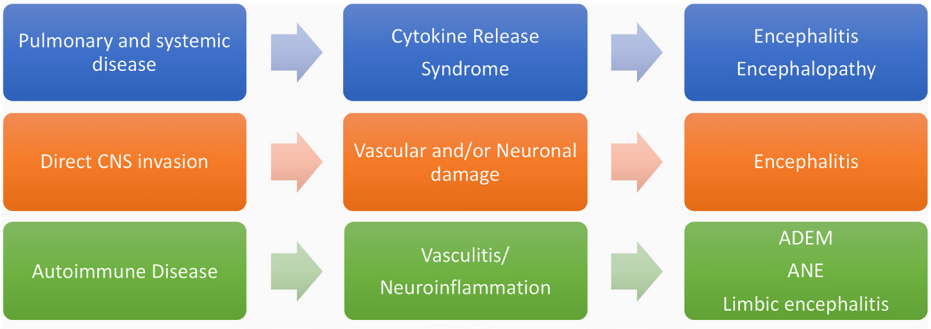
Acute necrotizing encephalopathy (ANE) is a rare neurological complication secondary to para-infectious and hyperimmune response to SARS-CoV-2 infection. This clinico-radiological syndrome affects patients with severe COVID-19 infection and occurs between one to two weeks after the onset of the upper respiratory tract infection[33,34]. The true incidence is unknown due to under-recognition of the syndrome and difficulties in obtaining timely neuroimaging studies due to patients' disease severity. Neurological manifestations of coma and persistent encephalopathy dominated clinical presentation, followed by seizures and focal deficits[22,33,34]. Neuroimaging findings in most patients showed patchy bilateral periventricular hypoattenuation on CT. MRI imaging showed multifocal diffusion restriction, periventricular confluent T2/FLAIR hyperintensities, and diffuse microhemorrhages. The pathophysiology of COVID-19-related ANE is unclear. Although the exact pathophysiology remains obscure, the lack of the typical features of viral and post-viral encephalitides in most ANE cases argues against the hypothesis that the virus directly damages the CNS and, as such, prompts speculation that, after a latent period following the infectious illness, SARS-CoV-2 might induce a secondary, parainfectious process that is responsible for many neurological manifestations. Several mechanisms were hypothesized, including hypercoagulable state from systemic inflammation,

the so-called "cytokine storm", post-infectious immune-mediated responses, direct viral-induced endotheliopathy leading to angiopathy, and microthrombosis. Viral particles have been isolated from the endothelium of various tissues, including the brain. "Cytokine storm"-mediated immunoglobulin G (IgG) production and breakdown of the blood-brain-barrier (BBB) are likely contributory mechanisms[22].

Mechanisms of COVID-19-related encephalomyelitis

There are three proposed mechanisms of the pathophysiology of encephalomyelitis as a complication of COVID-19 (Figure 7.2). The most important mechanism for the acute forms of encephalomyelitis is the systemic inflammation caused by the SARS-CoV-2 virus[36,38], which resembles Cytokine Release Syndrome (CRS).

Figure 7.2: Main mechanisms involved in encephalomyelitis



ADEM: acute disseminated encephalomyelitis; ANE: acute necrotizing encephalitis; CNS: central nervous system.

This is a potentially fatal complication of various infectious (e.g., influenza, SARS, Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis) and non-infectious diseases (e.g., multiple organ dysfunction syndrome, multiple sclerosis). It is triggered by an initial release of proinflammatory cytokines from activated T and/or B cells[37]. The release of cytokines activates bystander immune cells and endothelial cells to produce proinflammatory molecules. CRS-driven neurological disturbances have been described following CAR-T cell therapy and are termed immune effector cell-associated neurotoxicity syndrome (ICANS). There are various clinical manifestations of ICANS and these include encephalopathy (confusion or delirium), expressive aphasia or language disturbance, motor weakness, tremor, headache, seizures, depressed level of consciousness, and,

more rarely, diffuse cerebral edema[39,40]. Some neurological signs/symptoms such as expressive aphasia appear to be very specific to ICANS. Symptoms may progress to seizures or depressed level of consciousness/obtundation to the point of requiring intubation for airway protection. There have been rare cases of diffuse cerebral edema, often developing rapidly over hours with few antecedent clinical warning signs. However, most ICANS symptoms are transient and can fully resolve within the first 3-4 weeks of treatment; persistent abnormalities are uncommon[39]. Severe ICANS occurs almost exclusively in patients who develop CRS and almost always after the first fever. ICANS can occur at the same time as CRS or days later after CRS abates. Brain MRI in ICANS revealed the presence of acute T2/FLAIR hyperintensities suggestive of interstitial edema of varying severity and small (mm-scale) ischemic strokes[39]. More importantly, proinflammatory cytokines such as IL-6 have been shown to lead to endothelial damage and BBB dysfunction in this clinical entity and there is evidence that severe ICANS is associated with elevated CSF protein levels, likely reflecting increased blood-CSF barrier permeability. Accordingly, SARS-CoV-2 infection also activates the innate immune system, causing the release of large amounts of inflammatory cytokines. This causes the phenomenon known as "cytokine storm," which results in systemic inflammatory response syndrome[41]. Evidence to support this theory has been demonstrated by a recent study on CSF. Patients with encephalitis showed increased CSF levels of IL-8, IL-6, TNF-α, and β2-macroglobulin[42]. A second mechanism is direct invasion of the SARS-CoV-2 virus into the brain parenchyma that could cause the development of encephalitis[43,44]. SARS-CoV-2 could enter the brain parenchyma via a trans-synaptic propagation or via hematogenous invasion. In trans-synaptic propagation, SARS-CoV-2 binds to the angiotensin II (ACE-II) receptor on the cell membrane of peripheral nerve cells and enters cells via receptor-mediated endocytosis. It then uses active axonal machinery to travel retrogradely to the CNS[46]. One such route is via the olfactory epithelium, where SARS-CoV-2 invades the olfactory primary sensory neurons and travels to the cribriform plate of the ethmoid bone. From there, it crosses into the anterior cranial fossa and may later spread throughout the brain parenchyma to cause encephalitis[45].

During hematogenous invasion, SARS-CoV-2 crosses the BBB to enter the brain parenchyma. SARS-CoV-2 first invades vascular endothelial cells that express the ACE-II receptor[2,32]. It then interacts with ACE-II on surrounding neurons, glial cells, and other vascular cells, beginning a cycle of viral budding. This causes damage to both vascular and neuronal tissue, compromising the BBB and allowing the SARS-CoV-2 virus to enter the CNS.

Alternatively, hematogenous invasion could also occur through the infection of leukocytes[45]. Lymphocytes, monocytes, and granulocytes all express the ACE-II receptor, making way for possible infection with SARS-CoV-2. Once infected, these leukocytes travel in the blood vessels and cross the BBB,

entering the CNS and taking the SARS-CoV-2 virus with them, where they can infect other cell types within the CNS to cause encephalitis. However, it has been suggested that direct invasion of SARS-CoV-2 into the CNS may be less likely to be the main mechanism causing encephalomyelitis in COVID-19, as most of these patients have had a negative CSF PCR against SARS-CoV-2[2,4,45].

A third proposed mechanism for encephalomyelitis as a complication of COVID-19 is molecular mimicry[46]. In response to infection with SARS-CoV-2, there is an expansion of host antibodies and lymphocytes. Although these immune molecules are supposed to be specific for SARS-CoV-2 viral antigens, some of them are cross-reactive and can attack self-antigens[47]. When cells in the vascular endothelium and brain parenchyma are affected, there is widespread damage to the CNS, which may cause the development of encephalitis[32,46]. There have also been reports of acute hemorrhagic necrotizing encephalopathy which is known to develop via molecular mimicry, further supporting the theory of molecular mimicry as the pathophysiology of encephalitis as a complication of COVID-19[32].

Conclusive remarks

A variety of neurological manifestations have been reported in COVID-19, which include encephalopathy, encephalitis, and myelitis. Various clinical presentations have been described among which altered mental state and delirium are the most frequent, though these are not always clearly detected. The incidence is relatively low, but higher compared to other viral infections. Different mechanisms have been proposed according to onset and the relationship with COVID-19 symptoms. Most encephalitis, closely related to the onset of respiratory problems were likely due to a cytokine release syndrome. Direct invasion of SARS-CoV-2 is an unlikely mechanism but a few neuropathological studies have shown that this might happen in selected cases. Many cases of encephalomyelitis have occurred after the onset of COVID-19 and were likely immune-mediated. Different mechanisms have been identified but the heterogenous clinical picture still needs to be better understood. A key challenge in any epidemiological investigation is the precise definition of patients' clinical phenotypes. Clinicians should be aware that the diagnostic work-up should be as detailed and exhaustive as possible in order to rule out causes other than SARS-CoV-2 infection before including cases in epidemiological analyses. This requires, for example, a distinction between patients with clear evidence of brain inflammation (encephalitis) and patients with encephalopathy, and a careful characterization of all patients with suspected disease of the spinal cord by CSF examination, neurophysiological studies and, when needed, spinal imaging. Although this careful characterization is not always easy to achieve, especially in severely affected individuals, it should be noted that such a rigorous diagnostic approach was not applied in many of the studies published to date, with the obvious consequence

of phenotypic heterogeneity which compromised the reliability of the findings. A useful experimental approach would be, at least, a large-scale case-control study to compare homogeneous groups of patients with confirmed SARS-CoV-2 infection with non-infected individuals; however, this approach would present design challenges, as exposure to SARS-CoV-2 is high in the general population and widespread antibody testing would be needed to ascertain seroprevalence. In addition, neuropathological examination of patients with COVID-19 after death should be performed, as this approach might provide clues as to the mechanisms underlying nervous system injury. Finally, although an emphasis has been put on recovery from the acute phase of the infection, the potential long-term neurological effects of COVID-19 should not be overlooked. If SARS-CoV-2 invades the CNS, neurological manifestations could recur in predisposed individuals after the virus has remained latent for a long time. Longitudinal neurological assessments of patients after recovery will be crucial in understanding the natural history of SARS-CoV-2 in the CNS and monitoring for potential neurological sequelae. Evidence from animal and human studies of other coronaviruses suggests that, in some at-risk individuals, the inflammatory response elicited in acute or chronic infection might trigger or accelerate subclinical mechanisms that underlie the earliest stages of many neurological diseases. Accordingly, longitudinal studies should include careful neurological, imaging, laboratory, and neuropsychological evaluation in order to determine the interplay between central and systemic infection driving CNS damage and neurological alterations.

Take-home message

- COVID-19 infection is associated with increased risk of encephalitis and myelitis through different mechanisms.
- The spectrum of SARS-CoV-2-related encephalitides includes inflammatory-mediated and rare antibody-mediated forms.
- A prompt diagnosis of encephalitis and myelitis in COVID-19 is pivotal for early treatment.
- High-dose steroid treatment should be discussed on the basis of clinical and biological features as treatment options for non-infectious encephalitis/myelitis concomitant COVID-19 disease.

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report-51. 2020. Available from: https://www.who. int/docs/default- source/ coronaviruse/situationreports/ 20200311-sitrep-51-covid-19.pdf?sfvrsn= 1ba62e57_10. Last accessed: 10.07.2021.
2. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 2020;382:1177-1179.
3. World Health Organization. Report of the WHO China Joint Mission on Coronavirus Disease 2019 (COVID-19). 2020. Available from: https://www.who.int/publications/i/item/report-of-the-who-china-joint-mission-on-coronavirusdisease-2019-(covid-19)
4. Grant MC, Geoghegan L, Arbyn M, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta-analysis of 148 studies from 9 countries. *PLoS One*. 2020;15(6):e0234765.
5. 5. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
6. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Oto-Rhino-Laryngology*. 2020;277(8):2251-2261.
7. Yan CH, Faraji F, Prajapati DP, et al. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol*. 2020;10(7):806-813.
8. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(21):2268-2270.
9. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143(10):3104-3120.
10. Pilotto A, Benussi A, Libri I, et al. COVID-19 impact on consecutive neurological patients admitted to the emergency department. *J Neurol Neurosurg Psychiatry*. 2020;92(2):218-220.
11. Benussi A, Pilotto A, Premi E, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology*. 2020;95:e910-e920.
12. Michalicova A, Bhide K, Bhide M, Kovač A. How viruses infiltrate the central nervous system. *Acta Virol*. 2017;61(04):393-400.
13. Al-Obaidi MMJ, Bahadoran A, Wang SM, et al. Disruption of the blood brain barrier is vital property of neurotropic viral infection of the central nervous system. *Acta Virol*. 2018;62(1):16-27.
14. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection

with COVID-19 and other coronaviruses. *Brain Behav Immun*. 2020;S0889-1591(20)30357-3.

15. Ellul M, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol*. 2020;19:767-83.
16. 16. Lau KK, Yu WC, Chu CM, et al. Possible central nervous system infection by SARS corona-virus. *Emerg Infect Dis*. 2004;10:342344.
17. Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome coronavirus (MERS-CoV). *Infection*. 2015;43:495-501.
18. Meijer WJ, Linn FH, Wensing AM, et al. Acute influenza virus-associated encephalitis and encephalopathy in adults: a challenging diagnosis. *JMM Case Rep*. 2016;3:e005076.
19. Benameur K, Agarwal A, Auld SC, et al. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. *Emerg Infect Dis*. 2020;26:2016-2021.
20. Varatharaj A, Thomas N, Ellul MA, et al. UK-wide surveillance of neurological and neuropsychiatric complications of COVID-19: the first 153 patients. *Lancet Psychiat*. 2020;7:875882.
21. Siow I, Lee KS, Zhang JJY, et al. Encephalitis as a neurological complication of COVID-19: A systematic review and meta-analysis of incidence, outcomes, and predictors. *Eur J Neurol*. 2021. doi: 10.1111/ene.14913. [Preprint]
22. Pilotto A, Masciocchi S, Volonghi I, et al. Clinical Presentation and Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2-Related Encephalitis: The ENCOVID Multicenter Study. *J Infect Dis*. 2021;223(1):28-37.
23. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus 2. *Int J Infect Dis*. 2020;94:5558.
24. Venkatesan A, Tunkel AR, Bloch KC, et al. International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the International Encephalitis Consortium. *Clin Infect Dis*. 2013;57:1114-1128.
25. Venkatesan A, Johnson RT. Infections and multiple sclerosis. *Handb Clin Neurol*. 2014;122:151-171.
26. Abu-Rumeileh S, Garibashvili T, Ruf W, et al. Exacerbation of chronic inflammatory demyelinating polyneuropathy in concomitance with COVID-19. *J Neurol Sci*. 2020;418:117106.
27. Munz M, Wessendorf S, Koretsis G, et al. Acute transverse myelitis after COVID-19 pneumonia. *J Neurol*. 2020;267(8):2196-2197.
28. Zachariadis A, Tulbu A, Strambo D, et al. Transverse myelitis related to COVID-19 infection. *J Neurol*. 2020;267(12):3459-3461.
29. Chow CCN, Magnussen J, Ip J, Su Y. Acute transverse myelitis in COVID-19 infection. *BMJ Case Rep*. 2020;13(8):e236720.

30. Sarma D, Bilello LA. A case report of acute transverse myelitisfollowing novel coronavirus infection. *Clin Prac Cases Emerg Med.* 2020:4(3):321-323.

31. Román GC, Gracia F, Torres A, et al. Acute Transverse Myelitis (ATM): Clinical Review of 43 Patients With COVID-19-Associated ATM and 3 Post-Vaccination ATM Serious Adverse Events With the ChAdOx1 nCoV-19 Vaccine (AZD1222). *Front Immunol.* 2021;12:653786.

32. Reichard RR, Kashani KB, Boire NA, et al. Neuropathology of COVID-19: A spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol.* 2020;140:1-6.

33. Dixon L, Varley J, Gontsarova A, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. *Neurol Neuroimmunol Neuroinflamm.* 2020;26:789.

34. Mullaguri N, Sivakumar S, Battineni A, et al. COVID-19 Related Acute Hemorrhagic Necrotizing Encephalitis: A Report of Two Cases and Literature Review. *Cureus.* 2021;13(4):e14236.

35. Zubair AS, McAlpine LS, Gardin T, et al. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* 2020;77:1018-1027.

36. Mehta P, McAuley DF, Brown M, et al. COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression. *Lancet.* 2020;395(10229):1033-1034.

37. Tisoncik JR, Korth MJ, Cameron PS, et al. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev.* 2012;76(1):16-32.

38. Moore BJB, June CH. Cytokine release syndrome in severe COVID-19. *Science.* 2020;368(6490):473-474.

39. Santomasso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov.* 2018;8(8):958-997.

40. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.

41. Espíndola OM, Gomes YCP, Brandão CO, et al. Inflammatory Cytokine Patterns Associated with Neurological Diseases in Coronavirus Disease 2019. *Ann Neurol.* 2021;89(5):1041-1045.

42. Pilotto A, Masciocchi S, Volonghi I, et al. SARS-CoV-2 encephalitis is a cytokine release syndrome: evidences from cerebrospinal fluid analyses. *Clin Infect Dis.* 2021. doi:10.1093/cid/ciaa1933. [Preprint]

43. Cataldi M, Pignataro G, Taglialatela M. Neurobiology of coronaviruses: potential relevance for COVID-19. *Neurobiol Dis.* 2020;143:105007.

44. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. *Nat Rev Neurol.* 2020;16(11):636-644.

45. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological Features of

Covid-19. *N Engl J Med*. 2020;383(10):989-992.

46. Cappello F. COVID-19 and molecular mimicry: The Columbus' egg? *J Clin Neurosci*. 2020;77:246.
47. Franke C, Ferse C, Kreye J, et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain Behav Immun*. 2021;93:415-419.

Chapter 8. Stroke

Angelo Cascio Rizzo, Alessandro Innocenti, Giuditta Giussani, Francesca Lanzani, Elio Clemente Agostoni

Introduction

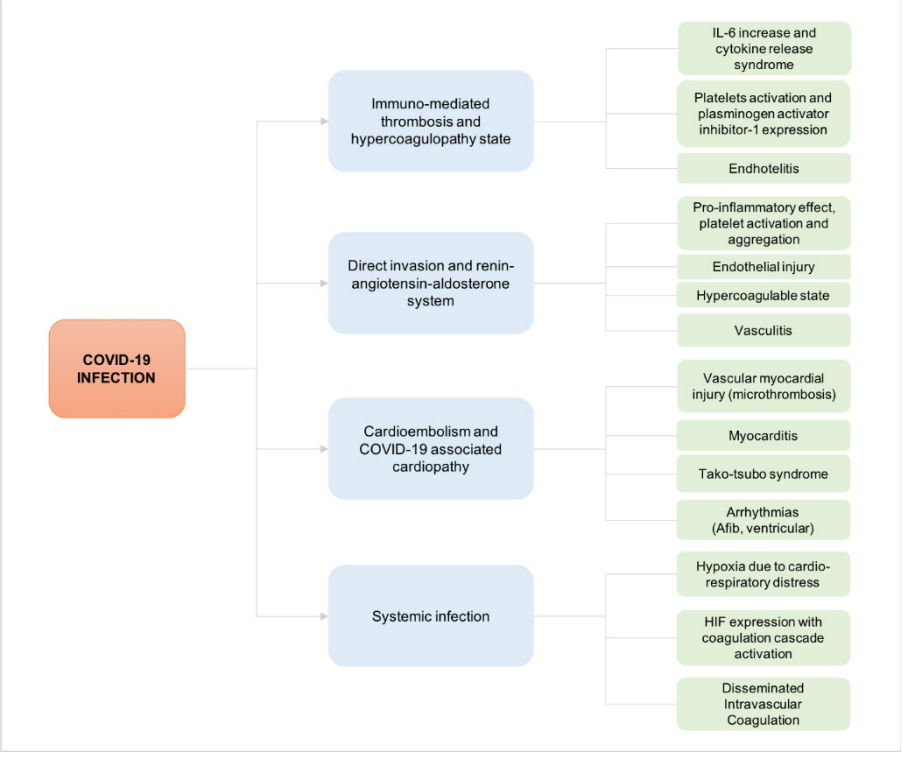
Coronavirus disease 2019 (COVID-19) has been associated with an increased risk of venous and arterial thromboembolic complications, including stroke. Patients affected by the illness may develop clinically significant coagulopathy probably mediated by several factors such as hyperinflammation, endothelial dysfunction, thrombin generation and platelet activation. Since the spread of the outbreak, a series of early reports indicated an association between COVID-19 and cerebrovascular disease, particularly ischemic stroke. In a case series of individuals admitted to a hospital in Wuhan, China, during the emergency, six patients (3%) presented stroke; five out of six strokes were ischemic and only one was hemorrhagic[1]. A series of five cases of severe large-vessel stroke (mean National Institutes of Health Stroke Scale [NIHSS] score: 17) in patients under 50 years of age was described in New York City[2] drawing attention to the potential relationship between large-vessel stroke and COVID-19 in young patients. From then, several studies have been published showing that the COVID-19 outbreak has had a considerable impact on stroke incidence and etiology.

Epidemiology

Incidence of ischemic stroke among COVID-19 admissions in clinical series is approximately 0.9-2.7%[3-7]. A lower incidence has been reported for intracranial hemorrhage (range 0.2-0.9%)[8,9] and for cerebral venous thrombosis (0.08%)[10]. Moreover, there is a higher occurrence of stroke among patients with COVID-19 compared to patients with other viral respiratory infections (SARS-CoV-1 or Influenza)[11]. Although there is evidence to suggest a high rate of cerebrovascular complications in patients with SARS-CoV-2 infection, the actual frequency of stroke among patients with COVID-19 has probably been underestimated because of the phenomenon of missed stroke diagnoses due to possible falling rates of new ischemic stroke admissions. Patients have been less likely to go to hospital

to ask for medical assistance, especially in the presence of mild symptoms. In addition, stroke diagnosis has been missed in those patients with severe respiratory involvement who were not extubated (thus clinical neurological symptoms could not be detected) or who did not survive mechanical ventilation. Finally, the number of stroke cases were probably underestimated due to fewer MRIs being carried out. Stroke generally developed later, after a mean 1-2 weeks from onset of COVID-19 symptoms. In a metanalysis, neurological symptoms related to stroke represented the reason for hospital admission in 37.7% and the median delay of stroke from onset of COVID-19 symptoms was 8.8 days[12]. In a UK study, fever, cough or dyspnea occurred a median 6 days before stroke onset[13]. This delay between stroke onset and COVID-19 infection is probably secondary to the development of the increased hypercoagulable and inflammation state as trigger mechanisms of cerebrovascular complications.

Figure 8.1: Pathophysiological processes related to stroke in patients with COVID-19 infection



HIF = hypoxia-inducible transcription factor; IL-6 = Interleukin 6.

COVID-19 and cerebral vascular disease: pathophysiological mechanisms

Various mechanisms can lead to involvement of the nervous system in COVID-19[14]. Many reports demonstrated a link between COVID-19 and cerebrovascular disease[1,15], and a recent meta-analysis showed a 5-fold increase in stroke risk for patients with severe COVID-19[12]. COVID-19 patients with ischemic stroke frequently have large vessel occlusion due to either cryptogenic or cardioembolic strokes. However, there is a higher risk even for minor or lacunar strokes. This clinical diversity probably also reflects pathophysiological heterogeneity. Several pathophysiological processes seem to be related to stroke in patients with COVID-19: a) an immunomediated thrombosis and hypercoagulopathy; b) direct invasion of the nervous system; c) heart disease with increased cardioembolic risk; and d) the consequences of systemic infection.

a) Immuno-mediated thrombosis and hypercoagulopathy state

S proteins are expressed on the surface of SARS-CoV-2 that bind the receptor for the enzyme that converts angiotensin (ACE2), also expressed in epithelial alveolar cells and endothelial cells.

In the lung, the virus is recognized by Toll like receptor (TLR) and upregulates pro-interleukin-1β expression of macrophages[16]. Macrophages cause the release of pro-inflammatory acute-response cytokines (tumor necrosis factor and IL-1β) and a sustained increase in IL-6. In turn, IL-6 supports the inflammatory process, similar to what happens in cytokine release syndrome[17]. During this hyper-inflammatory state, activated platelets induce the extrinsic coagulation cascade, leading to thrombin formation. The cytokine storm also promotes expression of plasminogen activator inhibitor-1 from the endothelium, thus inhibiting the formation of plasmin inhibiting fibrinolysis[18]. Simultaneously, circulating viruses, binding endothelial cells, facilitate endothelial and vascular inflammation (endothelitis)[19]. In turn, damaged endothelial cells also release Von Willebrand factor, causing platelet hyperactivation. The pro-inflammatory state, platelet and coagulation activation, and endothelitis result in hypercoagulability and microvascular immune-mediated thrombosis[20]. In some patients, hypercoagulopathy is also determined by the presence of antiphospholipid antibodies or lupus anticoagulant[21]. High D-dimer levels and elevated fibrinogen without hypofibrinogenemia characterize COVID-19 hypercoagulopathy. Furthermore, prolonged inflammation determines oxidative stress with the production of reactive oxygen species (ROS) which in turn enhance the inflammatory response[22].

b) Direct invasion and renin-angiotensin-aldosterone system

As mentioned above, S proteins on the surface of SARS-CoV-2 bind ACE2, which is expressed not only in the lung and endothelium but also in the Central

Nervous System (CNS), especially in the olfactory bulb, in the cingulate cortex, the temporo-mesial lobe, the substantia nigra, in cerebral capillaries, smooth muscle cells, and microglia. Direct CNS invasion by a virus probably occurs in several ways, but mainly through the olfactory nerve and olfactory bulb[23]. The hematogenous spread of a virus by crossing the blood-brain barrier could also cause direct damage. ACE2 counteracts the renin–angiotensin–aldosterone system by degrading angiotensin I and II and promoting vasodilating and an-inflammatory effects. By binding ACE2, SARS-CoV-2 downregulates ACE2 expression and higher formation of angiotensin II causes the migration of leukocytes into the tissues with a pro-inflammatory effect, promoting platelet aggregation[24]. These effects, together with endothelitis, cytokine storm, complement, platelet and neutrophil activation, may affect both the stability of already vulnerable atherosclerotic plaques and contribute to a hypercoagulable state and arterial embolism[25]. In addition, direct infection of the cerebrovascular endothelium and immune dysregulation could cause a viral cerebral vasculitis in the brain[26]. Direct (viral invasion) or indirect (inflammatory cytokine, prothrombotic factors, activation of coagulation cascades) endothelial damage increases not only the thrombotic risk, but also contributes to vascular fragility. This, associated with blood brain barrier dysfunction, can result in a cerebral hemorrhage[27].

c) Cardioembolism and COVID-19-associated cardiopathy

Pro-inflammatory pattern and cytokine storm may lead to myocardial injury, elevating microthrombi genesis[28]. In addition to vascular myocardial damage, several studies report an increased incidence of myocarditis and Tako-tsubo syndrome in COVID-19 patients[29,30]. Myocardial damage, whether vascular or non-vascular, causes left ventricular dysfunction, which is a well-known cause of embolic stroke. Furthermore, myocardial damage associated with a systemic infection can result in atrial fibrillation or in malignant ventricular arrhythmias, which in turn can be a potential cause of cardioembolism.

d) Systemic infection

COVID-19 is known to be a systemic disease. Therefore, disease-related brain damage is also closely linked to the systemic alterations caused by the disease. Hypoxia due to cardio-respiratory distress increases the risk of ischemic stroke. Furthermore, systemic hypoxia promotes the expression of Hypoxia Inducible Factor (HIF), which in turn activates the coagulation cascade via extrinsic coagulation pathway, maintaining hypercoagulability in hypoxic regions[18]. Sepsis with high D-dimer levels can result in sepsis-induced Disseminated Intravascular Coagulation. Furthermore, co-pathologies play an important role: severe disease is usually seen in older patients who often have comorbidities

that increase their risk of stroke (diabetes, hypertension, obesity, smoking habit), and these have a significant negative effect on prognosis.

Risk factor of stroke in COVID-19 patients

Some early reports observed that ischemic stroke frequently occurred in young patients with COVID-19. In a retrospective cohort study of consecutive patients with ischemic stroke who were hospitalized within a major health system in New York, among the 32 patients with COVID-19 and stroke, the median age was 62.5 years[2,4]. In a systematic review and metanalysis, patients with COVID-19 and stroke were younger than patients with stroke without infection with a pooled median difference for age of 6.0 years[12]. In the largest study, comprehensively reporting the characteristics and subtypes of stroke in SARS-CoV-2–infected patients from the Multinational COVID-19 Stroke Study Group, in a population of 323 patients with acute ischemic stroke, 36.2% were <55 years of age[31]. However, these data have not been confirmed by subsequent studies and systematic analysis which have shown a higher mean age of COVID-19 patients with stroke of over 65 years[7,32]. In the Global COVID-19 Stroke Registry study[33], median age was 71.2 years.

Male sex is more frequently associated with stroke and COVID-19 infection[34] and in several studies the proportion of Black people was higher[32,35,36]. Earlier observations from smaller case series also suggested that patients with COVID-19 who developed acute ischemic stroke did not have pre-existing cardiovascular risk factors[4].

However, subsequent studies and metanalysis showed stroke risk in Covid-19 was higher in patients with cardiovascular risk factors, with patients developing cerebrovascular diseases having greater likelihood of a smoking habit, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary artery disease, and congestive heart failure[12,32].

Stroke in COVID-19 patients seems to be associated with more severe infectious disease. In a retrospective study in patients admitted to the intensive care unit (ICU), incidence of stroke was 5.7% compared to 0.8% of patients with a non-severe disease course. Siepmann et al.[37] conducted a meta-analysis of 741 patients showing severe COVID-19 infection was associated with an increased risk of acute stroke. In a recent systematic review and meta-analysis of 5,266 patients, according to the severity of the disease, patients with severe COVID-19 had an increased risk of acute ischemic stroke compared with patients with non-severe disease: total stroke rate 3.37% and 0.61%, respectively[38]. Moreover, patients with severe manifestations of COVID-19 have significantly more frequent ischemic strokes with multivascular territorial distribution, hemorrhagic transformation, and simultaneous infarction and intracranial hemorrhage[36]. Stroke in severe COVID-19 is also associated with significantly higher

C-reactive protein and ferritin levels, elevated D-dimer levels, and more frequent lymphopenia and renal and hepatic injury, supporting the proposed pathogenic mechanisms of hyperinflammation activating a prothrombotic state, particularly in those with severe disease[36].

COVID-19 and stroke characteristics

Patients with COVID-19 and stroke have a higher prevalence of moderate-severe stroke with higher admission NIHSS score. In an early report from a hospital in New York, median NIHSS score was 19 in COVID-19 patients compared to 8 in patients not infected[4]. Sahajouel et al.[31] reported that, in a population of 323 acute ischemic strokes, up to 74% of patients had a NIHSS score ≥5. The high prevalence of more severe strokes can be explained by a greater prevalence of large vessel occlusions (LVO) that is twice as frequent as previously reported (up to 47%), with higher prevalence across all age groups, even in the absence of risk factors or comorbidities[7,31]. Up to 68.8% of young patients present a LVO[7]. Considering published data, young patients probably represent only a small proportion of the entire population of COVID-19 stroke patients and show specific features with respect to older individuals, such as lower prevalence of traditional vascular risk factors and higher incidence of LVO.

In COVID-19 patients, strokes usually present cortical and lobar location and multiterritorial involvement, and associated brain hemorrhage (hemorrhagic transformation or simultaneous hemorrhage and infarction) is common[39]. With regards to stroke etiology, cryptogenic subtype is the most frequently reported from several studies with a prevalence of 50-63%[4,40,41]. Around 50% have no identifiable source and are categorized as embolic stroke of unknown source (ESUS)[42]. In a recent metanalysis, patients infected by SARS-CoV-2 appear to have increased odds of cryptogenic stroke when compared to contemporary or historical non-infected controls[43]. The higher incidence of cryptogenic strokes and ESUS is probably due to blood hyperviscosity and a hypercoagulable state; these have been linked to an immune-mediated response following SARS-CoV-2 infection. In fact, high levels of biomarkers of inflammatory response (neutrophils, C-reactive protein, IL-6) and coagulation defects (high level of D-Dimer, low platelet count, elevated PT and aPTT) were found in patients with cryptogenic strokes[3,4,41], and significantly higher levels of CRP and D-dimer were found in patients with more severe infection, suggestive of an acquired thrombophilia[36]. Moreover, a temporal correlation has been identified between stroke onset and the peak of acute phase reactants, including C-reactive protein, ferritin, and D-dimer, supporting the hypothesis that ischemic stroke is due to an underlying endotheliopathy and thrombosis[44]. An association with newly

positive antiphospholipid antibodies has also been observed although the cause of this is uncertain[21,35].

Other possible embolic sources are probably related to cardiac dysfunction associated with critical illness and prolonged stay in the ICU; hypotension and inadequate cerebral perfusion, septic embolization, atrial fibrillation, cardiac dysfunction, stress cardiomyopathy, myocarditis are sometimes underdiagnosed in severely compromised patients. Compared to SARS-CoV-2-negative patients, patients with COVID-19 infection more often have cardioembolism, especially related to atrial fibrillation, as the likely cause of brain ischemia[34]. In fact, atrial arrhythmias have been associated with severe COVID-19 infection[45]. Patients with ischemic stroke under 50 years of age frequently have elevated cardiac troponin, a marker of acute or chronic myocardial injury strongly associated with the risk of stroke and usually secondary to underlying heart disease at baseline or to a myocardial ischemia. In a cohort of young stroke patients with COVID-19, 80% had high troponin. Considering that 44.8% of them had no prior risk factors, these high levels are probably the consequence of acute myocardial injury, which could play a role in the pathophysiology of acute ischemic stroke in young patients with COVID-19[7].

Among other stroke etiologies, cardioembolism represented the second most frequent subtype, while large vessel atherosclerosis and small artery stroke were less frequently reported[12]. In one study, no difference was found in the prevalence of large-artery and lacunar stroke between patients with and those without COVID-19[33].

However, any discussion of the distribution of stroke etiologies during the Covid-19 outbreak has to take into account some epidemiological bias. A high prevalence of cryptogenic strokes is probably related to an underestimation of the frequency of other subtypes. This could partly be explained by some confounding factors such as a relatively low number of diagnostic studies performed during the outbreak and an underestimation of mild stroke (often due to small vessel disease) because individuals with only mild symptoms would avoid going to hospital because of fear of contagion.

Stroke therapy in COVID-19 patients

Acute reperfusion therapies

Safety issues related to thrombolysis have not been specifically studied in the setting of COVID-19 infection. A reduction in the total number of patients treated with Alteplase has been observed, likely related to the lockdown in Milan, which made it difficult for stroke patients to access medical assistance. A study from Italy on treated patients with thrombolysis or bridging therapy, reported higher rates of unfavorable outcomes at 1-month compared to previous

data from the pre-COVID-19 literature. However, there was no increase in risk of symptomatic intracerebral hemorrhage[46]. Therefore, intravenous thrombolytic therapy should be evaluated, as for any patient with acute ischemic stroke, according to current guidelines. A similar approach should be adopted for mechanical thrombectomy. However, as for thrombolysis, the number of unfavorable outcomes after endovascular therapies was also higher compared to previous data. A French study showed an increased risk of reocclusion after initial endovascular recanalization in patients with COVID-19 that could have been related to hypercoagulability associated with the infection[47]. A European study investigated the efficacy and safety of mechanical thrombectomy in patients with acute ischemic stroke and LVO associated with COVID-19 infection and observed a 29% rate of 30-day mortality after treatment; in more than 50%, the primary cause of mortality was neurological associated with ICH or malignant cerebral infarction/edema[48].

Antithrombotic therapy

Up to now, no clear guidelines on antithrombotic therapy in patients with COVID-19 and stroke have been published. Strokes, particularly those resulting from large vessel occlusion, are associated with certain prothrombotic states in COVID-19 infection. On the other hand, anticoagulation is associated with an increased risk of hemorrhagic transformation in COVID-19 patients[49].

Pharmacological venous thromboembolism prophylaxis is strongly advised for all COVID-19 patients[50]. For patients with ischemic stroke with a strong indication for full-dose anticoagulation (atrial fibrillation, severe heart failure, intraventricular thrombus), early initiation is probably reasonable given the high thrombotic risk seen in patients with COVID-19, to be weighed up with the bleeding risk according to the size of the ischemic lesion.

For other patients with cryptogenic stroke, involvement of multiple vascular territories (suggesting an embolic phenomenon), presence of other potential thrombotic events, an assessment of the severity of systemic illness assessed by measurement of coagulation (fibrinogen and D-dimer) and inflammation markers, should all be considered when deciding between antiplatelet therapy or anticoagulation, always bearing in mind the higher bleeding risk in these patients.

Outcome

The prognosis for COVID-19-associated ischemic strokes is extremely poor. Patients often had severe illness requiring ICU admission and mechanical ventilation[3,4]. The prognosis was particularly bleak in those patients with high levels of D-dimer[5]. Patients have a longer hospital stay with a greater rate of neurological worsening during admission because of a higher rate of neurological

and cardiovascular events during hospitalization including cerebral edema, intracerebral hemorrhage, myocardial infarction, or multisystem involvement[32]. In one study, up to 51% of patients with COVID-19 had severe disability at discharge (median mRS 4 vs. 2) compared with patients without COVID-19[33], and more COVID-19-positive patients suffer in-hospital death[3,40,51]. Friedman et al.[7] reported that a clinical phenotype characterized by older age, a higher burden of comorbid conditions, and severe COVID-19 respiratory symptoms was associated with the highest in-hospital mortality (58.6%) and a 3 times higher risk of death than the rest of the cohort.

COVID-19 and hemorrhagic stroke

COVID-19-related hemorrhagic strokes are much less common than ischemic strokes. In a recent analysis from the COVID-19 cardiovascular disease registry of 21,483 patients, only 48 (0.2%) had had an intraparenchymal hemorrhage[9]. Most were elderly male patients with comorbidities and more vascular risk factors, the most common being systemic hypertension[9,52]. Intraparenchymal hemorrhage was the most common variety[52]. A significant proportion of patients with intracerebral hemorrhage were on some form (therapeutic or prophylactic dose) of anticoagulation therapy, which could have predisposed them to the development of the hemorrhage[40,53,54]. In one study, anticoagulation was associated with a 5-fold increase of intracerebral hemorrhage in COVID-19 patients[54]. Patients with intracerebral hemorrhage are more likely to require ICU admission, mechanical ventilation, extracorporeal membranous oxygenation, and have a higher mortality[9,31]. Higher hemorrhagic risk in COVID-19 patients could be explained by several hypotheses: invasion and direct damage of cerebral blood vessels by SARS-CoV-2, hypertensive effect induced by marked reduction in ACE-2 levels, or systemic hyperinflammatory syndrome characterized by fulminant hypercytokinemia which may mediate vascular damage[26,27].

Niguarda Hospital, Milan: the COVID-19 experience

A retrospective analysis was performed on 901 COVID-19 patients who attended the Niguarda Hospital in Milan[55]. In this case series, 53 patients (5.9%) had a stroke. As expected, our patients with stroke were older and with more comorbidities, and these factors could partially explain the observed higher fatality rate. It should also be noted that a mortality of 37.7% is considerably higher that that reported in the literature, where it ranges from 11% to 19%, and it is higher than previous mortality rates reported at our center (7.7% in 2019). Our data agree with the literature in that there is a substantially higher

mortality in individuals with both COVID-19 and stroke than that observed in patients with stroke without SARS-CoV-2 infection.

Stroke care and assisting patients with COVID-19 infection

Despite the association of SARS-CoV-2 infection with an increased risk of ischemic stroke, in Spring 2020, numbers of inpatient stroke decreased. A decline in acute stroke code activations (Figure 8.1), stroke hospitalizations, and mechanical thrombectomy volumes have been reported in a paper by Friedlich et al.[56] at local, regional, and national levels compared with most reports from comprehensive stroke centers (CSC) in high income countries (*paper has been recently retracted because of lack of written consent from the American Heart Association to use the 'Get with the Guidelines' dataset*).

Primary stroke centers and centers with higher COVID-19 inpatient volumes experienced steeper declines. The reasons for this decrease are not completely understood but may relate to patients with stroke symptoms not seeking care due to fear of contracting SARS-CoV-2 in the emergency room, lack of recognition of stroke symptoms due to isolation from social distancing, misdiagnosis of stroke in the setting of SARS-CoV-2 encephalopathy, or other factors[56,57].

Since the outbreak began, specific measures have been taken to contain the spread of the disease, including lockdown, converting general medical wards to quarantine wards, and reorganizing in-hospital clinical activities for the emergency management and treatment of acute conditions. One such measure has been to concentrate a large proportion of acute stroke patients in a restricted number of hospitals.

The initial lull in stroke volume allowed centers to develop and implement new processes and protocols to care for stroke patients with SARS-CoV-2 infection with the goal of reducing the duration and frequency with which the staff directly interacted with infectious patients. These changes have the dual benefits of not only reducing staff exposure to potential infection, but also helped to conserve personal protective equipment[58]. Recovery of stroke hospitalization but not intravenous thrombolysis volume was noted in the later phase of the initial pandemic wave and was associated with lower COVID-19 hospital burden, high volume, and higher use of comprehensive stroke centers[59-61]. Furthermore, Rinkel et al.[62] show that there was no change in the proportion of stroke patients treated with intravenous thrombolysis (28% vs. 30%, $p = 0.58$) or endovascular thrombectomy (11% vs. 12%, $p = 0.82$) or associated treatment times, confirming that there is no evidence for a decrease in the quality of acute stroke care. In contrast, Siegler et al.[63] report that evaluation for acute ischemic stroke during the COVID-19 period in pooled clinical data of consecutive adult stroke patients from 14 US comprehensive stroke centers was associated with a small but significant delay in intravenous thrombolysis but no significant delay

in thrombectomy time metrics. The analysis in a prospective multicenter cohort study used data from the Thrombolysis in Ischemic Stroke Patients (TRISP) registry of patients with acute ischemic stroke treated with reperfusion therapies indicates the solid stability of key quality performance measures between 2019 and 2020 that may confirm the resilience of acute stroke care services during the lockdown, at least in well-established European stroke centers[64].

Several studies confirm that patients with COVID-19 have more severe strokes and poorer outcomes despite similar acute management to other stroke patients. A well-established stroke care network helps to diminish the impact of such an outbreak in stroke care, reducing secondary transfers and allowing maintenance of reperfusion therapies, with a minor impact on door-to-puncture times, which were longer in patients who underwent chest computed tomography. The findings of these studies can inform medical preparedness and local policies in the event of a new COVID-19 surge or future pandemic.

Take-Home message

- Patients with COVID-19 have higher prevalence of moderate-severe stroke with large vessel occlusions, cortical and lobar location, multiterritorial involvement and associated brain hemorrhage (hemorrhagic transformation or simultaneous hemorrhage and infarction).
- Cryptogenic stroke is the most frequent subtype, probably related to a hypercoagulable state with high levels of inflammatory and coagulation biomarkers (neutrophils, C-reactive protein, IL-6, D-dimer, PT and aPTT).
- The acute management of ischemic or hemorrhagic stroke in COVID-19 patients should follow the same standards of care as for non-COVID-19 patients, adopting the necessary precautions related to infection control.
- Pharmacological venous thromboembolism prophylaxis should be strongly considered for all COVID-19 patients.
- In patients with cryptogenic stroke, involvement of multiple vascular territories (suggesting an embolic phenomenon), presence of other arterial or venous thrombotic events, elevated coagulation markers should be taken into consideration when deciding whether to initiate anticoagulation therapy, always bearing in mind the higher bleeding risk in these patients.

References

1. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683-690.
2. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med.* 2020;;382(20):e60.
3. Qin C, Zhou L, Hu Z, et al. Clinical Characteristics and Outcomes of COVID-19 Patients With a History of Stroke in Wuhan, China. *Stroke.* 2020;51(7):2219-2223.
4. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. *Stroke.* 2020;51(7):2002-2011.
5. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* 2020;191:9-14.
6. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147.
7. Fridman S, Bres Bullrich M, Jimenez-Ruiz A, et al. Stroke risk, phenotypes, and death in COVID-19: Systematic review and newly reported cases. *Neurology.* 2020;95(24):e3373-e3385.
8. Sweid A, Hammoud B, Bekelis K, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. *Int J Stroke.* 2020;15(7):733-742.
9. Leasure AC, Khan YM, Iyer R, et al. Intracerebral Hemorrhage in Patients With COVID-19: An Analysis From the COVID-19 Cardiovascular Disease Registry. *Stroke.* 2021;52(7):e321-e323.
10. Baldini T, Asioli GM, Romoli M, et al. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: A systematic review and meta-analysis. *Eur J Neurol.* 2021. doi: 10.1111/ene.14727. [Preprint]
11. Merkler AE, Parikh NS, Mir S, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. *JAMA Neurol.* 2020;77(11):1-7.
12. Nannoni S, de Groot R, Bell S, et al. Stroke in COVID-19: A systematic review and meta-analysis. *Int J Stroke.* 2021;16(2):137-149.
13. Perry RJ, Smith CJ, Roffe C, et al. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry.* 2021;92(3):242-248.
14. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol.* 2020;19(9):767-783.
15. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. *Brain Behav Immun.* 2020;87:115-119.
16. Bauernfeind FG, Horvath G, Stutz A, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J Immunol.* 2009;183:787-791.

17. Panigrahy D, Gilligan MM, Huang S, et al. Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Rev.* 2020;39:337-340.

18. Zhang S, Zhang J, Wang C, et al. COVID-19 and ischemic stroke: mechanisms of hypercoagulability (review). *Int J Mol Med.* 2021;47(3):21.

19. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020;395:1417-1418.

20. Gencer S, Lacy M, Atzler D, et al. Immunoinflammatory, Thrombohaemostatic, and Cardiovascular Mechanisms in COVID-19. *Thromb Haemost.* 2020;120(12):1629-1641.

21. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med.* 2020;382:e38.

22. Che Mohd Nassir CMN, Hashim S, Wong KK, et al. COVID-19 Infection and Circulating Microparticles-Reviewing Evidence as Microthrombogenic Risk Factor for Cerebral Small Vessel Disease. *Mol Neurobiol.* 2021;:58:4188-4215.

23. Zubair AS, McAlpine LS, Gardin T, et al. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. *JAMA Neurol.* 2020;77(8):1018-1027.

24. Fraga-Silva RA, Pinheiro SV, Gonçalves AC, et al. The antithrombotic effect of angiotensin-(1- 7) involves mas-mediated NO release from platelets. *Mol Med.* 2008;14:28-35.

25. Sagris D, Papanikolaou A, Kvernland A, et al. COVID-19 and ischemic stroke. *Eur J Neurol.* 2021. doi: 10.1111/ene.15008. [Preprint]

26. Gutierrez Amezcua JM, Jain R, Kleinman G, et al. COVID-19-induced neurovascular injury: a case series with emphasis on pathophysiological mechanisms. *SN Compr Clin Med.* 2020;2:2109-2125 .

27. Margos NP, Meintanopoulos AS, Filioglou D, et al. Intracerebral hemorrhage in COVID-19: A narrative review. *J Clin Neurosci.* 2021;89:271-278.

28. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2019;5(7):811-818.

29. Zeng J-H, Liu Y-X, Yuan J, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. *Infection.* 2020. doi: 10.1007/s15010-020-01424-5. [Preprint]

30. Sala S, Peretto G, Gramegna M, et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. *Eur Heart J.* 2020;41:1861-1862.

31. Shahjouei S, Tsivgoulis G, Farahmand G, et al. SARS-CoV-2 and Stroke Characteristics: A Report From the Multinational COVID-19 Stroke Study Group. *Stroke.* 2021;52(5):e117-e130.

32. Qureshi AI, Baskett WI, Huang W, et al. Acute Ischemic Stroke and COVID-19: An Analysis of 27 676 Patients. *Stroke.* 2021;52(3):905-912.

33. Ntaios G, Michel P, Georgiopoulos G, et al. Characteristics and Outcomes in Patients With COVID-19 and Acute Ischemic Stroke: The Global COVID-19 Stroke Registry. *Stroke*. 2020;51(9):e254-e258.

34. Pezzini A, Grassi M, Silvestrelli G, et al. STROKOVID group. SARS-CoV-2 infection and acute ischemic stroke in Lombardy, Italy. *J Neurol*. 2021. doi: 10.1007/s00415-021-10620-8. [Preprint]

35. Rothstein A, Oldridge O, Schwennesen H, et al. Acute Cerebrovascular Events in Hospitalized COVID-19 Patients. *Stroke*. 2020;51(9):e219-e222.

36. Katz JM, Libman RB, Wang JJ, et al. COVID-19 Severity and Stroke: Correlation of Imaging and Laboratory Markers. *AJNR Am J Neuroradiol*. 2021;42(2):257-261.

37. Siepmann T, Sedghi A, Simon E, et al. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. *Eur J Neurol*. 2021;28(1):238-247.

38. Lu Y, Zhao JJ, Ye MF, et al. The relationship between COVID-19's severity and ischemic stroke: a systematic review and meta-analysis. *Neurol Sci*. 2021;42(7):2645-2651. .

39. Katz JM, Libman RB, Wang JJ, et al. Cerebrovascular Complications of COVID-19. *Stroke*. 2020;51(9):e227-e231.

40. Dhamoon MS, Thaler A, Gururangan K, et al. Mount Sinai Stroke Investigators. Acute Cerebrovascular Events With COVID-19 Infection. *Stroke*. 2021;52(1):48-56.

41. Ramos-Araque ME, Siegler JE, Ribo M, et al. SVIN Multinational Registry and Task Force. Stroke etiologies in patients with COVID-19: the SVIN COVID-19 multinational registry. *BMC Neurol*. 2021;21(1):43.

42. Grewal P, Pinna P, Hall JP, et al. Acute Ischemic Stroke and COVID-19: Experience From a Comprehensive Stroke Center in Midwest US. *Front Neurol*. 2020. doi: 10.3389/fneur.2020.00910. [Preprint]

43. Katsanos AH, Palaiodimou L, Zand R, et al. The Impact of SARS-CoV-2 on Stroke Epidemiology and Care: A Meta-Analysis. *Ann Neurol*. 2021;89(2):380-388.

44. McAlpine LS, Zubair AS, Maran I, et al. Ischemic Stroke, Inflammation, and Endotheliopathy in COVID-19 Patients. *Stroke*. 2021;52(6):e233-e238.

45. Colon CM, Barrios JG, Chiles JW, et al. Atrial arrhythmias in COVID-19 patients. *JACC Clin Electrophysiol*. 2020;6:1189-1190.

46. Cappellari M, Zini A, Sangalli D, et al. Thrombolysis and bridging therapy in patients with acute ischaemic stroke and Covid-19. *Eur J Neurol*. 2020;27(12):2641-2645.

47. Escalard S, Maïer B, Redjem H, et al. Treatment of Acute Ischemic Stroke due to Large Vessel Occlusion With COVID-19: Experience From Paris. *Stroke*. 2020;51(8):2540-2543.

48. Cagnazzo F, Piotin M, Escalard S, et al. ET-COVID-19 Study Group. European Multicenter Study of ET-COVID-19. *Stroke*. 2021;52(1):31-39.

49. Dogra S, Jain R, Cao M, et al. Hemorrhagic stroke and anticoagulation in

COVID-19. *J Stroke Cerebrovasc Dis*. 2020. doi: 10.1016/j.jstrokecerebrovasdis.2020.104984. [Preprint]

50. Ma A, Kase CS, Shoamanesh A, et al. Stroke and Thromboprophylaxis in the Era of COVID-19. *J Stroke Cerebrovasc Dis*. 2021. doi: 10.1016/jstrokecerebrovasdis.2020.105392. [Preprint]
51. de Havenon A, Ney JP, Callaghan B, et al. Characteristics and Outcomes Among US Patients Hospitalized for Ischemic Stroke Before vs During the COVID-19 Pandemic. *JAMA Netw Open*. 2021. doi: 10.1001/jamanetworkopen.2021.10314. [Preprint]
52. Cheruiyot I, Sehmi P, Ominde B, et al. hemorrhage in coronavirus disease 2019 (COVID-19) patients. *Neurol Sci*. 2021;42(1):25-33.
53. Kvernland A, Kumar A, Yaghi S, et al. Anticoagulation use and Hemorrhagic Stroke in SARS-CoV-2 Patients Treated at a New York Healthcare System. *Neurocrit Care*. 2021;34(3):748-759.
54. Melmed KR, Cao M, Dogra S, et al. Risk factors for intracerebral hemorrhage in patients with COVID-19. *J Thromb Thrombolysis*. 2021;51(4):953-960.
55. Travi G, Rossotti R, Merli M, et al. Niguarda COVID-19 Group. Neurological manifestations in patients hospitalized with COVID-19: A retrospective analysis from a large cohort in Northern Italy. Eur J Neurosci. 2021;53(8):2912-2922.
56. Friedlich D, Newman T, Bricker S. Impact of the COVID-19 Pandemic on Stroke Epidemiology and Clinical Stroke Practice in the US. *J Stroke Cerebrovasc Dis*. 2021. doi: 10.1016/j.jstrokecerebrovasdis.2021.105639. [Preprint]
57. De Sousa DA, Sandset EC, Elkind MSV. The curious case of the missing strokes during the COVID-19 pandemic. *Stroke*. 2020;51:1921-1923.
58. Adelman EE, Leppert MH. Inpatient Stroke Care in the Time of COVID-19. *Stroke*. 2021;52:1871-1873.
59. Pezzini A, Grassi M, Silvestrelli G, et al. Impact of SARS-CoV-2 on reperfusion therapies for acute ischemic stroke in Lombardy, Italy: the STROKOVID network. *J Neurol*. 2021. ;1-8 doi: 10.1007/s00415-021-10497-7. [Preprint]
60. Nogueira LG, Qureshi MM, Abdalkader M et al. Global Impact of COVID-19 on Stroke Care and IV Thrombolysis. *Neurology*. 2021;96(23):e2824-e2838.
61. Kansagra AP, Goyal MS, Hamilton S, et al. Collateral effect of Covid- 19 on stroke evaluation in the United States. *N Engl J Med*. 2020;383:400-401.
62. Rinkel LA, Prick JCM, Slot RER, et al. Impact of the COVID-19 outbreak on acute stroke care. *J Neurol*. 2021;268:403-408.
63. Siegler JE, Zha A, Czap ALl et al. Influence of the COVID-19 Pandemic on Treatment Times for Acute Ischemic Stroke The Society of Vascular and Interventional Neurology Multicenter Collaboration. *Stroke*. 2021;52:40-47.
64. Altersberger VL, Stolze LJ, Heldner MRl et al. Maintenance of Acute Stroke Care Service During the COVID-19 Pandemic Lockdown. *Stroke*. 2021;52:1693-1701.

Chapter 9. Seizures and EEG

Valentina Chiesa*, Gemma Tumminelli*, Maria Paola Canevini
*These authors equally contributed to this work

Introduction

Many neurological symptoms, such as encephalopathy, seizures and status epilepticus, have been reported in patients with COVID-19[1-4]. Even if the acquisition of an Electroencephalogram (EEG) in SARS-CoV-2 positive patients presents some particular limitations, mainly due to the risk of infection, many papers describing electroencephalographic patterns of those patients have been published in the last year.

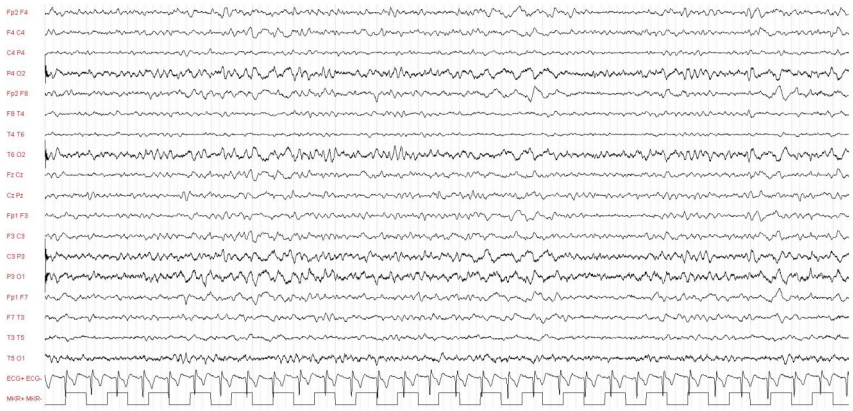
EEG findings

Although changes in mental status have been frequently reported in patients with COVID-19[5-11] together with other neurological symptoms, including clinical and subclinical seizures and status epilepticus[12-16], EEG studies have been significantly underused in these patients due to the risk of infection. Three studies showed that EEG services have been widely disrupted by the COVID-19 pandemic[17-19]. On the other hand, studies conducted using the scarce EEG data available showed that many of the patients with COVID-19 and encephalopathy/seizures had epileptiform discharges/seizures in their EEG examinations[7,20,21]. In a review of 617 patients from 84 reports, Antony and Haneef[22] found that EEG abnormalities in COVID-19 patients were common, comprising a wide variety of findings such as background abnormalities, periodic and rhythmic activity, and other epileptiform abnormalities[7,23,24]. Diffuse background slowing was the most frequent EEG finding, reported in two-thirds of patients, indicating that a diffuse, non-specific encephalopathy is the most constant brain abnormality in this condition (Figure 9.1).

These findings are in line with those of Roberto et al.[25] and those of Kubota et al.[26] who found that the proportion of abnormal background activity was even higher. These results confirm that patients infected with COVID-19 who required EEG may likely have encephalopathy. In fact, also in the meta-analysis

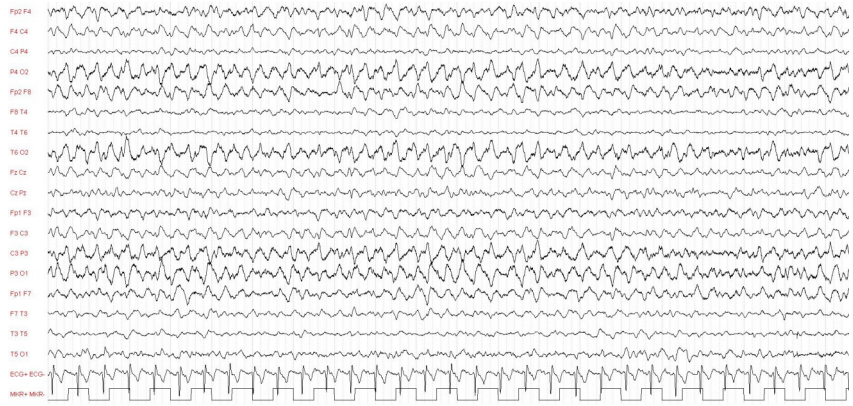
of Kubota et al.[26], the most common indication for EEG was altered mental status (68.4% of cases).

Figure 9.1



Male patient, aged 58, admitted for an episode of loss of consciousness; detection of COVID-19 at swab test at admission. EEG showed diffuse background slowing and sporadic sharp waves. 20 sec/page, 100 μm amplitude.

Figure 9.2



Female patient, aged 55, admitted for confusion and altered mental status appeared 24 hours after onset of low-grade fever and malaise in COVID-19 infection. EEG showed sub-continuous rhythmic delta activity. 20 sec/page, 100 μm amplitude.

Other EEG features suggesting diffuse encephalopathy included generalized rhythmic delta activity (GRDA)[7,9], generalized periodic discharges (GPD) with triphasic morphology[9,27], and discontinuous/burst suppression/background suppression. Kubota and colleagues found discontinuous / burst suppression / background suppression and GPDs in 5.33% and 16.5% of the patients, respectively[26].

Lateralized periodic and rhythmic abnormalities have also been reported, suggesting a co-existent focal dysfunction in some patients. Epileptiform discharges were common, indicating underlying cortical irritability predisposing to seizures[22].

Several studies reported abnormalities in the frontal region[7,22,27-29] including focal slowing, periodic discharges and rhythmic delta activity (Figure 9.2).

In the systematic review conducted by Antony and Henef[22], half of all status epilepticus and focal slowing originated in the frontal lobe. Most of the authors considered these frontal findings to be aspecific[25]. Others have described a specific EEG pattern characterized by continuous, slightly asymmetric, monomorphic, diphasic, delta slow waves with greater amplitude over both frontal areas and with a periodic organization[22,29] proposing this pattern as a potential biomarker. Some authors hypothesize that the common frontal location of focal abnormalities in COVID-19 patients correlates with the purported entry of the virus into the brain[7,27,28,30]. Early clinical manifestations of COVID-19 like anosmia and ageusia are thought to be due to viral entry in the nasal and oral mucosa facilitated by ACE-2 receptors[31]. Subsequent spread to the orbitofrontal region[31,32] via afferent nerves leads to preferential involvement of the olfactory bulb and orbitofrontal/frontal regions and can explain the preponderance of frontal EEG findings. This theory is also corroborated by frontal hypometabolism seen in PET scans in these patients[33].

Technical recommendations for EEG

Although much information may be gained from an EEG, the value of this information in the diagnosis and management of the patient must be weighed against the risks of infection from COVID-19 for the technologist. In this setting, reduced EEG montages using single-use subdermal EEG needle electrodes may be used in comatose patients. A full 10-20 EEG complement of electrodes with an ECG derivation remains the standard in all other cases. Under COVID-19 conditions, an expedited study that adequately screens for generalized status epilepticus, most types of regional status epilepticus, encephalopathy or sleep, may serve for most clinical questions, and using simplified montages may limit the risk of infection to EEG technologists[34]. Carrying out an EEG should be assessed in accordance with clinical urgency, setting, status of SARS-CoV-2 infection, and phase of governmental restrictions. In the most

critical phases of the pandemic, EEGs should be limited to patients with acute / subacute neurological symptoms, and outpatient examinations should be suspended. Risk of infection could be reduced by limiting contact between staff through rescheduling work shifts, and the use of disposable electrodes and of dedicated EEG devices for COVID-19-positive patients[35]. (International League Against Epilepsy [ILAE]'s Guidance for EEG investigation is available online at https://www.ilae.org/patient-care/covid-19-and-epilepsy/for-clinicians.)

Mechanisms of seizures in SARS-CoV-2

Many case series report an association between seizures and SARS-CoV-2 infection[15,24,36-38]. Three different mechanisms have been theorized by which seizures can develop in patients infected with SARS-CoV-2: a direct mechanism, am indirect mechanism, and an exacerbation of seizure in patients with epilepsy[39].

Direct mechanism

SARS-CoV-2 is capable of entering directly and infecting the central nervous system, leading to meningitis and encephalitis, and consequent seizures[39-41] through different ways. One of them involves Angiotensin converting-enzyme-2 (ACE-2) receptors[42], which are located on cells throughout the body, including the cardio-respiratory neurons of the brainstem, glial cells, basal ganglia, motor cortex, raphe, and endothelial cells of the brain. SARS-CoV-2 can infect the endothelial cells of the blood-brain barrier and then accumulate in the various previously mentioned brain regions causing direct infection with neurological complications[40,43]. Another pathway through which SARS-CoV-2 is thought to enter the central nervous system (CNS) is the olfactory nerve via the nasal cavity. In fact, it has been shown that, within seven days of infection, SARS-CoV-2 is able to reach the cerebrospinal fluid (CSF) and brain through the olfactory nerve causing inflammation and demyelinating reactions with potential subsequent seizures[43,44].

Indirect mechanism

Downregulation of ACE-2 expression - ACE-2 receptors may play a role also in an indirect mechanism. The overloading of these receptors by SARS-CoV-2 infection leads to a downregulation of ACE-2 expression, dysfunction of the renin-angiotensin system with overproduction of angiotensin II resulting in a cascade of biochemical events that eventually cause severe acute lung injury, vasoconstriction, and oxidative processes that promote brain damage with the possible occurrence of seizures[42,43].

Cytokine storm - Another possible indirect mechanism derives from the impairment of natural killer and cytotoxic T-cell function which results in excessive secretion of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), and interleukins (IL) 1, 4, 6, 8, 10, and 18. This cytokine storm results in an exaggerated inflammatory response leading to vascular permeability, edema, and widespread inflammation with consequent damage to multiple organs with progression to multi-organ failure[41,45].

Hypoxia and hypoperfusion - Also, hypoxia can potentiate encephalopathy, which can further play a role in the development of seizures. Ischemic brain injury also contributes to cerebral tissue hypoperfusion and may lead to seizures[46].

Exacerbation of seizure in patients with epilepsy

The effects of COVID-19 on patients with epilepsy (PWE) are still not clear. The ILAE has issued a declaration that PWE are not likely to be more susceptible to getting COVID-19 nor are they inclined to suffer through severe manifestations of SARS-CoV-2 infection[47]. Even if PWE are exposed to SARS-CoV-2, it is unlikely that the frequency of seizures increases. Nevertheless, management of COVID-19 in PWE requires certain precautions, and guidelines need to be followed in order to avoid a worsening of the condition; maintaining control of epilepsy with anti-seizure medication (ASM) is crucial as mortality associated with epilepsy is higher in patients with uncontrollable seizures. In particular, potential drug-drug interaction that may occur on concomitant administration of ASM along with the drugs used to treat COVID-19 need to be taken into account[48,49], since an increasing number of medications are being considered for the management of COVID-19[50-52]. Information about drug-drug interactions is also of particular relevance for intensive care unit management of critically ill COVID-19 patients who may develop acute seizures during a severe disease course.

Some drugs currently used as anti-COVID-19 medications may increase the risk of seizures, although this is rare. The mechanisms of seizure facilitation can be manifold: effects of anti-COVID-19 drugs on seizure threshold, effects of infection on ASM pharmacokinetics, and drug-drug interaction. Furthermore, common adverse effects of anti-COVID-19 drugs (such as diarrhea) could lower plasma ASM concentration. Lastly, immunomodulation by ASMs has also been hypothesized[53].

Moreover, COVID-19 infection could be related to impaired hepatic and renal function. This means that critically ill patients in particular may require ASM plasma concentrations to be monitored and possible dose adjustment. Major interactions relate to strong hepatic enzyme-inducing ASMs (phenobarbital, primidone, phenytoin and carbamazepine), but other mechanisms of drug-drug interaction have also been reported (i.e., P-glycoprotein way)[54].

Possible drug interactions between more common anti-COVID-19 medications and ASMs are summarized in Table 9.1.

Table 9.1: Possible interactions between anti-COVID-19 drugs (some of them not currently used) and most the commonly used ASMs, and recommendations for their combinations

	Drug interaction	Cardiac side effects	Recommendations
Chloroquine/ Hydroxychloroquine	BRV, CBZ, ESL, FBM, OXC, PHT, PB, PRM	Possible dysrhythmias if associated to FBM	Avoid co-administration with CBZ, PHT, PB, PRM
Lopinavir/Ritonavir	BRV, CBZ, CLN, CLB, DZP, ESL, FBM, LTG, MDZ, OXC, PER, PHT, PB, PRM, VPA	Possible dysrhythmias if associated to ESL or LCS	Avoid co-administration with MDZ. If in combination with CBZ, administer twice daily instead of once daily. If co-administered with LTG, therapeutic monitoring of LTG is required.
Tocilizumab	CBZ, CLB, CLN, DZP, LZP, MDZ, PHT, PRM, VPA		
Remdesivir	CBZ, ESL, OXC, PHT, PB, PRM		Avoid co-administration with CBZ, PHT, PB, PRM
Azithromycin	PHT	Possible dysrhythmias if associated to PRG	Dose adjustment and monitoring may be required if administered with PHT
Prednisone/dexamethasone	PB		Monitor plasma concentrations of PB if co-administered; dose of corticosteroids may have to be increased if administered with PB
DOACs	CBZ, ESL, LEV, FBM, OXC, PB, PHT, PRM, TPM, VPA		If associated with CBZ, PB, PHT or PRM caution and surveillance are needed, in addition to possible increases in DOAC dose; low molecular weight heparin or unfractionated heparin may be used in these cases.
	Drug interaction	Cardiac side effects	Recommendations
Chloroquine/ Hydroxychloroquine	BRV, CBZ, ESL, FBM, OXC, PHT, PB, PRM	Possible dysrhythmias if associated to FBM	Avoid co-administration with CBZ, PHT, PB, PRM
Lopinavir/Ritonavir	BRV, CBZ, CLN, CLB, DZP, ESL, FBM, LTG, MDZ, OXC, PER, PHT, PB, PRM, VPA	Possible dysrhythmias if associated to ESL or LCS	Avoid co-administration with MDZ. If in combination with CBZ, administer twice daily instead of once daily. If co-administered with LTG, therapeutic monitoring of LTG is required.
Tocilizumab	CBZ, CLB, CLN, DZP, LZP, MDZ, PHT, PRM, VPA		

Remdesivir	CBZ, ESL, OXC, PHT, PB, PRM		Avoid co-administration with CBZ, PHT, PB, PRM
Azithromycin	PHT	Possible dysrhythmias if associated to PRG	Dose adjustment and monitoring may be required if administered with PHT
Prednisone/dexamethasone	PB		Monitor plasma concentrations of PB if co-administered; dose of corticosteroids may have to be increased if administered with PB
DOACs	CBZ, ESL, LEV, FBM, OXC, PB, PHT, PRM, TPM, VPA		If associated with CBZ, PB, PHT or PRM caution and surveillance are needed, in addition to possible increases in DOAC dose; low molecular weight heparin or unfractionated heparin may be used in these cases.

AMSs - BRV: brivaracetam; CBZ: carbamazepine; CLB: clobazam; CLN: clonazepam; DZP: diazepam; ESL: eslicarbaz: epine; FBM: felbamate; LEV: levetiracetam; LTG: lamotrigine; LZP: lorazepam; MDZ: midazolam; OXC: oxcarbazepine; PER: perampanel; PHT: phenytoin; PB: phenobarbital; PRG: pregabalin; PRM: primidone; TPM: topiramate; VPA: valproic acid.

Seizures and SARS-CoV-2

Seizures and/or status epilepticus (SE) were often recorded in patients without any evidence of acute or chronic brain injury on imaging and without any alteration in CSF; in those patients, seizures have been recorded mainly in the frontal lobe[55] or in the fronto-central region[15,56]. Moreover, non-convulsive SE (NCSE) has been reported in the frontal region, unilaterally[30,57], or bilaterally[38] or in the fronto-temporal region[58].

Seizures and/or SE were recorded more rarely in patients with acute CNS lesions on brain imaging and/or significant CSF abnormalities, of either vascular or inflammatory origin, and in those cases, seizures or SE were often described as arising from the posterior regions. Occipital focal seizures or NCSE were described by Parauda et al.[59] in patients with posterior reversible encephalopathy syndrome (PRES). In other cases, seizures starting from the right fronto-temporal region were recorded in a patient with diffuse CNS demyelinating lesions on brain and spine imaging[60] or multifocal and bilateral seizures were detected in a patient with an acute disseminated encephalomyelitis[61]. Finally, Bernard-Valnet et al.[62] reported the case of a patient with lymphocytic meningitis diagnosed by CSF analysis, with normal brain Magnetic Resonance Imaging (MRI), whose EEG showed a focal anterior NCSE.

Seizures and/or SE were also reported in patients with neurological and radiological sequelae but without any acute lesions, arising from an area of previous cerebral insult, for example, due to prior surgery or to remote herpes simplex virus1 encephalitis[16,56].

Status epilepticus and SARS-CoV-2

Hung et al. reported the first case of status epilepticus associated with SARS, with the evidence of SARS-CoV RNA in both the CSF and serum[63]. Since then, over the last few months, there has been an increased reporting of seizures associated with SARS-CoV-2.

A review which analyzed published data of SE in COVID-19 infection[64] found that only a small proportion (6.4%) of patients who develop SE had prior history of epilepsy. Time of onset of SE may vary. Most of the patients developed SE after COVID-19 respiratory / gastrointestinal symptoms; in a minority of cases (14.9%), SE appeared before other systemic symptoms. The cause of SE was unknown in the majority of cases; acute symptomatic and multifactorial etiologies have been reported. Although motor symptoms represented the most frequent manifestation of SE, about one-third of the reported SE were non-convulsive SE. EEG abnormalities were mostly localized in the frontal lobe, followed by the temporal lobe. Most frequent EEG abnormalities consisted of continuous epileptiform activity, recorded in about half the patients; EEG slow-wave continuous activity was also reported in some patients. Cerebral imaging (CT or MRI) detected abnormal findings in 29-42% of patients reported having SE in the context of COVID-19 syndrome, including inflammatory lesions (17%), PRES (8.5%), brain atrophy or cerebral hemorrhage in two patients respectively (4.3%), brain tumor and cerebral hemorrhage in one patient (2.1%). Acute seizures and SE can arise from febrile status, hypoxia, or metabolic derangements. Nevertheless, according to the available data, such etiologies are infrequent, and are generally associated with a milder form of SE, with a good response to treatment and a favorable outcome. In SE, the most frequently used medication was levetiracetam, probably for its favorable tolerance profile, few drug-drug interactions and on the whole, an absence of respiratory depression, making it preferable to benzodiazepine in patients with COVID-19 pneumonia. Outcome was positive in the majority of cases reported (96%) (Table 9.2)[64].

A recent epidemiological study[65] has shown that the incidence of SE during the pandemic was no different from the general SE incidence recorded in the previous five years, even if it is probable that the real frequency of SE, and in particular of NCSE in SARS-CoV-2 infection, has been underestimated due to problems in using adequate diagnostic tools and in having prompt access to EEG recording during the pandemic.

Table 9.2: Status epilepticus features

Onset	Intra-hospital	30	63.8%
	Extra-hospital	12	25.5%
	NA	5	10.6%
Etiology	Acute	19	
	-Vascular	7	14.9%
	-Septic	5	10.6%
	-Inflammatory	4	8.6%
	-Multifactorial	3	6.4%
	Unknown	26	55.3%
	NA	2	4.3%
Semiology	Motor onset		
	-GCSE	11	23.4%
	-GCSE evolving to NCSE	2	4.3%
	-FMSE	2	4.3%
	-FMSE evolving to NCSE	6	12.8%
	-MSE evolving to NCSE	1	2.1%
	Non-motor onset		
	-NCSE	8	17%
	Unknown	17	36.2%
EEG Pattern	GPDs	5	10.6%
	LPDs	2	4.3%
	LPDs PLUS	2	4.3%
	BILPD	2	4.3%
	GRDA	2	4.3%
	NA	34	72.3%

Modified from Dono et al.[64]. BILPDs: bilateral independent periodic discharges; FMSE: focal motor status epilepticus; GCSE: generalized convulsive status epilepticus; GPDs: generalized periodic discharges; GRDA: generalized rhythmic delta activity; MSE: motor status epilepticus; NCSE: non-convulsive status epilepticus; LPDs: lateralized periodic discharges; NA: not available.

Treatment suggestions

In relation to the complexity of COVID-19 disease, to the variety of neurological symptoms, and to the possible interactions between ASMs and anti-COVID-19 drugs, the decision as to the best treatment for seizures should take into account the specific characteristics, the comorbidity, and the current clinical condition of the patient. As a general rule, it would be reasonable to choose ASMs with less known interactions (i.e., avoiding strong hepatic

enzyme-inducing ASMs), and giving preference to those with an intravenous formulation.

Conclusions

Neurological complications in patients with COVID-19 are common and may manifest as seizures. However, the underlying mechanism for development of seizure in patients with COVID-19 is still unclear.

EEG remains a crucial tool in the management of patients with neurological manifestations of COVID-19, especially encephalopathy, seizures, and status epilepticus. Abnormalities, when present, include slowing, periodic discharges, epileptiform discharges, seizures and status epilepticus, indicating the presence of a localized dysfunction, non-specific encephalopathy and cortical irritability in this condition. Several EEG patterns have been reported in seizures and SE associated with COVID-19, including periodic (LPDs, LPDs "plus", BiLPDs, and GPDs) and rhythmic (GRDA) patterns. However, based on the available evidence, no single EEG pattern appears to be specific in relation to this viral infection, even though a prevalent frontal lobe localization has been described.

Seizure or SE during SARS-CoV-2 infection can occur before any other symptom of respiratory and systemic involvement of COVID-19, although more frequently they occur within the context of a clinically overt respiratory infection. The lack of prompt access to EEG recordings may lead to an underestimation of the incidence of epileptic complications, particularly for NCSE. The etiology of SARS-CoV-2-related SE remains mostly unknown. A direct role of SARS-CoV-2 invasion in the CNS or the systemic inflammatory syndrome due to cytokine release has been proposed as a possible explanation.

The clinician should always prioritize identification of any inciting factors (hypoxia, fever, sepsis, electrolyte derangements) and aim to manage seizures in patients with COVID-19 with the application of principles of general management of seizures and status epilepticus. When an AED is initiated, consideration should be given to the pharmacokinetics of the drug, drug interactions, and medication-associated adverse effects. Patient factors such as age, along with any renal and/or hepatic impairment, should also be taken into account.

Further research into the relation of the EEG findings to the clinical status and short- or long-term prognosis of COVID-19 patients may be conducted to help clinicians identify which patients require an EEG procedure and would eventually require treatment, with the ultimate aim of improving their clinical outcomes.

Take-home message

- No specific EEG pattern has been described in COVID-19 patients: diffuse background slowing is the most frequent EEG finding.
- COVID-19 infection does not seem to increase seizure frequency in patients with epilepsy.
- Seizures and/or status epilepticus are often recorded in patients without any evidence of acute or chronic brain injury on imaging and without any alteration in CSF.
- There is no specific anti-seizure medication for COVID-19 patients. ASMs with no/few interactions and with available intravenous formulation should be preferred.

References

1. Asadi-Pooya AA, Simani L, Shahisavandi M, et al. COVID-19, de novo seizures, and epilepsy: a systematic review. *Neurol Sci*. 2021;42(2):415-431.
2. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. *J Neurol Sci*. 2020;413:116832.
3. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol*. 2020; 70(9):311-322.
4. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683-690.
5. Pinna P, Grewal P, Hall JP, et al. Neurological manifestations and COVID-19: experiences from a tertiary care center at the frontline. *J Neurol Sci*. 2020;415:116969.
6. Nalleballe K, Reddy Onteddu S, Sharma R, et al Spectrum of neuropsychiatric manifestations inCOVID-19. *Brain Behav Immun*. 2020;88:71-74.
7. Galanopoulou AS, Ferastraoaru V, Correa DJ, et al. EEG findings in acutely ill patients investigated for SARS-CoV-2 / COVID-19: a small case series preliminary report. *Epilepsia Open*. 2020;5:314-324.
8. Cecchetti G, Vabanesi M, Chieffo R, et al. Cerebral involvement in COVID-19 is associated with metabolic and coagulation derangements: an EEG study. *J Neurol*. 2020;267:3130-3134.
9. Vespignani H, Colas D, Lavin BS, et al. Report of EEG Finding on Critically Ill Patients with COVID-19. *Ann Neurol*. 2020;88(3):626-630.
10. Scullen T, Keen J, Mathkour M, et al. Coronavirus 2019 (COVID-19)-associated Encephalopathies and cerebrovascular disease: the New Orleans experience. *World Neurosurg*. 2020;S1878-8750(20):31163.
11. Pilotto A, Odolini S, Masciocchi S, et al. Steroid-responsive encephalitis in coronavirus disease 2019. *Ann Neurol*. 2020;88(2):423-427.
12. Lyons S, O'Kelly B, Woods S, et al. Seizure with CSF lymphocytosis as a presenting feature of COVID-19 in an otherwise healthy young man. *Seizure*. 2020;80:113-114.
13. Farhadian S, Glick LR, Vogels CBF, et al. Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19. *BMC Neurol*. 2020;20:248.
14. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis / encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55-58.
15. Hepburn M, Mullaguri N, George P, et al. Acute symptomatic seizures in critically ill patients with COVID-19: is there an association? *Neurocrit Care*. 2020;34(1):139-143.
16. Vollono C, Rollo E, Romozzi M, et al. Focal status epilepticus as unique clinical feature of COVID-19: a case report. *Seizure*. 2020;78:109-112.
17. Granata T, Bisulli F, Arzimanoglou A, et al. Did the COVID-19 pandemic silence the needs of people with epilepsy? *Epileptic Disord*. 2020;22(4):439-442.

18. Wirrell EC, Grinspan ZM, Knupp KG, et al. Care delivery for children with epilepsy during the COVID-19 pandemic: an international survey of clinicians. *J Child Neurol*. 2020;35:924-933.
19. Assenza G, Lanzone J, Brigo F, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol*. 2020;11:737.
20. Anand P, Al-Faraj A, Sader E, et al. Seizure as the presenting symptom of COVID-19: a retrospective case series. *Epilepsy Behav*. 2020;112:107335.
21. Pilato MS, Urban A, Alkawadri R, et al. EEG findings in coronavirus disease. *J Clin Neurophysiol*. 2020;00:1-7.
22. Antony AR, Haneef Z. Systematic review of EEG findings in 617 patients diagnosed with COVID-19. *Seizure*. 2020;83:234-241.
23. Helms J, Kremer S, Merdji H, et al. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care*. 2020;24:491.
24. Louis S, Dhawan A, Newey C, et al. Continuous electroencephalography characteristics and acute symptomatic seizures inCOVID-19 patients. *Clin Neurophysiol*. 2020;131:2651-2656.
25. Roberto KT, Espiritu AI, Fernandez MLL, et al. Electroencephalographic findings in COVID-19 patients: A systematic review. *Seizure*. 2020;82:17-22.
26. Kubota T, Gajera PK, Kuroda N. Meta-analysis of EEG findings in patients with COVID-19. *Epilepsy Behav*. 2021;115:107682.
27. Petrescu AM, Taussig D, Bouilleret V. Electroencephalogram (EEG) in COVID-19: a systematic retrospective study. *Neurophysiol Clin*. 2020;50:155-165
28. Ayub N, Cohen J, Jing J, et al. Clinical electroencephalography findings and considerations in hospitalized patients with coronavirus SARS-CoV-2. *MedRxiv*. 2020. doi: 10.1101/2020.07.13.20152207. [Preprint]
29. Vellieux G, Rouvel-Tallec A, Jaquet P, et al. COVID-19 associated encephalopathy: Is there a specific EEG pattern? *Clin Neurophysiol*. 2020;131:1928-1930.
30. Le Guennec L, Devianne J, Jalin L, et al. Orbitofrontal involvement in a neuro-COVID-19 patient. *Epilepsia*. 2020;61(8):e90-e94.
31. DosSantos MF, Devalle S, Aran V, et al. Neuromechanisms of SARS-CoV-2: a review. *Front Neuroanat*. 2020;14:37.
32. Bohmwald K, Galvez NMS, Ríos M, et al. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci*. 2018;12:386.
33. Haseli S, Karimi-Galougahi M. Reply to "MRI Evaluation of the Olfactory Clefts in Patients with SARS-CoV-2 Infection Revealed an Unexpected Mechanism for Olfactory Function Loss. *Acad Radiol*. 2020;27:1192.
34. Gélisse P, Rossetti A, Genton P, et al. How to carry out and interpret EEG recordings in COVID-19 patients in ICU? *Clin Neurophysiol*. 2020;131(8):2023-2031.
35. Grippo A, Assenza G, Scarpino M, et al. Electroencephalography during SARS-CoV-2 outbreak: practical recommendations from the task force of the Italian Society of Neurophysiology (SINC), the Italian League Against Epilepsy (LICE),

and the Italian Association of Neurophysiology Technologists (AITN). *Neurol Sci.* 2020;41(9):2345-2351.

36. Pellinen J, Carroll E, Friedman D, et al. Continuous EEG findings in patients with COVID-19 infection admitted to a New York academic hospital system. *Epilepsia.* 2020:epi.16667.
37. Pasini E, Bisulli F, Volpi L, et al. EEG findings in COVID-19 related encephalopathy. *Clin Neurophysiol.* 2020;131:2265-2267.
38. Chen W, Toprani S, Werbaneth K, et al. Status epilepticus and other EEG findings in patients with COVID-19: a case series. *Seizure*. 2020;81:198-200.
39. Narula N, Joseph R, Katyal N et al. Seizure and COVID-19: Association and review of potential mechanism. *Neurol Psychiatry Brain Res.* 2020;38:49-53.
40. Desforges M, Le Coupanec A., Dubeau P, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses*. 2020;12(1):14.
41. Fotuhi M, Mian A, Meysami S, et al. Neurobiology of COVID-19. *J Alzheimers Dis.* 2020;76(1):3-19.
42. Kuba K, Imai Y, Rao S, et al. Lessons from SARS: Control of acute lung failure by the SARS receptor ACE2. *J Mol Med.* 2006;84(10):814-820.
43. Iroegbu JD, Ifenatuoha CW, Ijomone OM. Potential neurological impact of coronaviruses: Implications for the novel SARS-CoV-2. *Neurol Sci.* 2020;41:1329-1337.
44. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* 2020;87:18-22.
45. Wan S, Yi Q, Fan S, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *MedRxiv*, 2020. doi: 10.1101/2020.02.10.20021832. [Preprint]
46. Connors JM, Levy, JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost.* 2020;18:1559-1561.
47. International League Against Epilepsy. COVID-19 information for clinicians. Available from: https://www.ilae.org/patient-care/covid-19-and-epilepsy/for-clinicians
48. Patsalos PN, Spencer EP, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy: A 2018 Update. *Ther Drug Monit*, 2018;40:526-548.
49. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord.* 2014;16(4):409-431.
50. Huff JS, Seizure MN. 2020. StatPearls [Updated 2020 Mar 20]. Available from: Treasure Island (FL): StatPearls Publishing https://www.ncbi. nlm.nih.gov/books/NBK430765/
51. Russo E, Iannone L. Clinically relevant Drug-Drug interaction between AEDs and medications used in the treatment of COVID-19 patients. 2020. Available from: www.ilae.org/files/ dmfile/Antiepileptic-drugs-interactions_in_COVID-19.pdf.
52. Sveinsson O, Andersson T, Mattsson P, et al. Clinical risk factors in SUDEP: A nationwide population-based case–control study. *Neurology.* 2020;94:e419-e429.

53. Epstein D, Noyman I, Fahoum F, et al. Treating epilepsy patients with investigational anti-COVID-19 drugs: reccomendations by the Israeli Chapter of the ILAE. *Isr Med Assoc J*. 2020;11(22):665-672.

54. Welty T, Gidal B. *Managing Patients with Epilepsy during COVID-19 - Pharmacotherapy-related Recommendations*. American Epilepsy Society, 2020. [Updated 1 June 2020]

55. Balloy G, Leclair-Visonneau L, Péréon Y, et al. Non-lesional status epilepticus in a patient with coronavirus disease 2019. *Clin Neurophysiol*. 2020;131(8):2059-2061.

56. Somani S, Pati S, Gaston T, et al. De novo status epilepticus in patients with COVID-19. *Ann Clin Trans Neurol*. 2020;7:1240-1244.

57. Flamand M, Perron A, Buron Y, et al. Pay more attention to EEG in COVID-19 pandemic. *Clin Neurophysiol*. 2020;131:2062-2064.

58. Rodrigo-Armenteros P, Uterga-Valiente JM, Zabala-Del-Arco J, et al. Non-convulsive status epilepticus in a patient with COVID-19 infection. *Clin.Neurophysiol*. 2020;131:2588-2590.

59. Parauda SC, Gao V, Gewirtz AN, et al. Posterior reversible encephalopathy syndrome in patients with COVID-19. *J Neurol Sci*. 2020;416:117019.

60. Zanin L, Saraceno G, Panciani P, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochir*. 2020;16:1491-1494.

61. Hussein O, Abd Elazim A, Torbey MT. Covid-19 systemic infection exacerbates pre-existing acute disseminated encephalomyelitis (ADEM). *J Neuroimmunol*. 2020;349:577405.

62. Bernard-Valnet R, Pizzarotti B, Anichini A, et al. Two patients with acute meningoencephalitis concomitant with SARS-CoV-2 infection. *Eur J Neurol*. 2020;27(9):e43-e44.

63. Hung EE, Chim SS, Chan PK, et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem*. 2020;49:2108-2109.

64. Dono F, Nucera B, Lanzone J. Status epilepticus and COVID-19: A systematic review. *Epilepsy Behav*. 2021;118:107887.

65. Leitinger M, Poppert KN, Mauritz M, et al. Status epilepticus admissions during the COVID-19 pandemic in Salzburg-A population-based study. *Epilepsia*. 2020;61(12):e198-e203.

Chapter 10. Delirium

Chiara Manfredi, Elisabetta Bernardi, Fabrizio Luiso,
Alberto Priori, Emma Scelzo

Background and epidemiology

Delirium, defined as a disturbance of consciousness or cognitive function with acute onset and fluctuating course, is widely known to be one of the commonest complications of hospitalization in older patients also outside the context of the COVID-19 pandemic[1].

Recently, there has been an increasing recognition of neuropsychiatric manifestations of SARS-CoV-2 infection. Early studies indicate that 20-30% of COVID-19 patients will present with or develop delirium or mental status changes during their hospitalization, with rates of 60-70% in cases of severe illness at all ages[2-4].

The results of a study by Mendes et al. revealed that, although COVID-19 is not associated with a higher prevalence of delirium than other acute illnesses, its development is strongly associated with a higher mortality[5]. Recently, a British study has found that delirium is common and yet under-recognized in hospitalized patients with COVID-19. Out of 31 patients with delirium, only 19 cases had been recognized by the clinical team. Moreover, at 4-week follow-up, delirium was significantly associated with worse functional outcomes independent of pre-morbid frailty[6]. Another study raised the question of whether atypical symptoms of COVID-19 could impact the quality of care, reducing early recognition of symptoms and hospitalization. Among these patients, the clinical presentation of COVID-19 was mostly atypical, and the most frequent symptom of onset was delirium, especially in the hypoactive form[7].

Acute encephalopathy appears to be even more common in critically ill patients. In a recent international cohort study on 2,088 patients with a SARS-CoV-2 infection admitted to an intensive care unit (ICU), Pun et al. described that delirium occurred in 55%[8].

In another recent case series of 58 severe COVID patients, Helms et al. reported that 84% developed neuropsychiatric symptoms[3]. In a cohort analysis of 140 ICU patients described by the same group, the prevalence of delirium was 79.5% in patients admitted to an ICU for acute respiratory distress syndrome (ARDS) due to COVID-19, with a worse prognosis than patients without delirium[9].

Pathogenesis

A major question remains as to whether delirium in COVID-19 represents a primary CNS manifestation, heralding the invasion of the brain by the virus, or whether it simply constitutes a symptom of a secondary encephalopathy caused by inflammation or other systemic effects of SARS-CoV-2[10].

The severity of the systemic illness in some COVID-19 patients, and the associated metabolic derangements and inflammatory cascades, is presumably sufficient to cause the toxic-metabolic encephalopathy often seen in hospitalized patients. However, the presentation of patients with severe confusional states in the absence of respiratory symptoms or other organ failure has raised questions about alternative mechanisms of CNS injury[11].

Several investigators have proposed multiple potential mechanisms by which SARS-CoV-2 may induce changes in mental status, including infection spreading to the CNS by retrograde transport or hematogenous route, a dysregulation of the cytokine activation leading to CNS inflammation, an induction of cell-mediated CNS inflammation, postinfectious autoimmune reactions via molecular mimicry, and hypoxemic/thrombotic neuronal injury[12].

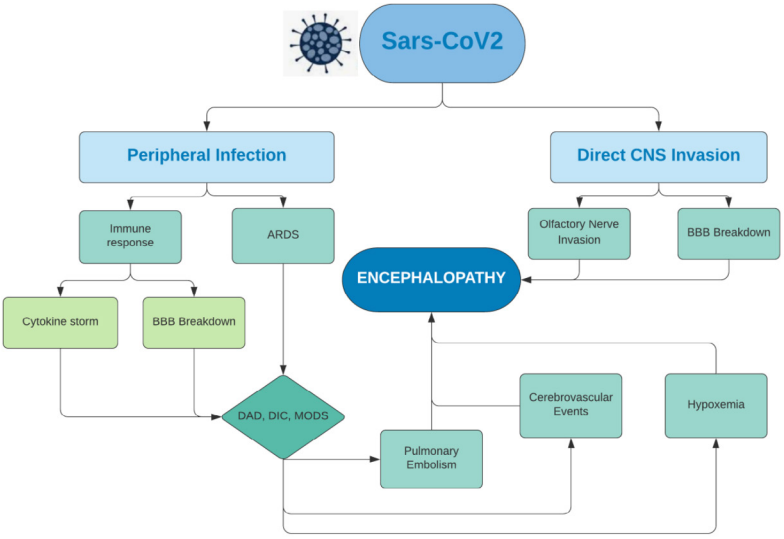
a. *Primary neuro-invasive hypothesis*: neurotropism of coronaviridae has been demonstrated during SARS and MERS epidemics. During the 2002-2003 SARS epidemic, older subjects presented not only with respiratory symptoms and typical febrile response, but also with decreased general well-being, poor feeding, and delirium. Given the fact that SARS-CoV and SARS-CoV-2 are similar in terms of pathogenicity, it is quite likely that SARS-CoV-2 has a similar ability to cause delirium[13]. There are two distinct proposed mechanisms for SARS-CoV-2 invading the CNS to cause a primary encephalopathy: entry route for the virus into the brain may be directly through intra-nasal access via olfactory nerves, or indirectly by crossing the blood-brain barrier (BBB) via hematogenous or lymphatic spread[14]. The first hypothesis would be consistent with the observation of high rates of anosmia and ageusia, which are thought to be caused by the involvement of the olfactory bulb. Given the anatomical positioning, one could imagine the virus travelling along the olfactory bulb toward the uncinate fasciculus and reaching the anterior cingulate and basal forebrain directly via that pathway. Such neuro-invasive potential of SARS-CoV-2 has been postulated to contribute to the respiratory failure observed in infected patients[10]. On the other hand, SARS coronaviruses enter human host cells mainly via the cellular receptor for the angiotensin-converting enzyme 2 (ACE2), predominantly expressed in the entire respiratory tract, but also in the upper esophagus, by the enterocytes and in the brain. In particular, ACE2 receptors have been detected in both neurons and glial cells, which makes them vulnerable to SARS-CoV-2 invasion, but they are also expressed by endothelial cells, and endothelitis has also been implicated in

the pathology of the virus as a result of both direct and indirect mechanisms: general inflammatory response to virus infection impairs BBB integrity leading to massive infiltration of renin-angiotensin components to the brain[15].

b. *Secondary-systemic mechanism hypothesis:* secondary neurological effects include increased CNS inflammatory mediators, cerebral hypoxia, cerebrovascular involvement, multiple organ failure, pyrexia, neurotransmitter imbalance, dehydration, and metabolic dysregulation. Immunologic responses to SARS-CoV-2 are mediated by an acute cytolytic T-cell activation which might also cause an autoimmune encephalopathy[10].

c. *Hybrid model:* a final possibility is a hybrid model, in which the virus may cause either a primary or secondary encephalopathy, or both. This combination would suggest a similarity to human immunodeficiency virus (HIV). Indeed, HIV is known to invade the circumventricular region via two mechanisms: direct and indirect invasion. The circumventricular fenestrated endothelial areas represent the major thoroughfares for diapedesis of HIV-infected macrophages into the brain, and the regions adjacent to these areas determine the neuropsychiatric symptoms. Invasion of the area postrema makes the patient vulnerable to depression and delirium due to selective vulnerability of midbrain neurotransmitter cell bodies, involvement of the pineal gland disrupts the sleep-wake cycle, and the organum vasculosum directly abuts the pregenual anterior cingulate. If SARS-CoV-2 enters the brain directly via disrupted circumventricular fenestrated endothelium or along an olfactory nerve track, we might expect a similar pathophysiological pathway to that seen in HIV encephalopathy[10]

Figure 10.1: Hypotheses of encephalopathy pathogenesis in COVID-19



ARDS: acute respiratory distress syndrome; BBB: blood-brain barrier; DAD: diffuse alveolar damage; DIC: disseminated intravascular coagulation; MODS: multi-organ dysfunction syndrome.

Clinical features and implications

Delirium is usually characterized by a disturbance of consciousness and an alteration of the cognitive state which typically develops over a short period of time (over hours to days) and tends to fluctuate during the course of the day. The features of delirium are unstable, usually becoming most severe in the evening and at night.

Generally, a change in the level of awareness and in the ability to focus, sustain, or shift attention are often described as the earliest manifestations of delirium. Otherwise, in the hypoactive forms, patients could appear drowsy, lethargic, or even semicomatose.

Delirium by COVID-19 may present in its hyperactive form, with agitation requiring sedation, or can otherwise manifest with somnolence and a decreased level of consciousness[4,9]. It could be implied by a variety of clinical manifestations, including psychomotor agitation, sleep-wake reversals, irritability, anxiety, emotional lability, and hypersensitivity to lights and sounds. In a study by Mendes et al. on 235 patients, those who presented with delirium showed hypoactive features in 41.6% of cases and hyperactive or mixed traits in 35.4% and 23.0% of cases, respectively[5].

The clinical aspects of delirium in COVID-19 may be heterogeneous, crossing over the features of encephalitis and meningitis. Some studies show the concomitant presence of pyramidal signs and/or meningeal irritation signs, such as enhanced deep tendon reflexes, ankle clonus, bilateral extensor plantar response, and neck stiffness with positive Brudzinski sign[3,16]. Interestingly, a multifocal myoclonus was found to be more frequent than would typically be observed in delirium[10].

Unfortunately, features of delirium in COVID-19 patients do not significantly differ from other conditions and, especially in the hypoactive form, may be mistaken as secondary to respiratory or sepsis symptoms. For example, in our experience, many patients were diagnosed with delirium several days after the onset of neuropsychiatric symptoms as they had been interpreted as being related to pneumonia or respiratory failure. This was more frequent in patients already affected by neurological diseases such as dementia or Parkinson's disease. Moreover, patients who experience delirium often have cognitive and perceptual problems, including memory loss, disorientation, and difficulty with language and speech, so it is vital to understand the patient's level of functioning prior to the onset of delirium from reliable informants since a mild cognitive impairment could frequently underly delirium. However, collecting complete anamnestic data about previous cognitive disturbances is made difficult by restrictions put in place during hospitalization of COVID-19 patients, thus delaying the diagnosis and treatment of delirium.

Seizures are described along with encephalopathy in patients with COVID-19, just as they can occur in toxic-metabolic encephalopathy in other settings. In a retrospective case series by Somani et al., the authors reported 2 COVID-19 women patients with *de novo* status epilepticus; in one of them, status epilepticus was the initial presentation in an otherwise asymptomatic individual[17]. In a case report by Lyons et al., a young man who had tested positive for SARS-CoV-2 presented with a generalized tonic-clonic seizure three days after complaining of myalgia, lethargy and fever; in the wake of the seizure, he was confused and aggressive, and required sedation[18].

Although in most cases encephalopathy develops in patients who become critically ill, it might also be the primary symptom of COVID-19[19-21]. In a study of 817 older COVID-19 patients (median age 78 years) evaluated in the emergency department, 37% of patients with encephalopathy did not have typical COVID-19 symptoms such as fever or dyspnea[19]. Additionally, after a review of the neurological symptoms of COVID-19 patients, Leonardi et al. found that in a cohort of 2,660 hospitalized patients, 6 (0.22%) presented with acute encephalopathy as the first and only symptom[21].

Ticinesi et al. conducted a retrospective study on 852 patients to assess the incidence of delirium in a large number of patients hospitalized for COVID-19 in Northern Italy. The aim of the study was to verify its clinical correlations and determine its impact on in-hospital mortality. In their study, 11% of the sample developed delirium during the hospital stay. These patients were usually older, were less likely to have common respiratory symptoms (such as cough), more frequently presented atypical symptoms (such as syncope, postural instability and thoracic pain), and had lower oxygen saturation values on room air. Patients who developed delirium also had a higher prevalence of dementia and epilepsy, and had lower functional autonomy in daily activities[22].

Potential factors contributing to delirium during the COVID-19 pandemic

Studies conducted so far in the pandemic consistently show that there are some risk factors associated to delirium in COVID-19 patients.

– *Old age:* COVID-19 is more common in older people, and this is probably due to the synergistic effects of aging, frailty, and comorbidities. In particular, aging of the immune system is characterized by a chronic systemic inflammatory state or 'inflammaging', marked by elevated inflammatory markers, such as IL-6 and C-reactive protein. Frailty is characterized by multisystem dysregulation that leads to reduced physiologic reserve and increased risk of adverse health outcomes. The combined effects of these

factors, added to a high rate of comorbidities, not only increase the risk of severe illness but also lead to an increased risk of delirium as a non-typical presentation of COVID-19[10]. Mendes et al., in a study on 235 Caucasian patients, found that older patients with COVID-19 on admission to acute medical wards had a global prevalence of delirium of 20.4% with the main risk factor being previous cognitive impairment[5].

- *Comorbidities:* comorbidities can facilitate the onset of an acute confusional state[23]. In a case study on ICU patients presented by Van Rompaey et al.[24], the relative prevalence of specific comorbidities was 16.9% for hypertension, 53.7% for other cardiovascular diseases, 1.9% for cerebrovascular diseases, 8.2% for diabetes. In another study involving 509 hospitalized COVID-19 patients, Liotta et al. found that nearly 32% developed encephalopathy. These patients were more likely to have risk factors (including a history of any neurological disorder) than those without encephalopathy[25].
- *Hospitalization and isolation:* long hospital stay along with hospitalization complications such as sleep deprivation, constipation, dehydration, urinary retention, and superinfections increase the risk of delirium in COVID-19. Additionally, hospitals have instituted an extremely limited visitors' policy and have limited interaction with hospital staff, which may increase the sense of isolation and induce patients' disorientation and reduced awareness. While created to minimize contagion, policies that increase isolation and immobility for hospitalized patients, combined with acute illness, produce a high-risk environment for delirium[26,27]. This can be particularly difficult for older people, who are less likely to resort to virtual or electronic methods of interpersonal communication[24,28]. Furthermore, this can lead to apathy, undermining the will to mobilize, further increasing the risk of delirium[13]. In addition, the use of personal protective equipment by staff members can depersonalize them and possibly has a frightening effect on older people, especially those with pre-existing cognitive impairment or dementia. Isolation in the ICU and the need for mechanical ventilation may also further increase the risk of delirium. Earlier epidemiological studies have shown that up to 75% of patients undergoing mechanical ventilation in ICUs suffer from delirium at some point during their hospitalization[14]. It has also been shown that medical personnel devote less time to isolated patients, and less frequently draw attention to the difficulties arising from the need to take precautionary measures, such as wearing personal protective equipment, which may ultimately hinder physical examination[26]. Therefore, respiratory isolation of COVID-19 patients may decrease the frequency and quality of delirium screening, increasing the risk for delirium to persist undetected in vulnerable patients[13,29].

– *Psychological factors*: additional factors triggering the occurrence of delirium may be related to fear, anxiety, and disorientation. Patients presenting to the hospital are often aware of the high volume of patients passing through in a limited period of time and fear a risk of contagion. They are conscious of how severe the disorder can be and know that when admitted to the hospital they will not be able to see their loved ones. Moreover, COVID-19 patients suffer from respiratory distress, and difficulties in breathing can trigger anxiety. Finally, uncertainty about the future and a sense of disorientation may be factors associated with delirium, especially due to the lack of religious or spiritual support[15].
– *Iatrogenic factors*: this group of factors includes elements related to treatment requirements, such as the use of deep sedation or muscle relaxants to enable mechanical ventilation and the prone position[30]. Indeed, the use of centrally acting drugs, including benzodiazepines and propofol or opioids, may induce the occurrence of sedation-related delirium[31]. Finally, the use of medications with an anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients[13]. Prolonged mechanical ventilation and immobilization also greatly contribute to increasing the risk of delirium in the ICU[32] because there is no possibility of full-scale physiotherapy during active infection[13].

Diagnostic work-up

The main aspects of the diagnostic evaluation of delirium include recognition of the disorder and uncovering the potential underlying medical illnesses. As previously mentioned, clinicians often fail to recognize delirium[6]. An early identification of delirium is critical in COVID-19 patients because it could be an early symptom of a worsening respiratory failure or a sign of the spreading of the infection to the CNS.

Neurological examination should always be the first step in the diagnostic work-up to identify focal clinal signs and assess the severity of the clinical picture. Clinicians must pay attention to any changes in the level of consciousness, which could be the first observable clue, and to the ability of the patient to focus, sustain, or shift attention during a conversation. Conversation with the patient may also elicit memory loss, disorientation, or tangential or incoherent speech. Determining whether cognitive impairment or perceptual problems are due to a prior or progressing dementia can be challenging and requires knowledge of the patient's baseline level of functioning. We thus suggest the application of screening tools (i.e., the 4 As Test), that are simple to administer and that require no formal training, to improve the diagnosis of delirium.

Due to the heterogeneity of predisposing factors and plausible causes of delirium in COVID-19, the diagnostic work-up for these patients should include

a complete assessment of prescribed medication and relative collateral effects, metabolic function, hypoxemia, systemic factors (sepsis, liver and renal function, cardiac dysfunction), coagulopathy and hydration status, aiming to investigate all the potential reversible causes of delirium (Table 10.1). Indeed, successful treatment of delirium depends on the early identification of the reversible contributing factors. Medications such as benzodiazepines, propofol, opioids or corticosteroids, commonly prescribed to COVID-19 patients, are the most common reversible cause of neuropsychiatric symptoms, especially in the elderly. Metabolic or systemic abnormalities, such as dehydration, may also be associated to COVID-19-related respiratory failure.

Table 10.1: Potential reversible causes of delirium

Drug and toxins Prescribed medications (sedatives, antipsychotics) Withdrawal states Alcohol Adverse drug reactions	**Metabolic derangements** Electrolyte or endocrine disturbances Hyper/hypoglycemia Hypoxemia Wernicke encephalopathy, folate or B12 deficiency
Infections and sepsis	Brain disorders (See Alternative Diagnosis)
Systemic conditions Cardiac failure Acute or chronic liver failure Renal failure Coagulopathy Pulmonary disease with respiratory failure	**Physical disorders** Burns Hyperthermia Hypothermia Dehydration

Once the potential reversible causes for delirium have been excluded, further investigations such as magnetic resonance imaging (MRI), electroencephalography and lumbar puncture should be considered inorder to rule out a primary CNS involvement. Indeed, COVID-19-related neuropsychiatric symptoms may theoretically be associated with both acute encephalitis caused by direct SARS-CoV-2 CNS invasion or autoimmune encephalopathy[15].

Although autoptic studies confirmed a pronounced CNS involvement with lymphocytic panencephalitis, diffuse petechial hemorrhages, and brainstem neuronal cell damage in COVID-19 patients[33], in most *in vivo* studies, neuroimaging and analysis of cerebrospinal fluid (CSF) were not performed[4,9].

Despite the fact that most patients with encephalopathy typically have no evidence of brain inflammation on neuroimaging studies, a brain CT or MRI should be performed. A spectrum of aspecific neuroimaging abnormalities, such as focal or diffuse subarachnoid abnormalities and contrast enhancement, bilateral fronto-temporal hypoperfusion, but also white matter abnormalities and microbleeds, have been found in patients with COVID-19-related neuropsychiatric symptoms[3,9,34]. Cerebral microhemorrhages, often associated with concomitant leukoaraiosis, seem to be more common in patients with severe respiratory involvement[35]. Cytotoxic alterations in the splenium of the corpus

callosum have also been described in adult patients with COVID-19-related encephalopathy as well as in multi-system inflammatory syndrome in children with COVID-19[36]. Although most of the described radiological abnormalities are likely to be chronic or unrelated alterations, neuroimages may sometimes indicate a specific alternative diagnosis for the patient's mental state, such as stroke, encephalitis, or posterior reversible encephalopathy (PRES)[9,37-39], thus influencing patient management. For example, in a case series of 64 patients with COVID-19-related encephalopathy, ischemic alterations were identified in 17 patients (27%), 10 of whom with focal or lateralizing signs on examination, which suggested possible cerebrovascular accident[38].

CSF testing is suggested at least in cases of suspected viral or autoimmune encephalitis. Although robust data are lacking, CSF analysis was unremarkable in most patients with neuropsychiatric symptoms and the RNA viral load was found only in a few patients[9,37,39]. Only a small proportion of patients showed elevated intrathecal IgG and mildly elevated protein levels[9].

Patients who have undergone electroencephalography have typically demonstrated non-specific findings which, thus far, appear to be largely consistent with the diffuse slowing of background activity expected in encephalopathy[9,40,41]. However, electroencephalography should be considered in patients with unexplained and persistent altered consciousness to rule out Non-Convulsive Status Epilepticus (NCSE) or with clinical suspicion of epileptic seizures.

Table 10.2: Delirium mimics: possible alternative neurological diagnosis in COVID-19 patients

Focal syndromes (encephalitis, stroke, PRES)	Patients with delirium/acute encephalopathy typically have no evidence of brain inflammation on neuroimaging studies. Sometimes MRI findings indicate a specific, alternative diagnosis. CSF testing is suggested at least in cases of suspected viral or autoimmune encephalitis.
Non-convulsive status epilepticus	Electroencephalography should be considered in patients with unexplained and persistent altered consciousness to rule out non-convulsive seizures or with clinical suspicion of epileptic seizures.
Primary psychiatric illnesses	*Depression:* similar to delirium could be associated with sleep disturbance and difficulty with concentration. However, depression is associated with dysphoria, and there is less fluctuation than in delirium. *Mania*: can be confused with hyperactive delirium with agitation, delusions, and psychotic behavior. However, mania is usually associated with a positive history for psychiatric disease.

In conclusion, delirium in the COVID-19 patient is mostly a diagnosis of exclusion of the potential medical reversible causes and the alternative diagnosis (Table 10.2). When in doubt, the most useful rule is to assume delirium and attempt to rule out common medical etiologies. Delirium may be mimicked by acute or subacute brain lesions (such as stroke, encephalitis, or PRES, which

must be ruled out even in the absence of focal deficits on examination) or by a NCSE (facial twitching, unexplained eye movements, automatisms and acute aphasia or neglect without a structural lesion could imply an underlying epileptic condition). Early identification of the key features such as acute onset, fluctuating course, altered consciousness, and cognitive decline should help to distinguish delirium from other neuropsychiatric conditions, such as depression, psychotic illness, and dementia, remembering that even patients with a known psychiatric illness are susceptible to delirium when acutely ill.

Treatment strategies

Non-pharmacological approaches

Every patient admitted to the hospital with COVID-19 should be considered at potential risk of developing delirium, thus prevention strategies should be optimized[42]. Unfortunately, during the COVID-19 pandemic, systematic delirium monitoring using the recommended validated tests may not be put in place[15], probably due to the fact that the main emphasis is placed on organizational issues, such as the lack of ventilators, setting priorities, and the shortage of personal protective equipment[43]. For this reason, it could be useful to implement easy screening tools for delirium, in order to provide prompt treatment. Baller et al. performed a narrative review setting out preliminary guidance for delirium management in COVID-19 patients. Similar to general delirium management, behavioral modifications are first line, but pharmacological options might be necessary for the treatment of psycho-motor agitation and perceptual disturbances[12]. Non-pharmacological interventions, such as regular orientation despite social separation, are actually going to prove vitally important, given the new limitations and challenges related to clinical staff and visitor restrictions in the hospital during the COVID-19 pandemic[15]. It is essential that patients have supervised access to fully charged mobile phones or a tablet to communicate with their families and caregivers, in addition to standard environmental and stimulus control, early ambulation, and care clustering[42].

Moreover, in ICU patients, the concomitant factors which increase the risk of delirium must be managed using standard approaches towards adequate pain management, avoiding urinary retention and constipation, ensuring early identification and treatment of hospital-acquired sepsis, and maintaining adequate oxygenation[15].

Pharmacological treatment strategies

When behavioral strategies alone are not enough to guarantee control of the symptoms, in particular in cases of hyperactive delirium with important behavioral issues, pharmacological management should be considered[44] (Table 10.3).

In COVID-19 patients, the treatment of delirium poses additional challenges considering that sedative agents might further compromise respiratory function, increasing the risk of secondary infections. Furthermore, there could be a considerable risk of drug interactions, particularly regarding QTc prolongation, as these patients are already considered to be at increased risk of torsades de pointes because of the direct effect of the disease on the heart[12].

Nevertheless, antipsychotics are to be considered first-line treatment for the management of delirium in COVID-19 patients. While the National Institute for Health and Care Excellence (NICE) recommend haloperidol[45], the COVID-19 Delirium Workgroup at Massachusetts General Hospital[12] support the prescription of second-generation agents, like olanzapine and quetiapine, due to concerns about extrapyramidal syndrome (EPS). Baller et al. also encourage the use of melatonin due to its action as a sleep regulator, its immunomodulatory role and its good safety profile[46], and of alpha-2 agonists due to their analgesic properties and safety.

In particular, dexmedetomidine, currently restricted to ICU settings, seems to improve delirium, and shorten the time to recovery[47]. Its administration via IV infusion allows for quick titration, and it could be particularly beneficial in ARDS patients because it does not interfere with respiratory function. Drugs with anti-histaminergic and anti-cholinergic profiles can effectively induce short-term sedation, but there may be significant long-term risks, such as daytime sedation, respiratory distress, and further worsening of cognitive performance[44]. The use of benzodiazepines, such as lorazepam, is recommended for patients who are severely agitated, in combination with antipsychotic agents[45]. However, these must be managed with extreme caution given the risk of respiratory suppression in cases with pneumonia or ARDS. Other treatment, such as antidepressants (i.e., trazodone) and antiepileptic drugs (valproic acid) can be considered in patients who may not tolerate antipsychotic agents[12].

Outcome and long-term complications

Delirium itself appears to be a risk factor for poor outcome. Evidence consistently shows that delirium is associated with adverse outcomes in hospitalized patients with COVID-19. Delirium has been associated with post-discharge functional and cognitive decline[48], but its long-term implications in COVID-19 are still unknown.

Liotta et al., in a study of 509 consecutive hospitalized COVID-19 patients with neurological manifestations, found that patients with encephalopathy had longer hospital stay, worse functional impairment at hospital discharge, and a higher mortality rate compared with those without encephalopathy. In particular, even adjusting for the severity of the COVID-19 illness, age, and length of hospital stay, the occurrence of encephalopathy remained independently associated with a higher risk of death at 30 days[25].

Table 10.3: Medications for the treatment of delirium in COVID-19 patients

Medication	Mechanism	Prevalent Use	Sedation	QTc prolongation	Advantages	Disadvantages	Daily doses
Melatonin	Circadian rhythm regulation anti-inflammatory	Add on therapy	-	-	Good safety profile	PO formulation only; caution in immunosuppressed	1-3 mg
Antipsychotics							
Aripiprazole	D2 partial agonist	⬇ agitation in dementia and acute psychosis	-	Low risk	Low risk of EPS	Long half-life	10-30 mg
Chlorpromazine	H1, α1, muscarinic, 5HT2A D2 antagonism	⬇ agitation in acute psychosis	High risk	Moderate risk	PO, IV, IM Lower risk of EPS	Hypotension Anticholinergic side effects	25-300 mg (max 75 mg/die in elderly)
Haloperidol	D2 antagonism	⬇ agitation in acute psychosis	Low risk	Moderate risk	PO, IV, IM	High risk of EPS with PO formulation	1-10 mg (0.5-5 mg in elderly)
Olanzapine	D2, H1, α1, muscarinic antagonism	⬇ agitation in acute psychosis	Moderate risk	Low risk	Fast acting	Anticholinergic side effects	2.5-5 mg
Promazine	H1, muscarinic, 5HT2A, D2 antagonism	⬇ agitation in acute psychosis	High risk	Moderate risk	PO, IV, IM lower risk of EPS	Hypotension Anticholinergic side effects	100-200 mg x 4 (25-50 mg in elderly)
Quetiapine	H1, α1, α2, 5HT2A, D1, D2 antagonism 5HT1A partial agonism	⬇ agitation in dementia and acute psychosis ICU patients	Moderate risk	Low risk	Wide dose range Minimal EPS	PO only	25-20 mg
Risperidone	5HT2A , D2 antagonism	⬇ agitation in dementia and acute psychosis	Low risk	Low risk		High risk of EPS	0.5-2 mg
Benzodiazepines							
Lorazepam	GABA agonism	Add on in severe agitation	Moderate risk	-	PO, IV, IM Rapid onset	Respiratory suppression Can worsen delirium	1-4 mg (0.5-2 mg in elderly)
Other drugs							
Dexmetomidine	α2 agonist	ICU patients	High risk	Moderate risk	IV, rapid titration Analgesic properties	Expensive Restricted to ICU patients Hypotension, bradycardia	0.2-1.4 mcg/Kg/h
Trazodone	α1, 5HT2A antagonism	Ipnotic in geriatric patients	High risk	Low risk	Low risk of EPS	PO only	50-150 mg
Valproic acid	Sodium channel blocker	⬇ agitation	Low risk	Low risk	PO, IV Useful in comorbid seizure	Contraindicated in patients with pancreatic or hepatic failure	250-1200 mg (weight-based loading possible)

EPS = extrapyramidal symptoms; ICU = intensive care unit; IM = intramuscular; IV = intravenous; PO = per os;

These results were confirmed by Garcez et al. in a cohort of 707 patients aged ≥50 years admitted consecutively to a COVID-19 hospital in Sao Paulo, Brazil. They found that the overall occurrence of delirium was independently associated with in-hospital death, length of hospital stay, admission to an ICU, and mechanical ventilation[48].

As with other critically ill patients, neurological dysfunction may persist after acute illness symptoms have resolved. The development of a 'post-intensive care syndrome' (PICS), a new and/or the worsening of previous symptoms which lead to an impairment in any physical, cognitive, or mental domain after critical illness or intensive care[49] has frequently been reported. In particular, a PICS with cognitive impairment is described in 30-80% of ICU patients, and includes memory loss and a dysexecutive syndrome with difficulty in concentration, comprehension, and critical thinking[50.] The major risk factors for the development of PICS appear to be ARDS, sepsis, delirium, prolonged mechanical ventilation, and multi-organ failure[51]. Surviving patients with COVID-19 treated in the ICU should be considered at higher risk for developing PICS given the restraints on social support, prolonged mechanical ventilation with exposure to greater use of sedatives, and limited mobilization[52].

To date, the long-term neurological prognosis of patients with COVID-19-related encephalopathy still needs to be clarified. Prospective cognitive and neurological-focused evaluations through specialized clinics dedicated to further diagnostic assessment are needed and could play a significant role in recovery from this pandemic[25].

Take-home message

- Delirium is common and is still under-recognized in hospitalized patients with COVID-19.
- 20-30% of COVID-19 patients will present with or develop delirium or changes in mental status during hospitalization.
- Although the pathogenesis remains unknown, delirium is thought to be related to a COVID-19 primary CNS manifestation or a secondary encephalopathy, caused by inflammation or other systemic effects of SARS-CoV-2.
- When behavioral strategies alone are not enough to guarantee control of symptoms, pharmacological management should be considered.
- Delirium itself appears to be a risk factor for poor outcome.

References

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383:911-922.
2. Docherty AB, Harrison EM, Green CA, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020. doi: 369:m1985. [Preprint]
3. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020;382(23):2268-2270.
4. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
5. Mendes A, Serratrice C, Herrmann FR, et al. Predictors of In-Hospital Mortality in Older Patients With COVID-19: The COVIDAge Study. *J Am Med Dir Assoc*. 2020;21(11):1546-1554.e3.
6. Mcloughlin BC, Miles A, Webb TE, et al. Functional and cognitive outcomes after COVID-19 delirium. *Eur Geriatr Med*. 2020;11:857-862.
7. Bianchetti A, Rozzini R, Guerini F, et al. Clinical Presentation of COVID19 in Dementia Patients. *J Nutr Health Aging*. 2020;24(6):560-562.
8. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. 2021;9(3):239-250.
9. Helms J, Kremer S, Merdji H, et al. Delirium and encephalopathy in severe COVID-19: acohort analysis of ICU patients. *Crit Care*. 2020;24(1):491.
10. Beach SR, Praschan NC, Hogan C, et al. Delirium in COVID-19: A case series and exploration of potential mechanisms for central nervous system involvement. *Gen Hosp Psychiatry*. 2020;65:47-53.
11. Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain Behav Immun*. 2020. doi: 10.1016/j.bbi.2020.04.024. [Preprint]
12. Baller EB, Hogan CS, Fusunyan MA, et al. Neurocovid: Pharmacological Recommendations for Delirium Associated With COVID-19. *Psychosomatics*. 2020;61(6):585-596.
13. Kotfis K, Williams Roberson S, Wilson J, et al. COVID-19: What do we need to know about ICU delirium during the SARS-CoV-2 pandemic? *Anaesthesiol Intensive Ther*. 2020;52(2):132-138.
14. Emmerton D, Abdelhafiz A. Delirium in Older People with COVID-19: Clinical Scenario and Literature Review. *SN Compr Clin Med*. 2020. doi: 10.1007/s42399-020-00474-7. [Preprint]
15. Kotfis K, Williams Roberson S, Wilson JE, et al. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care*. 2020;24(1):176.
16. Ye G, Pan Z, Pan Y, et al. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. *J Infect*. 2020;80(5):e14-e17.

17. Somani S, Pati S, Gaston T, et al. De Novo Status Epilepticus in patients with COVID-19. *Ann Clin Transl Neurol.* 2020;7(7):1240-1244.

18. Lyons S, O'Kelly B, Woods S, et al. Seizure with CSF lymphocytosis as a presenting feature of COVID-19 in an otherwise healthy young man. *Seizure.* 2020;80:113-114.

19. Kennedy M, Helfand BKI, Gou RY, et al. Delirium in Older Patients With COVID-19 Presenting to the Emergency Department. *JAMA Netw Open.* 2020;3(11):e2029540.

20. Alkeridy WA, Almaghlouth I, Alrashed R, et al. A Unique Presentation of Delirium in a Patient with Otherwise Asymptomatic COVID-19. *J Am Geriatr Soc.* 2020;68(7):1382-1384.

21. Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: a review and a call for action. *J Neurol.* 2020;267(6):1573-1576.

22. Ticinesi A, Cerundolo N, Parise A, et al. Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. *Aging Clin Exp Res.* 2020;32(10):2159-2166.

23. Trzepacz PT, Mittal D, Torres R, et al. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci.* 2001;13(2):229-242.

24. Van Rompaey B, Elseviers MM, Schuurmans MJ, et al. Risk factors for delirium in intensive care patients: a prospective cohort study. *Crit Care.* 2009;13(3):R77.

25. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol.* 2020;7(11):2221-2230.

26. Abad C, Fearday A, Safdar N. Adverse effects of isolation in hospitalised patients: a systematic review. *J Hosp Infect.* 2010;76(2):97-102.

27. Cipriani G, Danti S, Nuti A, et al. A complication of coronavirus disease 2019: delirium. *Acta Neurol Belg.* 2020;120(4):927-932.

28. Bannon L, McGaughey J, Clarke M, et al. Impact of non-pharmacological interventions on prevention and treatment of delirium in critically ill patients: protocol for a systematic review of quantitative and qualitative research. *Syst Rev.* 2016;5:75.

29. Marra A, Kotfis K, Hosie A, et al. Delirium Monitoring: Yes or No? That Is The Question. *Am J Crit Care.* 2019;28(2):127-135.

30. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* 2020;382(8):727-733.

31. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology.* 2006;104(1):21-26.

32. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA.* 2004;291(14):1753-1762.

33. von Weyhern CH, Kaufmann I, Neff F, et al. Early evidence of pronounced brain

involvement in fatal COVID-19 outcomes. *Lancet*. 2020;395(10241):e109.

34. Helms J, Kremer S, Meziani F. More on neurologic features in severe SARSCoV-2 infection. *N Engl J Med*. 2020;382(26):e110.
35. Agarwal S, Jain R, Dogra S, et al. Cerebral Microbleeds and Leukoencephalopathy in Critically Ill Patients With COVID-19. *Stroke*. 2020;51(9):2649-2655.
36. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. *JAMA Neurol*. 2020;77(11):1440-1445.
37. Moriguchi T, Norikazu H, Junko G, et al. A first case of meningitis/ encephalitis associated with SARS-Coronavirus-2. *Int J Infectious Dis*. 2020;94:55-58.
38. Kremer S, Lersy F, Anheim M, et al. Neurologic and neuroimaging findings in patients with COVID-19: A retrospective multicenter study. *Neurology*. 2020;95(13):e1868-e1882.
39. Kandemirli SG, Dogan L, Sarikaya ZT, et al. Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection. *Radiology*. 2020;297(1):E232-E235.
40. Gélisse P, Rossetti AO, Genton P, et al. How to carry out and interpret EEG recordings in COVID-19 patients in ICU? *Clin Neurophysiol*. 2020;131(8):2023-2031.
41. Vespignani H, Colas D, Lavin BS, et al. Electroencephalographic Findings in Critically Ill Patients with COVID-19. *Ann Neurol*. 2020;88(3):626-630.
42. LaHue SC, James TC, Newman JC, et al. Collaborative Delirium Prevention in the Age of COVID-19. *J Am Geriatr Soc*. 2020;68(5):947-949.
43. Emanuel EJ, Persad G, Upshur R, et al. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med*. 2020;382(21):2049-2055.
44. Ostuzzi G, Gastaldon C, Papola D, et al. Pharmacological treatment of hyperactive delirium in people with COVID-19: rethinking conventional approaches. *Ther Adv Psychopharmacol*. 2020;10:2045125320942703.
45. NICE guideline. *COVID-19 rapid guideline: managing COVID-19*. [NG191], Published: 23 March 2021.
46. Zhang R, Wang X, Ni Li, et al. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci*. 2020. 2020.. doi: 10.1016/j.lfs.2020.117583. [Preprint]
47. Skrobik Y, Duprey MS, Hill NS, et al. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium. A Randomized, Placebo-controlled Trial. *Am J Respir Crit Care Med*. 2018;197(9):1147-1156.
48. Garcez FB, Aliberti MJR, Poco PCE, et al. Delirium and Adverse Outcomes in Hospitalized Patients with COVID-19. *J Am Geriatr Soc*. 2020;68(11):2440-2446.
49. Ohtake PJ, Coffey Scott J, Hinman RS, et al. Impairments, activity limitations and participation restrictions experienced in the first year following a critical illness: protocol for a systematic review. *BMJ Open*. 2017;7(1):e013847.
50. Colbenson GA, Johnson A, Wilson ME. Post-intensive care syndrome: impact, prevention, and management. *Breathe* (Sheff). 2019;15(2):98-101.
51. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. *Crit Care Med*. 2011;39(2):371-379.

52. Biehl M, Sese D. Post-intensive care syndrome and COVID-19 - Implications post pandemic. *Cleve Clin J Med*. 2020. doi: 10.3949/ccjm.87a.ccc055. [Preprint]
53. Sato K, Mano T, Iwata A, et al. Neuropsychiatric adverse events of chloroquine: a real-world pharmacovigilance study using the FDA Adverse Event Reporting System (FAERS) database. *Biosci Trends*. 2020;14(2):139-143.
54. Abad C, Fearday A, Safdar N. Adverse effects of isolation in hospitalised patients: a systematic review. *J Hosp Infect*. 2010;76(2):97-102.
55. Courtin E, Knapp M. Social isolation, loneliness and health in old age: a scoping review. *Health Soc Care Community*. 2017;25(3):799-812.

Chapter 11. Psychiatry and psychopathology

Bernardo Dell'Osso, Benedetta Demartini, Beatrice Benatti, Veronica Nisticò, Nicolaja Girone, Orsola Gambini

There is a wide consensus that the current COVID-19 pandemic is affecting not only physical health, but also mental health and well-being, leading to considerable psychosocial consequences. The aim here is to give readers an update on the main research findings on the impact of COVID-19 on the principal psychiatric disorders.

Mood disorders

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are common mental disorders characterized by enhanced comorbidity, mortality, and risk of suicide. Several authors suggested that people with a previous history of mood disorder are at high risk of their symptoms worsening during the COVID-19 pandemic, given their greater vulnerability to changes in daily routine due to quarantine and fear of illnesses compared to the general population[1-4]. A study by Van Rheenen and colleagues showed that depressive symptoms, anxiety, stress and general distress were heightened in patients with affective disorders compared to healthy controls, with higher rates of anxiety in patients with BD compared to those with MDD[5] (Table 11.1). Another recent study by Fiorillo and colleagues based on an online survey conducted between March and May 2020 in the Italian population highlighted that symptoms of depression, anxiety and stress significantly worsened from the week April 9–15th to the week April 30th- May 4th. Moreover, female respondents and people with pre-existing mental health problems were at higher risk of developing severe depression and anxiety symptoms[6]. In this perspective, as regards patients with pre-existing affective disorders, higher levels of depressive symptoms and general distress emerged in male patients with BD compared to females[5]. This latter finding is in contrast with several prior studies showing the opposite gender effect under non-pandemic conditions[7-9], leading to the hypothesis that male patients with BD could be presenting a worse clinical profile during the COVID-19crisis.

In addition, specific aspects of this pandemic, and of the measures necessary for its control, may be of particular concern for patients with affective

disorders, particularly regarding risk of relapse. More precisely, the course of BD is sensitive to disruption of biological and social rhythms, an effect mediated through mechanisms related to circadian rhythm regulation[10]; these alterations are a central element of BD and have been implicated in the genesis of the illness[11-13]. Some measures that have been adopted to curtail the spread of COVID-19, such as home confinement, social distancing, lockdowns and quarantine, may potentially disrupt both habitual sleep patterns and the number and quality of social contacts and activities. This could have a deleterious influence on the risk of both manic and depressive relapses[3]. In this regard, recent studies found that rigid lockdown was associated with specific sleep dysregulations in BD patients, with greater impairment in patients experiencing a depressive episode, suggesting that the social isolation, lockdown and consequent lack of emotional support might introduce biorhythm dysregulation leading to higher vulnerability to depression[14,15].

In addition, the close relationship between affective disorders and substance use, particularly alcohol use, requires consideration. During the COVID-19 pandemic, many nations have opted to continue alcohol sales for home consumption, leading to a potential increase in use in vulnerable individuals. In patients with affective disorder, this could lead to increased symptom severity, as well as adverse outcomes such as suicide[3,16]. Indeed, lifestyle behaviors are key mediators of physical and cognitive health, which is typically compromised in BD and MDD[17,18]. There is evidence that increased alcohol intake, together with sleep loss and cessation of exercise, could amplify cardiometabolic dysfunction by altering biochemical and inflammatory marker profiles[19,20]. Thus, the maladaptive lifestyle changes in response to COVID-19 might not only contribute to emotional decline and cognitive impairment, but may further compound the risk of severe SARS-CoV-2 infection and associated medical complications[21].

There is evidence of an association between positivity for coronaviruses and the risk of mood episodes. Though the significance of this association is still unclear, it may be related to the neurotrophic potential of respiratory coronaviruses or to their ability to provoke a systemic inflammatory reaction, both of which may be associated with mood dysregulations[3,22]. In particular, the presence of somatic symptoms prompt researchers to consider the psychoneuroimmunological (PNI) framework of COVID-19. COVID-19 may, indeed, cause acute respiratory syndrome with consequent release of pro- inflammatory cytokines, including interleukin (IL)-1β and IL-6 from the respiratory tract[23]; these cytokines were frequently found to be increased in MDD[23].

Finally, other issues of concern in patients with affective disorders include the general distress associated with a disease outbreak and the reduced access to treatment during an epidemic, both of which could trigger a relapse. Confinement measures considered necessary to curtail the spread of

SARS-CoV-2, may disrupt daily routines including reduced access to healthcare, therefore exacerbating affective disorders under frequent follow-up[24].

Psychotic disorders

Psychotic disorders affect 1–2% of all adults; schizophrenia[25], schizoaffective disorder[26] and acute/transient psychotic disorders[27] are the most common diagnosis. Schizophrenia involves several symptoms that differ in terms of severity of positive, negative, and cognitive impairment and the corresponding risk of the presence of depression and hostility. In addition, individuals with schizophrenia are often less educated, have lower self-control and self-care than average and inadequate understanding of their problem[28]. These elements may have influenced the greater difficulty shown by these patients in finding correct information about COVID-19 and in preventing possible contagion with appropriate behaviors[29] (Table 11.1).

In this regard, risk perception and adherence to protective measures in individuals diagnosed with schizophrenia should be of particular concern for their caregivers. A literature review by Brown and colleagues focused on the impact of successive epidemics throughout history (including SARS, MERS, Ebola, and swine flu) on psychosis. The research found that patients diagnosed with schizophrenia are less likely to be vaccinated and isolated. In addition, a positive correlation between psychotic symptoms and poor adherence with protective measures was found[30].

As regards patients presenting with a first episode of psychosis (FEP), a recent report on a 62-patient sample hospitalized between March and July 2020 compared to patients with FEP hospitalized during the same timeframe in 2019 found that the 2020 FEP patients were significantly older than patients with FEP in 2020 and presented with significantly less substance abuse. These findings suggest a major role of aging as a vulnerability factor to the stressful environment during the pandemic compared to common factors such as substance abuse[31].

From an organic perspective, people suffering from schizophrenia historically resulted more vulnerable to the adverse consequences of new infections. More than 70% of patients have experienced at least one other clinical condition, such as type-2 diabetes, chronic lung disease, or heart disease. This would increase the mortality rate caused by COVID-19 in individuals with schizophrenia[32]. Moreover, even the choice of neuroleptic therapy may expose patients to a higher risk of COVID-19 infection. For example, the use of clozapine (a second-generation antipsychotic particularly effective in the treatment of refractory schizophrenia) has been placed among the potential contraindications for schizophrenic patients due to the risk of agranulocytosis, a dangerous side effect[32].

The medium- and long-term social effects of COVID-19 may disproportionately impact people with psychosis or those at risk of psychotic disorder: social isolation, unemployment, homelessness, relationship breakdown (divorce/separation), domestic violence, and worsened physical health may all particularly affect people with psychosis, given their vulnerability to social determinants of health[33]. Moreover, the massive modifications in social networking present a surreal scenario to which it is difficult to become accustomed. For those who suffer from psychotic disorders, this new reality may exacerbate feelings of perplexity, anxiety, and paranoia. Furthermore, the current situation may be assimilated into the typical delusional contents of patients diagnosed with schizophrenia[29]. In addition, social distancing practices could have a particularly negative impact on individuals with schizophrenia. Typically, individuals with schizophrenia have on average smaller and poorer-quality social networks than the general population[34]. Thus, they may be more able to comply with, and tolerate, social distancing directives. However, social support has been associated with higher scores on recovery measures in schizophrenia and broad community support structures, including casual contacts at stores, have also been associated with improved recovery and community integration scores in schizophrenia[35]. These casual contacts have been disrupted by social distancing during the COVID-19 pandemic. In addition, social distancing may also disproportionately impact the ability of people with schizophrenia to satisfy their basic needs, given their high reliance on income support and other community services that have become more difficult to access[36].

Conversely, some recent studies have shown that COVID-19 distancing policies have not produced significant symptomatic changes for patients with schizophrenia or other serious mental illnesses[37-39], suggesting three possible hypotheses: first, an unexpected demonstration of resilience from this class of patients; second, generalized social isolation may reassure patients suffering from persecution delusions; lastly, social isolation may be absorbed within the patient's delusion[28]. Considering the above, the consequences of the pandemic in individuals diagnosed with schizophrenia are variable and subjective, and are highly dependent on each patient's symptomatology.

Table 11.1: Mood Disorders, Psychotic Disorders and COVID-19

First author, Year	Site and dates	Methods	Participants	Main findings
Fiorillo et al., 2020 [6]	Italy, March and May 2020	Online self-report questionnaire	20,720 participants, general population	12.4% of respondents reported severe/extremely severe levels of depressive symptoms and 17.6% reported anxiety symptoms. Female respondents and people with pre-existing mental health problems were at higher risk of developing severe depression and anxiety symptoms.
Ma et al., 2020 [38]	China, January-April, 2020	Online self-report questionnaires	30 patients with schizophrenia subjected to isolation; 30 patients with schizophrenia not subjected to isolation	Patients in isolation experience higher levels of stress, anxiety, and depressive symptomatology, compared to patients not in isolation. PANSS scale scores between the two groups are not significantly different, meaning that no relevant changes in schizophrenic symptomatology were detected.
Pinkham et al., 2020 [37]	USA, April-June, 2020	Online self-report survey	92 patients with schizophrenia, 56 with affective disorders	No significant changes in mood or psychotic symptoms and sleep duration emerged. A significant increase in the number of substances used emerged in patients. Patients showed a significant increase in well-being after the pandemic onset.
Van Rheenen et al., 2020 [5]	Australia, April 2020	Online self-report survey	1292 BD/ MDD, 3167 controls	Higher psychological distress in the mood disorder group vs controls. Stress and depression are further elevated in patients BD vs MDD. Higher levels of depression emerged in BD men vs BD women.
Yocum et al., 2020 [15]	USA, April 20 and May 20, 2020	Online self-report survey	413 BD patients, 147 controls	BD patients reported greater impact, with an increase in mood symptoms and a slower global improvement over time compared to healthy controls.

MDD: Major Depressive Disorder; BD: Bipolar Disorder; PANSS: Positive and Negative Symptom Scale.

Anxiety disorders

COVID-19 has been linked to increased anxiety, health anxiety, depression, stress[40-42] and suicidal ideation both in the general population[43-44] and among patients with pre-existing psychiatric disorders[45-47], particularly due to disruptions in main routines and mental health care (Table 11.2). The main consequences were represented by relapse or exacerbation of symptoms[1,4,48].

Although some studies showed that, in patients with severe/chronic mental health disorders, the COVID-19 pandemic did not exacerbate pre-existing symptoms[49-51], a study by Asmundson and colleagues focused on the impact of pandemic-related stress, scored using the COVID Stress Scales (CSS), on patients with pre-existing anxiety disorders (e.g., generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, panic disorder)[52]. These patients exhibited higher CSS total scores and higher scores on fears about danger and contamination, socioeconomic consequences, xenophobia, and traumatic stress symptoms scales. In particular, patients with pre-existing anxiety disorders were more likely to self-isolate and to make more active efforts at coping with self-isolation distress, despite there being no evidence of any appreciable benefit for the methods they adopt to cope compared to controls.

Obsessive-compulsive disorder

Among patients with mental illness, those with Obsessive-Compulsive Disorder (OCD) showed significant clinical worsening as a result of the COVID-19 pandemic. OCD is characterized by recurrent and intrusive thoughts or images (i.e., obsessions) associated with behavioral efforts aimed at neutralizing the anxiety caused by obsessions (i.e., compulsions)[53]. Moreover, among the most common OCD symptoms is the fear of contamination leading to excessive cleaning behaviors[54,55]; indeed, frequent compensatory behaviors in OCD are compulsive hand washing, avoidance behavior with regard to touching objects considered contaminated, and cleansing rituals.

During large-scale outbreaks of infectious disease such as transnational pandemics, patients with OCD are prone to increase their dysfunctional cleaning and organizing beliefs[56,57]. The current global outbreak of COVID-19 and the consequent high fear of contamination have represented a precipitating factor for the potential increase in obsessions and compulsions, also due to the reinforced cleansing habits of patients with OCD[58] (Table 11.2). Indeed, given the high risk of contamination, better hygiene habits have been encouraged by governments and the media, generating

plausible justifications for intensifying compulsive cleaning rituals, usually considered excessive or irrational, and now legitimate and socially accepted[59]. However, this kind of information can have drastic implications for individuals with OCD, since cognitive distortions and compensatory strategies (cleansing rituals) generate plausible validation for the intensification of compulsive cleaning rituals[60], as well as excessive feelings of responsibility, and exaggerated risk assessment[61,62].

The exacerbation of OCD symptomatology has been well-documented during previous outbreaks, such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Influenza[63].

As expected, COVID-19-related stress has been significantly associated with OCD-like stress symptoms[41], intrusive thoughts, reassurance-seeking[64], intolerance of uncertainty, OCD symptoms, health anxiety[62], anxiety symptoms, and avoidance behaviors [65-67]. The effects of the current COVID-19 pandemic on OCD have been shown to worsen OC symptom severity, with serious clinical consequences[56,57,67-71] and changed the manifestation of OC symptoms, leading to the development of new and past obsessions and compulsions in the context of the pandemic. The onset of new and past obsessions and compulsions could be related to the need for greater control against potential contamination or the increase in spare time during the lockdown, leading to an increase in repetitive behaviors. Moreover, high rates of avoidance behaviors, mostly related to the fear of possible contamination, family accommodation, job difficulties, sleep disturbances, more psychiatric comorbidities and increased rates of suicidal ideation emerged in OCD patients during the pandemic[68].

Moreover, it is important to note that the intensification of obsessions, a sense of hopelessness, depressive symptoms and anxiety have been historically associated with high rates of suicide in individuals with OCD[72,73], and fear and stress related to COVID-19 may contribute to a rise in the risk of suicide[44,74]. Additional COVID-related factors that could potentially increase this risk include a recent increase in OCD severity, the effects of quarantine, loneliness or social isolation distress[68,75]. Furthermore, the OC dimensions of responsibility for harm and unacceptable obsessional thoughts, along with general OCD severity, have been linked to increased suicidal ideation during the pandemic[67].

Table 11.2: Anxiety Disorders, Obsessive Compulsive Disorder and COVID-19

First author, Year	Site and dates	Methods	Participants	Main findings
Asmundson et al., 2020 [52]	Canada/ USA, March-April 2020	Online self-report survey	700 patients with anxiety-related disorders, 368 mood disorders, 500 controls	Patients with anxiety-related disorders reported greater fears of danger and contamination, socioeconomic consequences, xenophobia, and traumatic stress symptoms than the other groups.
Benatti et al., 2020 [68]	Italy, March-April, 2020	Semi-structured interview conducted by telephone	123 OCD patients	Clinical worsening of OCD in more than one-third of the sample. New and past obsessions and compulsions phenotype, suicidal ideation, increased Internet checking, sleep disturbances, avoidance behaviors, work difficulties, and need of therapy adjustment emerged in OCD patients with clinical worsening.
Hao et al., 2020 [45]	China, February, 2020	Online self-report questionnaires	12 MDD patients, 19 with anxiety-related disorders, 45 with mixed anxiety and depressive disorders, 109 controls	Psychiatric patients were significantly more likely to show higher levels of PTSD, depression, anxiety, stress, and insomnia scores.
Højgaard et al., 2021 [70]	Denmark, March and April, 2020	Online self-report questionnaires	201 patients with OCD	61.2% of OCD patients reported an increase in OCD severity. Female gender, contamination symptoms, and psychiatric comorbidity were found to have a significant association with increasing OCD severity.

Khosravani et al., 2021 [67]	Iran, June 5 and October 30, 2020	Self-report questionnaires	304 patients with OCD	OCD patients with OC symptom dimensions of responsibility for harm and unacceptable obsessional thoughts and severe OCD were more likely to have suicidal ideation during the pandemic.
Littman et al., 2020 [69]	Israel, March 29 and April 20, 2020	Online self-report survey	65 patients with OCD	Most OCD patients have either been unaffected by the COVID-19 crisis or have even experienced symptomatic improvement.
Matsunaga et al., 2020 [115]	Japan, April 7 and May 2, 2020	Semi-structured interview	60 fully/partially remitted OCD patients	10% of OCD patients reported an increase in OCD severity. Patients with OCD worsening showed higher trait anxiety, depressive status, higher prevalence of generalized anxiety disorder, and contamination/washing symptoms.

MDD = Major depressive disorder; OCD = Obsessive-compulsive disorder

Eating disorders

Eating disorders (EDs) are characterized by persistent irregular eating behaviors causing a deficit in food intake or absorption, ultimately leading to a significant impairment of physical health and psychosocial functioning. anorexia nervosa, bulimia nervosa and binge-eating disorder are the most frequent EDs, and all three are characterized by irregular eating habits, along with severe distress or concern about body weight or shape[53].

In the context of the COVID-19 pandemic and the consequent lockdown measures imposed by local governments worldwide, patients both suffering and recovered from EDs have been considered by the scientific community to be at high risk of their symptoms worsening or of relapse. Scientific evidence suggested that during the first lockdown (March-May 2020) patients with EDs suffered from high levels of anxiety, along with increased dietary restriction behaviors, binge eating, purging, and exercise behaviors[76-78] (Table 11.3); a re-emergence of symptoms of Bulimia Nervosa was also reported in patients who were recovering from this condition[76]. Several factors have been suggested to play a major role in the exacerbation of ED symptoms[79]. First, food insecurity, defined by the Food and Agriculture Organization of the United Nations in 2019 as the "scarcity, reduced access to, or difficulty acquiring safe, nutritionally adequate foods"[79]; since

governments worldwide recommended limiting trips to the supermarket as much as possible, a large part of the population stormed stores to stockpile groceries, leaving shelves almost empty. Hence, even individuals from western countries, who have never experienced food insecurity before, for the first time had to face the anxiety (enhanced by media reports) of having limited access to food[80], which contributed to the so-called "feast or famine" pattern: periods of food abundance, hoarding, and overconsumption are alternated with compensatory behaviours, such as skipping meals[81]. Overall, food insecurity represents a risk factor for both the onset of an ED, and the worsening of pre-existing EDs symptoms, especially in populations from low socioeconomic backgrounds[82,83].

Second, the few opportunities for physical activity due to the closure of fitness centers and the difficulties in training outside while maintaining physical distancing. On one hand, this might lead to increased anxiety about gaining weight even in the general population; on the other hand, individuals suffering from EDs (especially Anorexia Nervosa) often use compulsive physical exercise both as a strategy to control their body shape, and as a coping method for negative emotions[84]. Therefore, when deprived of physical activity, patients with EDs often adopt other unhealthy compensatory behaviors, such as greater cutting down on calories or purging[79,85].

Third, the need to stay at home and the consequent disruption ofone's own routine, both physiological (i.e., eating and sleeping pattern) and social need to be considered[84]. Since March 2020, all non-essential workers and students have been asked to work and study from home. Family members with different time schedules were forced to reorganize spaces that they had routinely shared, which were often not adequate. On one hand, the lack of defined spaces and times to have one's own meals could negatively impact the recovery of patients with Eds. On the other hand, in order to meet the needs of the entire family, mealtimes often had to be organized several times through the day; this inevitably increased the time spent handling and speaking about food, which, in turn, may increase the risk for disordered eating behaviors[84,86]. In a psychosocial perspective, Castellini and colleagues[76] also found that the forced confinement at home often led to general domestic tensions that predicted the increase in ED symptoms in patients known for these types of disorder. In particular, patients with an insecure attachment and a history of trauma during childhood resulted more vulnerable to severe COVID-19-related post-traumatic symptomatology. Investigating the impact of social distancing on patients with EDs, it was suggested that lockdown measures might be initially thought as a potential short-term relief. In fact, having fewer social interactions also implies having fewer occasions to show in one's own body in public[79,87]. However, the authors also highlighted that, despite the short-term mitigation of interpersonal social triggers, the risk for patients with EDs to experience a worsening of their symptoms during the COVID-19 outbreak was still high, probably because social

support and adaptive coping strategies, known to be protective factors against the increase in ED symptoms, were lacking during this period[84]. Hence, it was also suggested to investigate the potential benefit of the end of the lockdown. In line with these considerations, our research group further hypothesized that the confinement at home might have represented a specific trigger for patients with EDs in terms of having more time to think about food and to compulsively gaze at one's own body in the mirror. We conducted a longitudinal study over two time points: 1) during the first lockdown in Italy - April 2020; and 2 a month after restrictions were eased - June 2020. The study aimed to assess the levels of stress, anxiety, depression, and symptoms related to post-traumatic stress disorder (PTSD) and EDs in patients with EDs. In this context, we found that patients with EDs, compared to a group of healthy controls, reported experiencing a heightened fear of losing control over eating, more discomfort at seeing their own body, and spending more time thinking about their body during the lockdown than before. We also found that, at the end of the lockdown, PTSD-related symptoms of patients with EDs significantly diminished with respect to the lockdown period, and patients reported feeling significantly better at the end of lockdown, although high levels of anxiety persisted[88].

Fourth, the restricted access to healthcare[84]. Despite the increased need for social and psychological support, healthcare services worldwide had to face the outbreak of a highly infectious disease, which led most of the hospitals to convert their departments into acute and subacute intensive care units and to block all but urgent outpatient services. In Italy, authorities were ordered to maintain full functionality of mental health and substance use services, officially recognizing inpatient and outpatient mental health services as being fundamental to the community during a global pandemic[89]. In our mental health department, second-level and third-level outpatient units, including the those dealing with EDs, were closed and switched to telemedicine programs; phone calls and video conference-based visits were organized only for emergencies or specific patient requests, and patients were encouraged to continue psychotherapy via video conference[89]. However, telehealth visits restrict the capacity to monitor weight change, vital signs, and carry out other key physiological assessments[79]. Moreover, it was reported that the discomfort of an online visit may have been a reason for avoiding mental healthcare services, especially for individuals who are at the onset of a mental health disorder[84].

In conclusion, here we have examined specific risk factors which might lead patients with EDs to experience a worsening of their symptoms during the COVID-19 pandemic. These should be taken into account when designing both therapeutic interventions tailored to the single patient, and large-scale preventive interventions.

Table 11.3: Eating Disorders and COVID-19 (experimental studies only)

First Author, year	Site and dates	Methods	Participants	Main findings
Castellini et al., 2020 [76]	Florence (Italy) T0: January – September 2019 (enrolment); T1: November 2019 – January 2020 (pre-lockdown) T2: April - May 2020 (during lockdown)	T0 and T1: self-report questionnaires, face-to face clinical interviews; T2: online questionnaires, video calls.	37 AN 37 BN 97 HC	EDs patients reported increased compensatory exercise during lockdown; household arguments and fear for the safety of loved ones predicted a higher increase in pathological physical exercise and in binge-eating episodes, respectively. In BN patients, pathways towards recovery were interrupted and previously remitted patients showed re-exacerbation of binge eating. BN patients also reported severe COVID-19-related post-traumatic symptomatology, predicted by childhood trauma and insecure attachment.
Fernandez-Aranda et al. 2020 [77]	Barcelona (Spain), first two weeks of lockdown.	Telephone survey	32 EDs patients	Most of the patients showed enhanced worries over uncertainties, for the possible negative impact of the pandemic on their work and their treatment, and fear of contagion (for themselves or their loved ones). 38% reported impairments in EDs symptoms; 52% reported additional anxiety symptoms (4 of these patients explicitly reported that stress made it difficult for them to control emotional eating).
Nisticò et al., 2020 [88]	Milan (Italy) T0: April 2020 (during lockdown) T1: June 2020 (after lockdown)	Online questionnaire	T0: 59 EDs patients and 43 HC T1: 40 EDs patients (a subset of t0)	At T0, EDs patients, compared to HC, experienced a heightened fear of losing control over eating, more discomfort at seeing their own body, and spent more time thinking about their body during the lockdown than before. At T1, in EDs patients, post-traumatic symptomatology diminished with respect to the lockdown period, and patients reported feeling significantly better, although high levels of anxiety persisted.
Phillipou et al. 2020 [78]	Australia, April 2020	Online questionnaire (national survey)	5,469 participants, 180 of whom self-reported an eating disorder history.	Since the very beginning of the COVID-19 pandemic 64.5% of the EDs patients reported more food restriction; 35.5% increased binge eating; 18.9% increased purging; 47.3% increased exercising. On the other hand, a small portion of the sample also reported decreased restricting (8%) and binge eating (8%). EDs symptoms should be strictly monitored for potential long-term consequences.

AN: Anorexia Nervosa; BN: Bulimia Nervosa; Eds: Eating Disorders; HC: Healthy Controls.

Autism spectrum disorders

The diagnostic category of autism spectrum disorders (ASDs) refers to a wide variety of conditions, affecting both children and adults, sharing the common core of "persistent deficits in social communication and social interaction across multiple contexts"[53]. These conditions can be thought of as a continuum, ranging from a severe delay in cognitive, social, and emotional development, to where individuals show selective impairment in understanding and responding to social cues, such as the tendency to avoid eye contact and a struggle in picking up cues about social context and the intentions of others, but do not present intellectual disabilities or cognitive impairment (Intelligence Quotient >70)[90]. The current literature aims at investigating how the COVID-19 pandemic and the consequent social restrictions impact on children and adults with autism, and with their caregivers.

Children with ASDs

With respect to pediatric samples, a systematic review including children with and without ASDs recently showed that, during the pandemic, children with a pre-existing diagnosis of ASDs and attention deficit hyperactivity disorder (ADHD) had a high probability of their behavioral symptoms worsening, along with presenting anxiety, depression, irritability, boredom, inattention, and fear of COVID-19[91]. It was also reported that, over the last year, children with ASDs presented symptoms resembling PTSD, in terms of increased stereotypes, aggression, hypersensitivity, and disturbance of sleep patterns and appetite[92]. However, when considering the severity of ASDs symptoms, Lugo-Marin et al.[93] also found that individuals with ASDs Level 1 (DSM-5-based) scored significantly lower in a questionnaire investigating symptoms of withdrawal and depression after the lockdown started, compared to before. Since this scale mostly investigates shyness, withdrawal, and a preference for being alone, the authors hypothesized that the drastic decrease in social demands during the lockdown had played a major role in their findings. In other words, children and adolescents with ASDs Level 1 might have partially benefited from the social distancing measures.

With respect to therapeutic interventions, although recent studies endorsed the use of video consultations for the follow-up of children with ASDs[94], White and colleagues showed that, in their sample of 3,502 children with ASDs in the United States, the majority of them experienced significant, ongoing disruptions to their therapies during the pandemic, with a consequent worsening of ASD symptoms and a heightened family distress, as reported by patients' caregivers[95]. Along the same line, Mutluer and colleagues[92] revealed that 92% of their sample, consisting of 87 individuals with ASDs in Turkey, stopped receiving special education support during this period. The authors underlined

the urgent need to develop special distance learning services also for children with special educational needs, possibly involving professionals specialized in both ASDs and trauma, in order to efficiently address the trauma-related symptomatology that emerged in their sample of children with ASDs.

Adults with ASDs

As mentioned above, moving along the autism spectrum, individuals with different degrees of symptom severity can be found. There is little literature on adult individuals with a diagnosis of severe ASDs in the context of the COVID-19 pandemic. Brondino et al. investigated the response of a sample of 18 adults with ASDs who attended a day-care center in Lombardy to new strict social routines implemented in order to keep the service running even during the lockdown. They increased the time spent performing individual physical activity, split the initial laboratory group into smaller groups, and reduced non-essential transfers to other facilities[96]. Authors assessed the patients' daily level of irritability, lethargy, social withdrawal, stereotypic behavior, hyperactivity, and inappropriate speech, and compared their findings with pre-lockdown scores. Despite the restrictions, the scores were not higher than before. These results might suggest that, when new routines are gradually and carefully introduced, people with severe ASDs might be able to adapt to them[96].

Moreover, few studies investigated the psychological impact of the pandemic on adults with high functioning ASDs. On one hand, a general increase in symptoms of anxiety and depression was reported; adults with autism showed a greater increase in worries about their work, medications and food supply, and their own safety/security, along with an increase in stress related to their loss of routine[97]. In particular, Bal et al.[98] showed that, among a sample of 396 adults with ASDs, the areas of their lives that experienced the greatest impact from the pandemic were, in order: i) employment ii) school; and iii) social life. On the other hand, a decrease in stress levels related to reduced sensory and social overload was also found[93,97]. Lugo-Marin and colleagues found a general improvement in levels of psychopathology, investigated through the Symptoms-Checklist-90-Revised (SCL-90-R), when comparing the scores of adult individuals with ASDs during the lockdown to those collected before; this was especially true in young adults (18- 30 years old). Adults aged over 30 years apparently also benefited from the social distancing measures, as demonstrated by improved scores on the SCL-90-R "Interpersonal Sensitivity", ascale that refers to feelings of inferiority and inadequacy. Only anxiety symptoms showed no significant improvement during the lockdown[93]. In fact, as reported by Oomen et al., the need to constantly adjust one's own behaviors and routines due to continuous changes in the recommendations of the authorities led several adults with ASDs to experience high levels of anxiety and distress[97].

Consistent with these findings, in our clinical practice, we observed that patients with difficulties in social interaction (e.g., patients with social phobia) often reported an improvement in their psychological well-being in relation to the imposed lockdown. This observation led our research group to hypothesize that specific groups of individuals might be able to handle social distancing better than the general population[87]. This might be the case of individuals with ASDs without intellectual disabilities. For example, previous studies showed that patients with ASDs without intellectual disabilities perform better in environments where they can work alone with a high degree of autonomy in a clearly defined and intellectually challenging job. In contrast, work settings that are highly variable from day-to-day and require teamwork and interaction with colleagues are the most challenging to secure or maintain for individuals with this ASD[99]. Preliminary results of our research, involving a sample of individuals with ASDs without intellectual disabilities and a group of neurotypical adults as control group, showed that individuals with ASDs presented significantly higher levels of stress, anxiety and depression than neurotypical adults in the first two months of the COVID-19 lockdown in Italy. However, neurotypical adults reported a higher perceived change in lifestyle during the lockdown than ASD participants. Intriguingly, with respect to the control groups, ASD individuals reported feeling more comfortable during the lockdown period in relation to the social distancing measures adopted by the Italian authorities, and said they arrived at the end of their study or working day significantly less tired during the lockdown than they had the month before (Nisticò et al., submitted paper, 2020).Trying to identify risk and protective factors for individuals with ASDs, Bal and colleagues[98] found that autistic adults who were younger, female, had a mental health diagnosis before the pandemic, and who knew someone directly infected by COVID-19, reported a greater impact of the pandemic on their life, and a corresponding greater difficulty in of coping with it. Moreover, they found that greater psychological distress was predicted by the feeling of receiving little benefit from online counselling services. In fact, as in the pediatric field and in most aspects of healthcare, services of consultation and psychological support had to rapidly reorganize and were either cancelled (as reported by the 46% of individuals interviewed by Oomen et al.[97]) or switched to remote telecommunication. Investigating the efficacy of telecommunication, Adamou and colleagues[100] reported that, in their sample of 117 adults with ASDs and ADHD in the United Kingdom, although the users subjectively found remote telecommunication to be useful, effective, reliable and satisfactory, almost half of them stated a general preference for face-to-face consultations.

Somatic symptom and related disorders

Somatic symptoms and related disorders are characterized by an intense focus on physical (somatic) symptoms that causes significant distress and/or interferes with patients' daily functioning. The DSM-5 includes in this category: i) somatic symptom disorders; ii) illness anxiety disorders; iii) conversion disorders (also called functional neurological disorders, FNDs); iv) psychological factors affecting other medical conditions; and v) factitious disorders. Recent studies have shown that the economic impact of somatic symptom and related disorders on national health systems is very high, both because of the elevated number of investigations that patients undergo (the so-called "doctor shopping" phenomenon), and because of the level of disability caused by the disorders themselves, often leading to loss of employment and need for disability benefit payments[101]. In particular, FNDs are often encountered in neurological and neuropsychiatric practice[101]. They are characterized by the presence of neurological symptoms (e.g., motor, sensory or loss of consciousness) that cannot be explained by typical neurological diseases or other medical conditions, nevertheless determining clinically significant discomfort or impairment in patients' social and/or occupational functioning[53]. FNDs encompass different phenotypes, including functional movement disorders (FMDs), in which the critical symptom relates to movement (e.g., tremor, dystonia, paralysis, gait disorders), and psychogenic non-epileptic seizures (PNES), paroxysmal events resembling epileptic attacks, although not associated with abnormal electrical activity in the brain. Several issues concerning the impact of the COVID-19 pandemic and consequent lockdown on FNDs have been raised in the literature and these will be discussed here.

The psychological impact of the pandemic on patients with pre-existing FNDs

Few studies have investigated the state of general physical and mental health in patients with pre-existing FNDs during the first lockdown (March-June 2020)[102-104] (Table 11.4). With respect to functional neurological symptoms, between 11% and 34% of patients assessed in this period reported a worsening of their symptoms; between 54% and 61% of patients reported no change in the frequency and intensity of their symptoms, and between 12% and 28% of patients felt that their symptoms had even improved during the lockdown period. Overall, an increase in stress, in poor quality of sleep, and in symptoms of anxiety was reported, which, in some cases, was associated with functional symptoms deterioration[105] but not in all[103] (Table 11.4). In an attempt to explain the stability or even the improvement of FNDs symptoms during the COVID-19 pandemic, several hypotheses were proposed. On one hand, Delgado and colleagues suggested that these findings might be caused by reduced self-monitoring, a phenomenon thought to play a significant role in the pathophysiology

of FNDs. In other words, as in everyday life, FNDs symptoms decrease when patients are distracted. During the pandemic these symptoms remained stable or even improved since patients with FNDs diverted their attention from their body to the global health crisis. On the other hand, as mentioned above, our group recently hypothesized that specific populations of patients, such as those with difficulties in social interactions, comorbid anxiety, or alexithymic personality traits, might have benefited from the lockdown, since they did not have to deal with external factors (e.g., comparison with colleagues or social relationships)[105].

Table 11.4: Pre-existing FNDs and COVID-19

First Author, year	Site and dates	Methods	Participants	Main findings
Asadi-Pooya et al., 2021 [108]	Shiraz, Iran. 2008 - 2021	Review of electronic medical records	388 PNES	94% patients were diagnosed before and 6% patients during the pandemic. PNES patients diagnosed during the COVID-19 pandemic less frequently had generalized motor seizures and had higher seizure frequencies than patients diagnosed before the pandemic.
Delgado et al., 2020 [102]	Madrid, Spain	Online survey	41 FMD	22 patients (54%) reported no change in their FMD, 5 (12%) improved and 14 (34%) worsened during lockdown. General health condition was worse or much worse in 20 patients; 15 (37%) remained stable, and 6 (15%) improved. 50% of the patients reported increased anxiety, insomnia, and lower mood, but none of these variables was associated with FMD symptoms.
Fredwall et al., 2021 [113]	Columbus, OH USA, March - June 2020	Tele-medicine program for diagnosis and support	23 PNES children and adolescents	20 patients completed their visits. At the 3-month follow up, all but 2 patients reported improvement in event frequency.
Hull et al., 2021 [106]	Houston, Texas March – October 2020	Review of electronic medical records	45 FND patients	2020: 550 new patients were evaluated; 8.2% received a diagnosis of FMD. 2019: 665 new patients were evaluated: 5.1% were diagnosed with FMD.

Mahawish et al., 2020 [107]	New Zealand January - August 2020	Review of electronic medical records	22 FND	2020: 22 patients were admitted and diagnosed with FND of whom: 9 acknowledged recent psychological stressors; a third was 70 years of age or older. 2019: 5 patients were admitted and diagnosed with FND.
Nisticò et al., 2020 [103]	Italy May 2020	Online survey	8 PNES 10 FMD 18 healthy controls	Patients with FMD showed higher levels of stress, anxiety, and symptoms related to post-traumatic stress disorder than healthy controls, but patients with PNES did not. 11.1% of patients with FND reported their functional symptoms to have worsened or to be much worsened during the previous two months, 61.1% to have remained stable, and 27.8% to have improved or to be much improved. 27.8 % of patients with FND reported their general health to have worsened or to be much worsened during the previous two months, 38.9% to have remained stable, and 33.3% to have improved or much improved.
Valente et al., 2021 [104]	Brazil, April -June 2020	Structured interviewed conducted by phone.	54 PNES	28% reported increased frequency of PNES during the pandemic; PNES aggravation was predicted by higher levels of stress, anxiety, depression, and poor sleep quality.

FND: Functional Neurological Disorders; FMS: Functional Motor Disorders; PNES: Psychogenic Non-Epileptic Seizures.

The incidence of FNDs during the COVID-19 pandemic

Retrospective review of electronic medical records of major hospitals[106,107] showed a general increase in the incidence of FNDs in 2020. In an adult and pediatric tertiary-care movement disorders clinic in Houston,Texas, USA, out of 550 new patients who were referred for evaluation between March and October 2020, 45 (8.2%) received a diagnosis of FMDs of whom 75.6% were females. This percentage is considerably higher than that of the previous years (2019), when only 5.1% of the referred patients were diagnosed with FMDs[106]. A similar increase was registered on the other side of the globe; amongst the entire population who referred to the MidCentral District Health Board in New Zealand, 22 patients received a diagnosis of FNDs between January and August 2020. These numbers are remarkable, since in the same months in 2019 only 5 patients were diagnosed with the same conditions. The authors also reported that a third of these patients were over the age of 70, leading them to hypothesize that this incidence might reflect the increasing social isolation experienced by the elderly during the lockdown. Assessing the characteristics of patients diagnosed with PNES during the COVID-19 pandemic, Asadi-Pooya and

Farazdaghi[108] from the Shiraz University of Medical Sciences,Iran, found that the patients diagnosed with PNES during the pandemic showed less frequently generalized motor seizures and had higher seizure frequency than patients diagnosed before the pandemic.

Interestingly, a case report of Piscitelli and colleagues from Italy documented the case of a 39-year-old woman who presented functional tremor in her lower limb after being diagnosed with COVID-19 and being forced into quarantine (Table 11.5)[109]. During the neuropsychiatric examination, which confirmed the diagnosis of FMD, the patient recalled that she had previously experienced a similar sudden tremor in her legs while rock climbing. This led the authors to hypothesize that her FMD might be the expression of her inability to verbally describe her feeling of anxiety which was instead expressed by a physical symptom. Similar cases of somatic symptoms and related disorders in the context of the COVID-19 pandemic have been reported from around the world[110-112] and are further detailed in Table 11.5.

The efficacy of telemedicine and online counselling services for patients with FNDs

So far, only one study conducted in a United States clinic has investigated the efficacy of telemedicine in patients with FNDs during the pandemic. Fredwall and colleagues reported that, from March to June 2020, the Psychogenic Nonepileptic Events Clinic of their hospital switched from the typical in-person visits to a telemedicine format, including a series of video-calls with neurologists and psychologists[113] (Table 11.5). Comparing data collected in this period to previously published results of in-persons visits, the authors showed that: i) there were just as many referrals to their clinic during the pandemic as before, and the rate of patients who completed the cycle of visits was also similar; ii) after 3 months, patients seen by telemedicine had similar acceptance rates, and the rate of improvement in PNES frequency even increased. However, there was a decrease in connection to psychological counselling: only 63% of the telemedicine cohort was linked with counselling in comparison to the historical control of 73%, which might be due to additional limitations in access during the pandemic. Importantly, the authors noted that visits conducted only via phone (and not video-call) were visibly less effective in both communicating the diagnosis and facilitating its acceptance among the families. Overall, telemedicine (provided with a video-call) proved to be a valid alternative to in-person visits.

Table 11.5: FNDs and SSDs emerged during the COVID-19 pandemic

First author, Year	Site and dates	Age, biological sex	Presentation	Diagnosis	Authors' comment
Buselli et al. 2020 [110]	Pisa, Italy March – May 2020	50-year-old Female	The patient (a nurse) presented with a history of fatigue and persistent dysphonia. She had previously been infected with COVID-19, which lasted about 2 months with pulmonary and extrapulmonary symptoms but, at the assessment, her test for SARS-CoV-2 was negative. No organic alterations emerged at specialist 's examination.	Given the personal vulnerability to somatization, a fact which emerged from the anamnestic interview, she was diagnosed with psychogenetic dysphonia related to COVID-19.	The authors highlight the importance of medical follow-up and psychological support for patients who tested positive for COVID-19, in particular in high-risk categories such as health care workers.
Colizzi et al. 2020 [111]	Verona, Italy, March 2020	16-year-old male	The patient, already in psychological treatment for an emerging eating disorder, presented at the Emergency Department with symptoms compatible with COVID-19. Despite testing negative for the presence of SARS-CoV-2, the patient kept presenting with psychomotor agitation and aggressivity. He responded rapidly to a low dose of antipsychotic and an antidepressant.	Based on his medical history and current presentation, he was diagnosed with SSD.	The authors highlight the importance of differentially diagnosing a possible exacerbation of a pre-existing SSD, triggered by fear of being infected, also to prevent a further burden to the healthcare system.
Jawowroski et al. 2021 [112]	Shaare Zedek Medical Centre, Jerusalem, Israel. Spring 2020	17-year-old. female	The patient, initially admitted to the ER in a rush, happily claimed to have tried to infect herself with COVID-19 by using the same thermometer as an infected patient; no evidence on the hospital security camera footage in the ER to verify her claims were founded, nor did she show any symptom compatible with COVID-19.	She was diagnosed with factitious disorder with underlying alexithymia.	The authors hypothesized that her feigning of illness might have been motivated by an unconscious need for the emotional support, she would have received as a COVID-19 patient.

Piscitelli et al. 2020 [109]	Italy, March – May 2020	39-year-old. female	The patient (a nurse), with no history of psychiatric disorder, was infected with SARS-CoV-2 and, while in quarantine, developed a lower limb tremor with variable frequency and amplitude, with abnormal movements while sitting, walking and at rest. No tremor in the upper limbs or in the cephalic district emerged; neurological and instrumental examination were normal. She showed entrainment phenomenon and effect of distractibility on the intensity of movement disorder. After testing negative for COVID-19, tremor intensity and frequency decreased.	She was diagnosed with FMD.	Since the patient recalled that she had previously experienced a similar sudden tremor in her legs while rock climbing, the authors hypothesized that her FMD might be the expression of her inability to verbally describe her feeling of anxiety which were instead expressed by a physical symptom.

FND: Functional Neurological Disorders; FMS: Functional Motor Disorders; SSD: Somatic Symptoms Disorder.

Functional neurological symptoms and COVID-19 vaccinations

Kim and colleagues[114] recently published a paper commenting on the news reported by newspapers and circulating on social media that at least one patient received the diagnosis of Conversion Disorder after experiencing continuous movement of the trunk and limbs, along with walking difficulties, after receiving the first shot of COVID-19 vaccine. The authors reminded the readers that FNDs can actually be triggered by emotional and/or physical events, including surgical procedures and vaccinations, but these cannot be considered the direct cause of FNDs. In other words, the substances contained in the vaccine cannot cause FNDs [114].

In conclusion, during the first year of the COVID-19 pandemic, the incidence of FNDs significantly increased with respect to previous years. The majority of patients with pre-existing FNDs reported no change in the frequency or intensity of their symptoms, although a global increase in stress, poor quality of sleep and symptoms of anxiety was reported. Telemedicine appears to be a promising alternative to in-person initial consultation. In the near future, the efficacy of online counselling for psychological distress should be further investigated.

Take-home message

- The current COVID-19 pandemic is having a major impact on mental health and well-being, both in the general population and in patients with pre-existing psychiatric symptomatology.
- Strict lockdown measures, leading to disruption of individual physiological and social routine (i.e., less social support, altered sleeping and eating patterns, etc.) are associated with higher risk of worsening of and relapse of mood, eating and psychotic disorders.
- The high fear of contamination and reinforced cleansing habits are severe precipitating factors for obsessions and compulsions. As in previous epidemics, individuals with obsessive-compulsive disorders showed a significant clinical worsening during the COVID-19 pandemic, and must be considered at high risk of suicide.
- Individuals with difficulties in social interaction (such as adults with high functioning autism spectrum disorders) showed, on one hand, a general increase in symptoms of anxiety and depression but, on the other hand, a decrease in stress levels related to reduced sensory and social overload.
- With respect to previous years, in 2020, the incidence of somatic symptom disorders and functional neurological disorders significantly increased; this might be due to paying greater attention towards one's own body in the context of the pandemic.

References

1. Druss B. Addressing the COVID-19 Pandemic in Populations With Serious Mental Illness. *JAMA Psychiatry*. 2020;77:891-892.
2. Chatterjee S, Barikar C M, Mukherjee A. Impact of COVID-19 pandemic on pre-existing mental health problems. *Asian J Pyschiatr*. 2020;51:102071.
3. Rajkumar R. Bipolar disorder, COVID-19, and the risk of relapse. *Bipolar Disord*. 2020;22:640.
4. Yao H, Chen J, Xu Y. Patients with mental health disorders in the COVID-19 epidemic. *Lancet Psychiatry*. 2020;7:e21.
5. Van Rheenen T, Meyer D, Neill E, et al. Mental health status of individuals with a mood-disorder during the COVID-19 pandemic in Australia: Initial results from the COLLATE project. *J Affect Disord*. 2020;27:69-77.
6. Fiorillo A, Sampogna G, Giallonardo V, et al. Effects of the lockdown on the mental health of the general population during the COVID-19 pandemic in Italy: Results from the COMET collaborative network. *Eur Psychiatry*. 2020;63(1):e87.
7. Arnold J, Martinez C, Zavala J, et al. Investigating symptom domains of bipolar disorder for Spanish-speakers using the Bipolar Inventory of Symptoms Scale. *J Affect Disord*. 2016;205:239-244.
8. Nivoli A, Pacchiarotti I, Rosa A, et al. Gender differences in a cohort study of 604 bipolar patients: The role of predominant polarity. *J Affect Disord*. 2011;133:443-449.
9. Parker G, Fletcher K, Paterson A, et al. Gender differences in depression severity and symptoms across depressive sub-types. *J Affect Disord*. 2014;167:351-357.
10. Crowe M, Inder M, Swartz H, et al. Social rhythm therapy—A potentially translatable psychosocial intervention for bipolar disorder. *Bipolar Disorder*. 2020;22:121-127.
11. Liu S, Yang L, Zhang C, et al. Online mental health services in China during the COVID-19 outbreak. *Lancet Psychiatry*. 2020;7:e17-e18.
12. Bottai T, Biloa-Tang M, Christophe S, et al. [Thérapie interpersonnelle et aménagement des rythmes sociaux (TIPARS): du concept anglo-saxon à l'expérience française.] *Encephale*. 2010; 36:S206-S217.
13. Lopes MC, Boarati MA, Fu IL. Sleep disturbance in bipolar disorder: neuroglia and circadian rhythms. *Frontiers Psychiatry*. 2020;10:1021.
14. Xue S, Husain MI, Ortiz A, et al. COVID-19: Implications for bipolar disorder clinical care and research. *SAGE Open Med*. 2020;8:2050312120981178.
15. Yocum A, Zhai Y, McInnis M, Han P. Covid-19 pandemic and lockdown impacts: A description in a longitudinal study of bipolar disorder. *J Affect Disord*. 2021;282:1226-1233.
16. Frye M, Salloum I. Bipolar disorder and comorbid alcoholism: prevalence rate and treatment considerations. *Bipolar Disord*. 2006;8:677-685.
17. Evans D, Charney D, Lewis L, et al. Mood Disorders in the Medically Ill: Scientific

Review and Recommendations. *Biol Psychiatry*. 2005;58:175-189.

18. McIntyre RS, Konarski JZ, Soczynska JK, et al. Medical comorbidity in bipolar disorder: implications for functional outcomes and health service utilization. *Psychiatr Serv*. 2006;57:1140-1144.
19. Booth F, Laye M, Lees S, et al. Reduced physical activity and risk of chronic disease: the biology behind the consequences. *Eur J Appl Physiol*. 2008;102:381-390.
20. Lippi G, Henry B, Sanchis-Gomar F. Physical inactivity and cardiovascular disease at the time of coronavirus disease 2019 (COVID-19). *Eur J Prev Cardiol*. 2020;27:906-908.
21. Zaman S, MacIsaac A, Jennings G, et al. Cardiovascular disease and COVID-19: Australian and New Zealand consensus statement. *Med J Aust*. 2020;213:182-187.
22. Okusaga O, Yolken R, Langenberg P, et al. Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts. *J Affect Disord*. 2011;130:220-225.
23. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34:327-331.
24. Lazzerini M, Barbi E, Apicella A, et al. Delayed access or provision of care in Italy resulting from fear of COVID-19. *Lancet Child Adolesc Health*. 2020;4(5):e10-e11.
25. Mueser K, McGurk S. Schizophrenia. *Lancet*. 2004;363:2063-2072.
26. Averill P, Reas D, Shack A, et al. Is Schizoaffective Disorder a Stable Diagnostic Category: A Retrospective Examination. *Psychiatric Quarterly*. 2004;75:215-227.
27. Marneros A, Pillmann F, Haring A, et al. Is the psychopathology of acute and transient psychotic disorder different from schizophrenic and schizoaffective disorders? *Eur Psychiatry*. 2005;20:315-320.
28. Caponnetto P, Benenati A, Maglia M. Psychopathological Impact and Resilient Scenarios in Inpatient with Schizophrenia Spectrum Disorders Related to Covid Physical Distancing Policies: A Systematic Review. *Behav Sci*. 2021;11:49.
29. Shinn A, Viron M. Perspectives on the COVID-19 Pandemic and Individuals With Serious Mental Illness. *J Clin Psychiatry*. 2020;81:20com13412.
30. Brown E, Gray R, Lo Monaco S, et al. The potential impact of COVID-19 on psychosis: A rapid review of contemporary epidemic and pandemic research. *Schizophr Res*. 2020;222:79-87.
31. Esposito CM, D'Agostino A, Dell Osso B, et al. Impact of the first Covid-19 pandemic wave on first episode psychosis in Milan, Italy. *Psychiatry Res*. 2021. doi: 10.1016/j.psychres.2021.113802. [Preprint]
32. Khosoravi M. COVID-19 Pandemic: What are the Risks and Challenges for Schizophrenia? *Clin Schizophr Relat Psychoses*. 2020;14:58-59.
33. Anglin D, Galea S, Bachman P. Going Upstream to Advance Psychosis Prevention and Improve Public Health. *JAMA Psychiatry*. 2020;77:665-666.
34. Degnan A, Berry K, Sweet D, et al. Social networks and symptomatic and functional outcomes in schizophrenia: a systematic review and meta-analysis. *Soc Psychi-*

atry Psychiatr Epidemiol. 2018;53:873-888.

35. Townley G, Miller H, Kloos B. A little goes a long way: the impact of distal social support on community integration and recovery of individuals with psychiatric disabilities. *Am J Community Psychol.* 2013;52:84-96.
36. Hakulinen C, Webb RT, Pedersen CB, et al. Association Between Parental Income During Childhood and Risk of Schizophrenia Later in Life. *JAMA Psychiatry.* 2020;77:17-24.
37. Pinkham AE, Ackerman RA, Depp CA, et al. A Longitudinal Investigation of the Effects of the COVID-19 Pandemic on the Mental Health of Individuals with Pre-existing Severe Mental Illnesses. *Psychiatry Res.* 2020;294:113493.
38. Ma J, Hua T, Zeng K, et al. Influence of social isolation caused by coronavirus disease 2019 (COVID-19) on the psychological characteristics of hospitalized schizophrenia patients: a case-control study. *Transl Psychiatry.* 2020;10:411.
39. Quittkat H, Düsing R, Holtmann F, et al. Perceived Impact of Covid-19 Across Different Mental Disorders: A Study on Disorder-Specific Symptoms, Psychosocial Stress and Behavior. *Front Psychol.* 2020. doi: 10.3389/fpsyg.2020.586246. [Preprint].
40. Nikčević A, Marino C, Kolubinski D, et al. Modelling the contribution of the Big Five personality traits, health anxiety, and COVID-19 psychological distress to generalised anxiety and depressive symptoms during the COVID-19 pandemic. *J Affect Disord.* 2021;279:578-584.
41. Taylor S, Landry C, Paluszek M, et al. COVID stress syndrome: Concept, structure, and correlates. *Depress Anxiety.* 2020;37:706-714.
42. Taylor S, Landry C, Paluszek M, et al. Development and initial validation of the COVID Stress Scales. *J Anxiety Disord.* 2020;72:102232.
43. Gunnell D, Appleby L, Arensman E, et al. Suicide risk and prevention during the COVID-19 pandemic. *Lancet Psychiatry.* 2020;7:468-471.
44. Leaune E, Samuel M, Oh H, et al. Suicidal behaviors and ideation during emerging viral disease outbreaks before the COVID-19 pandemic: A systematic rapid review. *Prev Med.* 2020;141:106264.
45. Hao F, Tan W, Jiang L, et al. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. *Brain Behav Immun.* 2020;87:100-106.
46. Jefsen O, Rohde C, Nørremark B, Østergaard S. COVID-19-related self-harm and suicidality among individuals with mental disorders. *Acta Psychiatr Scand.* 2020;142:152-153.
47. Gobbi S, Płomecka MB, Ashraf Z, et al. Worsening of Preexisting Psychiatric Conditions During the COVID-19 Pandemic. *Front Psychiatry.* 2020;11:581426.
48. Chatterjee S, Barikar CM, Mukherjee A. Impact of COVID-19 pandemic on pre-existing mental health problems. *Asian J Pyschiatr.* 2020;51:102071.
49. Plunkett R, Costello S, McGovern M, et al. Impact of the COVID-19 pandemic

on patients with pre-existing anxiety disorders attending secondary care. *Ir J Psychol Med.* 2020;38(2):123-131.

50. Pan KY, Kok AAL, Eikelenboom M, et al. The mental health impact of the COVID-19 pandemic on people with and without depressive, anxiety, or obsessive-compulsive disorders: a longitudinal study of three Dutch case-control cohorts. *Lancet Psychiatry*. 2021;8:121-129.
51. Tundo A, Betro' S, Necci R. What Is the Impact of COVID-19 Pandemic on Patients with Pre-Existing Mood or Anxiety Disorder? An Observational Prospective Study. *Medicina*. 2021;57(4):304.
52. Asmundson G, Paluszek M, Landry C, et al. Do pre-existing anxiety-related and mood disorders differentially impact COVID-19 stress responses and coping? *J Anxiety Disord*. 2020. doi: 10.1016/j.janxdis.2020.102271. [Preprint]
53. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, 2013.
54. Bloch M, Landeros-Weisenberger A, Rosario M, et al. Meta-Analysis of the Symptom Structure of Obsessive-Compulsive Disorder. *FOCUS*. 2015;13:232-243.
55. Cordeiro T, Sharma M, Thennarasu K, Reddy Y. Symptom Dimensions in Obsessive-Compulsive Disorder and Obsessive Beliefs. *Indian J Psychol Med*. 2015;37:403-408.
56. Davide P, Andrea P, Martina O, et al. The impact of the COVID-19 pandemic on patients with OCD: Effects of contamination symptoms and remission state before the quarantine in a preliminary naturalistic study. *Psychiatry Res*. 2020. doi: 10.1016/j.psychres.2020.113213. [Preprint]
57. Tanir Y, Karayagmurlu A, Kaya İ, et al. Exacerbation of obsessive compulsive disorder symptoms in children and adolescents during COVID-19 pandemic. *Psychiatry Res*. 2020. doi: 10.1016/j.psychres.2020.113363. [Preprint]
58. Sulaimani M, Bagadood N. Implication of coronavirus pandemic on obsessive-compulsive-disorder symptoms. *Rev Environ Health*. 2020;36:1-8.
59. Ornell F, Braga D, Bavaresco D, et al. Obsessive-compulsive disorder reinforcement during the COVID-19 pandemic. *Trends Psychiatry Psychother*. 2021;43(2):81-84.
60. Tibi L, van Oppen P, van Balkom AJLM, et al. The relationship between cognitions and symptoms in obsessive-compulsive disorder. *J Affect Disord*. 2018;225:495-502.
61. Salkovskis P, Shafran R, Rachman S, Freeston M. Multiple pathways to inflated responsibility beliefs in obsessional problems: possible origins and implications for therapy and research. *Behav Res Ther*. 1999;37:1055-1072.
62. Wheaton M, Abramowitz J, Berman N, et al. The relationship between obsessive beliefs and symptom dimensions in obsessive-compulsive disorder. *Behav Res Ther*. 2010;48:949-954.
63. Banerjee D. The other side of COVID-19: Impact on obsessive compulsive disorder (OCD) and hoarding. *Psychiatry Res*. 2020. doi: 10.1016/j.psychres.2020.112966. [Preprint]

64. Shafran R, Coughtrey A, Whittal M. Recognising and addressing the impact of COVID-19 on obsessive-compulsive disorder. *Lancet Psychiatry*. 2020;7(7):570-572.

65. McKay D, Yang H, Elhai J, Asmundson G. Anxiety regarding contracting COVID-19 related to interoceptive anxiety sensations: The moderating role of disgust propensity and sensitivity. *J Anxiety Disord*. 2020. doi: 10.1016/janxdis.2020.102233. [Preprint]

66. Nissen J, Højgaard D, Thomsen P. The immediate effect of COVID-19 pandemic on children and adolescents with obsessive compulsive disorder. *BMC Psychiatry*. 2020;20:511.

67. Khosravani V, Aardema F, Samimi Ardestani S, et al. The impact of the coronavirus pandemic on specific symptom dimensions and severity in OCD: A comparison before and during COVID-19 in the context of stress responses. *J Obsessive Compuls Relat Disord*. 2021. doi: 10.1016/j.jocrd.2021.100626. [Preprint]

68. Benatti B, Albert U, Maina G, et al. What Happened to Patients With Obsessive Compulsive Disorder During the COVID-19 Pandemic? A Multicentre Report From Tertiary Clinics in Northern Italy. *Front Psychiatry*. 2020. doi: 10.3389/fpsyt.2020.00720. [Preprint]

69. Littman R, Naftalovich H, Huppert J, Kalanthroff E. Impact of COVID-19 on obsessive-compulsive disorder patients. *Psychiatry Clin Neurosci*. 2020;74(12):660-661.

70. Højgaard D, Duholm C, Nissen J, et al. Immediate reactions to the covid-19 pandemic in adults with obsessive-compulsive disorder: a self-report survey. *Nordic J Psychiatry*. 2021. doi: 10.1080/08039488.2021. [Preprint]

71. Fontenelle L, Miguel E. The impact of coronavirus (COVID-19) in the diagnosis and treatment of obsessive-compulsive disorder.*Depress Anxiety*. 2020;37(6):510-511.

72. Angelakis I, Gooding P, Tarrier N, Panagioti M. Suicidality in obsessive compulsive disorder (OCD): A systematic review and meta-analysis. *Clin Psychol Rev*. 2015. doi: 10.1016/j.cpr.2015.03.002. [Preprint]

73. De La Vega D, Giner L, Courtet P. Suicidality in Subjects With Anxiety or Obsessive-Compulsive and Related Disorders: Recent Advances. *Curr Psychiatry Rep*. 2018. doi: 10.1007/s11920-018-0885-z. [Preprint]

74. Mamun M, Sakib N, Gozal D, et al. The COVID-19 pandemic and serious psychological consequences in Bangladesh: A population-based nationwide study. *J Affect Disord*. 2020;279:462-472.

75. Fineberg N, Van Ameringen M, Drummond L, et al. How to manage obsessive-compulsive disorder (OCD) under COVID-19: A clinician's guide from the International College of Obsessive Compulsive Spectrum Disorders (ICOCS) and the Obsessive-Compulsive and Related Disorders Research Network (OCRN) of the European College of Neuropsychopharmacology. *ComprPsychiatry*. 2020. doi: 10.1016/j.comppsych.2020.152174. [Preprint]

76. Castellini G, Cassioli E, Rossi E, et al. The impact of COVID-19 epidemic on eating disorders: A longitudinal observation of pre versus post psychopathologi-

cal features in a sample of patients with eating disorders and a group of healthy controls. *Int J Eat Disord.* 2020;53:1855-1862.

77. Fernández-Aranda F, Casas M et al. COVID-19 and implications for eating disorders. *Eur Eat Disord Rev.* 2020;28(3):239-245.
78. Phillipou A, Meyer D, Neill E, et al. Eating and exercise behaviors in eating disorders and the general population during the COVID-19 pandemic in Australia: Initial results from the COLLATE project. *Asian J Pyschiatr.* 2020;53:1158-1165.
79. Cooper M, Reilly EE, Siegel JA, et al. Eating disorders during the COVID-19 pandemic: An overview of risks and recommendations for treatment and early intervention. *Eat Disord.* 2020. doi: 10.1080/10640266.2020.1790271. [Preprint].
80. Loopstra R. Vulnerability to food insecurity since the COVID-19 lockdown. *Food Foundation Report.* London: The Food Foundation, 2020.
81. Bove CF, Olson CM. Obesity in low-income rural women: qualitative insights about physical activity and eating patterns. *Women Health.* 2006;44(1):57-78.
82. Becker CB, Middlemass K, Taylor B, et al. Food insecurity and eating disorder pathology. *Int J Eat Disord.* 2017;50:1031-1040.
83. Lydecker JA, Grilo CM. Food insecurity and bulimia nervosa in the United States. *Int J Eat Disord.* 2019;52:735-739.
84. Rodgers RF, Lombardo C, Cerolini S, et al. The impact of the COVID-19 pandemic on eating disorder risk and symptoms. *Int J Eat Disord.* 2020;53:1166-1170.
85. Dalle Grave R, Calugi S, Marchesini G. Compulsive exercise to control shape or weight in eating disorders: Prevalence, associated features, and treatment outcome. *Compr Psychiatry.* 2008;49:346-352.
86. Heriseanu AI, Hay P, Corbit L, Touyz S. Grazing in adults with obesity and eating disorders: A systematic review of associated clinical features and meta-analysis of prevalence. *Clin Psychol Rev.* 2017;58:16-32.
87. Demartini B, Fortunato F, Nisticò V, et al. COVID-19 and mental health: the other side of the coin. *J Affect Disord.* 2020;282:695-696.
88. Nisticò V, Bertelli S, Tedesco R, et al. The psychological impact of COVID-19-related lockdown measures among a sample of Italian patients with eating disorders: a preliminary longitudinal study. *Eat Weight Disord.* 2021. doi: 10.1007/s40519-021-01137-0. [Preprint]
89. D'Agostino A, Demartini B, Cavallotti S, Gambini O. Mental health services in Italy during the COVID-19 outbreak. *Lancet Psychiatry.* 2020;7(5):385-387.
90. Ameli R, Courchesne E, Lincoln A, et al. Visual memory processes in high-functioning individuals with autism. *J Autism Dev Disord.* 1988;18:601-615.
91. Panda PK, Gupta J, Chowdhury SR, et al. Psychological and Behavioral Impact of Lockdown and Quarantine Measures for COVID-19 Pandemic on Children, Adolescents and Caregivers: A Systematic Review and Meta-Analysis. *J Trop Pediatr.* 2021. doi: 10.1093/tropej/fmaa122. [Preprint]
92. Mutluer T, Doenyas C, Genc HA. Behavioral Implications of the COVID-19 Process for Autism Spectrum Disorder, and Individuals' Comprehension of and Re-

actions to the Pandemic Conditions. *Front Psychiatry*. 2020;11:561882.

93. Lugo-Marín J, Gisbert-Gustemps L, Setien-Ramos I, et al. COVID-19 pandemic effects in people with Autism Spectrum Disorder and their caregivers: Evaluation of social distancing and lockdown impact on mental health and general status. *Res Autism Spectr Disord*. 2021. doi: 10.1016/j.rasd.2021.101757. [Preprint]
94. Dahiya AV, DeLucia E, McDonnell CG, Scarpa A. A systematic review of technological approaches for autism spectrum disorder assessment in children: Implications for the COVID-19 pandemic. *Res Dev Disabil*. 2021. doi: 10.1016/j.ridd.2021.103852. [Preprint]
95. White LC, Law JK, Daniels AM, et al. Brief report: impact of COVID-19 on individuals with ASD and their caregivers: a perspective from the SPARK cohort. *J Autism Dev Disord*. 2021. doi: 10.1007/s10803-020-04816-6. [Preprint]
96. Brondino N, Damiani S, Politi P. Effective strategies for managing COVID-19 emergency restrictions for adults with severe ASD in a daycare center in Italy. *Brain Sci*. 2020;10(7):436.
97. Oomen D, Nijhof AD, Wiersema JR. The psychological impact of the COVID-19 pandemic on adults with autism: a survey study across three countries. *Molecular Autism*. 2021;12:1-21.
98. Bal VH, Wilkinson E, White LC, et al. Early pandemic experiences of autistic adults: Predictors of psychological distress. *Autism Res*. 2021;14:1209-1219.
99. Hensel C, Vanzo R, Martin M, et al. Analytical and Clinical Validity Study of FirstStepDx PLUS: A Chromosomal Microarray Optimized for Patients with Neurodevelopmental Conditions. *PLoS Curr*. 2017. doi: 10.1371/currents.eogt.7d92ce775800ef3fbc72e3840fb1bc22. [Preprint]
100. Adamou M, Jones SL, Fullen T, et al. Remote assessment in adults with Autism or ADHD: A service user satisfaction survey. *PloS One*. 2021. doi: 10.1371/journal.pone.0249237. [Preprint]
101. Carson A, Lehn A, Epidemiology. *Handb Clin Neurol*. 2016;139:47-60.
102. Delgado C, Pareés I, Jiménez-Huete A, Kurtis MM. Impact of the Coronavirus Disease 2019 Pandemic on Functional Movement Disorders: Lessons From a Specialized Clinic. *Mov Disord*. 2020;35(10):1723-1724.
103. Nisticò V, Goeta D, Gambini O, Demartini B. The psychological impact of COVID-19 among a sample of Italian patients with functional neurological disorders: A preliminary study. *Parkinsonism Relat Disord*. 2020;78:79-81.
104. Valente KD, Alessi R, Baroni G, et al. The COVID-19 outbreak and PNES: The impact of a ubiquitously felt stressor. *Epilepsy Behav*. 2021;117:107852.
105. Demartini B, Nisticò V, Edwards MJ, et al. The pathophysiology of functional movement disorders. *Neurosci Biobehav Rev*. 2021;120:387-400.
106. Hull M, Parnes M, Jankovic J. Increased Incidence of Functional (Psychogenic) Movement Disorders in Children and Adults Amidst the COVID-19 Pandemic: A Cross-Sectional Study. *Neurology Clinical Practice*. 2021. doi: 10.1212/CPJ.0000000000001082. [Preprint]

107. Mahawish KM, Watson I. Functional stroke-like presentations in the time of COVID-19. *N Z Med J*. 2020;133(1525):123-126.

108. Asadi-Pooya AA, Farazdaghi M. Effects of the COVID-19 pandemic on characteristics of functional (psychogenic) seizures. *Psychosom Res*. 2021. doi: 10.1016/j.jpsychores.2021.110514. [Preprint]

109. Piscitelli D, Perin C, Tremolizzo L, et al. Functional movement disorders in a patient with COVID-19. *Neurol Sci*. 2020;41:2343-2344.

110. Buselli R, Corsi M, Necciari G, et al. Sudden and persistent dysphonia within the framework of COVID-19: The case report of a nurse. *Brain Behav Immun Health*. 2020. doi: 10.1016/j.bbih.2020.100160. [Preprint]

111. Colizzi M, Bortoletto R, Silvestri M, et al. Medically unexplained symptoms in the times of COVID-19 pandemic: A case-report. *Brain Behav Immun Health*. 2020. doi: 10.1016/j.bbih.2020.100073. [Preprint]

112. Jaworowski S, Abramov C, Malka M, Gropp C. Factitious disorder of a 17-year-old female during COVID-19 pandemic. *J Paediatr Child Health*. 2021. doi: 10.1111/jpc.15362. [Preprint]

113. Fredwall M, Terry D, Enciso L, et al. Short-term outcomes in pediatric and adolescent patients with psychogenic nonepileptic events seen by telemedicine during the COVID-19 pandemic. *Epilepsy Behav*. 2021. doi: 10.1016/j.yebeh.2020.107739. [Preprint]

114. Kim DD, Kung CS, Perez DL. Helping the Public Understand Adverse Events Associated with COVID-19 Vaccinations: Lessons Learned From Functional Neurological Disorder. *JAMA Neurol*. 2021;78(7):789-790.

115. Matsunaga H, Mukai K, Yamanishi K. The acute impact of the pandemic of COVID-19 on the phenomenological features in the full or partial remitted patients with obsessive-compulsive disorder (OCD). *Psychiatry Clin Neurosci*. 2020;74(10):565-566.

116. Prestia D, Pozza A, Olcese M, et al. The impact of the COVID-19 pandemic on patients with OCD: Effects of contamination symptoms and remission state before the quarantine in a preliminary naturalistic study. *Psychiatry Res*. 2020;291:113213.

Chapter 12. Cognitive dysfunction and rehabilitation

Michelangelo Dini, Alberto Priori, Roberta Ferrucci

Introduction

COVID-19 is a respiratory disease which ranges from mild to severe and presents a wide clinical spectrum. It is primarily characterized by pneumonia and respiratory distress but can be accompanied by numerous other complications. Of these, we will focus on examining the role and relevance of cognitive dysfunction. Cognitive dysfunction is typically defined as the presence of deficits which affect one or more cognitive functions: memory, language, executive functions, attention, visuospatial abilities, etc. Cognitive dysfunction can be classified according to the severity (subjective, mild cognitive impairment, dementia), type of onset (insidious, acute), and course (progressive, chronic, transient) of illness. The causes may be many and diverse in nature, as cognitive deficits can represent the clinical manifestation of underlying neurodegenerative processes, hypoxia, hyperinflammation, cerebrovascular events, or traumatic injury being the most commonly reported.

Evidence from previous coronavirus-related respiratory diseases, such as the SARS and MERS epidemics in 2002 and 2012, respectively, has alerted scientists all over the world about the neuroinvasive potential of SARS-CoV-2. For this reason, studies aimed at assessing the incidence of neurological symptoms have been conducted since the earliest phases of the pandemic. Additionally, the fact that severe COVID-19 requires admission to the intensive care unit (ICU) and, in the most severe cases, invasive mechanical ventilation and sedation, suggests that cognitive deficits might be linked to prolonged respiratory distress, which can cause hypoxia-related brain injury. Finally, other pathological processes, such as hyperinflammation and hypercoagulability, have also been proposed as possible causes of cognitive dysfunction in COVID-19.

Rationale for cognitive dysfunction in COVID-19

As outlined above, there are many different types of pathological mechanisms that could determine cognitive dysfunction in COVID-19 patients (Figure 12.1)[1]. Therefore, it is difficult to establish exactly whether cognitive dysfunction in COVID-19 is associated with direct viral neuronal injury, or whether it results from the presence of a severe systemic disorder characterized by a combination of sepsis, hypoxia, hyperpyrexia, hypercoagulability and critical illness[2,3].

During the SARS and MERS epidemics, studies reported the presence of neurological symptoms such as altered mental status in the acute phase[4] and cognitive complaints in recovered patients[5]. A metanalysis of 72 studies on both acute and post-acute neuropsychiatric effects of coronavirus infection[6] highlighted the presence of delirium in the acute phase, and impaired concentration and memory in the long-term (range of follow-up from 6 weeks to 39 months).

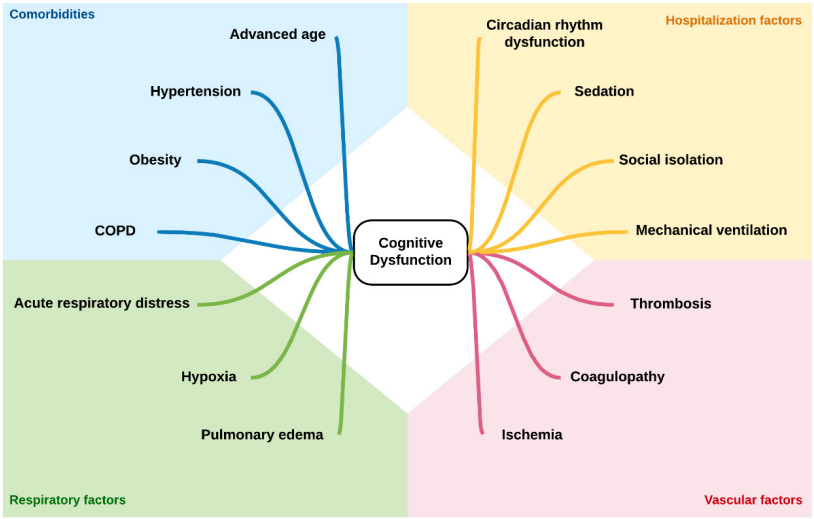
Evidence from studies on patients hospitalized for acute respiratory distress syndrome (ARDS) has highlighted a higher prevalence of delirium in intubated patients with ARDS (72%) compared to intubated patients without ARDS (53%), and non-intubated ICU patients (21%)[7]. With regards to long-term cognitive outcomes, a review of the literature has observed that there is a high prevalence of ARDS-related cognitive dysfunction and that prevalence correlates inversely with time since recovery, ranging from 70-100% in the post-acute phase and decreasing to 46-78% at 1-year follow-up, to 25-47% at two years, and to ~20% at five years[8]. The domains most affected were memory, attention, concentration, processing speed, and executive functioning[8–10]. Furthermore, studies have observed that hypoxia is associated with neuronal atrophy and subsequent ventricular enlargement, which are particularly associated with memory impairment[11,12], likely due to the demonstrated sensitivity of hippocampal neurons to hypoxic damage[13]. However, it should be noted that other authors have also found a strong association between hypoxia and executive functions deficits[10].

In addition to ARDS, it has been suggested that hyperinflammation plays a significant role in determining the severity and mortality of COVID-19[3,14]. Aberrant stress responses to acute infection have been linked to cognitive impairment through the activation of a systemic inflammation pathway associated with elevated interleukins serum levels[15], and may represent a distinct pathological pathway. This implies that the etiology of COVID-19-related acute cognitive dysfunction might be both inflammatory and non-inflammatory[16]. Indeed, evidence from *in vitro* studies shows that coronavirus-infected glial cells secrete large quantities of inflammatory factors (IL-6, IL-12, IL-15 and TNF-α)[17]. Last but not least, the cases of acute cerebrovascular disease observed in COVID-19 may themselves be linked to cytokine storm syndromes[3], but they could also result from increased D-dimer levels and severe platelet reduction[18].

Notably, risk factors associated with a higher risk of severe COVID-19 (advanced age, hypertension, obesity, diabetes)[19,20] are also associated with higher risk of cognitive impairment[21]. Finally, multiple factors related to hospital care for COVID-19 (i.e., prolonged mechanical ventilation, sedation, social isolation) are known to increase the risk of delirium[22,23], which in turn is recognized to be a potentially modifiable risk factor for long-term cognitive dysfunction[24,25].

For these reasons, clinicians should be particularly watchful for cognitive dysfunction in hospitalized COVID-19 patients, both during the acute phase and in the long term.

Figure 12.1: Factors contributing to long-term cognitive dysfunction in COVID-19 survivors



COPD: Chronic Obstructive Pulmonary Disease.

Cognitive dysfunction in COVID-19: the state of the art

Acute cognitive impairment

Evidence regarding the presence of cognitive impairment during the acute clinical phase of COVID-19 was provided as early as March 2020 by Chen et al.[26] who reported the presence of delirium in 26 of 274 (9%) patients admitted for COVID-19. Notably, they also observed that the prevalence of delirium was much higher in patients who later died (22%) compared to those who recovered (1%). Another study[27] found that, as of February 2020, 16 of 214 (7.5%) patients admitted to hospital for COVID-19 manifested impaired consciousness. This study also confirmed that the presence of impaired consciousness was associated with a greater severity of illness, as the prevalence was significantly higher in patients

with severe COVID-19 compared to other patients (14.8% vs. 24%, $p < 0.001$)[27]. Some authors have noted that the observed percentages may underestimate the actual incidence of acute cognitive dysfunction, since the main clinical focus during this period of crisis lay in pressing organizational issues (i.e., shortages of personal protective equipment, prioritization of limited ventilation options), which may have resulted in a reduction in resources allocated to delirium prevention and management[22].

Between February and April 2020, as the epicenter of the COVID-19 pandemic began shifting towards Europe, neurologists became ever more aware of the incidence of neurological manifestations of COVID-19. In April 2020, the European Academy of Neurology (EAN) core COVID-19 Task Force[28] posted a survey asking clinicians to report the prevalence of neurological symptoms in COVID-19 patients. They collected responses from 2,343 clinicians (82% of which were neurologists) who reported the presence of impaired consciousness (29.3% of patients), psychomotor agitation (26.7%), encephalopathy (21.3%), and cerebrovascular disease (21.0%)[28]. During the same period, Helms et al.[29] reported the results of an observational study on a series of consecutive COVID-19 patients hospitalized in the ICU for ARDS. Among other neurological symptoms, the authors observed the presence of a dysexecutive syndrome, characterized by disorientation, inattention, and poorly organized behavioral response to commands, in over one-third of patients (14/39; 36%)[29].

In conclusion, according to studies published so far, the clinical profile of cognitive dysfunction in COVID-19 patients during the acute phase appears to be characterized primarily by the presence of delirium and dysexecutive syndromes. (For a more detailed discussion of delirium in COVID-19, please see the dedicated chapter.) However, to the best of our knowledge, there have been no reports of the presence of milder and more specific cognitive deficits in the acute phase of COVID-19 (i.e., during hospitalization) in the scientific literature. While there are many brief neuropsychological tools designed to rapidly assess a broad range of cognitive functions at the bedside (Mini-Mental State Examination – MMSE[30], Montreal Cognitive Assessment – MoCA[31], Frontal Assessment Battery – FAB[32], to cite some of the most widely used), several factors would have rendered their use challenging and often unfeasible. One of these is the fact that hospitals faced enormous pressure to manage a large influx of critical and infectious patients, and therefore had to prioritize pressing clinical concerns, leaving aside all those assessments that were not urgently required in order to save patients' lives. Furthermore, other environmental, structural, and organizational limitations could have made the evaluation impossible even for patients who were not being treated in the ICU (busy, noisy wards, impossibility of moving patients, mandatory use of personal protective equipment that made verbal communication difficult, etc.). For these reasons, studies that have performed formal neuropsychological assessment in COVID-19 patients have done so exclusively in the post-acute phase.

Post-acute cognitive impairment

The ongoing COVID-19 pandemic continues to affect an increasing number of people worldwide. Thanks to the advances in the clinical management of acute symptoms, there has been a parallel increase in the numbers of patients who have recovered, who nevertheless often experience persisting symptoms. This so-called "Long-COVID" syndrome is often characterized by physical symptoms (fatigue, joint and bone pain), behavioral alterations (anxiety, insomnia), and, crucially, neurological symptoms (headache, paresthesia, cognitive impairment)[33,34]. Therefore, during the course of the pandemic, researchers have begun studying the cognitive outcomes associated with COVID-19 in order to establish, not only the prevalence and quality of these deficits, but also the presence of relevant clinical, physiological, and pathological associations.

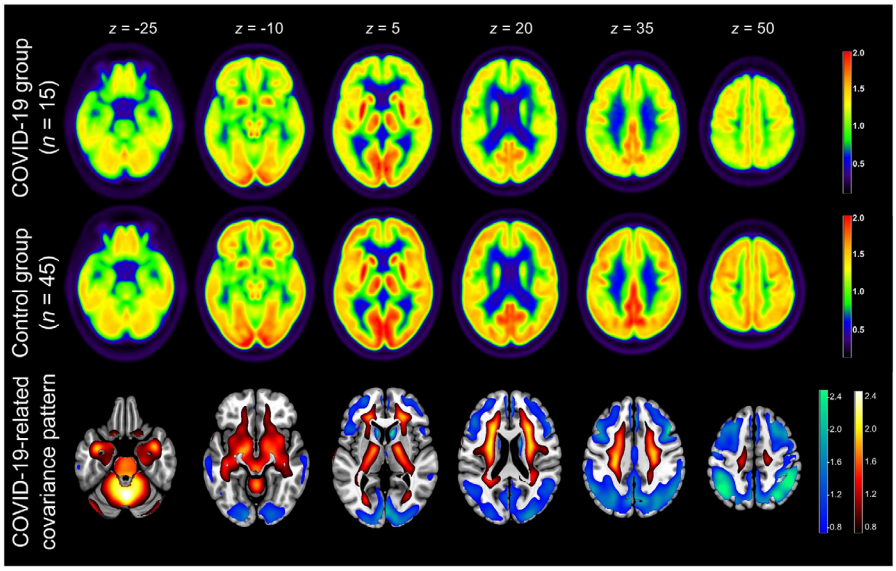
One of the first studies to report the presence of cognitive deficits following recovery from COVID-19 symptoms was conducted by Zhou et al.[35]. They observed that, between two and three weeks after clinical recovery, patients exhibited slower reaction times and performed worse in a test of continuous and selective attention compared to healthy controls. Interestingly, the authors also found a positive correlation between C-reactive protein (CRP) levels and reaction times; higher CRP levels correlated with slower reaction times[35]. Researchers in Spain[36] performed a complete neuropsychological assessment of 35 patients who recovered from COVID-19 between April and June 2020 (aged 24-60 years; mean age: 47.6±8.9 years; 19 females). Of these 35 patients, 21 (60%) had required oxygen and 7 (20%) had required admission to the ICU; the neuropsychological assessment was conducted between two and five weeks after clinical recovery. The study found deficits of memory, attention and semantic fluency in 5.7%, deficits of working memory and mental flexibility in 8.6%, and phonemic fluency deficits in 11.4%. The authors also observed that patients who had required oxygen therapy (n = 21) had lower scores in memory, attention, and executive functions, compared to other patients (n = 14)[36].

We assessed the presence of cognitive dysfunction in recovered COVID-19 patients at approximately five months from hospital discharge, by performing a complete neuropsychological assessment of 38 patients (aged 22-74 years;mean age: 53.45±12.64 years; 11 females)[37]. We found that 60.5% of our sample had deficits in at least one cognitive test, with attention and processing speed being the most affected domains (42.1% of patients). However, we also observed a significant prevalence of both verbal and visuospatial long-term memory deficits (26.3% and 18.4% of patients, respectively)[37]. Interestingly, patients who suffered from ARDS showed significantly lower scores in tests of verbal memory, and there was a positive correlation between PaO_2/FiO_2 levels and verbal memory performance. After recruiting more patients (n = 77), we observed a general stability of the cognitive profile, with an increase in the prevalence of memory deficits, likely due to the fact that we also

recruited patients who had required NIV and intubation, which confirms the link between memory deficits and ARDS (M Dini et al., 2021, unpublished data).

Other studies have assessed cognitive dysfunction in patients who have recovered from COVID-19 (see Table 12.1 for a summary). Notably, Hosp et al.[38] studied 29 patients (mean age: 65.2±14.4 years; 11 females) in the subacute phase (i.e., around one month after symptom onset) and found impaired global cognition in 18/26 patients (69%), as seen by MoCA scores <26; cognitive dysfunction was confirmed in 15 patients via detailed neuropsychological testing. The authors also performed ^{18}FDG PET scans on patients who had presented with at least 2 neurological symptoms, revealing a pattern of predominant frontoparietal hypometabolism in 10/15 (66%) patients, confirmed by comparison with a control sample via voxel-wise principal components analysis (Figure 12.2), which showed a positive correlation ($R^2 = 0.62$) with MoCA scores. Additionally, post-mortem assessment of a patient deceased for extracerebral causes revealed the presence of pronounced microgliosis with absence of neuroinflammation[38].

Figure 12.2: Result of 18FDG PET group analysis



Top and middle row: Transaxial sections of group averaged and spatially normalized ^{18}FDG PET scans in patients with COVID-19 and healthy controls. *Bottom row*: COVID-19-related spatial co-variance pattern of cerebral glucose metabolism constructed by Principal component analysis of the aforementioned groups. Reproduced from [38] with permission.

Table 12.1: Summary of data from studies on post-acute cognitive dysfunction in COVID-19 patients

Authors	Sample size	Demographic characteristics	Clinical characteristics	Illness - assessment delta	Tests used	Results
Almenia et al.[36]	35	Mean age = 47.6 ± 8.9 M/F = 16/19	60% required O_2, 20% ICU care	2-5 weeks	TAVEC, Visual Reproduction of the WMS- IV, Digit span, Letter and Numbers, TMT-A and -B, SDMT, Stroop, Phonemic and Semantic fluency, BNT	T-score < 30 in memory domains, attention and semantic fluency 5.7%, in working memory and mental flexibility (8.6%) and in phonetic fluency (11.4%)
Zhou et al.[27]	29 patients - 29 controls	Mean age = 47 ± 10.54 M/F = 18/11 - Mean age = 42.48 ± 6.94 M/F = 12/17	n/a	2-3 weeks	TMT, SCT, CPT, Digit span	Patients with COVID-19 scored lower in the correct number of the second and third parts of CPT, they also scored higher in the missing number of the third part of CPT (all $p < 0.05$).
Ferrucci et al.[37]	38	Mean age = 53.45 ± 12.64 M/F = 27/11	23.7% = no O_2 76.3% = low-flow O_2	5 months	MoCA, Rao's Brief Repeatable Battery	60.5% had at least one deficit, 42.1% had processing speed and attention deficits, 26.3% had long-term verbal memory deficits. ARDS was associated with worse verbal memory performance.
Hosp et al.[38]	29	Mean age = 65.2 ± 14.4 M/F = 18/11	10% = endotracheal intubation, 7% = NIV	1 month	MoCA, HV-LT-R, TMT-A and -B, Stroop test, Digit span, SDMT, verbal fluences	MoCA performance was impaired in 18/26 patients (mean score 21.8/30)
Beaud et al.[39]	13	Mean age = 64.8 M/F = 10/3	all received mechanical ventilation	5-6 days	MoCA, FAB	MoCA= normal cognitive performances in 4 patients, mild deficits in 4 and moderate to severe deficits in 5. FAB= executive dysfunction in 8 patients.
Miskowiak et al.[40]	29 patients - 100 controls	Mean age = 56.2 ± 10.6; M/F = 17/12 - Mean age = 56 ± 6.9 M/F = 41/59	n/a	3-4 months	SCIP TMT-B	Cognitive impairment ranged from 59% to 65% depending on the applied cut-off, with verbal learning and executive functions being most affected

Méndez et al.[41]	179	Median age = 57 M/F = 105/74	49.7% = no O_2, 11.2% = nasal cannula 21.2% venturi mask 4.5% = NIV 12.8% = intubation	4 months	Immediate, and delayed memory subtests from the SCIP, animal naming test (ANT), Digit Span backward	58.7% of patients had neurocognitive impairment in at least one function. Immediate verbal memory and learning = 38%, delayed verbal memory = 11.8%, verbal fluency = 34.6%, working memory = 6.1%
Blazhenets et al.[42]	8	Mean age = 66 ± 14.23 M/F = 6/2	n/a	T1= subacute T2= 6 months	MoCA	MoCA (mean ± SD) = 19.1 ± 4.5 at the subacute stage, 23.4 ± 3.6 at 6 months. 5/8 patients remained below the normative threshold (<26/30).
Ortelli et al.[43]	12 patients 12 healthy controls (HC)	Mean age = 67 ± 9.6 M/F = 10/2 Mean age = 64.3 ± 10.5 M/F = 8/4	n/a	2-3 months	MoCA, FAB	Significantly poorer MoCA and FAB scores in patients compared to HC ($p < 0.001$).
Mattioli et al.[44]	120 COVID+ healthcare workers - 30 healthy healthcare workers	Mean age = 47.86 M/F = 30/90 - Mean age = 45.73 M/F = 8/22	118 = no O_2 1 = NIV 1 = intubation	4 months	MMSE, COWA, CVLT, TEA attention test, TOL	At least 1 impaired test: 30% (COVID-19 subjects) vs. 23.3% (non-COVID subjects). There was no statistical difference in mean scores of all the neuropsychological tests between COVID-19 and non-COVID-19 subjects
Cristillo et al.[45]	101	Age = 63.62 ± 12.9 M/F = 73/28	18 = no O_2, 68 = low-flow, 13 = NIV, 2 = intubation	6 months	MoCA	Patients with hyposmia exhibited lower MoCA score (23.2 ± 3.4 vs. 25.7 ± 2.5)

ARDS: acute respiratory distress syndrome; BNT: Boston Naming Test; COWA: Controlled Oral Word Association by categories; CPT: Continuous Performance Test; CVLT: California Verbal Learning Test; FAB: Frontal Assessment Battery; HVLT-R: Hopkins Verbal Learning Test Revised; ICU: intensive care unit; MMSE: Mini-mental State Examination; MoCA: Montreal Cognitive Assessment; NIV: Non-invasive ventilation; SCIP: Screen for Cognitive Impairment in Psychiatry; SCT: Sign Coding Test ; SDMT: Symbol Digit Modalities Test; TAVEC: Test de Aprendizaje Verbal Espana-Complutense; TMT: Trail-making Test; TOL: Tower of London test; WMS-IV: Wechsler Memory Scale –IV.

The authors conducted a follow-up study[42], repeating[18] FDG PET scans in 8 patients after six months, and observed a significant reduction in the initial pattern of frontoparietal hypometabolism, as well as an increase in temporal cortical ^{18}FDG uptake, compared to the acute phase; these results were accompanied by a significant improvement in cognition. They remarked that, although an improvement can be observed from neurophysiological data, some patients still exhibit residual impairment at six months, which is confirmed by the fact that 5/8 (62.5%) obtained MoCA scores below the normative cut-off[42]. The studies discussed so far are characterized by small samples, mainly due to the limitations imposed by the pandemic. More recent studies, however, have managed to collect data from larger samples. Méndez et al.[41], for example, studied cognitive dysfunction in a sample of 179 patients at four months after clinical recovery. Patients (median age: 57 years; 105 males) had been hospitalized for COVID-19 between March and April 2020 and had required different levels of oxygen therapy (no support: 49.7%; nasal cannula: 11.2%; venturi mask: 21.2%; NIV: 4.5%; mechanical ventilation: 12.8%). The authors found that 58.7% of patients had impairment in at least one domain, and that the most frequently impaired functions were immediate verbal memory and learning (38%), and verbal fluency (34.6%), while they found a lower prevalence of delayed verbal memory (11.8%) and working memory (6.1%) deficits. Delirium during hospitalization occurred in 8 (4.5%) patients, and was associated with an increased risk of cognitive dysfunction (OR [95%CI] = 4.05 [1.03 – 16.4])[41].

Another large sample of patients was assessed by Cristillo et al.[45] who studied a sample of 101 recovered patients at six months after discharge. Eighteen patients required no oxygen therapy, 68 required low-flow oxygen therapy, 13 required NIV oxygen therapy, while only 2 required orotracheal intubation. The authors focused on the association between hyposmia, dysgeusia and cognitive dysfunction, observing that patients who reported hyposmia at six months also obtained lower MoCA scores (23.2 ± 3.4 vs. 25.7 ± 2.4, $p < 0.001$). There was no association between hyposmia and severity of the disease, which suggests that the long-term cognitive dysfunction associated with COVID-19 might also have a non-respiratory component.

Mattioli et al.[44] conducted a study in which they assessed 120 healthcare workers who had had mild-moderate COVID-19 and 30 healthy controls, in order to assess cognitive dysfunction at four months from the diagnosis of COVID-19. The authors found that 30% of COVID-19 patients had at least one cognitive deficit at four months compared to controls (23%), although this difference was not significant. Notably, of the 120 patients, only 2 had required oxygen therapy (one NIV and one intubation); therefore, this sample is characterized by significantly milder disease severity compared to the studies discussed so far.

Methodological and practical considerations

Some key limitations need to be considered when interpreting the results of the studies which have been discussed so far. First and foremost, there is considerable variability in terms of sample size, with most studies characterized by small samples ($n < 40$). Additionally, most studies had an unbalanced males/female ratio, with male patients generally representing the majority of the sample, mainly because COVID-19 has been shown to affect males more severely[46] this results in higher hospitalization rates. The only exceptions were Zhou et al.[35], who studied 16 males and 19 females, and Almeria et al.[36] who studied 30 males and 90 females. There is also significant variability with regards to age as some studies assessed patients who were, on average, under 50 years of age[35,36,44], some assessed patients aged 50 – 60 years[37,40,41], and others focused on patients over 60 years of age[38,39,42,43,45]. Crucially, several studies differed in terms of the clinical characteristics of patients. Namely, some focused on patients who had recovered from severe COVID-19 (i.e., had required ICU treatment and mechanical ventilation)[39], while others focused on patients with milder illness severity[44]. The majority of studies, however, evaluated patient populations characterized by varying disease severity[36,37,41,45]. Crucially, some studies did not report the type of oxygen therapy patients received[35,40,43].

In terms of experimental design, most studies are observational in nature as they lack a control sample, and therefore they do not allow definitive conclusion regarding the role of COVID-19 on the observed cognitive dysfunction to be reached. Some conclusions may be drawn by comparing the performance of recovered patients with data from published normative studies relative to the various neuropsychological batteries and tests; this can be done either by calculating z-scores, or by categorizing patients based on published normative cutoffs. Another important methodological limitation is the fact that each study used different neuropsychological assessment batteries, which complicates the interpretation of results. Some studies administered only global assessment batteries (MoCA, FAB)[39,42,43,45] or a very limited selection of individual tests[35,40]gender- and education-matched healthy controls were also recruited. The cognitive functions of all subjects were evaluated by the iPad-based online neuropsychological tests, including the Trail Making Test (TMT, while others performed a more detailed assessment[36–38,44]. This, in addition to the fact that normative data differ across nationalities, language, and ethnicities, is likely to have contributed to the heterogeneity of the results. In conclusion, while rapid global neuropsychological tests (MoCA, MMSE, and FAB) should be considered for use during the acute phase, post-acute cognitive evaluation should be conducted using specific tests for the different cognitive domains in order to achieve greater sensitivity and to better characterize the qualitative profile of cognitive dysfunction.

Preliminary results of our study indicate that a MoCA score ≤ 25.50 at five months from clinical recovery predicted the presence of persistent cognitive

impairment (defined by the presence of deficits in at least two neuropsychological tests) at one year (sensitivity: 70.6%; scpecificity: 62.9%). Clinicians should be alerted to the risk of cognitive impairment not only when faced with patients falling below the established cut-offs, but also when observing patients who obtain borderline normal scores, since more detailed neuropsychological assessments might uncover impairment of specific cognitive domains.

Cognitive dysfunction at 1-year

As more than a year has now passed since the first peak of the pandemic, we should aim to assess the long-term course of cognitive dysfunction in recovered COVID-19 patients to establish first and foremost whether the observed deficits do persist in the long term, and secondly, whether specific patterns emerge (i.e., whether certain domains improve faster than others).

Following up on our first study[37], we recruited more patients and repeated the neuropsychological assessment at one year from hospital discharge in order to try and provide an answer to the questions outlined above. Preliminary data obtained from follow-up assessments (n: 52, T1: 5 months, T2: 12 months) highlight that the majority of patients show an improvement in all tests as time progresses, but it should be noted that a percentage of patients still exhibit cognitive deficits at one year from hospital discharge (Dini et al., unpublished data).

Cognitive rehabilitation

Considering what has been discussed so far, it is evident that cognitive rehabilitation must be included in multidisciplinary rehabilitation programs designed to improve the functional outcome of recovered COVID-19 patients[47,48]. As of today, however, few studies have assessed the effects of different cognitive rehabilitation programs in COVID-19.

An observational study[49] found that post-acute 3-week multidisciplinary rehabilitation improved respiratory, motor, and functional outcomes. Even though 29% of patients had cognitive deficits before enrolment, the authors did not report the results on cognitive functioning. Another study[50] on the effects of 6-week physical and educational rehabilitation interventions found that MoCA score significantly improved post treatment. However, since the study did not include formal cognitive rehabilitation, and did not include a control sample, it is difficult to say whether this improvement resulted from the rehabilitation intervention or from a spontaneous recovery of function. A recent study[51] assessing the effects of inpatient multidisciplinary rehabilitation interventions in patients who had recovered from COVID-19 who had required ICU treatment found improvements in cognition and speech, but also noted that a significant percentage of patients still exhibited deficits of attention, memory, and problem solving.

Given the ever-increasing number of recovered patients worldwide, rehabilitative interventions will play a significant role in determining the functional impact of the ongoing pandemic. As cognitive dysfunction represents a common symptom of the so-called "Long-COVID" syndrome, cognitive rehabilitation should be included in multidisciplinaruy rehabilitation programs. Finally, as subjective cognitive deficits can also significantly affect quality of life[52] and tend to be associated to psychological distress, anxiety and depression[53], rehabilitation programs may also benefit from the inclusion of techniques aimed at reducing psychological distress (e.g., mindfulness-based stress reduction [MBSR]).

Conclusions

Cognitive dysfunction can be observed not only during the acute phase of COVID-19, in the form of delirium and dysexecutive syndrome, but also in the post-acute phase of the disease, which is characterized by mild-moderate deficits. The qualitative profile of cognitive dysfunction is heterogeneous, probably as a result of differences between the various studies (socio-demographic variables, clinical variables, methodological differences) which are outlined above. Nevertheless, interesting results have been published linking the severity of cognitive dysfunction in the months following hospital discharge to clinical factors such as presence of ARDS[37], hyposmia[45], and inflammation[35]. It is likely that the cognitive functioning of these patients might improve as time progresses, and preliminary data seem to indicate that this is, indeed, the case. However, it is paramount that both clinicians and researchers be on the alert for the presence of cognitive dysfunction in people who had COVID-19, as it could represent a key factor in determining the functional outcome of a large number of patients worldwide.

Take-home message

- Cognitive dysfunction is common in patients with COVID-19.
- Cognitive deficits can be observed not only in the acute phase, but also in the months following recovery.
- ARDS, hyposmia/dysgeusia and hyperinflammation have all been linked with an increased risk of cognitive dysfunction.
- Cognitive deficits tend to be most severe in the first months from clinical recovery, and improve gradually in the long-term.
- Brief screening neuropsychological tests (MoCA, MMSE, FAB) may be unable to detect mild cognitive dysfunction in COVID-19 patients.

References

1. Baker HA, Safavynia SA, Evered LA. The 'third wave': impending cognitive and functional decline in COVID-19 survivors. *Br J Anaesth* [Internet] 2021;126(1):44–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33187638
2. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. *JAMA Neurol* [Internet] 2020. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32469387
3. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression [Internet]. *Lancet*. 2020;395(10229):1033–4. Available from: https://www.
4. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: A single-center experience in Saudi Arabia. *Int J Infect Dis* [Internet] 2014;29:301–6. Available from: http://dx.doi.org/10.1016/j.ijid.2014.09.003
5. Sheng B, Cheng SKW, Kwok KL, Ho LL, Chan ELY. The effects of disease severity, use of corticosteroids and social factors on neuropsychiatric complaints in severe acute respiratory syndrome (SARS) patients at acute and convalescent phases. *Eur Psychiatry* 2005;20(3):236–42.
6. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry* 2020;
7. Hsieh SJ, Soto GJ, Hope AA, Ponea A, Gong MN. The association between acute respiratory distress syndrome, delirium, and in-hospital mortality in intensive care unit patients. *Am J Respir Crit Care Med* 2015;191(1):71–8.
8. Wilcox EM, Brummel NE, Archer K, Wesley Ely E, Jackson JC, Hopkins RO. Cognitive dysfunction in ICU patients: Risk factors, predictors, and rehabilitation interventions. *Crit Care Med* 2013;41(9 SUPPL.1):81–98.
9. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-Lohr V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* [Internet] 1999;160(1):50–6. Available from: www.atsjournals.org
10. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: Long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* [Internet] 2012;185(12):1307–15. Available from: /pmc/articles/PMC3381234/?report=abstract
11. Herridge MS, Moss M, Hough CL, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers [Internet]. *Intensive Care Med*. 2016 [cited 2020 Oct 13];42(5):725–38. Available from: https://link.springer.com/article/10.1007/s00134-016-4321-8

12. Hopkins RO, Gale SD, Weaver LK. Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. *Brain Inj* [Internet] 2006;20(3):263–71. Available from: https://pubmed.ncbi.nlm.nih.gov/16537268/

13. Cervós-Navarro J, Sampaolo S, Hamdorf G. Brain changes in experimental chronic hypoxia. *Exp Pathol* 1991;42(4):205–12.

14. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* [Internet] 2020;46(5):846–8. Available from: https://doi.org/10.1007/s00134-020-05991-x

15. MacLullich AMJ, Ferguson KJ, Miller T, de Rooij SEJA, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. *J Psychosom Res* 2008;65(3):229–38.

16. Sasannejad C, Ely EW, Lahiri S. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care* 2019;23(1):352.

17. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci* 2018;12(October):1–15.

18. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol* [Internet] 2020;92(6):568–76. Available from: http://dx.doi.org/10.1002/jmv.25748

19. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* [Internet] 2020;395(10239):1763–70. Available from: http://dx.doi.org/10.1016/S0140-6736(20)31189-2

20. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with. Morb Mortal Wkly Report, US Dep Heal Hum Serv Dis Control Prev [Internet] 2020;69(15):458–64. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm

21. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment-A review of the evidence and causal mechanisms. *Ageing Res Rev* [Internet] 2013;12(4):840–51. Available from: http://dx.doi.org/10.1016/j.arr.2013.06.004

22. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care* [Internet] 2020;24(1):176. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03072-5

23. Riordan P, Stika M, Goldberg J, Drzewiecki M. COVID-19 and clinical neuropsychology: A review of neuropsychological literature on acute and chronic pulmonary disease [Internet]. *Clin. Neuropsychol.* 2020. Available from: https://www.tandfonline.com/doi/abs/10.1080/13854046.2020.1810325

24. Hopkins RO, Jackson JC. Assessing neurocognitive outcomes after critical illness: Are delirium and long-term cognitive impairments related? [Internet]. *Curr. Opin.*

Crit. Care. 2006; 12(5):388–94. Available from: https://pubmed.ncbi.nlm.nih.gov/16943714/

25. Pandharipande PP, Girard TD, Jackson JC, et al. Long-Term Cognitive Impairment after Critical Illness. *N Engl J Med* 2013;369(14):1306–16.
26. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. *BMJ* 2020;368.
27. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77(6):683–90.
28. Moro E, Priori A, Beghi E, et al. The international European Academy of Neurology survey on neurological symptoms in patients with COVID-19 infection. *Eur J Neurol* [Internet] 2020 [cited 2020 Jun 26];27(9):1727–37. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.14407
29. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 2020;382(23):2268–70.
30. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res [Internet] 1975;12(3):189–98. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1202204
31. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* [Internet] 2005;53(4):695–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1532-5415.2005.53221.x
32. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* [Internet] 2000; 55(11):1621–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11113214
33. Orrù G, Bertelloni D, Diolaiuti F, et al. Long-COVID Syndrome? A Study on the Persistence of Neurological, Psychological and Physiological Symptoms. *Healthcare* 2021;9(5):575.
34. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19 [Internet]. *J. Infect.* 2020;81(6):e4. Available from: /pmc/articles/PMC7445491/?report=abstract
35. Zhou H, Lu S, Chen J, et al. The landscape of cognitive function in recovered COVID-19 patients. *J Psychiatr Res* [Internet] 2020;129(April):98–102. Available from: https://doi.org/10.1016/j.jpsychires.2020.06.022
36. Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J. Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. *Brain, Behav Immun* - Heal [Internet] 2020;9(January):100163. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2666354620301289
37. Ferrucci R, Dini M, Groppo E, et al. Long-Lasting Cognitive Abnormalities after COVID-19. *Brain Sci* [Internet] 2021;11(2):235. Available from: https://doi.org/10.3390/brainsci11020235

38. Hosp JA, Dressing A, Blazhenets G, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain* [Internet] 2021;144(4):1263–76. Available from: https://academic.oup.com/brain/article/144/4/1263/6209743.

39. Beaud V, Crottaz-Herbette S, Dunet V, et al. Pattern of cognitive deficits in severe COVID-19. *J Neurol Neurosurg Psychiatry* 2021;92(5):567–8.

40. Miskowiak KW, Johnsen S, Sattler SM, et al. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. *Eur Neuropsychopharmacol* [Internet] 2021;46:39–48. Available from: https://doi.org/10.1016/j.euroneuro.2021.03.019

41. Méndez R, Balanzá-Martínez V, Luperdi SC, et al. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. *J Intern Med* 2021;1–11.

42. Blazhenets G, Schröter N, Bormann T, et al. Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients. *J Nucl Med* [Internet] 2021;jnumed.121.262128. Available from: http://jnm.snmjournals.org/lookup/doi/10.2967/jnumed.121.262128

43. Ortelli P, Ferrazzoli D, Sebastianelli L, et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *J Neurol Sci* [Internet] 2021;420(January):117271. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022510X20306079

44. Mattioli F, Stampatori C, Righetti F, Sala E, Tomasi C, De Palma G. Neurological and cognitive sequelae of Covid-19: a four month follow-up. *J Neurol* [Internet] 2021;(0123456789). Available from: https://doi.org/10.1007/s00415-021-10579-6

45. Cristillo V, Pilotto A, Cotti Piccinelli S, et al. Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID-19 infection. *J Am Geriatr Soc* [Internet] 2021;jgs.17296. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jgs.17296

46. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun* [Internet] 2020;11(1):1–10. Available from: http://dx.doi.org/10.1038/s41467-020-19741-6

47. Iannaccone S, Castellazzi P, Tettamanti A, et al. Role of Rehabilitation Department for Adult Individuals With COVID-19: The Experience of the San Raffaele Hospital of Milan. *Arch Phys Med Rehabil* [Internet] 2020;101(9):1656–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32505489

48. Simpson R, Robinson L. Rehabilitation after critical illness in people with COVID-19 infection. *Am J Phys Med Rehabil* 2020;99(6):470–4.

49. Puchner B, Sahanic S, Kirchmair R, et al. Beneficial effects of multi-disciplinary rehabilitation in postacute COVID-19: an observational cohort study. *Eur J Phys Rehabil Med* [Internet] 2021;57(2):189–98. Available from: https://www.minervamedica.it/index2.php?show=R33Y2021N02A0189

50. Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition – A cohort study. *Chron Respir Dis* 2021;18.

51. Olezene CS, Hansen E, Steere HK, et al. Functional outcomes in the inpatient rehabilitation setting following severe COVID- 19 infection. *PLoS One* [Internet] 2021;16(3 March 2021):8–15. Available from: http://dx.doi.org/10.1371/journal.pone.0248824

52. Hill NL, McDermott C, Mogle J, et al. Subjective cognitive impairment and quality of life: a systematic review. *Int psychogeriatrics* 2017;29(12):1965–77.

53. van Rijsbergen MWA, Mark RE, Kop WJ, de Kort PLM, Sitskoorn MM. Psychological factors and subjective cognitive complaints after stroke: Beyond depression and anxiety. *Neuropsychol Rehabil* [Internet] 2019; 29(10):1671–84. Available from: https://pubmed.ncbi.nlm.nih.gov/29502474/

Chapter 13. Disorders of cranial and spinal nerves

Tommaso Bocci*, Laura Campiglio*, Alberto Priori
* These authors equally contributed to this work

Non-length dependent neuropathies: Guillain-Barré-Strohl syndrome and COVID-19

Definition and epidemiology

Guillain-Barré-Strohl syndrome (GBS) is an acute, parainfectious autoimmune disease, either axonal or demyelinating, with rapid onset of 3-4 weeks following the primary infection. GBS has been described from the beginning of the COVID-19 pandemic and a number of typical features, both clinical and neurophysiological, have been reported[1-3]. GBS was reported in 0.1-0.4% of hospitalized patients,[4-6] and GBS and variants represent about 21% of the neurological case reports[7]. In general, the mean age, gender and COVID-19 features appear to reflect those of hospitalized COVID patients, while the disease course is more severe than non-COVID-related GBS[8,9]. The causal relationship between GBS and COVID-19 may be classified as possible or probable. In particular, a probable association is defined when: 1) the disease onset is within 6 weeks of acute infection; 2) either SARS-CoV-2 RNA is detected in any sample or there is antibody evidence of acute SARS-CoV-2 infection; and 3) there is no evidence of other commonly associated causes[10].

Clinical, biochemical and neurophysiological features

Overall, onset of COVID-related GBS seems to follow quickly from the primary infection, as compared to other parainfectious diseases, with neurological signs emerging just one week after respiratory failure. Moreover, in COVID patients, polyradiculoneuropathies primarily affect cranial nerves and are commonly related to an early and severe autonomic dysfunction[11-14]. In the first reports, axonal GBS was observed, including both acute motor axonal neuropathies (AMAN) and acute motor-sensory axonal neuropathies (AMSAN[11]). As the pandemic progressed on a global scale, there have also been increasing reports of demyelinating GBS, and the current percentages of axonal and

demyelinating forms are similar[3,8]. Nonetheless, axonal neuropathies are still more frequent when compared to other parainfectious GBS[9]. The immunological bases are not yet fully understood, and neither are the antibodies involved in the pathophysiology of the disease. However, as likely occurs for the Central Nervous System (CNS), we cannot rule out the possibility of a direct viral invasion of the peripheral nerves and myelin; this could explain the short delay between respiratory symptoms and the early development of neurological signs. As reported in some studies[2,11], a direct mechanism may also be suggested by the absence of serum anti-ganglioside antibodies, commonly engaged in the pathophysiology of immune-related disorders.

Putative pathophysiological mechanisms and comparison with other coronaviruses

As described above, the immuno-mediated nature of COVID-related GBS is still a subject of debate and we cannot exclude the possibility of a direct viral invasion. In this scenario, it is worth remembering that the receptor of the angiotensin-conversion enzyme (ACE), the main gate of entry of SARS-CoV-2 into the cells, is highly expressed not only on the neuronal and vascular endothelial surface, but also by Schwann's cells and central oligodendrocytes[15-17]. Moreover, to further support the concept of direct viral damage, a prion-like mechanism of neuroinvasion, both at a central and a peripheral level, has been extensively described for other coronaviruses, both in animals and humans[18-21]. These data also fit our recent combined neurophysiological and histopathological findings in severe COVID-19 showing an early involvement of the vagus nerve and respiratory nuclei, probably also accounting for the respiratory failure itself[22,23]. However, despite the particular abovementioned features of COVID-related GBS, whether COVID patients exhibit an increased risk is still under debate. Recent data suggest that the incidence of GBS in COVID is similar to that described following other infectious diseases[24, 25], while a larger multi-center study reports a 2.6 fold increased incidence of GBS in Italy during the first pandemic outbreak [26]. However, the risk of GBS in severe COVID-19 seems to be lower when compared to other emerging infections, such as Zika[27].

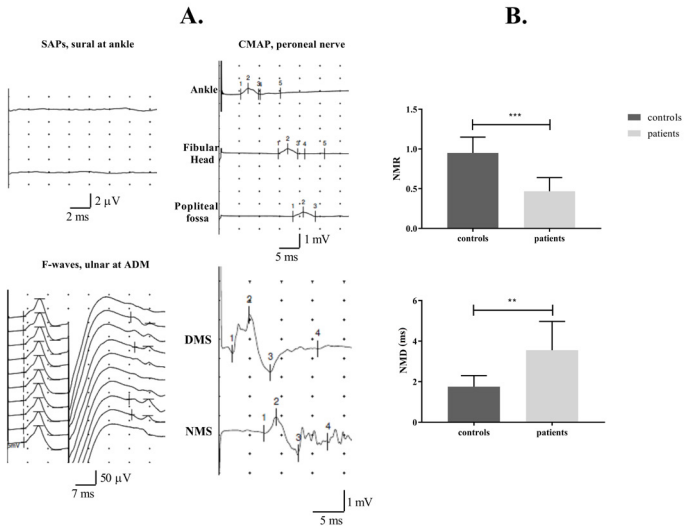
Length-dependent neuropathies

Among other diseases affecting the Peripheral Nervous System, an increasing body of literature has described "Critical Illness Polyneuropathies or Myopathies" (CIP/CIM) in COVID patients, during their stay in the Intensive Care Unit (ICU)[28-32].The main clinical features are difficulty in weaning the patient off the ventilator and flaccid weakness, thus resulting in areflexic quadriplegia[33-36]. Although pathophysiologic mechanisms still remain to be established, CIP/CIM usually follows a prolonged treatment of sepsis and may represent the neural manifestation of

multiple organ failure (MOF). Among other causes, high and prolonged doses of corticosteroids and/or non-depolarizing neuromuscular blockers are thought to be strongly associated with these neuromuscular abnormalities[34]. In non-COVID patients, signs of both neuropathy and myopathy are common, but the myopathic involvement seems to be more frequent and associated to a better clinical outcome[36,37].

In comparison with non-COVID patients, a higher percentage of CIP has been described in severe COVID-19[31,32,38]. This is of key importance given that CIP/CIM may have a different impact on the choice of strategies to be adopted for functional recovery and rehabilitation, possibly delaying ICU discharge for patients affecting by predominant neuropathies[39]. Critical illness neuropathies are probably related to the COVID-induced MOF, but other causes should be taken into consideration, including a possible vasculitic involvement of the *vasa nervorum* and a direct viral invasion of the peripheral nerves by SARS-CoV-2[39].

Figure 13.1: Neurophysiological features



The figure shows nerve conduction studies from a representative COVID-19 patient with critical illness neuropathy (CIP). Top: sensory action potentials (SAPs) from the right sural nerve (not recordable) and CMAP (reduced amplitude) derived from the right extensor digitorum brevis; at the bottom (left) F-waves from the left ulnar nerve are provided (with reduced amplitude and impaired representation). Bottom: (right), CMAPs obtained by either Direct Muscle Stimulation (DMS, top trace) or Nerve Motor Stimulation (NMS, bottom) are shown: the significant amplitude reduction, when NMS was compared to DMS, further confirms the predominace of a neuropathic rather than a myopathic pattern (modified from Bocci et al.[39], Fig. 1 p. 4).

Although sometimes limited by the very small sample size, studies in COVID-19 have shown that patients with high serum levels of Interleukin-6 (IL-6) and creatin-phosphokinase (CPK) are at the highest risk of developing both muscular and neuropathic impairment[31,40]. CPK itself is known to represent an independent factor associated with an overall worse clinical outcome and to the development of neurological complications, both at a central and a peripheral level[40].

Isolated involvement of the cranial nerves

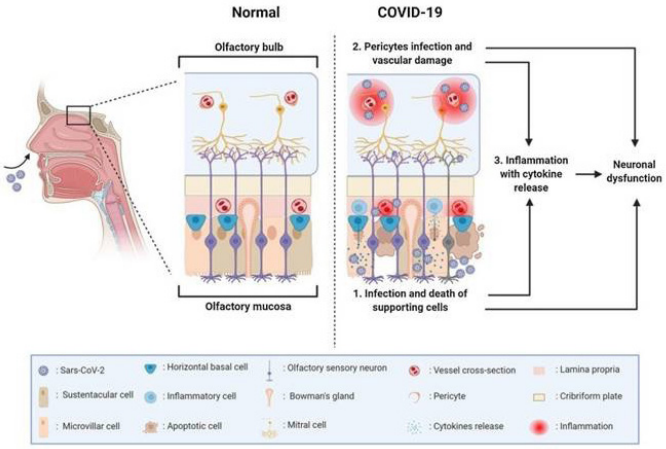
Since the beginning of the pandemic, authors around the world have reported COVID-associated cranial neuropathies, detected by clinical, radiological and neuropathological investigation[41-43]. In most cases, isolated cranial nerve involvement consisted of hyposmia and dysgeusia, but multiple polyneuritis cranialis or cranial nerves deficits in the context of Miller Fisher Syndrome (MFS) have been observed in a significant number of patients[13,44].

Smell and taste disorders

Hyposmia and/or hypogeusia are known to be the main symptoms of SARS-CoV-2 infection. Anosmia has been reported in about 5% of hospitalized patients[4,44,45], but its prevalence is considerably higher in dedicated studies, with a frequency ranging from 61% to 86%[46-49]. According to some studies, anosmia is the first symptom in about 25% of patients[50] and is nearly always associated with ageusia. These symptoms tend to have an unexpected onset[51,52] and, because they are often not accompanied by other symptoms, these deficits could be the only indication of infection in otherwise asymptomatic COVID-19[53]. Most patients report an improvement within the first week, but it is still not known whether some deficit could be permanent[52]. Some Authors propose that the persistence of anosmia is related to lasting SARS-CoV-2 in the olfactory mucosa, while others suggest a central mechanism[50,54].

The exact pathogenesis of olfactory dysfunctions is still not fully understood. Animal models have suggested an infection of sensory neurons by SARS-CoV-2 or retrograde brain invasion through the olfactory nerve, but the sudden onset and the fast recovery do not indicate any structural sensory neuron damage and published data are not always in agreement about this[55,56]. Current evidence suggests an indirect mechanism (infection and inflammation) to non-neural supporting cells of olfactory mucosa, particularly sustentacular and microvillar cells with high expression of ACE2 receptor[57].

Figure 13.2: Olfactory disorders in SARS-COV-2 infection



1) Local inflammation due to the involvement of supporting cells of the olfactory epithelium. 2) Involvement of endothelial cells and vascular pericytes, leading to hypoperfusion and inflammation. The recruitment of inflammatory cells, cytokine release and generation of neurotoxic compounds modulate the neuronal signaling (from Mastrangelo et al.[56], Fig. 1 p. 2. Reproduced from [56] with permission).

However, the possible occurrence of other mechanisms leading to chemosensory dysfunction and a direct sensory neuron invasion have been postulated[54,56]. Interestingly, a recent study on post-mortem samples revealed the co-localization of a coronavirus antigen and SARS-CoV-2 RNA in olfactory sensory neurons[58].

So far, published data on the pathogenesis of taste disorders remain limited. Some studies demonstrated that epithelial cells of the tongue express ACE-2 receptors, hypothesizing a key role for oral mucosa as an entry route for the virus[59]. For the moment there are few data available on the percentage of taste and smell disorders at follow-up. Recent studies seem to suggest that many patients recover quickly, but about 40% of those who experienced smell loss at disease onset may suffer from parosmia during the following six months[60-62]. This does not depend on the severity of primary infection and is not related to the persistence of other systemic dysfunctions during long-term follow-up.

Optic nerve disorders

Involvement of the optic nerve during COVID-19 is unusual and optic neuritis has rarely been described in patients with SARS-CoV-2 infection[63,64]. Patients presented with painful vision loss, relative afferent pupillary defect and, in severe cases, visual field defects and optic nerve enhancement on Magnetic Resonance Imaging (MRI)[64].

In some other COVID-19 patients, optic neuritis was associated with myelin oligodendrocyte glycoprotein (MOG) antibodies. In these cases, SARS-CoV-2

was not detected in the cerebrospinal fluid and researchers postulated that the viral infection triggered the autoimmune response [65,66].

Because SARS-CoV-2 is associated with endothelial damage, and thrombotic events are a well described complication of COVID-19, in the case of a sudden visual loss, central retinal artery occlusion and retinal vein occlusion need to be excluded[67,68].

Oculomotor nerves

Some cases of oculomotor nerve palsies have been described in patients diagnosed with COVID-19, most often associated with areflexia and ataxia in the context of Miller Fisher Syndrome (MFS)[69]. Case reports on isolated palsy of the III, IV and VI cranial nerves have also been published, and in some of these patients there was no other risk factor for nerve palsy other than SARS-CoV-2 infection[70]. Proposed pathogenetic mechanisms include immune response, ischemia or direct viral involvement of the CNS[70].

Facial and vestibulocochlear nerves

There has been an increase in the number of reports in the literature of Bell's palsy during SARS-CoV-2 infection but whether these conditions are directly linked or just coincidental is still a matter of debate. While some Authors suggest a higher occurrence of facial palsy during the COVID-19 outbreak, others did not report any significant difference as compared with other infectious disorders[71-73].

Although rare, nystagmus, tinnitus and sudden hearing loss have been reported in association with COVID-19[74].

Lower cranial nerves

Recently, the occurrence of lower cranial neuropathy in post-intubated severe SARS-CoV-2 patients has been reported[13,75], with asymmetric involvement of the IX, X, XI and XII cranial nerves leading to dysphagia, hoarseness, weakness of the soft palate, weakness of the trapezius/ sternocleidomastoid and tongue deviation.

Although these alterations have been previously described as the results of traumatic nerve involvement during prolonged intubation (e.g., stretching during lateral head flection in prone position or nerve compression against the cervical bones), recent neuropathological findings raised the hypothesis of nerve nuclei in the medulla oblongata or a multiple cranial neuropathy. In a post-mortem series, neuroinflammatory changes in the brainstem were the most common findings, with SARS-CoV-2 viral proteins detected in both isolated cells of the brainstem and lower cranial nerves originating from the medulla oblongata[22]. These data support the hypothesis of an involvement of the brainstem respiratory center in COVID-19 respiratory failure. According to this theory, failure to wean patients

off the ventilator and the respiratory dissociation seen in some patients after recovery from pneumonia could be due to central respiratory drive depression.

Practical recommendations for clinicians and personal experience

During the COVID-19 pandemic, the role and the guidelines for neurophysiological assessment changed rapidly. In particular, safety criteria have been extensively revised in terms of the management and the response of physicians and technicians, hygiene and personal protection standards, and use of technical equipment[76,77]. At the same time, there has been an increasing need for Telemedicine, not only as a high-specialized "second opinion".

In our experience, the main limitation was the duration of clinical and electrophysiological assessment for diseases affecting the Peripheral Nervous System. This is because, in COVID, a neurophysiological examination usually takes three times longer than for non-COVID patients, mainly because of safety concerns. Another limitation was the under-estimation of cranial neuropathies, which may frequently complicate the disease course. Moreover, as discussed above, GBS in COVID-19 frequently involves the cranial nerves, even at an early stage, and is more severe than non-COVID-related polyradiculopathies. The cranial nerves are not systematically evaluated in these patients; probably because the attention is usually switched toward the respiratory impairment. Furthermore, the presence of mechanical devices (continuous positive airway pressure or non-invasive ventilation devices) often makes the clinical investigation of cranial nerves very difficult to perform.

Take-home message

- The involvement of the Peripheral Nervous System (PNS) is frequent in severe COVID-19.
- This involvement comprises both length- and non-length dependent diseases, with particular clinical and neurophysiological features when compared to other para-infectious disorders.
- Converging histopathological, clinical and neurophysiological findings suggest that PNS disorders may be due to a direct invasion by SARS-CoV-2.
- PNS involvement can significantly impact the functional recovery and rehabilitation strategies for COVID patients.

References

1. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020:143(10):3104-3120.
2. Whittaker A, Anson M, Harky A. Neurological Manifestations of COVID-19: A systematic review and current update. *Acta Neurol Scand*. 2020;142(1):14-22.
3. Abu-Rumeileh S, Abdelhak A, Foschi M, et al. Guillain-Barre syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol*. 2021;268(4):1133-1170.
4. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*. 2020;95(8):e1060-e1070.
5. Mahammedi A, Saba L, Vagal A, et al. Imaging of Neurologic Disease in Hospitalized Patients with COVID-19: An Italian Multicenter Retrospective Observational Study. *Radiology*. 2020;297(2):E270-E273.
6. Guilmot A, Maldonado Slootjes S, Sellimi A, et al. Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. *J Neurol*. 2021;268(3):751-757.
7. Maury A, Lyoubi A, Peiffer-Smadja N, et al. Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: A narrative review for clinicians. *Rev Neurol*. (Paris) 2021;177(1-2):51-64.
8. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barre syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. *J Neurol Neurosurg Psychiatry*. 2020;92(7):751-756.
9. Caress JB, Castoro RJ, Simmons Z, et al. COVID-19-associated Guillain-Barre syndrome: The early pandemic experience. *Muscle Nerve*. 2020;62(4):485-491.
10. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol*. 2020;19(9):767-783.
11. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barre Syndrome Associated with SARS-CoV-2. *N Engl J Med*. 2020;382(26):2574-2576.
12. Gutierrez-Ortiz C, Mendez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology*. 2020;95(5):e601-e605.
13. Todisco M, Alfonsi E, Arceri S, et al. Isolated bulbar palsy after SARS-CoV-2 infection. *Lancet Neurol*. 2021;20(3):169-170.
14. Zito A, Alfonsi E, Franciotta D, et al. COVID-19 and Guillain-Barre Syndrome: A Case Report and Review of Literature. *Front Neurol*. 2020;11:909.
15. Yang Q, Hughes TA, Kelkar A, et al. Inhibition of SARS-CoV-2 viral entry upon blocking N- and O-glycan elaboration. *Elife*. 2020;9:e61552.
16. Choi JY, Lee HK, Park JH, et al. Altered COVID-19 receptor ACE2 expression in a higher risk group for cerebrovascular disease and ischemic stroke. *Biochem Biophys Res Commun*. 2020;528(3):413-419.
17. Han T, Kang J, Li G, et al. Analysis of 2019-nCoV receptor ACE2 expression in different tissues and its significance study. *Ann Transl Med*. 2020;8(17):1077.

18. Dube M, Le Coupanec A, Wong AHM, et al. Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43. *J Virol*. 2018;92(17):e00404-18.

19. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552-555.

20. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci*. 2020;11(7):995-998.

21. Baig AM, Khaleeq A, Nazim F. Targeting CNS Related Protist Pathogens: Calcium Ion Dependency in the Brain-Eating Amoebae. *ACS Chem Neurosci*. 2020;11(16):2385-2387.

22. Bulfamante G, Bocci T, Falleni M, et al. Brainstem neuropathology in two cases of COVID-19: SARS-CoV-2 trafficking between brain and lung. *J Neurol*. 2021. doi:10.1007/s00415-021-10604-8. [Preprint]

23. Bocci T, Bulfamante G, Campiglio L, et al. Brainstem clinical and neurophysiological involvement in COVID-19. *J Neurol*. 2021. doi:10.1007/s00415-021-10474-0. [Preprint]

24. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barre syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011;36(2):123-133.

25. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barre syndrome. *Brain*. 2021;144(2):682-693.

26. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barre syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. *J Neurol Neurosurg Psychiatry*. 2021;92(7):751-756.

27. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet*. 2016;387(10027):1531-1539.

28. Bagnato S, Boccagni C, Marino G, et al. Critical illness myopathy after COVID-19. *Int J Infect Dis*. 2020;99:276-278.

29. Tankisi H, Tankisi A, Harbo T, et al. Critical illness myopathy as a consequence of Covid-19 infection. *Clin Neurophysiol*. 2020;131(8):1931-1932.

30. Cabanes-Martinez L, Villadoniga M, Gonzalez-Rodriguez L, et al. Clinical and neurophysiological characterization of muscular weakness in severe COVID-19. *Neurol Sci*. 2021;42(6):2173-2178.

31. Bax F, Lettieri C, Marini A, Pellitteri G, Surcinelli A, Valente M, et al. Clinical and neurophysiological characterization of muscular weakness in severe COVID-19. Neurol Sci. 2021;42(6):2173-8. doi: 10.1007/s10072-021-05110-8.

32. Frithiof R, Rostami E, Kumlien E, et al. Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: A prospective study. *Clin Neurophysiol*. 2021;132(7):1733-1740.

33. Bolton CF. Neuromuscular conditions in the intensive care unit. *Intensive Care Med.* 1996;22(9):841-843.

34. De Jonghe B, Cook D, Sharshar T, et al. Acquired neuromuscular disorders in critically ill patients: a systematic review. Groupe de Reflexion et d'Etude sur les Neuromyopathies En Reanimation. *Intensive Care Med.* 1998;24(12):1242-1250.

35. Latronico N, Fenzi F, Recupero D, et al. Critical illness myopathy and neuropathy. *Lancet.* 1996;347(9015):1579-1582.

36. Lefaucheur JP, Nordine T, Rodriguez P, Brochard L. Origin of ICU acquired paresis determined by direct muscle stimulation. *J Neurol Neurosurg Psychiatry.* 2006;77(4):500-506.

37. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA.* 2002;288(22):2859-2867.

38. Tankisi H. Critical illness myopathy and polyneuropathy in Covid-19: Is it a distinct entity? *Clin Neurophysiol.* 2021;132(7):1716-1717.

39. Bocci T, Campiglio L, Zardoni M, et al. Critical Illness Neuropathy in severe COVID-19: a case series. *Neurol Sci.* 2021; https://doi.org/10.1007/s10072-021-05471-0.

40. De Rosa A, Verrengia EP, Merlo I, et al. Muscle manifestations and CK levels in COVID infection: results of a large cohort of patients inside a Pandemic COVID-19 Area. *Acta Myol.* 2021;40(1):1-7.

41. Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol.* 2020;19(11):919-929.

42. Doblan A, Kaplama ME, Ak S, et al. Cranial nerve involvement in COVID-19. *Am J Otolaryngol.* 2021;42(5):102999.

43. Correa DG, Hygino da Cruz LC Jr, Lopes FCR, et al. Magnetic resonance imaging features of COVID-19-related cranial nerve lesions. *J Neurovirol.* 2021;27(1):171-177.

44. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683-690.

45. Agarwal P, Ray S, Madan A, Tyson B. Neurological manifestations in 404 COVID-19 patients in Washington State. *J Neurol.* 2021;268(3):770-772.

46. Speth MM, Singer-Cornelius T, Oberle M, et al. Olfactory Dysfunction and Sinonasal Symptomatology in COVID-19: Prevalence, Severity, Timing, and Associated Characteristics. *Otolaryngol Head Neck Surg.* 2020;163(1):114-120.

47. Giacomelli A, Pezzati L, Conti F, et al. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. *Clin Infect Dis.* 2020;71(15):889-890.

48. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* 2020;277(8):2251-2261.

49. Sedaghat AR, Gengler I, Speth MM. Olfactory Dysfunction: A Highly Prevalent Symptom of COVID-19 With Public Health Significance. *Otolaryngol Head Neck Surg*. 2020;163(1):12-15.
50. Lorenzo Villalba N, Maouche Y, Alonso Ortiz MB, et al. Anosmia and Dysgeusia in the Absence of Other Respiratory Diseases: Should COVID-19 Infection Be Considered? *Eur J Case Rep Intern Med*. 2020;7(4):001641.
51. Russell B, Moss C, Rigg A, et al. Anosmia and ageusia are emerging as symptoms in patients with COVID-19: What does the current evidence say? *Ecancermedicalscience*. 2020;14:ed98.
52. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun*. 2020;87:18-22.
53. Kaye R, Chang CWD, Kazahaya K, et al. COVID-19 Anosmia Reporting Tool: Initial Findings. *Otolaryngol Head Neck Surg*. 2020;163(1):132-134.
54. Saussez S, Lechien JR, Hopkins C. Anosmia: an evolution of our understanding of its importance in COVID-19 and what questions remain to be answered. *Eur Arch Otorhinolaryngol*. 2021;278(7):2187-2191.
55. Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. *Neuroscientist*. 2020. doi: 10.1177/1073858420956905. [Preprint]
56. Mastrangelo A, Bonato M, Cinque P. Smell and taste disorders in COVID-19: From pathogenesis to clinical features and outcomes. *Neurosci Lett*. 2021. doi: 10.1016/j.neulet.2021.135694. [Preprint]
57. Chen M, Shen W, Rowan NR, et al. Elevated ACE-2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. *Eur Respir J*. 2020;56(3):2001948.
58. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci*. 2021;24(2):168-175.
59. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12(1):8.
60. Cook E, Kelly CE, Burges Watson DL, Hopkins C. Parosmia is prevalent and persistent amongst those with COVID-19 olfactory dysfunction. *Rhinology*. 2021;59(2):222-224.
61. Hopkins C, Surda P, Vaira LA, et al. Six month follow-up of self-reported loss of smell during the COVID-19 pandemic. *Rhinology*. 2021;59(1):26-31.
62. Carvalho-Schneider C, Laurent E, Lemaignen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*. 2021;27(2):258-263.
63. Benito-Pascual B, Gegundez JA, Diaz-Valle D, et al. Panuveitis and Optic Neuritis as a Possible Initial Presentation of the Novel Coronavirus Disease 2019 (COVID-19). *Ocul Immunol Inflamm*. 2020;28(6):922-925.
64. Rodriguez-Rodriguez MS, Romero-Castro RM, Alvarado-de la Barrera C, et al.

Optic neuritis following SARS-CoV-2 infection. *J Neurovirol.* 2021;27(2):359-363.

65. Sawalha K, Adeodokun S, Kamoga GR. COVID-19-Induced Acute Bilateral Optic Neuritis. *J Investig Med High Impact Case Rep.* 2020;8:2324709620976018.
66. Zhou S, Jones-Lopez EC, Soneji DJ, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Optic Neuritis and Myelitis in COVID-19. *J Neuroophthalmol.* 2020;40(3):398-402.
67. Murchison AP, Sweid A, Dharia R, et al. Monocular visual loss as the presenting symptom of COVID-19 infection. *Clin Neurol Neurosurg.* 2021;201:106440.
68. 68. Finsterer J, Scorza FA, Scorza CA, Fiorini AC. Vascular Damage May Mimic Retinitis and Optic Neuritis in COVID-19. *Curr Eye Res.* 2021. doi:10.1080/02713683.2021.1896743. [Preprint]
69. 69. Sen M, Honavar SG, Sharma N, Sachdev MS. COVID-19 and Eye: A Review of Ophthalmic Manifestations of COVID-19. *Indian J Ophthalmol.* 2021;69(3):488-509.
70. Anilkumar A, Tan E, Cleaver J, Morrison HD. Isolated abducens nerve palsy in a patient with asymptomatic SARS-CoV-2 infection. *J Clin Neurosci.* 2021;89:65-67.
71. Mutlu A, Kalcioglu MT, Gunduz AY, et al. Does the SARS-CoV-2 pandemic really increase the frequency of peripheral facial palsy? *Am J Otolaryngol.* 2021;42(5):103032.
72. Islamoglu Y, Celik B, Kiris M. Facial paralysis as the only symptom of COVID-19: A prospective study. *Am J Otolaryngol.* 2021;42(4):102956.
73. Codeluppi L, Venturelli F, Rossi J, et al. Facial palsy during the COVID-19 pandemic. *Brain Behav.* 2021;11(1):e01939.
74. Elibol E. Otolaryngological symptoms in COVID-19. *Eur Arch Otorhinolaryngol.* 2021;278(4):1233-1236.
75. Yatim N, Bonnet N, Wing Tin SN, et al. Persistent bilateral Tapia syndrome following critical COVID-19. *Clin Neurophysiol.* 2021;132(2):505-506.
76. Grippo A, Assenza G, Scarpino M, et al. Electroencephalography during SARS-CoV-2 outbreak: practical recommendations from the task force of the Italian Society of Neurophysiology (SINC), the Italian League Against Epilepsy (LICE), and the Italian Association of Neurophysiology Technologists (AITN). *Neurol Sci.* 2020;41(9):2345-2351.
77. Dubbioso R, Nobile-Orazio E, Manganelli F, et al. Dealing with immune-mediated neuropathies during COVID-19 outbreak: practical recommendations from the task force of the Italian Society of Neurology (SIN), the Italian Society of Clinical Neurophysiology (SINC) and the Italian Peripheral Nervous System Association (ASNP). *Neurol Sci.* 2020;41(6):1345-1348.

Chapter 14. COVID-19-related myopathy

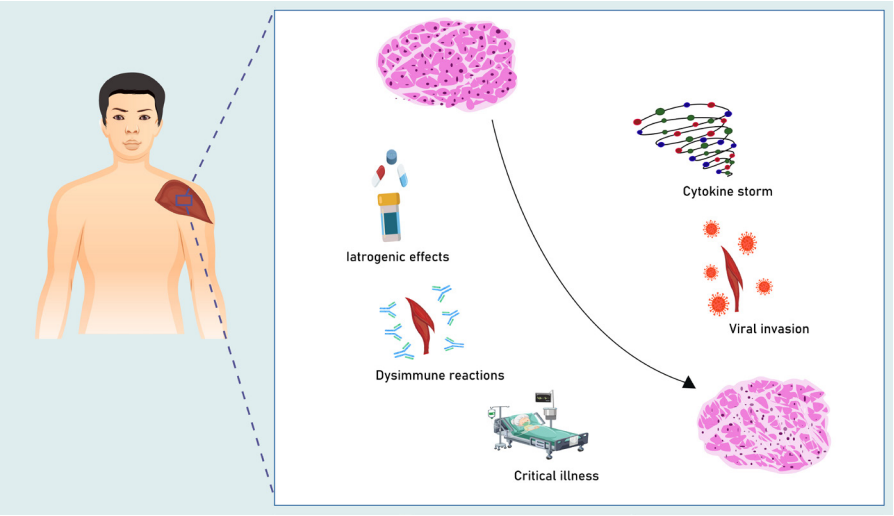
Gianluca Costamagna, Daniele Velardo, Giacomo Pietro Comi

Introduction

Various different viral infections can lead to muscle damage. These include influenza virus A and B, human immunodeficiency virus (HIV), coxsackievirus, cytomegalovirus (CMV), West Nile virus, Dengue virus, Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1), and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)[1-3]

The mechanisms leading to muscle involvement in SARS-CoV-2 infection are still poorly understood. Possible pathogenic mechanisms may involve an acute cytokine release, para- or post-dysimmune dysfunctions, side effects of pharmacologic treatments, critical illness-associated mechanisms, or a direct viral invasion (Figure 14.1).

Figure 14.1: Potential causes associated with SARS-CoV-2 muscle involvement



Different factors may play a role in SARS-CoV-2 myopathies, including iatrogenic effects from systemic drugs and critical illness-related muscular comorbidities. Systemic inflammatory responses known as "cytokine storms", SARS-CoV-2-triggered dysimmune reactions, or direct viral invasion may also lead to muscle damage.

SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) to infect human cells[4]. This receptor is expressed in different organs, including the lungs, the blood vessels, and the immune system[5]. Although there is still no evidence for a direct muscle invasion,skeletal muscles express ACE2 receptors[4], representing a potential viral entry point to the muscle as well. In parallel, SARS-CoV-2 can trigger an inflammatory cascade, increasing interleukin-1, interleukin-6, and tumor necrosis factor release[6] leading to widespread inflammation and possibly muscle damage. Different studies reported small arteriolar and venular thromboses in multiple organs with vasculopathy and vasculitis in severe SARS-CoV-2 infections[7] potentially linked to muscle damage.

Muscular involvement and SARS-CoV-2 infection

Muscular involvement in the context of SARS-CoV-2 infection includes myalgia[8], myositis[9–11] as well as critical-illness myopathies[14].

Myalgia

The literature on muscular involvement in the context of SARS-CoV-2 infection is highly heterogeneous, including mainly case reports and retrospective analyses (Table 14.1).

Most studies report myalgia as the most frequent muscular symptom. Muscle involvement was first described in a retrospective study of 214 Chinese patients[8] where 23 (10.7%) were reported with "skeletal muscle injury." No specific investigations were carried out to further characterize the type and pathophysiology of the muscle injury. In another study involving 41 infected Chinese patients, 18 (44%) complained about myalgia and fatigue. In particular, all 18 patients complained about myalgia as symptom onset; of these, 7 patients required admission to an intensive care unit (ICU)[8] for SARS-CoV-2 infection. In a retrospective study in a European cohort of 1,420 patients, Lechien et al. reported 887 (62.5%) patients with myalgia[15]. In a population of 48 patients with neuromuscular disorders with SARS-CoV-2 infection from different Italian centers, 14 (29.2%) reported myalgia (G Costamagna, unpublished data, 2021).

Table 14.1 Selected case reports/series and observational studies on SARS-CoV-2-associated myopathies

N. of patients	Age	Sex	Signs and symptoms	CK levels	EMG	Muscle biopsy	Ref.
887	NR	NR	Myalgia	NR	NR	NR	[15]
164	NR	NR	Myalgia, fatigue	≥200 U/L in 90	NR	NR	[16]
67	NR	NR	Myalgia	NR	NR	NR	[17]
48	NR	NR	Myalgia	NR	Normal	NR	[18]
23	NR	NR	Myalgia	>200 U/L in 23	NR	NR	[19]
18	NR	NR	Myalgia, fatigue	NR	NR	NR	[8]
11	NR	NR	Myalgia	NR	NR	NR	[20]
6	NR	NR	NR	NR	NR	Myositis	[21]
5	NR	NR	Myalgia	> 200 U/l in 6	NR	NR	[22]
5	NR	NR	NR	> 200 U/l in 5	NR	NR	[23]
4	8-15	2M, 2 F	Weakness	NR	Myogenic	NR	[24]
1	60	M	Weakness	11,842	NR	NR	[12]
1	58	F	Weakness	700	Fibrillations	Myositis	[25]
1	71	M	Weakness, Myalgia	8720	NR	NR	[26]
1	16	M	Weakness, fatigue	427,656	NR	NR	[27]
1	38	M	Myalgia	42,670	NR	NR	[28]
1	NR	M	Weakness, Myalgia	25,384	NR	NR	[9]
1	57	F	Weakness	15,000	Myogenic	Necrotizing myopathy	[29]
1	38	M	Weakness	29,000	NR	Type I Interferonopathy	[11]

CK: creatine kinase; EMG: electromyography; Ref.: reference; NR: not reported.

Available studies on myalgia and creatinine kinase (CK) levels in SARS-CoV-2 patients in different populations reported mixed results. In a cohort of 138 infected Chinese patients, including 48 subjects presenting with myalgia, CK levels were normal in most cases[18]. In a Chinese study on 1,099 patients, 164 (14.9%) reported myalgia. In another cohort, only 60 patients out of 657 (13.7%) presented increased CK to > 200 U/L[16]. In a sample of 1,150 SARS-CoV-2 patients in the US, 67 (26%) presented with myalgia. Increased CK was reported in some patients, although the exact number was not reported[17]. In a study of 351 European SARS-CoV-2 patients, 95 (27%) showed increased CK levels that were significantly correlated with inflammation markers and disease severity[30].

Altogether, these studies suggest the presence of myalgia and variable degrees of CK elevation to be associated with SARS-CoV-2 infection. However, the heterogeneous populations, the variable assessment of muscle involvement, and the absence of data from patient medical records on pre-infectious muscular diseases limit the generalizability of these findings. In addition, none of these studies prospectively investigated post-infectious muscle damage.

Myositis and rhabdomyolysis

Single case reports and small case series have described muscular damage in the context of SARS-CoV-2 infection presenting as myositis and rhabdomyolysis. Manzano et al. presented the case of a SARS-CoV-2 infected 38-year-old man with an acute-onset, generalized muscle weakness more severe proximally than distally, who was unable to walk. Laboratory testing showed markedly increased CK levels (29,000 U/L). Muscle biopsy revealed some features typically associated with type I interferonopathies, a group of autoinflammatory disorders with prominent enhanced type I interferon signaling[31]. Histopathological alterations included abnormal expression of major-histocompatibility-complex class I and abnormal myxovirus resistance protein A, suggesting a role for SARS-CoV-2 in causing type I interferonopathy-associated muscle damage[11]. Treatment with intravenous remdesevir and methylprednisolone followed by oral prednisone led to mild clinical improvement and improvement in CK levels.

A 16-year-old female patient presented with acute rhabdomyolysis and magnetic resonance imaging (MRI), electromyography (EMG), and bioptic signs of myositis in the context of SARS-CoV-2 infection (G Costamagna, unpublished observations, 2021). She was brought to the emergency department following a transitory loss of consciousness, new-onset mild fever, and severe muscle pain. She had complained about persistent, mild muscle pain in the proximal lower and upper limbs two months previously; no specific tests had been carried out. Upon arrival at our center, laboratory findings showed severe CK elevation (10,988 U/L), increased alanine aminotransferase (ALT), aspartate aminotransaminase (AST), troponin T and lactate dehydrogenase (LDH) levels. EKG and transthoracic echocardiogram ruled out acute myocardial infarction. Renal function was within normal limits. A nasal swab tested positive for SARS-CoV-2. A diagnosis of acute rhabdomyolysis associated with SARS-CoV-2 was made. Early aggressive fluid resuscitation with isotonic saline was initiated. A dermatological evaluation highlighted diffuse skin thickening and hardening on the neck, chest, and thighs consistent with cutaneous manifestations of systemic sclerosis (SS). Extensive autoimmune panel and comprehensive viral and bacterial serology showed ANA positivity (1:640) and SARS-CoV-2 IgM and IgG antibodies. Muscle MRI revealed diffuse muscle and fascial edema with mild and patchy contrast enhancement in the lower limbs. EMG documented diffuse fibrillation potentials with myogenic pattern in the lower limbs. Figure

14.2 shows muscle biopsy findings consistent with inflammatory myopathy (see histopathological studies). A diagnosis of acute rhabdomyolysis associated with SARS-CoV-2 infection in the context of an SS-related inflammatory myopathy was made. A 5-day course with intravenous methylprednisolone followed by high-dose oral dexamethasone led to clinical improvement.

Other reports described MRI-confirmed myositis associated with SARS-CoV-2 infection. A previously healthy patient complained about acute-onset, diffuse myalgias, and proximal lower limb muscle weakness associated with falls. Clinical examination and early laboratory findings including CK levels were consistent with an acute myopathy. Work-up for polymyositis, dermatomyositis and necrotizing autoimmune myopathies (NAM) with comprehensive autoimmunity screening were all negative. On day 7, lower limb MRI showed obturator muscle and quadricipital edema, suggesting a bilateral lower-limb myositis[9].

In another study, a 58-year-old female presented with limb and facial weakness, ptosis, CK elevation, diffuse muscle edema on muscle MRI and myogenic alteration on EMG, with a final diagnosis of myositis following muscle biopsy[25]. The authors reported an improvement in symptoms after a 5-day course of intravenous methylprednisolone and tocilizumab. Shabbir et al. highlighted the case of a middle-aged woman with a history of chronic myopericarditis presenting with SARS-CoV-2 pulmonary symptoms and central chest pain. She developed bilateral leg weakness and elevated CK levels up to 19,000 U/L six days after symptom onset. Lower limb MRI revealed generalized subcutaneous edema and symmetrical diffuse alterations in all muscle compartments, pointing to myositis. Cardiac MRI showed myocardial edema and pericardial effusion, consistent with myopericarditis. Following treatment with colchicine, ibuprofen, and prednisolone, the patient showed both cardiac and muscular improvement upon discharge. Similar to these findings, an MRI study on 7 SARS-CoV-2 infected patients showed intramuscular edema and/or enhancement, supporting the evidence of a possible lumbar spine myositis in some patients[10]. In a case series of 10 SARS-CoV-2 patients from Brazil, minimally invasive, ultrasound-guided, post-mortem morphological studies highlighted features of myositis in 60% of cases and necrotic muscle fibers in 80% of patients[21].

Although a thorough muscular diagnostic work-up was not performed, different authors have described SARS-CoV-2 patients with markedly increased levels of CK, suggesting acute rhabdomyolysis. For example, Zhang et al. highlighted the case of a 38-year-old man with SARS-CoV-2 pulmonary symptoms, muscle weakness, markedly elevated inflammatory markers, elevated ALT, LDH, and CK elevation up to 43,000 U/L[28]. Similarly, other manuscripts report patients with increased levels of CK at disease onset[32] or during hospital stay[12].

However, since these early reports lack a full muscle diagnostic workup (e.g., muscle MRI, EMG, muscle biopsy), confounding factors such as iatrogenic or critical illness-associated effects cannot be ruled out.

Necrotizing autoimmune myopathies

One case report described a possible association between necrotizing autoimmune myopathies (NAM) and SARS-CoV-2 infection. NAM refers to a subgroup of inflammatory myopathies displaying necrotic muscle fibers and absent or minimal inflammation on muscle biopsy. While NAM cases are usually idiopathic, patients taking statins or presenting viral infections or neoplastic diseases may develop this condition[33]. Though the exact pathophysiology of NAM is unknown, some studies suggest a role for an exaggerated inflammatory response, possibly as a result of viral infections[34].

Veyseh et al. described the case of a 57-year-old woman presenting with acute rhabdomyolysis, diffuse muscle weakness, and positive SARS-CoV-2 IgG titers one month from SARS-CoV-2-related, self-limiting, mild upper respiratory symptoms[29]. The patient was discharged with a final diagnosis of rhabdomyolysis in the setting of SARS-CoV-2 infection. Four months later, she presented to the hospital with progressive muscle weakness over 2 weeks. Lower limb MRI showed bilateral, diffuse signal abnormalities in the proximal muscles with edema of the myofascial layers, consistent with myositis. EMG displayed an irritative myogenic pattern in the tibialis anterior muscles. Muscle biopsy showed a few scattered necrotic myofibers with limited inflammatory cell infiltrates, suggesting NAM. Potential confounding factors including acute viral infections, electrolyte abnormalities, endocrinopathies, and statin use were ruled out. Serologic testing was positive for ANA (1:320, speckled pattern) and low titers of anti-Smith antibodies (considered secondary to SARS-CoV-2 infection) with negative titers for anti-Jo1, anti-HMG-CoA reductase (HMGCoAR), and anti-signal recognition particle (SRP). High-dose prednisone (1 mg/kg) led to an improvement in muscle strength and decreasing CK levels. The authors interpreted these findings as a SARS-CoV-2 IgG-related NAM.

Although this report suggests a possible post-SARS-CoV-2 autoimmune response targeting the muscles, there have been no reliable reports of viral-triggered autoimmune muscular disorders.

Critical illness myopathy

Available reports have described ICU-acquired weakness (ICUAW) in severe SARS-CoV-2 cases. ICUAW is typically generalized, symmetrical, affecting both limbs more proximally than distally, as well as respiratory muscles while sparing facial and ocular muscles[35,36]. Diaphragm dysfunction may develop more frequently than limb weakness[37]. Reduction in muscle tone and normal to reduced deep tendon reflexes complete the clinical presentation. Both neurogenic disorders known as critical illness polyneuropathy (CIP) and myogenic abnormalities referred to as critical illness myopathy (CIM) can cause ICUAW[36]. Bolton's and Lacomi's criteria support the diagnosis of these conditions[38,39].

Table 14.2 shows the typical features of CIP and CIM in electrophysiological and biopsy studies.

Table 14.2 Features of critical illness polyneuropathy and critical illness myopathy in electrophysiological and biopsy studies

	Critical illness myopathy	Critical illness neuropathy
CMAP amplitude	Decreased	Decreased
CMAP duration	Increased	Normal
SNAP amplitude	Normal	Decreased
Nerve conduction velocity	Normal or near normal	Normal or near normal
EMG at rest	Fibrillation potentials/positive sharp waves	Fibrillation potentials/positive sharp waves
MUP voluntary muscle activation	Short duration/low amplitude	Long duration, high amplitude, polyphasic
Repetitive nerve stimulation	Absence of decremental response	Absence of decremental response
Direct muscle stimulation	Reduced muscle excitability	Normal muscle excitability
Muscle biopsy	Different abnormalities: myofiber atrophy, angulated fibers, necrosis, fatty degeneration, local or diffuse lack of thick filaments.	Denervation atrophy of type 1 and 2 muscle fibers
Nerve biopsy	Normal	Primary distal axonal degeneration of sensory nerve fibers, no demyelination

CMAP: compound muscle action potential; SNAP: sensory nerve action potential; EMG: electromyography; MUP: muscle action potential.[36,40-42].

Several risk factors can contribute to CIM onset. Among these, the severity of the underlying illness, sepsis and inflammation, multiple organ failure, and mechanical ventilation play an important role[40,43-45]. In addition to these, hyperglycemia, parenteral nutrition, drugs such as corticosteroids, neuromuscular blocking agents, antibiotics (e.g., aminoglycosides and vancomycin), sedatives[46], as well as prolonged immobilization all represent important risk factors[47-49]

Assessment of weakness in patients with CIM includes mainly clinical and electrophysiological evaluations. The most widely used clinical approach is the 6-grade Medical Research Council (MRC) sum score[35]. Other less frequently used tools are the hand-held dynamometry, the Scored Physical Function in Intensive Care Test, the Functional Status Score for the ICU, and the Chelsea Critical Care Physical Assessment Tool[50,51]. The 6-minute walking distance test is useful for patients' performance at discharge or in post-ICU settings[51].

Electrophysiological studies may be valuable tools in unconscious / non-cooperative patients, such as severe SARS-CoV-2 cases. EMG, single-nerve conduction studies (NCS), and direct muscle stimulation (DMS) can help to differentiate CIM from CIP and other differential diagnoses[41,52].

Different case reports[14,53] and small retrospective studies present severe SARS-CoV-2 patients with ICUAW, including CIM. Van Aerde et al. reported a 70% incidence of weakness on awakening in a cohort of 50 SARS-CoV-2 patients requiring invasive mechanical ventilation[54]. Among 11 patients with severe SARS-CoV-2 and ICUAW, 7 received a diagnosis of CIM[55]. In particular, these patients presented mixed muscular electrophysiological alterations on EMG such as abundant spontaneous activity and short motor unit potentials with decreased amplitude and duration. Weak patients presented prolonged ventilation, higher mean morning glycemia, and higher exposure to corticosteroids, sedatives, and analgesics[54]. Madia et al. described 6 ventilator-dependent SARS-induced ARDS cases with acute-onset flaccid quadriplegia noted when attempts were made to reduce sedation[56]. Physical examination showed quadriplegia, weak tendon reflexes, no sensory abnormalities, and preserved extraocular, mimic, and tongue muscles. Electrophysiological studies including EMG and electroneurography (ENG) revealed myopathic abnormalities with fibrillation potentials and rapid recruitment of small, polyphasic motor units in proximal and distal limb muscles, as well as reduced compound muscle action potential (CMAP) amplitude. CK levels were normal or mildly elevated in all patients. One of the patients died due to sepsis, while the others showed improvement in the neurological examination at discharge after 14-20 days.

Taken together, these findings suggest the frequent association between muscle involvement and SARS-CoV-2 infection, particularly in severe cases in ICU settings.

Testing

Specific testing including imaging, electrodiagnostic and histopathological studies can help characterize SARS-CoV-2-associated myopathies.

Neuroimaging studies

MRI can support the diagnosis and evaluation of muscular manifestations and iatrogenic complications associated with SARS-CoV-2 infection[57]. Myositis can present with rhabdomyolysis following damage of the muscle (myonecrosis) and elevated levels of myoglobin in the blood (myoglobinemia). Rhabdomyolysis can be life-threatening, potentially leading to acute kidney failure, compartment syndrome, and disseminated intravascular coagulation[58].

In this context, MRI imaging is the modality of choice for supporting the diagnosis and delineating the site for muscle biopsy, preferably with 1.5-T or 3.0-T magnets, including multiplanar fluid-sensitive and anatomic sequences.

Myositis can be associated with different alterations on muscle MRI, such as muscle edema. Increased signal intensity on T2-weighted or short tau inversion recovery (STIR) sequences identifies muscle edema[59]. Two different radiological patterns define myositis, including homogeneous hyperintense signal and enhancement (type 1) and heterogeneous hyperintense signal and rim enhancement (type 2)[60]. Severe disease forms may display areas of necrosis and loss of muscle architecture. In particular, the "stipple sign" refers to a distinguishing sign of myonecrosis, presenting with dot-like, streaky, or curvilinear enhancing foci within a muscle separated from normal tissue by an enhancing rim61. Intramuscular hemorrhage may be present, identified by T1 hyperintensities or blooming artifacts on gradient-echo sequences[62].

In addition to myositis, CIM represents the most important differential diagnosis for muscle edema on muscle MRI in hospitalized SARS-CoV-2 patients. CIM is associated with non-specific imaging findings such as multifocal muscle edema and atrophy59. In contrast to SARS-CoV-2-related rhabdomyolysis, there is no evidence of necrosis on MRI. Clinical and imaging features of CIM in SARS-CoV-2-infected patients do not appear to differ from CIM in non-SARS-CoV-2 patients.

Imaging is also helpful to monitor diaphragm function. Patients with severe SARS-CoV-2 infection can present diaphragm dysfunction due to CIM, use of ventilators, or phrenic nerve injury, possibly from chest support devices. In addition, diaphragm impairment may be due to a direct SARS-CoV-2 involvement[63]. In an autopsy study on the human diaphragm of ICU SARS-CoV-2 patients, Shi et al. demonstrated the expression of ACE2, the presence of SARS-CoV-2 RNA, and the increased activity of genes related to fibrinogenesis. The fluoroscopy sniff test enables the evaluation of diaphragm excursion and ultrasound offers additional information on muscle atrophy, muscle thickening ratio, and excursion[59,64]. High-resolution ultrasound contributes to the assessment of the phrenic nerve in the neck region, helping in the differential diagnosis between neuropathic versus myopathic processes.

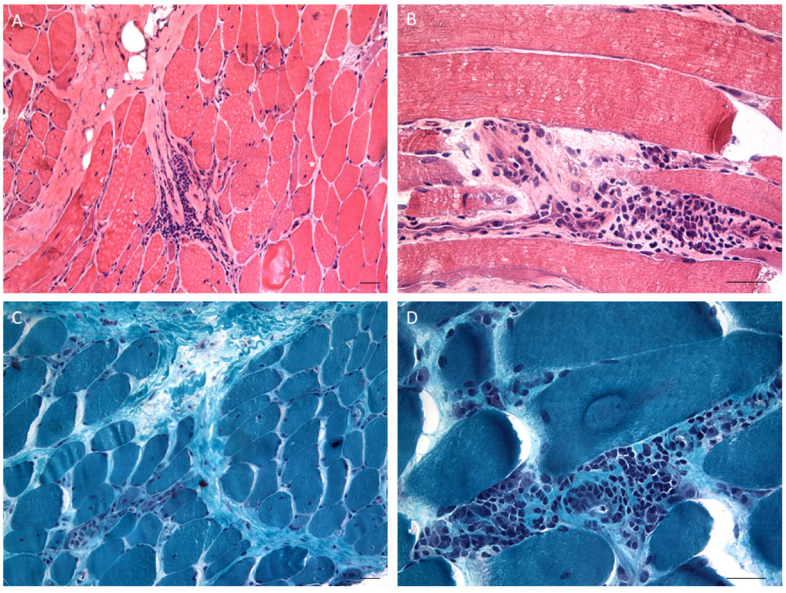
MRI imaging allows the evaluation of other SARS-CoV-2-associated muscular changes, such as sarcopenia and cachexia in patients with prolonged weakness. Sarcopenia is defined as muscle loss typically associated with aging, though other contributing factors include inactivity and poor nutrition. Cachexia is associated with muscle wasting due to chronic illness. Typical MRI findings, in this case, encompass muscle atrophy associated with decreased muscle size and fat infiltration[59].

Electrodiagnostic studies

Few studies have focused on the electrodiagnostic assessment of SARS-CoV-2 patients with muscle weakness. Most case reports / series included patients with severe SARS-CoV-2 infections, possibly presenting with CIM. Cabañes-Martínez performed electrodiagnostic assessment in a cohort of 12 ICU SARS-CoV-2

patients with ICUAW. Seven out of 12 patients showed some degrees of EMG abnormalities, including abundant spontaneous activity, motor unit potential with decreased amplitude and duration. Repetitive nerve stimulation was normal in all cases[55]. Similarly, in another study, 8 SARS-CoV-2 subjects out of 23 patients showed increased spontaneous activity on EMG[65]. A 62-year-old woman with severe SARS-CoV-2 presented motor unit action potentials (MUAPs) with short duration and low amplitude as well as early recruitment, more evident in the quadriceps. On DMS, the post-DMS CMAP was absent in the quadriceps and of reduced amplitude in the tibialis anterior. The ratio of the amplitudes of the CMAP achieved by motor nerve stimulation and DMS is useful to differentiate between neuropathic and myopathic processes, with values near 1 suggesting a myopathic disorder[66]. In this case, the ratio of the CMAP amplitudes achieved by peroneal nerve stimulation and DMS of the tibialis anterior was 0.96, supporting the diagnosis of SARS-CoV-2-related myopathy[14]. A case series of 3 patients with post-SARS-CoV-2 infection myalgia and fatigue showed EMG alterations consistent with myopathies, including MUAP with early recruitment, short duration, and low amplitude in proximal muscles[67].

Figure 14.2: Muscle biopsy of a 16-year-old female patient with a suspected systemic sclerosis-related inflammatory myopathy and SARS-CoV-2 infection



A (20x) and **B** (40x) show scattered necrotic fibers with macrophage infiltration. *Increased centralized nuclei and fiber splitting are also present (hematoxylin & eosin stain, light microscopy). **C** (20x) and **D** (40x) display perivascular inflammatory cell infiltrates and slightly increased endomysial fibrosis (Gomori's trichrome stain, light microscopy).

Overall, these studies suggest no specific electrodiagnostic patterns associated with SARS-CoV-2 myopathies. However, patients with severe SARS-CoV-2 infections may present a more abundant spontaneous activity if compared with patients in the ICU for other etiologies[55].

Histopathological studies

Muscle biopsy may be useful in the differential diagnosis of SARS-CoV-2-associated myopathies (Figure 14.2).

Manzano et al. performed a muscle biopsy of the left deltoid in a patient with a suspected SARS-CoV-2 inflammatory myopathy, showing mild perivascular inflammation in a few vessels without regenerating fibers or perifascicular atrophy. Immunohistochemical analysis displayed abnormal expression of the major histocompatibility complex class I antigen on sarcolemma and sarcoplasm. In addition, abnormal expression of the myxovirus resistance protein A on muscle fibers and capillaries was seen with no membrane attack complex deposition on muscle fibers or vessels. No SARS-CoV-2 RNA was present in the sample[11]. Myxovirus resistance protein A (a type I interferon-inducible protein) can accumulate in muscle fibers and capillaries as an early sign of dermatomyositis preceding muscular atrophy. However, its abnormal deposition may present also following viral infections, including SARS-CoV-2[68]. In addition, muscle tissue lacked deposition of membrane attack complex on capillaries, another sign of dermatomyositis. The authors made a final diagnosis of SARS-CoV-2-associated myopathy caused by type I interferonopathy.

Severe cases of SARS-CoV-2 infection may show consistent vascular pathology on histopathological assessment. In a post-mortem evaluation of a middle-aged woman with rapidly progressive and systemic SARS-CoV-2 infection, Hooper et al. detected diffuse fibrin microthrombi, perimysial microhemorrhages, muscle fiber vacuolar degeneration, and necrosis on muscle tissue[69]. Further analysis revealed no angulated atrophic fibers, basophilic regenerating fibers or increased central nuclei, and only minimal inflammatory infiltrates. Electron microscopy showed no clear signs of direct viral-induced muscle damage. In this case, muscle involvement was more likely due to endothelial injury and vascular damage rather than direct viral infection.

Similarly, in another report on a patient with a suspected SARS-CoV-2-associated myopathy presenting with acute proximal and bulbar weakness, muscle biopsy highlighted features consistent with an inflammatory etiology[25]. These included perivascular inflammatory infiltration with endomysial extension, regenerating fibers (as suggested by mild sarcoplasmic basophilia and enlargement of visible nuclei), and upregulation of human leukocyte antigen class ABC expression on non-necrotic fibers. Cytochrome oxidase / succinic dehydrogenase enzyme histochemistry was unrevealing.

In a case series including 3 muscle biopsies in severe SARS-CoV-2 cases, the findings suggested a non-specific degenerative-regenerative process, supporting a diagnosis of CIM[55]. In particular, 2 patients presented only occasional atrophic and regenerative fibers. One patient displayed scattered necrotic and regenerative fibers without inflammatory infiltrates. Most of the fibers presented an equal number of degenerative-regenerative alterations and no increase in fibers with internal nuclei. Oxidative histochemical analysis, ATP techniques, HLA as well as C5b9 staining were unremarkable. No signs of microvascular damage were detected.

Overall, muscle biopsies coupled with electrodiagnostic studies and imaging can be valuable tools in the multimodal assessment of SARS-CoV-2 patients with suspected myopathies.

Treatment

There are no specific treatments for SARS-CoV-2-associated myopathies. As a rule of thumb, inflammatory myopathies associated with SARS-CoV-2 infection should be treated with corticosteroids (e.g., intravenous methylprednisolone 1 g/die for 3-5 days followed by oral prednisone 1 mg/kg/die for 4 weeks with slow tapering)[11,25,70]. Although there is no high-quality evidence available, another report suggests the use of tocilizumab[25].

In the context of CIM, controlling risk factors and providing support therapies remain the mainstay of treatment. Avoiding hyperglycemia, certain drugs (vasoactive medications, corticosteroids, neuromuscular blocking agents, sedatives aminoglycosides, vancomycin), and limiting parenteral nutrition, as well as prolonged bed immobilization and mechanical ventilation reduce the risk of ICU-acquired CIM[71]. Intensive insulin therapy and early rehabilitation seem the most useful approaches for preventing CIM. There is no high-quality evidence supporting the use of corticosteroids or electric muscle stimulation in this setting[72].

Patients presenting with rhabdomyolysis are at increased risk for heme-induced acute kidney injury[73-75]. Early and aggressive fluid resuscitation is the major preventative measure. Patients presenting CK levels > 5,000 U/L or increasing values regardless of baseline values should receive intravenous fluids[76]. Isotonic fluids with an initial volume repletion at a rate of 1- 2 L/hour may be preferred over alternatives, such as colloids. There are some limited data to support the use of urine alkalinization with bicarbonate, loop diuretics, mannitol, and routine renal replacement therapy in severe rhabdomyolysis[76].

Take-home message

- Muscle involvement in the context of SARS-CoV-2 infection includes myalgia, myositis, rhabdomyolysis, as well as critical-illness myopathies[14].
- Rare SARS-CoV-2 cases with muscle involvement presented an inflammatory-like phenotype with some features of type I interferonopathies, a group of autoinflammatory disorders with prominent enhanced type I interferon signaling.
- Muscle MRI is valuable for assessing SARS-CoV-2-associated muscular changes, such as sarcopenia and cachexia in patients with prolonged weakness.
- Histopathological analysis of muscle biopsies from SARS-CoV-2 patients with muscle involvement may show inflammatory and/or chronic illness myopathy-related changes.
- There are no specific treatments for SARS-CoV-2-associated myopathies. Inflammatory-like forms should be treated similarly to inflammatory myositis, whereas critical illness myopathies require ICU-related risk factors to be controlled and the provision of support therapy.

References

1. Tsai L-K, Hsieh S-T, Chao C-C, et al. Neuromuscular Disorders in Severe Acute Respiratory Syndrome. *Arch Neurol.* 2004;61(11):1669-1673.
2. Ferrandi PJ, Alway SE, Mohamed JS. The interaction between SARS-CoV-2 and ACE2 may have consequences for skeletal muscle viral susceptibility and myopathies.*J Appl Physiol.* 2020;129(4):864-867.
3. Crum-Cianflone NF. Bacterial, Fungal, Parasitic, and Viral Myositis. *Clin Microbiol Rev.* 2008;21(3):473-494.
4. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. *PNAS.* 2020;117(21):11727-11734.
5. Yamamoto K, Takeshita H, Rakugi H. ACE2, angiotensin 1-7 and skeletal muscle: review in the era of COVID-19. *Clin Sci.* (Lond) 2020;134(22):3047-3062.
6. Coperchini F, Chiovato L, Croce L, et al. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev.* 2020;53:25-32.
7. McGonagle D, Bridgewood C, Ramanan AV, et al. COVID-19 vasculitis and novel vasculitis mimics. *Lancet Rheumatol.* 2021;3(3):e224-233.
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
9. Beydon M, Chevalier K, Tabaa OA, et al. Myositis as a manifestation of SARS-CoV-2. *Ann Rheum Dis.* 2021;80(3):e42-e42.
10. Mehan WA, Yoon BC, Lang M, et al. Paraspinal Myositis in Patients with COVID-19 Infection. *Am J Neuroradiol.* 2020;41(10):1949-1952.
11. Manzano GS, Woods JK, Amato AA. Covid-19–Associated Myopathy Caused by Type I Interferonopathy. *N Engl J Med.* 2020;383(24):2389-2390.
12. Jin M, Tong Q. Rhabdomyolysis as Potential Late Complication Associated with COVID-19. *Emerg Infect Dis.* 2020;26(7):1618-1620.
13. Chedid NR, Udit S, Solhjou Z, et al. COVID-19 and Rhabdomyolysis. *J Gen Intern Med.* 2020;35(10):3087-3090.
14. Bagnato S, Boccagni C, Marino G, et al. Critical illness myopathy after COVID-19. *Int J Infect Dis.* 2020;99:276-278.
15. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med.* 2020;288(3):335-344.
16. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New Engl J Med.* [Internet] 2020;382(18):1708-1720.
17. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet.* 2020;395(10239):1763-1770.

18. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
19. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
20. Chen Y, Zhao M, Wu Y, Zang S. Epidemiological analysis of the early 38 fatalities in Hubei, China, of the coronavirus disease 2019. *J Glob Health*. 2020;10(1):011004.
21. Duarte-Neto AN, Monteiro RAA, da Silva LFF, et al. Pulmonary and systemic involvement in COVID-19 patients assessed with ultrasound-guided minimally invasive autopsy. *Histopathology*. 2020;77(2):186-197.
22. Zhong Z-F, Huang J, Yang X, et al. Epidemiological and clinical characteristics of COVID-19 patients in Hengyang, Hunan Province, China. *World J Clin Cases*. 2020;8(12):2554-2565.
23. Khosla SG, Nylen ES, Khosla R. Rhabdomyolysis in Patients Hospitalized With COVID-19 Infection: Five Case Series. *J Investige Med High Impact Case Rep*. 2020;8:2324709620984603.
24. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. *JAMA Neurol*. 2020;77(11):1440.
25. Zhang H, Charmchi Z, Seidman RJ, et al. COVID-19-associated myositis with severe proximal and bulbar weakness. *Muscle Nerve*. 2020;62(3):E57-60.
26. Valente-Acosta B, Moreno-Sanchez F, Fueyo-Rodriguez O, Palomar-Lever A. Rhabdomyolysis as an initial presentation in a patient diagnosed with COVID-19. *BMJ Case Rep*. 2020;13(6):e236719.
27. Gefen AM, Palumbo N, Nathan SK, et al. Pediatric COVID-19-associated rhabdomyolysis: a case report. *Pediatr Nephrol*. 2020;35(8):1517-1520.
28. Zhang Q, Shan KS, Minalyan A, et al. A Rare Presentation of Coronavirus Disease 2019 (COVID-19) Induced Viral Myositis With Subsequent Rhabdomyolysis. *Cureus*. 2020;12(5):e8074.
29. Veyseh M, Koyoda S, Ayesha B. COVID-19 IgG-related autoimmune inflammatory necrotizing myositis. *BMJ Case Rep*. 2021;14(4):e239457.
30. Pitscheider L, Karolyi M, Burkert FR, et al. Muscle involvement in SARS-CoV-2 infection. *Eur J Neurol*. 2020. doi: abs/10.1111/ene.14564. [Preprint]
31. Crow YJ. Type I interferonopathies: Mendelian type I interferon up-regulation. *Curr Opin Immunol*. 2015;32:7-12.
32. Suwanwongse K, Shabarek N. Rhabdomyolysis as a Presentation of 2019 Novel Coronavirus Disease. *Cureus*. 2020;12(4):e7561.
33. Khan NAJ, Khalid S, Ullah S, et al. Necrotizing Autoimmune Myopathy: A Rare Variant of Idiopathic Inflammatory Myopathies. *J Investig Med High Impact Case Rep*. 2017;5(2):2324709617709031.
34. Fadila MF, Wool KJ. Rhabdomyolysis secondary to influenza a infection: a case report and review of the literature. *N Am J Med Sci*. 2015;7(3):122-124.

35. Latronico N, Herridge M, Hopkins RO, et al. The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med*. 2017;43(9):1270-1281.
36. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *Lancet Neurol*. 2011;10(10):931-941.
37. Dres M, Dubé B-P, Mayaux J, et al. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. *Am J Respir Crit Care Med*. 2017;195(1):57-66.
38. Lacomis D, Zochodne DW, Bird SJ. Critical illness myopathy. *Muscle Nerve*. 2000;23(12):1785-1788.
39. Bolton CF. Neuromuscular manifestations of critical illness. *Muscle Nerve*. 2005;32(2):140-163.
40. Latronico N. Critical illness polyneuropathy and myopathy 20 years later. No man's land? No, it is our land! *Intensive Care Med*. 2016;42(11):1790-1793.
41. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med*. 2014;370(17):1626-1635.
42. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med*. 2009;37(10 Suppl):S299-308.
43. Chlan LL, Tracy MF, Guttormson J, Savik K. Peripheral muscle strength and correlates of muscle weakness in patients receiving mechanical ventilation. *Am J Crit Care*. 2015;24(6):e91-98.
44. Wolfe KS, Patel BK, MacKenzie EL, et al. Impact of Vasoactive Medications on ICU-Acquired Weakness in Mechanically Ventilated Patients. *Chest*. 2018;154(4):781-787.
45. Yang T, Li Z, Jiang L, et al. Risk factors for intensive care unit-acquired weakness: A systematic review and meta-analysis. *Acta Neurol Scand*. 2018;138(2):104-114.
46. Lönnqvist P-A, Bell M, Karlsson T, et al. Does prolonged propofol sedation of mechanically ventilated COVID-19 patients contribute to critical illness myopathy? *Br J Anaesth*. 2020;125(3):e334-336.
47. Goossens C, Marques MB, Derde S, et al. Premorbid obesity, but not nutrition, prevents critical illness-induced muscle wasting and weakness. *J Cachexia Sarcopenia Muscle*. 2017;8(1):89-101.
48. Van den Berghe G, Schoonheydt K, Becx P, et al. Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology*. 2005;64(8):1348-1353.
49. Garnacho-Montero J, Madrazo-Osuna J, García-Garmendia JL, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. *Intensive Care Med*. 2001;27(8):1288-1296.
50. Denehy L, de Morton NA, Skinner EH, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). *Phys Ther*. 2013;93(12):1636-1645.

51. Huang M, Chan KS, Zanni JM, et al. Functional Status Score for the ICU: An International Clinimetric Analysis of Validity, Responsiveness, and Minimal Important Difference. *Crit Care Med.* 2016;44(12):e1155-1164.
52. Kelmenson DA, Quan D, Moss M. What is the diagnostic accuracy of single nerve conduction studies and muscle ultrasound to identify critical illness polyneuromyopathy: a prospective cohort study. *Crit Care.* 2018;22(1):342.
53. Tankisi H, Tankisi A, Harbo T, et al. Critical illness myopathy as a consequence of Covid-19 infection. *Clin Neurophysiol.* 2020;131(8):1931-1932.
54. Aerde NV, Berghe GV den, Wilmer A, et al. Intensive care unit acquired muscle weakness in COVID-19 patients. *Intensive Care Med.* 2020;46(11):2083-2085.
55. Cabañes-Martínez L, Villadóniga M, González-Rodríguez L, et al. Neuromuscular involvement in COVID-19 critically ill patients. *Clin Neurophysiol.* 2020;131(12):2809-2816.
56. Madia F, Merico B, Primiano G, et al. Acute myopathic quadriplegia in patients with COVID-19 in the intensive care unit. *Neurology.* 2020;95(11):492-494.
57. Yildiz OK, Yildiz B, Avci O, et al. Clinical, Neurophysiological and Neuroimaging Findings of Critical Illness Myopathy After COVID-19. *Cureus.* 2021;13(3):e13807.
58. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. *J Neurol.* 2020;267(4):877-882.
59. Ramani SL, Samet J, Franz CK, et al. Musculoskeletal involvement of COVID-19: review of imaging. *Skeletal Radiol.* 2021;50(9):1763-1773.
60. Jelinek JS, Murphey MD, Aboulafia AJ, et al. Muscle infarction in patients with diabetes mellitus: MR imaging findings. *Radiology.* 1999;211(1):241-247.
61. Lu C-H, Tsang Y-M, Yu C-W, et al. Rhabdomyolysis: magnetic resonance imaging and computed tomography findings. *J Comput Assist Tomogr.* 2007;31(3):368-374.
62. Kattapuram TM, Suri R, Rosol MS, et al. Idiopathic and diabetic skeletal muscle necrosis: evaluation by magnetic resonance imaging. *Skeletal Radiol.* 2005;34(4):203-209.
63. Shi Z, de Vries HJ, Vlaar APJ, et al. Diaphragm Pathology in Critically Ill Patients With COVID-19 and Postmortem Findings From 3 Medical Centers. *JAMA Intern Med.* 2021;181(1):122.
64. Guarracino F, Vetrugno L, Forfori F, et al. Lung, Heart, Vascular, and Diaphragm Ultrasound Examination of COVID-19 Patients: A Comprehensive Approach. *J Cardiothorac Vasc Anesth.* 2021;35(6):1866-1874.
65. Scarpino M, Bonizzoli M, Lazzeri C, et al. Electrodiagnostic findings in patients with non-COVID-19- and COVID-19-related acute respiratory distress syndrome. *Acta Neurol Scand.* 2021;144(2):161-169.
66. Rich MM, Bird SJ, Raps EC, et al. Direct muscle stimulation in acute quadriplegic myopathy. *Muscle Nerve.* 1997;20(6):665-673.
67. Daia C, Scheau C, Neagu G, et al. Nerve conduction study and electromyography findings in patients recovering from Covid-19 – Case report. *Int J Infect Dis.* 2021;103:420.

68. Pulia MS, O'Brien TP, Hou PC, et al. Multi-tiered screening and diagnosis strategy for COVID-19: a model for sustainable testing capacity in response to pandemic. *Ann Med.* 2020;52(5):207-214.

69. Hooper JE, Uner M, Priemer DS, et al. Muscle Biopsy Findings in a Case of SARS-CoV-2-Associated Muscle Injury. *J Neuropathol Exp Neurol.* 2021;80(4):377-378.

70. Shabbir A, Camm CF, Elkington AG, et al. Myopericarditis and myositis in a patient with COVID-19: a case report. *Eur Heart J Case Rep.* 2020;4(6):1-6.

71. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. *Intensive Care Med.* 2020;46(4):637-653.

72. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev.* 2014;(1):CD006832.

73. Warren JD, Blumbergs PC, Thompson PD. Rhabdomyolysis: A review. *Muscle Nerve.* 2002;25(3):332-347.

74. Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. *J Am Soc Nephrol.* 2000;11(8):1553-1561.

75. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine.* (Baltimore) 2005;84(6):377-385.

76. Michelsen J, Cordtz J, Liboriussen L, et al. Prevention of rhabdomyolysis-induced acute kidney injury – A DASAIM/DSIT clinical practice guideline. *Acta Anaesthesiol Scand.* 2019;63(5):576-586.

Chapter 15. Teleneurology in the COVID-19 era

Elena Moro, Sara Meoni

Introduction

Telemedicine is defined as the delivery of medical care by electronic communication between a health care professional (i.e., a physician or advanced practice provider) and a patient, each at different locations[1]. It has the potential to overcome geographical, physical, and biological barriers to health care access. Telemedicine has been shown to be a safe, efficient, timely, and convenient procedure[1,2]. For decades, it has provided medical care to rural and underserved areas[3], but only more recently has this field undergone an accelerated development. This has been due to advances in technologies and a broader Internet access.

The application of telemedicine to neurology (teleneurology) allows delivery of or additional neurological care to remote locations. It reflects the gap existing between the growing demand of neurological expertise and the lack of neurologists[4,5].

Over the last decades, teleneurology has been successfully applied in acute care, mostly for stroke ("telestroke")[6], in outpatient evaluation and in teleconsultations for chronic diseases such as movement disorders[7], epilepsy[8], multiple sclerosis[9], dementia[10] and headache[11].

However, before the advent of COVID-19, there were considerable limitations to the use of telemedicine: technological, regulatory, political and clinical considerations, reimbursement issues, and social barriers.

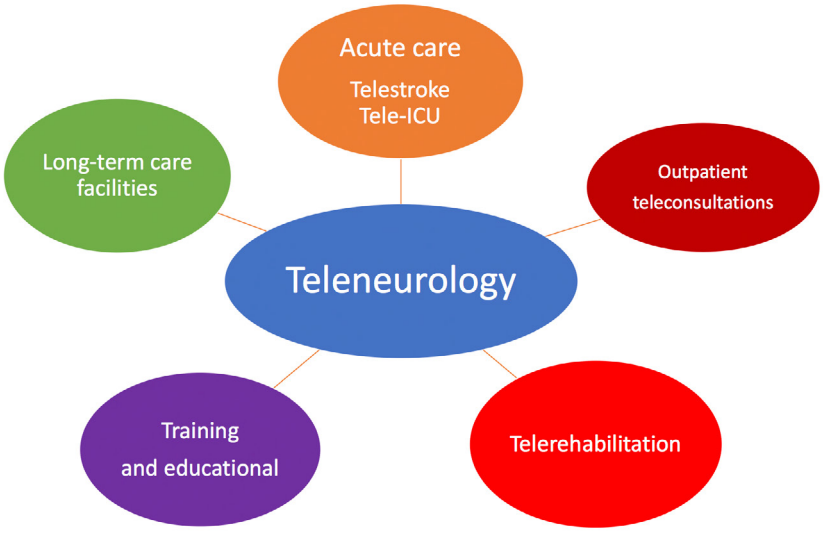
Since 2020, the COVID-19 pandemic and the new related challenges in health care have greatly pushed teleneurology forward[12].

Most of the hospitals and health systems around the world have modified their standard practices in telemedicine in order to assure care management of non-COVID neurological disorders[13]. The main objective of the adoption of telehealth during the pandemic is the safety of all the participants in their clinical encounters, including patients, family members, caregivers and health care teams. Several reimbursement and licenses issues which had limited teleneurology in the pre-COVID era, have been suspended or removed in order to deal with the worldwide health emergency. Most of the hospital consultations have

been replaced by teleconsultations using tablets, smartphones, mobile telehealth carts or cameras at patients' homes. New telemedicine tools have emerged to reduce the exposure to COVID-19 infection[13,14].

All the pandemic-related changes in neurology clinical practice have happened very quickly, in days or weeks, requiring the availability of adequate equipment and the rapid development of technology infrastructure to support the large expansion in the use of teleneurology. For example, at the epicenter of the pandemic, at NYU Langone Health, teleconsultations grew from a typical 50 visits per day to >7,000 daily visits within 10 days[15]. At the University of Pennsylvania Health System, nearly 400,000 telemedicine meetings across thousands of providers occurred in less than three months, requiring implementation of videoconferencing platforms, training, and development of new procedures for outpatient and inpatient management[16].

Figure 15.1: Teleneurology applications in the COVID-19 era



ICU: Intensive Care Unit.

Moreover, the pandemic has greatly impacted the scientific community and academic activities, as all the congresses, and educational training and teaching courses have been turned into virtual conferences and webinars, requiring a huge effort to change the routine practices in place up to the pre-COVID era.

In this chapter, we provide a summary of the available literature on teleneurology during the COVID-19 pandemic, its advantages and limitations, clinical implications, and future challenges.

Telestroke

Since the earliest stages of the pandemic, the risk of underestimating and undertreating several potentially treatable strokes emerged, leading health authorities to generate an appeal to the general population not to stay at home in case of onset of acute neurological symptoms[17]. However, studies in European countries[18,19], China[20] and the USA[21] reported a significant global reduction in admissions to the emergency department or stroke units for acute ischemic stroke in the first period of the emergency. This contraction has likely been secondary to policies minimizing provider-patient interactions as well as patients' reticence to come to the emergency departments during the pandemic.

At the same time, the COVID-19 crisis has required implementation of the use of telemedicine in the field of stroke at all treatment stages[22,23], and it could be the starting point for its large-scale use[24,25].

The continuum of care via telestroke has broadened to include prehospital, inter-facility and intra-facility hospital-based services, stroke telerehabilitation, and ambulatory telestroke[26].

Alternative stroke care models have been developed including protected stroke codes and streamlined triage for endovascular therapy[27-29] in order to maintain patient care in this pandemic setting.

Prehospital telestroke offers many advantages for acute stroke care in this context, such as the use of mobile systems limiting person-to-person contact in the prehospital stroke assessment, and ambulance-based telestroke. Emergency service providers can focus on personal protective equipment (PPE) and respiratory management, in parallel with a remote emergency provider or stroke specialist, who can assist with screening during ambulance transport[30]. The prehospital evaluation by the remote provider potentially reduces PPE usage limiting the need for multiple re-evaluations prior to acute treatment decisions. Prehospital triage with telestroke could further limit unnecessary exposures and PPE usage by identifying the appropriate hospital for the patient's needs. However, additional research is needed in order to optimize tele-triage protocols.

Inter-facility telestroke may also help during the pandemic, in order to limit unnecessary transfers of patients with mild stroke syndromes or stroke mimics in their local facilities and to reduce potential exposure to the patient and treatment teams. This is a key point, considering the higher risk of infection in stroke patients[31]. This model can also preserve bed availability at the hub for patients needing a higher level of care. Moreover, ambulance-based mobile systems can be used to support long distance transfers, particularly for "drip-and-ship" post-thrombolysis management, and for critically ill stroke patients[32].

During the COVID-19 crisis, several hospitals and stroke centers have developed intra-facility telestroke to help reduce provider and patient exposure and

PPE usage, and to cover workforce shortages due to COVID-19 related illness and quarantining of staff[13,14]. A new framework for COVID-19 screening and proper usage of PPE incorporated with stroke assessment, called "protected stroke code"[28] has emerged during the pandemic, which has also been applied at an intra-facility level. This model allows several team members to participate in the patient evaluation remotely, while preserving PPE and limiting staff-patient interactions. Moreover, some academic centers have also switched to virtual rounds using a teleconferencing platform[13], with table rounds first completed via teleconferencing, and with only one team member moving the workstation to each patient's room to carry out the examination, functioning as tele-presenter for the remote team. The virtual round model allows health-care providers to guarantee patients care even during therapeutic or prophylactic quarantine. In addition, this allows for a rotating schedule which can be used to address staff shortages.

Tele-ICU

Telemedicine enables remote monitoring of patients in intensive care units (ICUs) without continuous availability of critical care expertise, in order to expand coverage, similar to telestroke coverage of emergency departments. Management of neurological emergencies, such as status epilepticus, may be facilitated by telemedicine, thanks to remote access to subspecialty expertise.

In the pre-COVID-19 era, a metanalysis reported on a reduction in mortality and hospital lengths of stay with tele-ICU[33]. The neurological ICU population is not specifically addressed in most studies, although one report demonstrated reduced response times and shorter lengths of stay[34].

The pandemic has been the turning point for digital transformation also in neurocritical care. The tele-ICU solution can triage and manage patients in isolation, conserving PPE, avoiding infection, and optimizing human resources with constant remote monitoring. Close range telemedicine called 'ePPE' has evolved and wireless monitoring has been developed[35]. Mobile devices are used to communicate with patients who can be physically attended to immediately if needed. Workforce sustainability, fewer burnout episodes, and lower incidence of specialists having to quarantine are consequences of tele- ICUs. Video conferencing helps decrease infection risk during the pandemic. Moreover, tele-EEG monitoring can be used for diagnosing non-convulsive status epilepticus as a cause of unexplained consciousness in COVID-19 patients[36]. The remote reading of EEG helps reduce the risk of infection. Furthermore, telemedicine may also help to establish a dedicated command unit for critical care support by linking ICUs of COVID hospitals on a single platform[37].

Outpatient teleneurology

Studies across multiple neurological subspecialties report non-inferiority of outpatient evaluations by telemedicine compared with in-person evaluations in terms of patient and caregiver satisfaction and diagnostic accuracy[38].

Telemedicine has the potential to address challenges in the transition between hospital and home. In the pre-COVID-19 era, transitional care models had showed the potential to improve outpatient management, mostly for post-stroke patients[39]. However, these models were not really incorporated into global routine practice until today. Pre-pandemic barriers to widespread use of telemedicine for outpatient care have mostly been due to reimbursement challenges and lack of infrastructures[40].

With the pandemic, social distancing requirements and restrictions on non-essential visits to the clinic created an urgent need for outpatient telemedicine in the stroke population[25,41,42] and in several chronic neurological diseases, such as Parkinson's disease[7,4349], and other movement disorders[2,50-53], epilepsy[54-68], Alzheimer's disease[69-73], multiple sclerosis[74-81] and migraine[82–84].

The integration of telemedicine into outpatient practice has required a rapid adaptation of the standard clinic practice[85]. In the US, for example, a policy of expansion of Centers for Medicare and reimbursement for Medicaid Services in March 2020 led to the implementation of telestroke services[38]. Institutional support is strongly required for widespread adoption and sustainability of technology, such as hardware, audiovisual platforms, Electronic Health Records integration, and server support. Scheduling, billing and coding integration have also to be considered in any staffing changes. Training for providers and staff, patient education, and on-call technology assistance for both patients and providers must also be guaranteed. The main limitation of the application of teleneurology in outpatient care concerns its feasibility in elderly patients, frequently with motor and cognitive issues, and having little contact with the younger generation who are more experienced with technology.

Preliminary experience suggests positive results of telemedicine use during the pandemic, both via video and phone. However, disparities in health care delivery emerged, and these were exacerbated by inequalities in access to technology in socially or economically disadvantaged populations[86]. Lack of adequate access to technology, high-speed internet services and increased need for technology support will need to be addressed to achieve widespread improvements in access to care.

Teleneurology for long-term care facilities

Telemedicine can be applied to patients in long-term care and correctional facilities which have limited access to specialty care[87]. The COVID-19 pandemic

has raised a major concern in terms of a higher risk and exposure for this vulnerable population of patients and staff due to close living quarters and the need for frequent in-person assessments of healthcare needs. The use of telemedicine for post-acute care in long-term care settings has the advantage of staff support, which reduces the technological burden on patients, and on-site assistance with the physical examination. Telemedicine can also be useful to assess patients with stroke symptoms in these environments and to guide necessary triage decisions[88,89]. Telestroke could inform appropriate hospital destination choices for both thrombolytics and thrombectomy, minimizing the activation of emergency medical services and exposure of health care providers, and avoiding unnecessary transfer to the emergency room for high-risk patients.

Telerehabilitation

Telemedicine is important in rehabilitation[90]. During the pandemic, the standard model of in-person stroke rehabilitation, including physical, occupational, and speech and language therapies, has been reassessed. The drastic reduction in the availablity of rehabilitation facilities, due to their conversion to host COVID-19 patients, makes the telerehabilitation a key tool in this phase. On the Google trend engine, searches for the term "telerehab" grew by about 400% in the first week of March 2020.[91] Indeed, for COVID-19 patients with ischemic stroke, telerehabilitation has been shown to be beneficial[92] and it can dramatically lower the risk of infection without compromising post-stroke recovery.

Telerehabilitation has been performed with benefit in other neurological diseases such as Parkinson's disease[93-98] and multiple sclerosis[74,99,100].

Telerehabilitation might also have a role in achieving an adequate cognitive stimulation in several neurological diseases with associated cognitive issues in the era of social distancing due to the pandemic[101].

Terehabilitation is useful even for non-infected patients, reducing PPE consumption and the exposure of therapists and providers, and helping maintain patient safety in a fragile population[102]. The application of telerehabilitation may equally help patients in densely populated urban areas where the infection risk is higher, and for patients living in rural areas, with geographic barriers and shelter-at-home orders limiting their access to therapy and healthcare services[103].

New digital technologies

In parallel with the dramatic and far-reaching health crisis, the COVID-19 pandemic has boosted the integration of new digital technologies into our medical armamentarium for the management of several neurological disorders,

including stroke[104,105], Parkinson's disease,[106-108], epilepsy[109,110], multiple sclerosis[80,81] and dementia[73].

Novel applications for remote monitoring via e-diaries, sensors, vital sign monitoring, or even cardiac monitoring via smart watches have been applied for diagnostic, rehabilitation and research purposes and regular follow-up visits.

Stroke is the field which has probably seen a larger use of digital technologies compared to other neurological disciplines. Accelerometers and gyroscopes in smartphones have been shown to be effective in recording mechanical cardiac activity to support the diagnosis of atrial fibrillation (AF)[111].

Photoplethysmography with a smartphone camera has been applied for AF screening[112]. Apps specifically designed to record a rhythm strip using smartwatches have been seen to be accurate in differentiating AF from sinus rhythm[113]. More recently, an app for detecting AF has been applied in the Apple Heart Study[114].

Depending on the availability of the users, the telerehabilitation sessions can be performed by phone, via videoconferencing software or through dedicated apps (i.e., "REHABmyPatient," "myRehab," or "RehabPal")[91].

This pandemic might be the key moment in which to introduce a more widespread use of new technologies to improve management of neurological disorders.

Training and educational teleneurology

The COVID-19 pandemic greatly impacted neurology education and training, including lectures, grand rounds and international congresses.[115,116] With social distancing and closure of lecture halls, in-person teaching and lessons moved to on-line platforms, such as WebEx™, Zoom™ and Microsoft Teams™, requiring a rapid availablility for millions of people, the development of technology resources, and teachers and students had to adapt to these changes[117-119].

The advantages of this new educational delivery are the access to live/on demand lectures from any location or from different educational centers via virtual platforms[120] with no need to travel. The limitations include the reduction of trainees' exposure to elective procedures and bed-side teaching, resulting in a poorer clinical experience. Moreover, remote education for some neurological skills such as neurological examination may not be ideal.

The experience from the pandemic may be utilized to further improve neurology education and training, as current and future neurology education will likely consist of a mixture of in-person and virtual learning.

Practical implications and future directions

In the post-pandemic era, the major limitations to the widespread use of teleneurology might be the lack of evidence for its efficacy, and understanding its proper place when in-person care is also available. Although randomized trials are challenging in teleneurology[121], the high volume of virtual visits during the COVID-19 crisis should allow patients' outcomes using telemedicine and in-person visits to be compared. Moreover, the role of evaluation through physical examination, provider-patient interaction, and workflow changes using telemedicine will need to be established.

In some ways, we might use teleneurology after the pandemic to improve on in-person visits. Indeed, telemedicine promotes a team approach by virtually bringing together providers from various disciplines in different locations without traveling and saving time. Similarly, teleneurology can allow family members to take part in tele-vists; they can provide medical history and receive counseling, and can be included in the decision-making process even if the medical team is working in remote, far from the patient and provider. For neurological patients in rural areas and those with limited mobility, telemedicine might have an important role when an in-person visit is not practical or the alternative is reduced care or no care at all. Teleneurology consultations in such situations has the potential to improve outcomes and reduce costs while saving time for busy clinicians.

Today teleneurology is still in its infancy. Along with digital transformation in other industries, teleneurology has considerable possibilities for further improvement[122]. The COVID-19 experience will lead to the development of new applications in large networks with analytics and big data. Moreover, artificial intelligence may automate some of the processes now requiring training and proficiency, improving teleneurology, diagnosis and outcomes. The integrated use of the electronic medical records and wearable devices adds important new information to increase teleneurology capabilities. Although teleneurology has limitations in terms of the physical examination, it may be enhanced through observational aids or in some cases the assistance of family members on site[123,124]. The integration of digital sensors and activity monitors into routine practice might provide additional information on patient characteristics not available during an in-person visit. With the growing use of home monitoring and wearable devices, health providers will need to learn how to monitor and to manage patient-generated data. Consequently, hospitals and health services need to develop new, more powerful informatics systems to manage a large inflow of data and to integrate it into electronic health records.

The pandemic has highlighted the problems of access to health care for those patients living in underserved areas[125]. The efforts of health systems, including community and long-term care facilities should be scrutinized to ensure an equal distribution of services, keeping patients in their own environment and optimizing the use of high-technology tools.

Moreover, telemedicine could provide specialist support for patients with neurological diseases needing a high level of expertise, such as movement disorders, epilepsy or stroke, avoiding the need to direct them to hub hospitals for lower-acuity problems. The goal should be to guarantee to all patients within any single system the same level of excellent care. This could consolidate subspecialty centers, reducing costs and avoiding duplication of valuable resources.

The use of telemedicine in the COVID-19 crisis has also changed the approach of the medical system to the patient, which was provider-based in the pre-pandemic era; this has now become patient-focused. The patient remains in his environment, saving time spent on transfers and visits. Moreover, tele-consultations with videos allow the provider to obtain important information about the patients' home environment, improving their overall care.

In conclusion, teleneurology expands access and availability across the spectrum from outpatient to acute care and rehabilitation[1]. The temporary enabling policies that expire with the public health emergency will hopefully translate into lasting changes. Private payers are increasing the coverage, and countries are considering new approaches to telemedicine licensing. These advances could dramatically improve the landscape for telemedicine and teleneurology. Hopefully, national, regional, private, and public entities will join forces to keep the development of telemedicine moving forward.

Take home message

- The COVID-19 pandemic has greatly pushed the development of teleneurology forward, reducing or removing technological, regulatory, political and clinical considerations, reimbursement issues, and social barriers.
- Teleneurology has been successfully applied in the COVID-19 era to manage outpatients, inpatients, and for rehabilitation purposes in several neurological disorders.
- The COVID-19 pandemic has boosted the integration of new digital technologies into the medical armamentarium for the management of neurological disesases.
- The pandemic has greatly impacted the scientific community and the academic activities, as all the congresses, and educational training and teaching courses have been turned into virtual conferences and webinars.
- After the pandemic, teleneurology could be used to improve on in-person visits and in academic activities, and to integrate the new technologies into our clinical practice.

References

1. Wechsler LR. Advantages and limitations of teleneurology. *JAMA Neurol.* 2015;72(3):349-354.
2. Dorsey ER, Glidden AM, Holloway MR, et al. Teleneurology and mobile technologies: the future of neurological care. *Nat Rev Neurol.* 2018;14(5):285-297.
3. Levine SR, Gorman M. "Telestroke": the application of telemedicine for stroke. *Stroke.* 1999;30(2):464-469.
4. Dall TM, Storm MV, Chakrabarti R, et al. Supply and demand analysis of the current and future US neurology workforce. *Neurology.* 2013;81(5):470-478.
5. Freeman WD, Vatz KA, Griggs RC, Pedley T. The Workforce Task Force report: clinical implications for neurology. *Neurology.* 2013;81(5):479-486.
6. Waseem H, Salih YA, Burney CP, et al. Efficacy and Safety of the Telestroke Drip-And-Stay Model: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis.* 2021;30(4):105638.
7. Shalash A, Spindler M, Cubo E. Global Perspective on Telemedicine for Parkinson's Disease. *J Parkinsons Dis.* 2021;11(s1):S11-S18.
8. Kissani N, Lengané YTM, Patterson V, et al. Telemedicine in epilepsy: How can we improve care, teaching, and awareness? *Epilepsy Behav.* 2020;103(Pt A):106854.
9. Kane RL, Bever CT, Ehrmantraut M, et al. Teleneurology in patients with multiple sclerosis: EDSS ratings derived remotely and from hands-on examination. *J Telemed Telecare.* 2008;14(4):190-194.
10. Costanzo MC, Arcidiacono C, Rodolico A, et al. Diagnostic and interventional implications of telemedicine in Alzheimer's disease and mild cognitive impairment: A literature review. *Int J Geriatr Psychiatry.* 2020;35(1):12-28.
11. Pereira-Monteiro J, Wysocka-Bakowska M-M, Katsarava Z, Antonaci F. Guidelines for telematic second opinion consultation on headaches in Europe: on behalf of the European Headache Federation (EHF). *J Headache Pain.* 2010;11(4):345-348.
12. Patterson V. Neurological telemedicine in the COVID-19 era. *Nat Rev Neurol.* 2021;17(2):73-74.
13. Al Kasab S, Almallouhi E, Holmstedt CA. Optimizing the Use Of Teleneurology During the COVID-19 Pandemic. *Telemed J E Health.* 2020;26(10):1197-1198.
14. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. *N Engl J Med.* 2020;382(18):1679-1681.
15. Mann DM, Chen J, Chunara R, et al. COVID-19 transforms health care through telemedicine: Evidence from the field. *J Am Med Inform Assoc.* 2020;27(7):1132-1135.
16. Wechsler LR. The Teleneurology Revolution. *Ann Neurol.* 2020;88(4):656-657.
17. Baracchini C, Pieroni A, Viaro F, et al. Acute stroke management pathway during Coronavirus-19 pandemic. *Neurol Sci.* 2020;41(5):1003-1005.

18. Padmanabhan N, Natarajan I, Gunston R, et al. Impact of COVID-19 on stroke admissions, treatments, and outcomes at a comprehensive stroke centre in the United Kingdom. *Neurol Sci.* 2021;42(1):15-20.
19. Bersano A, Kraemer M, Touzé E, et al. Stroke care during the COVID-19 pandemic: experience from three large European countries. *Eur J Neurol.* 2020;27(9):1794-1800.
20. Zhao J, Rudd A, Liu R. Challenges and Potential Solutions of Stroke Care During the Coronavirus Disease 2019 (COVID-19) Outbreak. *Stroke.* 2020;51(5):1356-1357.
21. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral Effect of Covid-19 on Stroke Evaluation in the United States. *N Engl J Med.* 2020;383(4):400-401.
22. Lin JC, Humphries MD, Shutze WP, et al. Telemedicine platforms and their use in the coronavirus disease-19 era to deliver comprehensive vascular care. *J Vasc Surg.* 2021;73(2):392-398.
23. Ting DSW, Carin L, Dzau V, Wong TY. Digital technology and COVID-19. *Nat Med.* 2020;26(4):459-461.
24. Leira EC, Russman AN, Biller J, et al. Preserving stroke care during the COVID-19 pandemic: Potential issues and solutions. *Neurology.* 2020;95(3):124-133.
25. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke.* 2020;15(4):361-364.
26. Guzik AK, Martin-Schild S, Tadi P, et al. Telestroke Across the Continuum of Care: Lessons from the COVID-19 Pandemic. *J Stroke Cerebrovasc Dis.* 2021;30(7):105802.
27. Goyal M, Ospel JM, Southerland AM, et al. Prehospital Triage of Acute Stroke Patients During the COVID-19 Pandemic. *Stroke.* 2020;51(7):2263-2267.
28. Khosravani H, Rajendram P, Notario L, et al. Protected Code Stroke: Hyperacute Stroke Management During the Coronavirus Disease 2019 (COVID-19) Pandemic. *Stroke.* 2020;51(6):1891-1895.
29. Nguyen TN, Abdalkader M, Jovin TG, et al. Mechanical Thrombectomy in the Era of the COVID-19 Pandemic: Emergency Preparedness for Neuroscience Teams: A Guidance Statement From the Society of Vascular and Interventional Neurology. *Stroke.* 2020;51(6):1896-1901.
30. Russi CS, Heaton HA, Demaerschalk BM. Emergency Medicine Telehealth for COVID-19: Minimize Front-Line Provider Exposure and Conserve Personal Protective Equipment. *Mayo Clin Proc.* 2020;95(10):2065-2068.
31. Chamorro A, Urra X, Planas AM. Infection after acute ischemic stroke: a manifestation of brain-induced immunodepression. *Stroke.* 2007;38(3):1097-1103.
32. Mohamed A, Fatima N, Shuaib A, Saqqur M. Comparison of mothership versus drip-and-ship models in treating patients with acute ischemic stroke: A systematic review and meta-analysis. *Int J Stroke.* 2021;17474930211013284.
33. Wilcox ME, Adhikari NKJ. The effect of telemedicine in critically ill patients: systematic review and meta-analysis. *Crit Care.* 2012;16(4):R127.

34. Vespa PM, Miller C, Hu X, et al. Intensive care unit robotic telepresence facilitates rapid physician response to unstable patients and decreased cost in neurointensive care. *Surg Neurol.* 2007;67(4):331-337.

35. Arabi YM, Azoulay E, Al-Dorzi HM, et al. How the COVID-19 pandemic will change the future of critical care. *Intensive Care Med.* 2021;47(3):282-291.

36. Gélisse P, Rossetti AO, Genton P, et al. How to carry out and interpret EEG recordings in COVID-19 patients in ICU? *Clin Neurophysiol.* 2020;131(8):2023-2031.

37. Haranath SP, Ganapathy K, Kesavarapu SR, Kuragayala SD. eNeuroIntensive Care in India: The Need of the Hour. *Neurol India.* 2021;69(2):245-251.

38. Hatcher-Martin JM, Adams JL, Anderson ER, et al. Telemedicine in neurology: Telemedicine Work Group of the American Academy of Neurology update. *Neurology.* 2020;94(1):30-38.

39. Bushnell CD, Duncan PW, Lycan SL, et al. A Person-Centered Approach to Post-stroke Care: The COMprehensive Post-Acute Stroke Services Model. *J Am Geriatr Soc.* 2018;66(5):1025-1030.

40. Guzik AK, Switzer JA. Teleneurology is neurology. *Neurology.* 2020;94(1):16-17.

41. Vollmuth C, Miljukov O, Abu-Mugheisib M, et al. Impact of the coronavirus disease 2019 pandemic on stroke teleconsultations in Germany in the first half of 2020. *Eur J Neurol.* 2021. doi: 10.1111/ene.14787. [Preprint]

42. D'Anna L, Ellis N, Bentley P, et al. Delivering telemedicine consultations for patients with transient ischaemic attack during the COVID-19 pandemic in a comprehensive tertiary stroke centre in the United Kingdom. *Eur J Neurol.* 2021. doi: 10.1111/ene.14750. [Preprint]

43. Ferreira D, Azevedo E, Araújo R. Teleneurology in Parkinson's disease: A step-by-step video guide. *Acta Neurol Scand.* 2021;144(2):221-225.

44. Miele G, Straccia G, Moccia M, et al. Telemedicine in Parkinson's Disease: How to Ensure Patient Needs and Continuity of Care at the Time of COVID-19 Pandemic. *Telemed J E Health.* 2020;26(12):1533-1536.

45. Cubo E, Hassan A, Bloem BR, Mari Z. Implementation of Telemedicine for Urgent and Ongoing Healthcare for Patients with Parkinson's Disease During the COVID-19 Pandemic: New Expectations for the Future. *J Parkinsons Dis.* 2020;10(3):911-913.

46. van den Bergh R, Bloem BR, Meinders MJ, Evers LJW. The state of telemedicine for persons with Parkinson's disease. *Curr Opin Neurol.* 2021;34(4):589-597.

47. Shivkumar V, Subramanian T, Agarwal P, et al. Uptake of telehealth in Parkinson's disease clinical care and research during the COVID-19 pandemic. *Parkinsonism Relat Disord.* 2021;86:97-100.

48. Larson DN, Schneider RB, Simuni T. A New Era: The Growth of Video-Based Visits for Remote Management of Persons with Parkinson's Disease. *J Parkinsons Dis.* 2021;11(s1):S27-S34.

49. Motolese F, Magliozzi A, Puttini F, et al. Parkinson's Disease Remote Patient Monitoring During the COVID-19 Lockdown. *Front Neurol.* 2020;11:567413.

50. Houston E, Kennedy AG, O'Malley D, et al. Telemedicine in Neurology: A Scoping Review of Key Outcomes in Movement Disorders. *Telemed J E Health*. 2021. doi: 10.1089/tmj.2021.0117. [Preprint]
51. Esper CD, Scorr L, Papazian S, et al. Telemedicine in an Academic Movement Disorders Center during COVID-19. *J Mov Disord.* 2021;14(2):119-125.
52. Mulroy E, Menozzi E, Lees AJ, et al. Telemedicine in Movement Disorders: Leçons du COVID-19. *Mov Disord.* 2020;35(11):1893-1896.
53. Cilia R, Mancini F, Bloem BR, Eleopra R. Telemedicine for parkinsonism: A two-step model based on the COVID-19 experience in Milan, Italy. *Parkinsonism Relat Disord.* 2020;75:130-132.
54. Moura LMVR, Donahue MA, Smith JR, et al. Telemedicine Can Support Measurable and High-Quality Epilepsy Care During the COVID-19 Pandemic. *Am J Med Qual.* 2021;36(1):5-16.
55. Olivo S, Cheli M, Dinoto A, et al. Telemedicine during the SARS-Cov-2 pandemic lockdown: Monitoring stress and quality of sleep in patients with epilepsy. *Epilepsy Behav.* 2021;118:107864.
56. Nair PP, Aghoram R, Thomas B, et al. Video teleconsultation services for persons with epilepsy during COVID-19 pandemic: An exploratory study from public tertiary care hospital in Southern India on feasibility, satisfaction, and effectiveness. *Epilepsy Behav.* 2021;117:107863.
57. Datta P, Barrett W, Bentzinger M, et al. Ambulatory care for epilepsy via telemedicine during the COVID-19 pandemic. *Epilepsy Behav.* 2021;116:107740.
58. Madaan P, Sahu JK, Wanigasinghe J, et al. Teleneurology based management of infantile spasms during COVID-19 pandemic: A consensus report by the South Asia Allied West syndrome research group. *Epilepsy Behav Rep.* 2021;15:100423.
59. Banks J, Corrigan D, Grogan R, et al. LoVE in a time of CoVID: Clinician and patient experience using telemedicine for chronic epilepsy management. *Epilepsy Behav.* 2021;115:107675.
60. Stafstrom CE, Sun LR, Kossoff EH, et al. Diagnosing and managing childhood absence epilepsy by telemedicine. *Epilepsy Behav.* 2021;115:107404.
61. Pasca L, Zanaboni MP, Grumi S, et al. Impact of COVID-19 pandemic in pediatric patients with epilepsy with neuropsychiatric comorbidities: A telemedicine evaluation. *Epilepsy Behav.* 2021;115:107519.
62. Lima MC, Sander M, Dos Santos Lunardi M, et al. Challenges in telemedicine for adult patients with drug-resistant epilepsy undergoing ketogenic diet treatment during the COVID-19 pandemic in the public healthcare system in Brazil. *Epilepsy Behav.* 2020;113:107529.
63. Tailby C, Collins AJ, Vaughan DN, et al. Teleneuropsychology in the time of COVID-19: The experience of The Australian Epilepsy Project. *Seizure.* 2020;83:89-97.
64. Kuroda N. Decision Making on Telemedicine for Patients With Epilepsy During the Coronavirus Disease 2019 (COVID-19) Crisis. *Front Neurol.* 2020;11:722.

65. Panda PK, Dawman L, Panda P, Sharawat IK. Feasibility and effectiveness of teleconsultation in children with epilepsy amidst the ongoing COVID-19 pandemic in a resource-limited country. *Seizure.* 2020;81:29-35.

66. Conde-Blanco E, Centeno M, Tio E, et al. Emergency implementation of telemedicine for epilepsy in Spain: Results of a survey during SARS-CoV-2 pandemic. *Epilepsy Behav.* 2020;111:107211.

67. Brigo F, Bonavita S, Leocani L, et al. Telemedicine and the challenge of epilepsy management at the time of COVID-19 pandemic. *Epilepsy Behav.* 2020;110:107164.

68. Punia V, Nasr G, Zagorski V, et al. Evidence of a Rapid Shift in Outpatient Practice During the COVID-19 Pandemic Using Telemedicine. *Telemed J E Health.* 2020;26(10):1301-1303.

69. Macchi ZA, Ayele R, Dini M, et al. Lessons from the COVID-19 pandemic for improving outpatient neuropalliative care: A qualitative study of patient and caregiver perspectives. *Palliat Med.* 2021;2692163211017383.

70. Gosse PJ, Kassardjian CD, Masellis M, Mitchell SB. Virtual care for patients with Alzheimer disease and related dementias during the COVID-19 era and beyond. *CMAJ.* 2021;193(11):E371-377.

71. De Marchi F, Contaldi E, Magistrelli L, et al. Telehealth in Neurodegenerative Diseases: Opportunities and Challenges for Patients and Physicians. *Brain Sci.* 2021;11(2):237.

72. Geddes MR, O'Connell ME, Fisk JD, et al. Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19. *Alzheimers Dement.* (Amst) 2020;12(1):e12111.

73. Cuffaro L, Di Lorenzo F, Bonavita S, et al. Dementia care and COVID-19 pandemic: a necessary digital revolution. *Neurol Sci.* 2020;41(8):1977-1979.

74. Xiang XM, Bernard J. Telehealth in Multiple Sclerosis Clinical Care and Research. *Curr Neurol Neurosci Rep.* 2021;21(4):14.

75. Cerqueira JJ, Ladeira AF, Silva AM, et al. Multiple Sclerosis Patient Management During the COVID-19 Pandemic: Practical Recommendations From the Portuguese Multiple Sclerosis Study Group (GEEM). *Front Neurol.* 2021;12:613769.

76. Howard IM, Burgess K. Telehealth for Amyotrophic Lateral Sclerosis and Multiple Sclerosis. *Phys Med Rehabil Clin N Am.* 2021;32(2):239-251.

77. Corea F, Ciotti S, Cometa A, et al. Telemedicine during the Coronavirus Disease (COVID-19) Pandemic: A Multiple Sclerosis (MS) Outpatients Service Perspective. *Neurol Int.* 2021;13(1):25-31.

78. Alonso R, Carvajal R, Boaventura M, Galleguillos L. Experience of South American MS and/or NMOSD experts in practice during the COVID-19 pandemic: Focus on Telemedicine. *Mult Scler Relat Disord.* 2021;48:102702.

79. D'haeseleer M. Teleconsultation will replace most face-to-face interactions in the multiple sclerosis clinic - Commentary. *Mult Scler.* 2021;27(2):178-179.

80. Moccia M, Lanzillo R, Brescia Morra V, et al. Assessing disability and relapses in multiple sclerosis on tele-neurology. *Neurol Sci.* 2020;41(6):1369-1371.

81. Bonavita S, Tedeschi G, Atreja A, Lavorgna L. Digital triage for people with multiple sclerosis in the age of COVID-19 pandemic. *Neurol Sci.* 2020;41(5):1007-1009.
82. Chiang C-C, Halker Singh R, Lalvani N, et al. Patient experience of telemedicine for headache care during the COVID-19 pandemic: An American Migraine Foundation survey study. *Headache.* 2021;61(5):734-739.
83. Dias L, Martins B, Pinto MJ, et al. Headache teleconsultation in the era of COVID-19: Patients' evaluation and future directions. *Eur J Neurol.* 2021. doi: 10.1111/ene.14915. [Preprint]
84. Sharawat IK, Panda PK. Caregiver Satisfaction and Effectiveness of Teleconsultation in Children and Adolescents With Migraine During the Ongoing COVID-19 Pandemic. *J Child Neurol.* 2021;36(4):296-303.
85. Smith WR, Atala AJ, Terlecki RP, et al. Implementation Guide for Rapid Integration of an Outpatient Telemedicine Program During the COVID-19 Pandemic. *J Am Coll Surg.* 2020;231(2):216-222.e2.
86. Roberts ET, Mehrotra A. Assessment of Disparities in Digital Access Among Medicare Beneficiaries and Implications for Telemedicine. *JAMA Intern Med.* 2020;180(10):1386-1389.
87. Gray LC, Edirippulige S, Smith AC, et al. Telehealth for nursing homes: the utilization of specialist services for residential care. *J Telemed Telecare.* 2012;18(3):142-146.
88. Edge C, Black G, King E, et al. Improving care quality with prison telemedicine: The effects of context and multiplicity on successful implementation and use. *J Telemed Telecare.* 2019;1357633X19869131.
89. Edirippulige S, Martin-Khan M, Beattie E, et al. A systematic review of telemedicine services for residents in long term care facilities. *J Telemed Telecare.* 2013;19(3):127-132.
90. Peretti A, Amenta F, Tayebati SK, et al. Telerehabilitation: Review of the State-of-the-Art and Areas of Application. *JMIR Rehabil Assist Technol.* 2017;4(2):e7.
91. Iodice F, Romoli M, Giometto B, et al. Stroke and digital technology: a wake-up call from COVID-19 pandemic. *Neurol Sci.* 2021;42(3):805-809.
92. Chang MC, Boudier-Revéret M. Usefulness of Telerehabilitation for Stroke Patients During the COVID-19 Pandemic. *Am J Phys Med Rehabil.* 2020;99(7):582.
93. Garg D, Dhamija RK. Teleneurorehabilitation for Parkinson's Disease: A Panacea for the Times to Come? *Ann Indian Acad Neurol.* 2020;23(5):592-597.
94. Ganesan B, Fong KNK, Meena SK, et al. Impact of COVID-19 pandemic lockdown on occupational therapy practice and use of telerehabilitation - A cross sectional study. *Eur Rev Med Pharmacol Sci.* 2021;25(9):3614-3622.
95. Cornejo Thumm P, Giladi N, Hausdorff JM, Mirelman A. Tele-Rehabilitation with Virtual Reality: A Case Report on the Simultaneous, Remote Training of Two Patients with Parkinson Disease. *Am J Phys Med Rehabil.* 2021;100(5):435-438.
96. Langer A, Gassner L, Flotz A, et al. How COVID-19 will boost remote exercise-based treatment in Parkinson's disease: a narrative review. *NPJ Parkinsons Dis.* 2021;7(1):25.

97. Vila-Viçosa D, Clemente A, Pona-Ferreira F, et al. Unsupervised Walking Activity Assessment Reveals COVID-19 Impact on Parkinson's Disease Patients. *Mov Disord.* 2021;36(3):531-532.

98. Srivastav AK, Samuel AJ. E-Rehabilitation: One solution for patients with Parkinson's disease in COVID-19 era. *Parkinsonism Relat Disord.* 2020;75:128-129.

99. Nora M, Giannarelli M, Zicchinella C, et al. An Experience of Multiple Sclerosis Telerehabilitation During the COVID-19 Pandemic. *Am J Phys Med Rehabil.* 2021;100(3):214.

100. Zasadzka E, Trzmiel T, Pieczyńska A, Hojan K. Modern Technologies in the Rehabilitation of Patients with Multiple Sclerosis and Their Potential Application in Times of COVID-19. *Medicina.* (Kaunas) 2021;57(6).

101. Mantovani E, Zucchella C, Bottiroli S, et al. Telemedicine and Virtual Reality for Cognitive Rehabilitation: A Roadmap for the COVID-19 Pandemic. *Front Neurol.* 2020;11:926.

102. Prvu Bettger J, Thoumi A, Marquevich V, et al. COVID-19: maintaining essential rehabilitation services across the care continuum. *BMJ Glob Health.* 2020;5(5).

103. Middleton A, Simpson KN, Bettger JP, Bowden MG. COVID-19 Pandemic and Beyond: Considerations and Costs of Telehealth Exercise Programs for Older Adults With Functional Impairments Living at Home-Lessons Learned From a Pilot Case Study. *Phys Ther.* 2020;100(8):1278-1288.

104. Avelino PR, Menezes KKP, Nascimento LR, et al. Validation of the Telephone-Based Application of the ABILHAND for Assessment of Manual Ability After Stroke. *J Neurol Phys Ther.* 2020;44(4):256-260.

105. Chae SH, Kim Y, Lee K-S, Park H-S. Development and Clinical Evaluation of a Web-Based Upper Limb Home Rehabilitation System Using a Smartwatch and Machine Learning Model for Chronic Stroke Survivors: Prospective Comparative Study. *JMIR Mhealth Uhealth.* 2020;8(7):e17216.

106. Mishra R, Park C, York MK, et al. Decrease in Mobility during the COVID-19 Pandemic and Its Association with Increase in Depression among Older Adults: A Longitudinal Remote Mobility Monitoring Using a Wearable Sensor. *Sensors.* (Basel) 2021;21(9).

107. Alberts JL, Koop MM, McGinley MP, et al. Use of a Smartphone to Gather Parkinson's Disease Neurological Vital Signs during the COVID-19 Pandemic. *Parkinsons Dis.* 2021;2021:5534282.

108. Rammo R, Gostkowski M, Rasmussen PA, et al. The Need for Digital Health Solutions in Deep Brain Stimulation for Parkinson's Disease in the Time of COVID-19 and Beyond. *Neuromodulation.* 2021;24(2):331-336.

109. Feyissa AM. Hold the Smartphone! Tele-epilepsy in a Post-COVID-19 World. *Mayo Clin Proc.* 2021;96(1):4-6.

110. Tatum WO, Acton EK. Smartphones in Epilepsy: The New Age of Aquarius. *Mayo Clin Proc.* 2021:96(1):29-31.

111. Jaakkola J, Jaakkola S, Lahdenoja O, et al. Mobile Phone Detection of Atrial Fibrillation With Mechanocardiography: The MODE-AF Study (Mobile Phone Detection of Atrial Fibrillation). *Circulation.* 2018;137(14):15241527.

112. Brasier N, Raichle CJ, Dörr M, et al. Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-centre, clinical validation study (DETECT AF PRO). *Europace.* 2019;21(1):41-47.

113. Bumgarner JM, Lambert CT, Hussein AA, et al. Smartwatch Algorithm for Automated Detection of Atrial Fibrillation. *J Am Coll Cardiol.* 2018;71(21):2381-2388.

114. Perez MV, Mahaffey KW, Hedlin H, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med.* 2019;381(20):1909-1917.

115. Sandrone S, Albert DV, Dunham SR, et al. Training in Neurology: How Lessons Learned on Teaching, Well-being and Telemedicine During the COVID-19 Pandemic Can Shape the Future of Neurology Education. *Neurology.* 2021;96(24):e3007-e3010.

116. Zha AM, Chung LS, Song SS, et al. Training in Neurology: Adoption of resident teleneurology training in the wake of COVID-19: Telemedicine crash course. *Neurology.* 2020;95(9):404-407.

117. Di Lorenzo F, Ercoli T, Cuffaro L, et al. COVID-19 impact on neurology training program in Italy. *Neurol Sci.* 2021;42(3):817-823.

118. Gros P, Rotstein D, Kinach M, et al. Innovation in resident education - Description of the Neurology International Residents Videoconference and Exchange (NIRVE) program. *J Neurol Sci.* 2021;420:117222.

119. Franklin G, Martin C, Ruszaj M, et al. How the COVID-19 Pandemic Impacted Medical Education during the Last Year of Medical School: A Class Survey. *Life.* (Basel) 2021;11(4):294.

120. Weber DJ, Albert DVF, Aravamuthan BR, et al. Training in Neurology: Rapid implementation of cross-institutional neurology resident education in the time of COVID-19. *Neurology.* 2020;95(19):883-836.

121. Robb JF, Hyland MH, Goodman AD. Comparison of telemedicine versus in-person visits for persons with multiple sclerosis: A randomized crossover study of feasibility, cost, and satisfaction. *Mult Scler Relat Disord.* 2019;36:101258.

122. Duffy S, Lee TH. In-Person Health Care as Option B. *N Engl J Med.* 2018;378(2):104-106.

123. Ansary AM, Martinez JN, Scott JD. The virtual physical exam in the 21st century. *J Telemed Telecare.* 2019;1357633X19878330.

124. Grossman SN, Han SC, Balcer LJ, et al. Rapid implementation of virtual neurology in response to the COVID-19 pandemic. *Neurology.* 2020;94(24):1077-1087.

125. Gursky JM, Boro A, Escalante S, et al. Disparities in Access to Neurologic Telemedicine During the COVID-19 Pandemic: A Bronx Tale. *Neurol Clin Pract.* 2021;11(2):e97-101.

Chapter 16. Impact of COVID-19 on pre-existing neurological diseases

Paola Alberti, Simone Beretta, Laura Brighina,
Valeria Isella, Carlo Ferrarese

Introduction

Neurological sequelae and complications have been reported as being related to COVID-19[1-3]. Yet light should still be shed on the exact impact of COVID-19 on neurological diseases as well as on patients with an underlying neurological condition. To solve this unmet clinical and scientific need, large observational multicenter studies are warranted; one good example is the NEUROCOVID study proposed by Members of the Italian Society for Neurology (Società Italiana di Neurologia, SIN)[4].

In this chapter we address some potentially highly interesting topics related to COVID-19 and neurological patients.

Neuroinflammatory and neuro-oncological diseases

In this section we discuss issues related to some categories of frail neurological patients: those affected by neuroinflammatory and neuro-oncological conditions. As a general indication, basic safety rules apply. Social distancing is crucial, and given these are mainly chronic patients, appropriate logistic solutions should be put in place by the treating physician/center: minimizing trips to pharmacies, relying on telemedicine if appropriate and switching to home infusion of selected drugs (e.g., home-base intravenous immunoglobulin subcutaneous administration). In the next section we will examine the specific issues related to COVID-19 in categories of fragile patients.

Multiple sclerosis

Epidemiological studies are addressing the potential effects of COVID-19 in multiple sclerosis (MS) patients. A European multicenter trial reported 21.8% of 399 MS patients suffered from an infection clinically suggestive of COVID-19, and reported major symptoms of COVID-19[5]. MS is a chronic

immune-mediated demyelinating disease of the central nervous system which involves inflammation, blood-brain-barrier disruption, and autoreactive lymphocytes. Its treatment relies on disease-modifying therapies (DMTs) aiming at immunomodulation, immunosuppression, or cell depletion and/or alteration of inflammatory cell trafficking[6]. Relapse treatment is based on glucocorticoids and, occasionally, plasmapheresis cases of corticosteroid failures, with, of course, only short-term administration. Instead, DMTs are administered chronically to help prevent relapse and to slow progression. In basic terms, DMTs can be divided into[6]: *immunomodulatory drugs*, such as interferon-beta-1 (IFN-β1), glatiramer acetate (GA), and fumarates (i.e., dimethyl fumarate); *cell trafficking alterations molecules*, like S1P receptor modulators (i.e., fingolimod), and natalizumab, an anti-α4-integrin antibody; *cell depletion* (anti-CD20 antibodies [i.e., ocrelizumab, rituximab, ofatumumab], cladribine, and *anti-CD52 antibodies* [i.e., alemtuzumab]); *systemic immunosuppressants* (i.e., teriflunomide). The immunocompetence status of patients might play an important role in COVID-19 associated risks. It has been suggested that MS patients not receiving DMTs have the same risk of suffering from COVID-19 as the general population[7] and that the greatest risk of contracting the disease can be related to dosage and medication administered, in particular for second-generation therapies[8]. However, these observations were conducted on a relatively small cohort possibly biasing the results[8, 9]. From case series studies, immunosuppression has emerged as a risk factor for severe forms of COVID-19[10]. *Dimethyl fumarate*, for example, could potentially induce lymphopenia, mainly in the early treatment course[11], eventually increasing susceptibility to SARS-CoV-2 in case of moderate-to-severe lymphopenia, but it is considered likely to be safe in patients with no or mild lymphopenia (absolute lymphocyte count > 800/mm^3)[12]. Another drug, *natalizumab*, is considered to be low risk for severe forms of COVID-19[13] since it does not interfere with lymphocyte function. Other drugs with, however, a possible moderate risk for COVID-19 are those with a modulatory effect of the S1P receptor (*fingolimod, siponimod, and ozanimod*) and anti-CD20 monoclonal antibodies (*ocrelizumab and rituximab*)[13]. S1P modulators are capable of reducing peripheral lymphocytes, increasing susceptibility to coronavirus infection, as evidenced by the increased predisposition to other viral infections[13]. Anti-CD20 monoclonal antibodies could impair the anti-viral long-term immunity and increase the risk of reinfection[13]. For the same reasons, the greatest infection risk might be suggested for treatments acting on the lymphocyte population, such as alemtuzumab or cladribine; moreover, they potentially affect the early and long-term immunity against SARS-CoV-2, increasing infection susceptibility and re-infection rate[13].

Given these reflections, caution should be exercised when managing each individual patient both for acute relapse treatment, and management of confirmed COVID-19 cases. In case of acute relapse, single cases should be carefully

evaluated given that corticosteroids are associated with an increased risk of infections, including (of course) SARS-CoV-2 infection, and these accelerate the onset of relapses[11]. In patients with a relapsed MS and, at the same time, an ongoing COVID-19, the use of plasmapheresis was suggested[13]. However, in case of COVID-19 in a MS patient without an active neuroinflammatory status, it is generally suggested to continue DMTs if infection is mild. Suspension is to be evaluated in those with greater immunosuppressive effects or in patients with other risk factors for development of a more severe form of COVID-19. Careful risk assessment of rebound activity should always be considered in case of suspension of S1P modulators and natalizumab[11]. However, it should be noted that we are still gaining inferences on COVID-19 and MS patients as well as DMTs, therefore, it should be strongly encouraged to stay carefully updated on the indications of regulatory agencies and scientific societies on these products (see as an example those released by Associazione Italiana Sclerosi Multipla [AISM][14]).

Myasthenia gravis

Myasthenia gravis (MG) is a chronic autoimmune disorder characterized by fluctuating muscle weakness affecting ocular, bulbar and limb skeletal muscles[15]. The onset of MG has been related to several triggering factors including hepatitis B and C, herpes simplex, HIV, Epstein-Barr virus, West Nile and Zika virus. SARS-CoV-2 virus has given rise to some possible challenges in MG patients since it can lead to variable symptoms, ranging from mild to severe pneumonia, subsequently leading to acute respiratory distress syndrome (ARDS) and death in many cases[16]. The risk can be higher in MG patients for many reasons: a potential immunocompromised state related to MG therapies and possible respiratory muscle weakness[16]. Several reports in literature are available on MG patients suffering from COVID-19; Camelo-Filho et al.[17] published a large series of patients, revealing a rather severe disease course, requiring intensive care admission in 87% of cases, mechanical ventilation in 73%, and with a fatal outcome in 30%. However, clinical response of MG patients to COVID-19 represents a major challenge and outcome predictors are still lacking. Most notably, it has been pointed out that Treg/Th17 imbalance in the course of COVID-19 might increase or even trigger an excessive autoimmune response, and a possible role for hyper-inflammatory responses in COVID-19 might be crucial in respiratory failure[16]. Therefore, respiratory muscle function evaluation is crucial in deciding the timing of endotracheal intubation in MG patients affected by COVID-19. A non-invasive ventilation trial can be indicated and could avoid endotracheal intubation. But, in cases of excessive distress in breathing, or in case of the development of bulbar dysfunction or ARDS, early intubation and mechanical ventilation could be required. The current state of knowledge on the interaction between MG and COVID-19 is changing rapidly due to growing

experience with patients. The ongoing international registries will soon provide greater insight on this matter[18, 19]. For the moment, the best approach is for MG patients to continue their current treatment, unless specifically discussed with and approved by the treating physician; when deciding whether altering or stopping an existing immunosuppressive therapy, the increased disease activity and/or MG exacerbation or crisis, should be considered.

Inflammatory neuropathy

The relationship between COVID-19 and inflammatory neuropathies is quite complex. On one hand, patients affected by inflammatory neuropathies might be undergoing an immunomodulatory treatment, raising the same concerns discussed for other diseases so far; on the other hand, COVID-19 itself might trigger an immune reaction resulting in potential damage to the peripheral nervous system. Regarding chronic conditions, such as chronic inflammatory demyelinating polyneuropathy, a reflection is in order. Some standard treatments are not expected to increase the risk of COVID-19 or severe disease: immunoglobulin (either intravenous or subcutaneous), complement inhibitor therapy (e.g., eculizumab), therapeutic plasma exchange.

Notably, the inflammatory response driven by COVID-19 has started to raise concerns related to acute polyradiculoneuritis occurrence. Case reports and case series were reported at the beginning of the first COVID-19 outbreak[20,21]. As pointed out by Sheikh and co-authors[22] in a recent systematic review, acute polyradiculoneuritis could be considered one of the many presentations of COVID-19. However, there is no definite agreement on the robustness of the association between COVID-19 and acute polyradiculoneuritis. A recently published study by Keddie and collaborators[23] argues against SARS-CoV-2 as being causative. They based this statement comparing cases in the UK from 2016 to 2019 and cases reported during the COVID-19 outbreak. Nevertheless, authors recognized it is not possible to entirely rule out the possibility of a link, since acute polyradiculoneuritis incidence has fallen during the pandemic, probably due to lockdown measures reducing transmission of other pathogens associated with this condition. In general, despite the reported conflicting studies, it is highly important not to underestimate a diagnosis of acute polyradiculoneuritis related to COVID-19; acute polyradiculoneuritis raises specific challenges the treating physician should be aware of, especially in an intensive care setting.

Neuro-oncological patients

The COVID-19 pandemic has created major issues for cancer diagnosis and treatment, as well as in access to care; this is particularly true in the field of neuro-oncology. In the case of brain tumors, the perceived benefit of therapeutic interventions is often low, although this view is not always correct. As a consequence of the pandemic, the risk/benefit ratio has altered and major challenges

have been posed to health-care providers. In order to reduce risks to patients, different responses were evaluated: brain scans intervals were increased and radiotherapy schedules were adapted to hypofractionation. Another issue was raised by systemic chemotherapy given its immunosuppressive potential, raising some concerns, for example, on proposing temozolomide to glioblastoma patients lacking MGMT promoter methylation, given the risk of lymphopenia and repeated access to the hospital facilities (e.g., for blood tests), thus increasing the risk of developing COVID-19[24]. For brain cancer patients symptomatic for COVID-19, withholding systemic chemotherapy, unless entirely non-immunosuppressive, could be suggested until full recovery from COVID-19[24]. A careful evaluation of risk/benefit is needed, and moderate delays of systemic chemotherapy may be a preferred option, in case of patients positive for SARS-CoV-2, as part of a screening program, but asymptomatic. In any case, there is an urgent need to ensure treatment of neuro-oncological patients is not significantly delayed and initiating therapy should not be outweighed by COVID-19. Therefore, multidisciplinary initiatives are being undertaken to better navigate through pandemics and learn/adapt practice. As an example, Bernhardt and collaborators[25] proposed detailed consensus-based practice recommendations based on experts' opinion, including neuro-oncologists, neurosurgeons, radiation oncologists, and medical physicists. They suggest adapting treatments, proposing hypofractionated radiotherapy, and modifying chemotherapy to minimize immunosuppression.

Cerebrovascular diseases

COVID-19 patients with pre-existing cerebrovascular disease have been shown to have a significantly higher risk of in-hospital death, compared to COVID-19 patients without cerebrovascular comorbidity (relative risk 2.18)[26]. Moreover, patients with previous cerebrovascular disease had higher risk of severe COVID-19 than those without (relative risk 2.07) and requiring intensive care (relative risk 2.79). Both pharmacological and non-pharmacological therapies used for COVID-19 have increased risks or are less practicable in patients with previous stroke. Dexamethasone and tocilizumab increase the risk of bacterial infections,[27] hydroxychloroquine has a potential cardiac toxicity[28] and prone positioning is difficult to apply in conscious patients with previous motor disability.

The risk of first or recurrent stroke associated with COVID-19 is a matter of debate. The first studies during the early phase of the pandemic indicated an apparent increase in the number of stroke patients who were younger and with a lower vascular risk factor burden, as well as an apparent increase in stroke severity, but other cohorts did not identify this different patient profile.[29-34]

For patients with pre-existing cerebrovascular disease, who are more vulnerable to secondary events as a result of their poor vascular condition, the risk of recurrent stroke among individuals with COVID-19 remains to be determined. This issue is even more difficult to ascertain due to the approximately 30% decrease in the volume of stroke patients accessing hospitals during the COVID-19 pandemic, with an even larger decrease (up to 40-60%) for patients with transient ischemic attacks (TIA) and mild strokes.[35-37] Despite a true decline in stroke incidence that may be related to a reduced exposure to common viruses (well-known triggers of acute cerebrovascular events), during the lockdown periods,[38] the most likely explanation is that the reduced stroke presentation is a direct consequence of social distancing, decreasing early identification of stroke and patients' fears about coming to the hospital in the midst of a pandemic.[39] Hospital avoidance may have created a cohort of untreated stroke patients at risk of poorer outcomes and recurrent events. Notably, an alarming increase in lifestyle risk factors for cerebrovascular diseases, such as smoking, alcohol and physical inactivity was noticed during the months of confinement.[40, 41]

COVID-19 highlighted the long road that still has to be run towards a satisfactory education of the population for stroke. The World Stroke Organization issued an important campaign highlighting the importance of not wasting time in suspected first or recurrent stroke during the COVID pandemic.[42]

In particular, for patients who had already suffered a stroke and were likely to have reduced access to secondary prevention clinics and neurological rehabilitation therapies, the pandemic has highlighted the enormous potential of telemedicine in stroke care. Although still in their early stages, novel models of care have been implemented for telemedicine neurological consultations of TIA patients[43] and for video-guided telerehabilitation using home exercise programs.[44]

Epilepsy

Epilepsy is one of the most common chronic neurological conditions, with a prevalence of approximately 1% and a high incidence among elderly individuals and children[45]. Various factors surrounding epilepsy and epilepsy care may be affected by COVID-19.

A systematic review article showed that the rate of COVID-19 severity in people with epilepsy is lower than other neurological disorders such as dementia, cerebrovascular disease, and multiple sclerosis[46]. However, epilepsy is not a single disease; it has many causes and associations, some of which may debilitate the patient and increase the risk of respiratory impairment. Notably, patients with epilepsy associated with learning and developmental disabilities are exposed to a significantly higher risk of death due to a severe form of COVID-19 compared to other epilepsy patients[47].

Current evidence indicates that the incidence of acute symptomatic seizures due to COVID-19 is less than 1%,[48] suggesting that acute symptomatic seizures caused by COVID-19 are not particularly common compared with other viral diseases. However, a change in seizure frequency among patients with chronic epilepsy during the COVID-19 crisis has been reported, regardless of whether these patients were infected with COVID-19[49]. The proportion of patients experiencing increased seizures varied from 8% to up to 30%, and may reflect several contributing factors, besides COVID-19 infection itself: reduced compliance to antiepileptic drug schedule, difficulty in obtaining medicine due to lockdown or reduction in income, increased psychological stress and sleep problems. Indeed, the impact of the COVID-19 pandemic on psychological effects in epilepsy patients showed a high prevalence of depression (29%), anxiety (38%) and insomnia (29%)[50].

The social impact of COVID-19 has been seen also in epilepsy care facilities. Patient access to healthcare facilities has been greatly restricted because of the potential for patient-to-patient or healthcare provider-to-patient transmission of SARS-CoV-2. In a survey from 49 countries, more than 90% of physicians responding stated that in-person outpatient visits had decreased and use of telemedicine had increased[51].

The use of virtual epilepsy appointments became the standard of care in the lockdown periods in most countries and allowed an unprecedented assessment of this new care system, from both the patient's and the physician's perspective. Two large studies enrolling over 1,300 patients showed no backlog of appointments or loss of care continuity and strong levels of satisfaction expressed by clinicians for routing follow-up appointments, including adjustment of antiepileptic drugs and prescriptions of diagnostic testing[52, 53]. On the other hand, most physicians doubted the suitability of telemedicine for patients with newly diagnosed epilepsy and drug-resistant epilepsy. Up to 75% of patients reported positive experiences of telephone appointments comparing them favorably to face-to-face encounters. Beyond the pandemic, most patients reported a preference for continuing telemedicine if their epilepsy symptoms remained stable, while only 44.4% chose telemedicine should their symptoms worsen.

Dementia and movement disorders

Coexistence of coronavirus disease with degenerative cognitive and movement disorders has represented the crossroad of two pandemics. Neurodegenerative diseases like Parkinson's disease (PD) or, and above all, Alzheimer's disease (AD), are extremely frequent in older people, who were also the main target of COVID-19 infection. The impact of the virus in these clinical populations has been massive and diverse: during the quarantine these patients have shown a higher risk of contagion and a worse outcome of the infection, have suffered

the consequences of physical confinement and social deprivation, and also of greater caregiver burnout, and have experienced discontinuity in assistance due to overload or lockdown of medical and support services.

Results from meta-analyses and systematic reviews have shown that, compared with individuals with no dementia, dementia patients were at higher risk of COVID-19 infection, showed a more severe disease course, and had a higher mortality rate (with ORs ranging from 1.54 to 5.17)[46, 54-62]. Various elements have been indicated as causes of this increased vulnerability[63, 64]. Some were related to age (increased viral shedding, atypical presentations, such as lack of fever, that delay the diagnosis, or heavy comorbidity), while others were more specific to dementia. A case in point was delirium, which is particularly frequent in patients with a neurodegenerative disease in the course of an infection; this is a serious, potentially lethal condition. A second element was the fact that measures to prevent contagion, like wearing masks, frequent handwashing or avoiding social contact, are difficult to introduce to individuals with cognitive impairment. Third, potential biological mediators of major vulnerability to COVID-19 in AD were hypothesized[61, 62, 64-66]. For instance, Apolipoprotein E allele ε4, a known risk factor for AD, has been associated with increased COVID-19 severity, and expression of the ACE2gene, coronavirus binding protein for cell entry, has been found to be upregulated in the brain tissues of AD subjects. Moreover, and more importantly, cytokine-mediated neuroinflammation plays a central role in the pathogenesis of AD, and COVID-19 is known for causing a 'cytokine storm' that affects multiple organs, including the central and peripheral nervous system. These observations on biological common links between coronavirus and AD, however, are for the moment highly speculative, and will need to be verified empirically.

As far as PD is concerned, it remains unclear whether there was a major incidence of coronavirus disease in this disorder. Reports on prevalence of the infection varied greatly (according to geographical area, inclusion criteria, etc.), ranging from 0.6% to 8.5%[67], but in most studies it was below 1%, therefore equivalent to that of the general population. Risk factors for COVID-19 infection in PD were also similar to those seen in control populations, i.e., age, male gender, smoking, cardiovascular and chronic obstructive pulmonary diseases[67]. However, data are still insufficient to establish whether the similar prevalence was related to the same predisposition for COVID-19 infection, or to a higher level of attention and self-isolation in PD patients as an at-risk population[68, 69]. Interestingly, a few studies have actually reported that a subgroup of PD patients were less likely to be infected by COVID-19, namely those receiving amantadine[70, 71]. This finding has also received support from an *in vitro* drug screen gene expression study showing that amantadine decreased the virus rate of replication and degree of infectivity[72].

With regard to the prognosis, mortality rates were also highly variable (from 5% to 75%) according to sample size, and patients' socio-demographic and clinical characteristics (e.g., disease stage, involvement of community-dwelling, hospital-based or long-term care facilities series). However, they were generally higher in PD patients than in age-matched non-PD individuals[73], mostly because of restricted pulmonary capacity due to axial akinesia, and impaired cough reflex[74]. Interestingly in PD the detrimental interaction between coronavirus infection and neurodegeneration has appeared to be bi-directional, in the sense that the virus also seemed to have a negative impact on the course of the motor disorder, through various mechanisms. Dopamine neurons have in fact been shown to highly express the ACE2 receptor, which mediates COVID-19 entry to cells, and immune activation in the olfactory system, targeted by the virus, has been shown to eventually lead to the misfolding of α-synuclein in the central nervous system, possibly causing the development and/or progression of PD. In support of this hypothesis, four cases of parkinsonism have been reported, which manifested between five to 32 days from coronavirus infection and showed asymmetric decrease of dopamine uptake in the putamina and good response to dopamine replacement therapy[75, 76]. These cases of new-onset parkinsonism might have been related to unmasking subclinical PD. Large cohort studies will be needed to determine whether COVID-19 will also increase the incidence of PD in the long term.

The pandemic has had heavy consequences on patients with dementia and movement disorders also indirectly, through quarantine and isolation. During the lockdown declared in Italy as a containment measure of the first wave of the coronavirus pandemic, the COVID-19 Study Group of the Italian Society of Neurology for Dementia (SINdem) carried out a nation-wide survey on the impact of quarantine on cognitive, neuropsychiatric and motor symptoms of dementia, using a telephone interview with patients' family caregivers. Clinical worsening was reported in approximately two patients in three for behavioral aspects (mainly irritability and apathy), in one patient in two for cognitive functions (especially memory), and in one patient in three for motor disturbances (above all, in walking)[77, 78]. These findings are in line with a large bulk of literature also showing exacerbation of pre-existing neurological symptoms of dementia during and after quarantine[78]. Such an exacerbation appeared to be linked to multiple factors: movement restriction, reduced social interaction and activities that usually stimulate cognition and have a beneficial effect on mood and behavior, disruption of daily routine. A negative effect was also observed in terms of greater caregiver burnout, which has been reported repeatedly in the pandemic literature[79, 80], and quarantine due to the coronavirus disease 2019 (COVID-19, and this set off a vicious cycle with worsening of the patient's clinical condition.

Very similar findings have been reported for PD patients. Worsening of motor and non-motor symptoms has also been described in these patients, and attributed mainly to psychological distress, depression and anxiety, a reduction in physical activity, and social isolation, besides fear of being infected by COVID-19[81, 82]. A behavioral disturbance very typical of PD, Impulse Control Disorder (ICD), has also been found to increase during the COVID-19 lockdown[82].

The SINdem COVID-19 Study Group's report on the impact of quarantine on family caregivers of patients with dementia identified discontinuity in assistance as one of the main determinants of caregiver stress, causing a three-fold increase in feelings of isolation and abandonment and a two-fold increase in a sense of being overwhelmed and helpless[83]. This element has in fact emerged as one of the main causes of the extra burden resulting from the pandemic on patients with dementia[83], mostly on patients with PD[81, 82.] Redeployment of hospital units and lockdown of medical and assistance services (outpatient clinics, diagnostic departments, cognitive and motor rehabilitation centers, elderly daycare facilities, social support services) created a real emergency, with problems in the supply of medications and postponement of appointments for follow ups and for new referrals, leading to delays in diagnosis and initiation of appropriate management. PD patients seem to have been the most heavily penalized by this situation, due to the fact that, unlike other neurological groups, they need routine visits to the hospital for physical assessment and medication adjustments by movement disorder specialists. In particular, during the peak phases of the COVID-19 pandemic a significant decline was observed globally for PD Multimodal Complex Treatments (MCT), including levodopa/carbidopa intestinal gel, continuous subcutaneous apomorphine infusion and Deep Brain Stimulation (DBS). Patients treated by MCT require regular follow-up visits in highly specialized and multidisciplinary clinical settings, which appear to have been massively affected by social distancing and lockdown measures[84]. Beside reporting concern about problems of hospital access and the interruption of pharmacological and non-pharmacological treatments, patients treated with MCT were also worried specifically about management of stimulation devices. First of all, PD patients with implanted DBS systems require replacements of the Implantable Pulse Generator (IPG), especially if not rechargeable, every three to five years. More crucially, battery malfunction due to exhaustion or other device-related issues may occur unexpectedly and become an emergency requiring surgical intervention to avoid the risk of life-threatening complications such as malignant subthalamic nucleus-DBS withdrawal syndrome (similar to a neuroleptic malignant syndrome), acute dystonic crisis, and the reappearance of disabling PD symptoms, which can be refractory to medication. During the pandemic, both pre-planned and urgent hospitalizations for interventions on the device were extremely problematic.

Possible role of telemedicine

These issues lead straight to reflections about the need to identify and implement interventions aimed at providing care in current and future situations of physical distancing Telehealth must represent a very promising solution, as it helps in limiting virus circulation by decreasing person-to-person contact, while allowing remote delivery of a full spectrum of services to patients and caregivers[85, 86]. Indeed, a recent study showed that telemedicine was as efficacious as in-office visits, and PD patients even expressed an increased likelihood of participating in future clinical research studies if some visits could be conducted remotely[87]. Along these lines, the International Parkinson and Movement Disorder Society has developed a guide on how to set up telemedicine practice as a valid alternative method for consultations and remote assessments of PD patients[88]. History-taking, aspects of the neurological examination, a brief cognitive assessment, and medication reviews can be performed via videoconferencing. Virtual cognitive and also physical stimulation programs may also be arranged, and counseling or psychological support may be provided to patients, caregivers and family members through telephone or web meetings. Furthermore, PD patients may efficiently be assessed with wearable devices to complement remote MDS-UPDRS scores. However, telehealth has some limitations: the impossibility of performing a complete neuropsychological evaluation or physical examination (e.g., to assess rigidity, or to perform balance-related maneuvers, especially without the supervision/assistance of a trained caregiver); the lack of validation and norms for neuropsychological tools; the inability to conduct 'difficult conversations' (e.g., on palliative care) on the screen, or to check in with the caregiver without the presence of the patient; the problems in using audio-visual devices for older people and for subjects with major neurocognitive disorders or severe neurosensory deficits, or even the unavailability of such devices.

Patient and caregiver education programs

When and where telehealth is not a feasible or efficient solution, other interventions might help reduce the overall impact of coronavirus disease on neurological disorders, and particularly on dementia and PD populations[64, 89]. Patients and caregivers should first of all be educated to keep home a "clean zone" (e.g., contacts should receive an anti-COVID vaccine, have regular COVID-19 testing, wear appropriate personal protective equipment, strictly follow recommended prevention rules). Family members and caregivers should also be encouraged to monitor patients' clinical changes (including, for instance, worsening or onset of ICD in PD patients), and be advised on how to organize home-based activities like cognitive stimulating tasks (including arts and crafts or games) or simple exercise (e.g., walking, stretching). In fact, although the majority of physical rehabilitation programs for PD patients are conducted outside

the home in supervised settings (e.g., non-contact boxing programs, assisted aerobic or functional strength activities, yoga), many activities can be done at home[90]. Most of them have been shown to effectively reduce off-state motor signs even with minimal remote supervision, at least in patients with mild disease severity[91]. For PD patients, web-based exercise initiatives such as online singing and exercise or dancing classes have indeed been implemented during the pandemic, often initiated or supported by large patient associations.

Pharmacological interactions

On their part, clinicians should keep on the alert for atypical presentations of coronavirus infection, to promote timely diagnosis of the disease, and be able to adopt a targeted approach in those patients who do become infected. Special efforts should be made to monitor and prevent delirium, given the high prevalence and poor outcome of this condition in patients with a neurodegenerative disorder, and close attention should be paid to possible pharmacological interactions. Patients with dementia are often on a cocktail of cholinesterase inhibitors/memantine, antidepressants and antipsychotics that interact with liver enzymes and cause adverse events similar to those of antirheumatic (chloroquine and hydroxychloroquine), antiviral (ritonavir in particular) or antibiotic (e.g., azithromycin) drugs used for treating COVID-19[62]. Pharmacological choices should be guided by these observations. As an example, cholinesterase inhibitors might require adjusting, or replacing with memantine (which has lower hepatic interaction) if used in conjunction with antirheumatics, and ribavirin or favipiravir should be preferred to other antivirals as they can be administered more safely alongside treatments for AD. As to patients with PD, several case series and observational studies have reported a worsening of motor and non-motor symptoms during COVID-19 infection, which may be linked to acute systemic inflammatory response, or to changes in pharmacokinetics of oral therapy (e.g., reduced absorption due to diarrhea)[92]. Clinicians should be prepared to increase levodopa dose in these circumstances[92]. For patients treated with MCT, it is recommended to gradually reduce stimulation amplitude and increase levodopa dosage accordingly to avoid acute cessation when end of IPG life is approaching. Routine management of the device should also be reorganized, for instance through supplementation of programming-related follow ups with video teleconsultations, and with the use of patient-controlled programmers. Decision algorithms for patients with advanced therapies are available in the literature to improve PD work up in these difficult circumstances[93].

Reflections on COVID-19 vaccination in frail neurological patients

The ultimate defense against coronavirus infection is, of course, represented by vaccines.

Specialists managing patients with dementia should be aware that vaccination against COVID-19 is recommended to these patients above and beyond the general elderly population. Participation of patients with cognitive impairment or dementia in clinical trials on anti-COVID vaccines was probably null or negligible, since such conditions were explicit reasons for exclusion in the Oxford-AstraZeneca trial, and could be reasons for exclusion upon investigator's judgment in the Pfizer/BioNTech and Moderna trials[94], but without a doubt the risk-benefit ratio favors vaccination of patients with dementia against coronavirus. This has also been clearly confirmed in PD patients (see MDS/MDS COVID-19 Vaccine Statement for Patients[95]) since the benefits and risks of approved COVID-19 vaccinations do not appear to differ in individuals with this disorder from those observed in the general population, while the risks of life-threatening complications of the infection do appear to be higher for persons living with advanced PD. Moreover, no changes in PD symptoms or responses to PD treatments following COVID-19 vaccination have been reported, whereas PD symptoms may worsen after COVID-19 infection. Finally, although longitudinal studies are warranted to explore the impact of vaccines on PD progression, no evidence has been found thus far suggesting a direct interaction of vaccine-induced immune response with the neurodegenerative process and, in particular, with inflammation associated with the pathogenesis of PD[96].

Some concern might arise in patients with underlying neuroinflammatory conditions when it comes to COVID-19 vaccines; the fear is that vaccination would trigger the immune system and lead to neurological adverse events. One of the main concerns is related to the possible onset of an acute polyradiculoneuritis following vaccination. Weighing the evidence to date, the potential COVID-19 specific consequences outweigh the risks of vaccination. The general recommendation is that patients with inflammatory neuropathies should be encouraged to have the vaccination[97] and, as stated by such experts as Lunn and co-authors[98], although an association of any vaccination to acute polyradiculoneuritis cannot be ruled out and we should stay vigilant, it is not necessarily to be expected. On the other hand, regarding those patients who are actively receiving an immunosuppressive/immunomodulatory treatment, such as, for example, MS patients, some concerns might arise as to the effect of these treatments on vaccine efficacy, reducing the ability of the individual patient to have an adequate immune response[99], especially for those which interfere with B-cell activity and antibody production. This gave rise to some indications by different scientific societies, for example the SIN, suggesting to wait 4-6 weeks after

the completion of the whole vaccination cycle before starting drugs such as alemtuzumab, rituximab, ocrelizumab, ofatumumab, cyclophosphamide, mitoxantrone[100]. However, this is just an example, and given that we are still obtaining evidence on COVID-19 and COVID-19 vaccination management (taking into account novel vaccines might be soon available), the best course of action is to rely on indications given by regulatory agencies, such as the European Medicine Agency (EMA) in Europe and the Food and Drug Administration (FDA) in the US, and to keep constantly updated on changes on data reported in the technical description of both DMTs and COVID-19 vaccine.

Take-home message

- SARS-CoV-2 virus, known to cause COVID-19, is having a dramatic impact on neurological patients, highlighting older and new frailties.
- Careful updates on growing evidence should be recommended for patients undergoing immunomodulatory/immunosuppressive treatments, relying on indications that continue to be released by regulatory agencies and scientific societies.
- There have been problems in treatment/care/follow up of frail patients (e.g., dementia patients) suggesting a possible role for telemedicine.
- COVID-19 should be carefully monitored for potential neurological complications and their exact impact will only be evaluated through large observational trails, such as the NEUROCOVID study proposed by the SIN.
- The ultimate defense against coronavirus infection is represented by vaccines. Considering the evidence so far, the potential COVID-19 specific consequences outweigh the risks of vaccination. Careful planning of vaccine administration should be undertaken for patients undergoing immunomodulant and/or immunosuppressive treatments.

References

1. Vakili K, Fathi M, Hajiesmaeili M, et al. Neurological Symptoms, Comorbidities, and Complications of COVID-19: A Literature Review and Meta-Analysis of Observational Studies. Eur Neurol 2021:1-18.
2. Yadav R, Srivastava DK, Bajpai PK, Kumar R. Systemic review of CNS involvement and its manifestations in SARS-CoV2 positive patients. *J Infect Public Health* 2021;14:734-739.
3. Camargo-Martínez W, Lozada-Martínez I, Escobar-Collazos A, et al. Post-COVID 19 neurological syndrome: Implications for sequelae's treatment. *J Clin Neurosci* 2021;88:219-225.
4. Ferrarese C, Silani V, Priori A, et al. An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEURO-COVID). *Neurol Sci* 2020;41:1355-1359.
5. Dalla Costa G, Leocani L, Montalban X, et al. Real-time assessment of COVID-19 prevalence among multiple sclerosis patients: a multicenter European study. *Neurol Sci* 2020;41:1647-1650.
6. Chaudhry F, Jageka C, Levy PD, Cerghet M, Lisak RP. Review of the COVID-19 Risk in Multiple Sclerosis. *J Cell Immunol* 2021;3:68-77.
7. Berger JR, Brandstadter R, Bar-Or A. COVID-19 and MS disease-modifying therapies. *Neurol Neuroimmunol Neuroinflamm* 2020;7.
8. Willis MD, Robertson NP. Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. *J Neurol* 2020;267:1567-1569.
9. Wijnands JMA, Zhu F, Kingwell E, et al. Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study. *J Neurol Neurosurg Psychiatry* 2018;89:1050-1056.
10. Boziki MK, Mentis AA, Shumilina M, Makshakov G, Evdoshenko E, Grigoriadis N. COVID-19 Immunopathology and the Central Nervous System: Implication for Multiple Sclerosis and Other Autoimmune Diseases with Associated Demyelination. *Brain Sci* 2020;10.
11. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology* 2020;94:949-952.
12. Zheng C, Kar I, Chen CK, et al. Multiple Sclerosis Disease-Modifying Therapy and the COVID-19 Pandemic: Implications on the Risk of Infection and Future Vaccination. *CNS Drugs* 2020;34:879-896.
13. Diaz de la Fe A, Peláez Suárez AA, Fuentes Campos M, et al. SARS-CoV-2 Infection and Risk Management in Multiple Sclerosis. *Diseases* 2021;9.
14. https://www.aism.it/raccomandazioni_aggiornate_sul_covid_19_le_persone_con_sclerosi_multipla_sm.
15. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. *Muscle Nerve* 2019;60:693-699.

16. Galassi G, Marchioni A. Myasthenia gravis at the crossroad of COVID-19: focus on immunological and respiratory interplay. *Acta Neurol Belg* 2021.
17. Camelo-Filho AE, Silva AMS, Estephan EP, et al. Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes. *Front Neurol* 2020;11:1053.
18. Muppidi S, Guptill JT, Jacob S, et al. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). *Lancet Neurol* 2020;19:970-971.
19. Jacob S, Muppidi S, Guidon A, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci* 2020;412:116803.
20. Paola, Maria ASBMPAK, Ferrarese LPPSMVGGFPDAMIAC. Guillain-Barré syndrome related to COVID-19 infection. *Neurol Neuroimmunol Neuroinflamm* [serial online] 2020;accepted paper.
21. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. *J Neurol Neurosurg Psychiatry* 2020.
22. Sheikh AB, Chourasia PK, Javed N, et al. Association of Guillain-Barre syndrome with COVID-19 infection: An updated systematic review. *J Neuroimmunol* 2021;355:577577.
23. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain* 2021;144:682-693.
24. Weller M, Preusser M. How we treat patients with brain tumour during the COVID-19 pandemic. *ESMO Open* 2020;4:e000789.
25. Bernhardt D, Wick W, Weiss SE, et al. Neuro-oncology Management During the COVID-19 Pandemic With a Focus on WHO Grade III and IV Gliomas. *Neuro Oncol* 2020.
26. Siepmann T, Sedghi A, Barlinn J, et al. Association of history of cerebrovascular disease with severity of COVID-19. *J Neurol* 2021;268:773-784.
27. Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2018;77:905-910.
28. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature. *Drug Saf* 2018;41:919-931.
29. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med* 2020;382:e60.
30. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg* 2020;12:648-653.
31. Escalard S, Maïer B, Redjem H, et al. Treatment of Acute Ischemic Stroke due to Large Vessel Occlusion With COVID-19: Experience From Paris. *Stroke*

2020;51:2540-2543.

32. Akhtar N, Abid FB, Kamran S, et al. Characteristics and Comparison of 32 COVID-19 and Non-COVID-19 Ischemic Strokes and Historical Stroke Patients. *J Stroke Cerebrovasc Dis* 2021;30:105435.
33. Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute Cerebrovascular Events in Hospitalized COVID-19 Patients. *Stroke* 2020;51:e219-e222.
34. Bekelis K, Missios S, Ahmad J, et al. Ischemic Stroke Occurs Less Frequently in Patients With COVID-19: A Multicenter Cross-Sectional Study. *Stroke* 2020;51:3570-3576.
35. Sacco S, Ricci S, Ornello R, et al. Reduced Admissions for Cerebrovascular Events During COVID-19 Outbreak in Italy. *Stroke* 2020;51:3746-3750.
36. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center. *J Stroke Cerebrovasc Dis* 2020;29:104953.
37. Hsiao J, Sayles E, Antzoulatos E, et al. Effect of COVID-19 on Emergent Stroke Care: A Regional Experience. *Stroke* 2020;51:e2111-e2114.
38. Schlachetzki F, Wilfling S, Hubert ND, et al. Decline and Recurrence of Stroke Consultations during the COVID-19 Pandemic Lockdown Parallels Population Activity Levels. *Cerebrovasc Dis* 2021;50:317-325.
39. Jasne AS, Chojecka P, Maran I, et al. Stroke Code Presentations, Interventions, and Outcomes Before and During the COVID-19 Pandemic. *Stroke* 2020;51:2664-2673.
40. Koopmann A, Georgiadou E, Reinhard I, et al. The Effects of the Lockdown during the COVID-19 Pandemic on Alcohol and Tobacco Consumption Behavior in Germany. *Eur Addict Res* 2021:1-15.
41. Chambonniere C, Lambert C, Tardieu M, et al. Physical Activity and Sedentary Behavior of Elderly Populations during Confinement: Results from the FRENCH COVID-19 ONAPS Survey. *Exp Aging Res* 2021:1-13.
42. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke* 2020;15:361-364.
43. D'Anna L, Ellis N, Bentley P, et al. Delivering telemedicine consultations for patients with transient ischaemic attack during the COVID-19 pandemic in a comprehensive tertiary stroke centre in the United Kingdom. *Eur J Neurol* 2021.
44. Wang CC, Chao JK, Wang ML, et al. Care for Patients with Stroke During the COVID-19 Pandemic: Physical Therapy and Rehabilitation Suggestions for Preventing Secondary Stroke. *J Stroke Cerebrovasc Dis* 2020;29:105182.
45. Correction: Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology* 2017;89:642.
46. Kubota T, Kuroda N. Exacerbation of neurological symptoms and COVID-19 severity in patients with preexisting neurological disorders and COVID-19: A systematic review. *Clin Neurol Neurosurg* 2021;200:106349.
47. Cummins L, Ebyarimpa I, Cheetham N, Tzortziou Brown V, Brennan K, Panovs-

ka-Griffiths J. Factors associated with COVID-19 related hospitalisation, critical care admission and mortality using linked primary and secondary care data. *Influenza Other Respir Viruses* 2021.

48. Lu L, Xiong W, Liu D, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. *Epilepsia* 2020;61:e49-e53.
49. Kuroda N. Epilepsy and COVID-19: Updated evidence and narrative review. *Epilepsy Behav* 2021;116:107785.
50. Lallana S, Fonseca E, Restrepo JL, et al. Medium-term effects of COVID-19 pandemic on epilepsy: A follow-up study. *Acta Neurol Scand* 2021.
51. Wirrell EC, Grinspan ZM, Knupp KG, et al. Care Delivery for Children With Epilepsy During the COVID-19 Pandemic: An International Survey of Clinicians. *J Child Neurol* 2020;35:924-933.
52. Banks J, Corrigan D, Grogan R, et al. LoVE in a time of CoVID: Clinician and patient experience using telemedicine for chronic epilepsy management. *Epilepsy Behav* 2021;115:107675.
53. Datta P, Barrett W, Bentzinger M, et al. Ambulatory care for epilepsy via telemedicine during the COVID-19 pandemic. *Epilepsy Behav* 2021;116:107740.
54. Smorenberg A, Peters EJ, van Daele P, Nossent EJ, Muller M. How does SARS-CoV-2 targets the elderly patients? A review on potential mechanisms increasing disease severity. *Eur J Intern Med* 2021;83:1-5.
55. Hariyanto TI, Putri C, Arisa J, Situmeang RFV, Kurniawan A. Dementia and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: A systematic review and meta-analysis. *Arch Gerontol Geriatr* 2021;93:104299.
56. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One* 2020;15:e0241955.
57. Liu N, Sun J, Wang X, Zhao M, Huang Q, Li H. The Impact of Dementia on the Clinical Outcome of COVID-19: A Systematic Review and Meta-Analysis. *J Alzheimers Dis* 2020;78:1775-1782.
58. Numbers K, Brodaty H. The effects of the COVID-19 pandemic on people with dementia. *Nat Rev Neurol* 2021;17:69-70.
59. Mok VCT, Pendlebury S, Wong A, et al. Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future. *Alzheimers Dement* 2020;16:1571-1581.
60. Emmerton D, Abdelhafiz AH. Care for Older People with Dementia During COVID-19 Pandemic. *SN Compr Clin Med* 2021:1-7.
61. McAlpine LS, Fesharaki-Zadeh A, Spudich S. Coronavirus disease 2019 and neurodegenerative disease: what will the future bring? *Curr Opin Psychiatry* 2021;34:177-185.
62. Yamamoto V, Bolanos JF, Fiallos J, et al. COVID-19: Review of a 21st Century Pandemic from Etiology to Neuro-psychiatric Implications. *J Alzheimers Dis*

2020;77:459-504.

63. Gil R, Arroyo-Anlló EM. Alzheimer's Disease and Face Masks in Times of COVID-19. *J Alzheimers Dis* 2021;79:9-14.
64. Meshkat S, Salimi A, Joshaghanian A, Sedighi S, Aghamollaii V. Chronic neurological diseases and COVID-19: Associations and considerations. *Transl Neurosci* 2020;11:294-301.
65. Wouk J, Rechenchoski DZ, Rodrigues BCD, Ribelato EV, Faccin-Galhardi LC. Viral infections and their relationship to neurological disorders. *Arch Virol* 2021;166:733-753.
66. Rahman MA, Islam K, Rahman S, Alamin M. Neurobiochemical Cross-talk Between COVID-19 and Alzheimer's Disease. *Mol Neurobiol* 2021;58:1017-1023.
67. Artusi CA, Romagnolo A, Ledda C, et al. COVID-19 and Parkinson's Disease: What Do We Know So Far? *J Parkinsons Dis* 2021;11:445-454.
68. Papa SM, Brundin P, Fung VSC, et al. Impact of the COVID-19 Pandemic on Parkinson's Disease and Movement Disorders. *Mov Disord* 2020;35:711-715.
69. Artusi CA, Romagnolo A, Imbalzano G, et al. COVID-19 in Parkinson's disease: Report on prevalence and outcome. *Parkinsonism Relat Disord* 2020;80:7-9.
70. Cortés-Borra A, Aranda-Abreu GE. Amantadine in the prevention of clinical symptoms caused by SARS-CoV-2. *Pharmacol Rep* 2021.
71. Cortés Borra A. Does amantadine have a protective effect against COVID-19? *Neurol Neurochir Pol* 2020;54:284-285.
72. Fink K, Nitsche A, Neumann M, Grossegesse M, Eisele KH, Danysz W. Amantadine Inhibits SARS-CoV-2 In Vitro. *Viruses* 2021;13.
73. Fearon C, Fasano A. Parkinson's Disease and the COVID-19 *Pandemic. J Parkinsons Dis* 2021;11:431-444.
74. Zhang Q, Schultz JL, Aldridge GM, Simmering JE, Narayanan NS. Coronavirus Disease 2019 Case Fatality and Parkinson's Disease. *Mov Disord* 2020;35:1914-1915.
75. Cohen ME, Eichel R, Steiner-Birmanns B, et al. A case of probable Parkinson's disease after SARS-CoV-2 infection. *Lancet Neurol* 2020;19:804-805.
76. Makhoul K, Jankovic J. Parkinson's disease after COVID-19. *J Neurol Sci* 2021;422:117331.
77. Rainero I, Bruni AC, Marra C, et al. The Impact of COVID-19 Quarantine on Patients With Dementia and Family Caregivers: A Nation-Wide Survey. *Front Aging Neurosci* 2020;12:625781.
78. Cagnin A, Di Lorenzo R, Marra C, et al. Behavioral and Psychological Effects of Coronavirus Disease-19 Quarantine in Patients With Dementia. *Front Psychiatry* 2020;11:578015.
79. Mioshi E, Foxe D, Leslie F, et al. The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2013;27:68-73.
80. Tsapanou A, Papatriantafyllou JD, Yiannopoulou K, et al. The impact of COVID-19 pandemic on people with mild cognitive impairment/dementia and

on their caregivers. Int J Geriatr Psychiatry 2021;36:583-587.

81. Helmich RC, Bloem BR. The Impact of the COVID-19 Pandemic on Parkinson's Disease: Hidden Sorrows and Emerging Opportunities. *J Parkinsons Dis* 2020;10:351-354.
82. Salari M, Zali A, Ashrafi F, et al. Incidence of Anxiety in Parkinson's Disease During the Coronavirus Disease (COVID-19) Pandemic. *Mov Disord* 2020;35:1095-1096.
83. Zucca M, Isella V, Lorenzo RD, et al. Being the Family Caregiver of a Patient With Dementia During the Coronavirus Disease 2019 Lockdown. *Front Aging Neurosci* 2021;13:653533.
84. Richter D, Scherbaum R, Bartig D, Gold R, Krogias C, Tönges L. Analysis of nationwide multimodal complex treatment and drug pump therapy in Parkinson's disease in times of COVID-19 pandemic in Germany. *Parkinsonism Relat Disord* 2021;85:109-113.
85. Geddes MR, O'Connell ME, Fisk JD, et al. Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19. *Alzheimers Dement (Amst)* 2020;12:e12111.
86. Gosse PJ, Kassardjian CD, Masellis M, Mitchell SB. Virtual care for patients with Alzheimer disease and related dementias during the COVID-19 era and beyond. *CMAJ* 2021;193:E371-E377.
87. Tarolli CG, Andrzejewski K, Zimmerman GA, et al. Feasibility, Reliability, and Value of Remote Video-Based Trial Visits in Parkinson's Disease. *J Parkinsons Dis* 2020;10:1779-1786.
88. https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide.htm.
89. Barry HE, Hughes CM. Managing medicines in the time of COVID-19: implications for community-dwelling people with dementia. *Int J Clin Pharm* 2021;43:275-279.
90. Vaartio-Rajalin H, Rauhala A, Fagerström L. Person-centered home-based rehabilitation for persons with Parkinson's disease: A scoping review. *Int J Nurs Stud* 2019;99:103395.
91. van der Kolk NM, de Vries NM, Kessels RPC, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol* 2019;18:998-1008.
92. Cilia R, Bonvegna S, Straccia G, et al. Effects of COVID-19 on Parkinson's Disease Clinical Features: A Community-Based Case-Control Study. *Mov Disord* 2020;35:1287-1292.
93. Fasano A, Antonini A, Katzenschlager R, et al. Management of Advanced Therapies in Parkinson's Disease Patients in Times of Humanitarian Crisis: The COVID-19 Experience. *Mov Disord Clin Pract* 2020;7:361-372.
94. Antonelli Incalzi R, Trevisan C, Del Signore S, et al. Are vaccines against COVID-19 tailored to the most vulnerable people? *Vaccine* 2021;39:2325-2327.

95. https://www.movementdisorders.org/COVID-19-Pandemic-MDS/MDS-COVID-19-Vaccine-Statement-for-Patients.htm.

96. Bloem BR, Trenkwalder C, Sanchez-Ferro A, et al. COVID-19 Vaccination for Persons with Parkinson's Disease: Light at the End of the Tunnel? *J Parkinsons Dis* 2021;11:3-8.

97. Doneddu PE, Spina E, Briani C, et al. Acute and chronic inflammatory neuropathies and COVID-19 vaccines: Practical recommendations from the task force of the Italian Peripheral Nervous System Association (ASNP). *J Peripher Nerv Syst* 2021.

98. Lunn MP, Cornblath DR, Jacobs BC, et al. COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations. *Brain* 2021;144:357-360.

99. Otero-Romero S, Ascherio A, Lebrun-Frénay C. Vaccinations in multiple sclerosis patients receiving disease-modifying drugs. *Curr Opin Neurol* 2021;34:322-328.

100. (http://www.neuro.it/web/lib/Download.cfm?dirdownload=E%3A%5Cgruppotesi%5Cdatasite%5Cnephromeet%5CDocs%5CNWSNEURO%5CATT%5C&filename=190%5FAggiornamentoRaccomandazioniSMeCovid%5F17052021%2Epdf&filesavename=Aggiornamento%20Raccomandazioni%20SM%20e%20Covid%5F17%2E05%2E2021%2Epdf&typeattach=inline.

Chapter 17. Neurological complications of vaccines for COVID-19

Laura Bertolasi, Maria Donata Benedetti

On January 30 2020, the World Health Organization (WHO) declared the outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) a public health emergency of international concern, reaching a pandemic status on March 11 2020[1]. In less than 12 months, several research teams rapidly developed candidate vaccines to prevent COVID-19, assessing their efficacy and safety in phases I, II, and, later, in phase III clinical trials[2-10]. Pfizer-BioNTech COVID-19, Moderna COVID-19, and J&J/Janssen COVID-19 vaccines were authorized for emergency use in rapid succession in the US (Food and Drug Administration [FDA]: December 11 2020[11], December 18 2020[12], and February 27 2021[13], respectively) and in Europe (European Medicines Agency [EMA]: December 21 2020[14], January 6 2021[15], and March 11 2021[16]), where a fourth vaccine, AstraZeneca COVID-19, was also authorized on January 29 2021[17]. The WHO recently authorized two vaccines developed in China: Sinopharm COVID-19[18] and Sinovac COVID-19[19]; authorization by the FDA and the EMA is still awaited. Overall, more than 100 candidate vaccines are currently under clinical development, while another three vaccines have been authorized and are used in several parts of the world (Sputnik V, Russia[20,21]; CanSino, China; Bharat Biotech, India[22]). As of June 18 2021, the worldwide cumulative number of COVID-19 cases was 177,108,695, the cumulative deaths 3,840,223, and a total of 2,378,482,776 vaccine doses had been administered worldwide[23]. Currently authorized COVID-19 vaccines are summarized in Table 17.1.

Despite the urgency related to the pandemic state, the safety profiles of candidate vaccine resulting from available clinical trials and all documents and product information submitted by companies, were rigorously and thoroughly evaluated by the WHO and regulatory agencies before authorization[24]. Nevertheless, clinical trials have a limited follow-up time and insufficient power to detect rare adverse events (AEs), or those occurring at a later time, or those emerging after large populations have been vaccinated. Post-marketing safety surveillance and monitoring allow recommendations and advice to be updated and modified.

Table 17.1: The anti-COVID-19 vaccines

Characteristics	Pfizer/BioNTech Vaccine	Moderna Vaccine	Astra-Zeneca Vaxzevria	Jonson & Jonson jNJ-78436735	Sputnik V	Sinopharm	Sinovach Biotech
Type of vaccine	mRNA (BNT 162b2)	mRNA (1273)	Chimpanzee Recombinant adenovirus vectored	Human Recombinant viral vector	Recombinant viral vector (2 different viruses)	Human inactivated coronavirus	Chimpanzee inactivated virus
Approval	Emergency authorization Dec 11, 2020 FDA	Emergency authorization Dec 18, 2020 FDA	Emergency authorization Jan 29, 2021 EMA	Emergency authorization March 12, 2021 EMA	Under evaluation	Under evaluation	Under evaluation
Number of injections	2 shots, 21 days apart	2 shots, 28 days apart	2 shots, 28 days apart	1 shots	2 shots, 21 days apart	2 shots, 21 days apart	2 shots, 21 days apart
Age group for vaccination	16 yrs and older	18 yrs and older	Recommended 60 yrs and older	18 yrs and older			
Effectiveness	95%	94%	62%-90%	77%-85%	91.4%	79.34%	78%
Mechanism of action	Elicits immune response to the S antigen	Elicits immune response to the S antigen	Elicits the immune response to the virus	Elicits the immune response to the virus	Elicits the immune response to the virus	Elicits the immune response to the virus	Elicits the immune response to the virus

Safety definitions

According to the WHO criteria for causality assessment, an AE following immunization (AEFI) is any untoward medical occurrence which follows vaccination and which does not necessarily have a causal relationship with the usage of the vaccine[25]. The AE may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease. Serious adverse events (SAE) are untoward events that at any dose result in death, are life-threatening, require hospitalization or prolongation of existing hospitalization, or result in persistent or significant disability/incapacity or birth defect, or AEs requiring medical attention, or leading to withdrawal from the trial. The AE

severity grading scale ranges from grade 1 (mild), grade 2 (moderate), and grade 3 (severe), to grade 4 (life-threatening). Reactogenicity is evaluated in terms of solicited local (injection site pain / tenderness / swelling) and systemic (fatigue, headache, myalgia, nausea, fever) AEs during the 7 days after vaccination, and unsolicited AEs over the 28 days post vaccination. AEs are further classified as AEs of Special Interest (AESI) or according to MedDRA (Medical Dictionary for Regulatory Activities) by system organ classes (SOC), e.g., nervous system disorders. Finally, investigators, independent committees of neurological experts, and regulatory agencies evaluated whether it is plausible that the reported AEs are or are not related to the vaccine under study. For the purpose of this discussion, AEs were searched in published trials and Supplementary Appendices, and FDA and EMA assessment reports.

Neurological complications of COVID-19 vaccines in clinical trials

1. BNT162b2 COVID-19 mRNA-based vaccine

The safety and efficacy of the BNT162b2 candidate vaccine (Pfizer and BioNTech) were assessed in phase I and II/III randomized, placebo-controlled clinical trials[2,7], where local and systemic events were generally milder in older than in younger participants and were greater after the second than after the first dose. The phase III trial enrolled 43,448 subjects aged 16 years and over from July to November 2020, randomized to receive BNT162b2 (n=21,720) or placebo (n=21,728) two doses, 21 days apart[7]. The safety population, followed for a median of 2 months after the second dose, included 37,706 subjects, median age 52 years, while reactogenicity was evaluated in a subgroup of 8,183 subjects. Related AEs were reported more frequently in vaccine recipients (20.7%) than in placebo (5.1%), largely due to reactogenicity events during the 7 days after vaccination. Among them, headache was reported more often after the second dose (52% vs 24% in placebo [16-55 years], and 39% vs 14% in placebo [>55 years]) than after the first dose (42% vs 34% in placebo [16-55 years], and 25% vs 18% in placebo [>55 years]). No severe AEs/SAEs of neurological interest occurred in the safety population. The investigators concluded that no deaths were to be considered to be related to the study interventions. In the FDA and EMA assessment reports (not in the published paper[7]), four cases of Bell's palsy were reported in the vaccine arm versus 0 in placebo, three occurring 3, 9 and 48 days after dose 2, and one 37 days after dose 1; the study investigators considered all four to be related to vaccination[11,14]. Sleep disturbances (insomnia/sleep disorder/abnormal dreams) were more frequent in the vaccine than in the placebo arm, possibly due to local/systemic reactogenicity[11,14]. Overall, systemic reactions

were transient and of short duration, mostly of mild or moderate intensity, and reported more often by younger subjects. The frequency of severe AEs, SAEs and AEs leading to trial discontinuation was low and equally distributed in both study arms.

Comment: the efficacy of Pfizer-BioNTech COVID-19 vaccine (Comirnaty in Europe) was considered high (95%) and the observed safety profile favorable, with a positive benefit-risk balance. The frequency of Bell's palsy in the vaccine group was consistent with the expected rate in the general population[11], with a possible relation to the vaccine[14]. Surveillance for cases of Bell's palsy and allergic (anaphylactic) reactions with deployment of the vaccine into larger populations was recommended.

2. mRNA-1273 MODERNA COVID-19 -based vaccine

This vaccine was evaluated in two small phase I studies[3,4] and in a large phase III, placebo-controlled clinical trial enrolling 30,420 subjects between July 2020 and October 2020, randomized to receive mRNA-1273 (n=15,185) two doses, 28 days apart, or placebo (n=15,166)[8]. The median follow-up after the second injection was 63 days; 25% of participants were ≥65 years of age. Reactogenicity was pronounced for both local and systemic adverse reactions, in particular after the second dose of vaccine, with mostly mild or moderate transient events[12,15]. Headache was more frequently reported in younger than in older persons, and after the second dose: 65.8% versus 25.3% in placebo (18-64 years) and 46.2% versus 17.5% in placebo (≥65 years), than after the first dose: 35.3% versus 29% in placebo (18-64 years) and 24.5% versus 19.3% in placebo (≥65 years). Unsolicited nervous system disorders during the 28 days after vaccination were reported by 4.5% in the vaccine arm (3.1% headache) and 4.1% in the placebo group (3% headache) (Supplementary Appendix: Tables S9-S11)[8]. Moreover, three cases of Bell's palsy were observed in the mRNA-group compared to one case in the placebo group, with timing suggesting a possible causal relationship to vaccination[15]. Treatment-related sensory disturbances (paresthesia, hypoesthesia, hyperesthesia) were more frequent in the vaccine than in the placebo arm (20 vs 7) as well as sleep disorders (insomnia abnormal dreams, nightmare) (30 vs 15). Finally, in vaccine recipients, three SAEs of cerebrovascular accident (1 placebo), 2 SAEs of embolic stroke (none in the placebo group), and 1 SAE of transient ischemic attack (none in the placebo group) were reported; the investigators did not consider any of them to be related to vaccination.

Comments: the efficacy of mRNA-1273 MODERNA COVID-19-based vaccine was high, and the safety profile was favorable, although this vaccine appeared more reactogenic than many of the standard vaccines in use. As for the COVID-19 vaccines, long-term safety data, interaction with other

vaccines, data on use in pregnancy and other subgroups require updates and surveillance for AEs[26].

3. ChAdOx1 nCoV-19 vaccine (AZD1222)

The safety and efficacy of the AstraZeneca COVID-19 vaccine, now called Vaxzevira, were evaluated in a phase I/II trial[5] and in the pooled interim analysis of four ongoing randomized, blinded, controlled trials carried out across the UK, Brazil, and South Africa between April 23 and Nov 4 2020[9]. The safety analysis included 23,745 participants randomly assigned to receive two doses of AZD1222 (n=12,021) or vaccine/placebo (n=11,724). Overall, in the safety population, 91.1% were aged 18-64 years, 8.9% were 65 years or over, 55.8% were female. The median follow-up from the first dose was 105 days in the AZD1222 treatment and 104 days in the control groups. Local and systemic AEs, generally mild or moderate, were reported more frequently in AZD1222 than in controls, and after the first dose than after the second. Headache was the second most frequently reported solicited systemic AE (57.5% vs 42.4% in control) after fatigue (62.3% vs 48% in control)[17], while among the unsolicited AEs, the frequency of nervous system disorders was higher in the vaccine group (9.3%, mostly of grade 1-2) than in controls (5.5%), including headache, lethargy, migraines, somnolence, dizzines[17]. In the category of AESI, five 'potential immune mediated conditions-neuroinflammatory disorders' are reported in the AZD1222 group (three Bell's palsy, one transverse myelitis, one multiple sclerosis) and four in controls (three Bell's palsy, one myelitis), while 'other neurologic events' reported in both vaccinated and control groups, although with a very low frequency (range <0.1 - <0.5%) included paresthesia, hypoesthesia, muscular weakness, visual impairment, followed by sensory disturbance (sensory loss, dysesthesia, hyperesthesia), gait disturbance, neuralgia (Supplementary Appendix Table S7)[9]. Of the six cases of Bell's palsy, only one in the vaccine and one in the control group were considered to be at least possibly related to vaccination based on the timing. Again, among the seven SAEs of neurological interest in the vaccine recipients (facial spasm, ischemic stroke, migraine, multiple sclerosis, transverse myelitis, presyncope, serotonin syndrome; one case each), and the four in controls (myelitis, subarachnoid hemorrhage, syncope, transient ischemic attack; one case each) (Supplementary Appendix Table S6), only the case of transverse myelitis in the AZD1222 group was reported as being possibly related to vaccination, resulting in temporarily pausing the trial, while multiple sclerosis was considered unrelated to study treatment as the MRI showed new and pre-existent brain lesions[9]. One case in each group had generalized convulsion, while a case of neuritis and a case of peripheral neuropathy were reported in the AZD1222 group.

Comment: in this trial the subjects in the control group were administered Meningococcus ACWY vaccine or saline, which complicates the comparison of data[17]. Only 3 of 175 SAEs were considered to be related to the vaccine or control. Thrombotic and neurovascular events were more frequent in controls (8 cases) than in the AZD1222 group.

4. Ad26.COV2.S COVID-19 vaccine

Immunogenicity was studied in a very small phase I trial[6], while the safety and efficacy of a single dose of Ad26.COV2.S (Janssen/Johnson & Johnson) vaccine were evaluated in a multicenter, placebo-controlled, phase III trial, enrolling 43,783 subjects aged 18 years and over from September 2020 to January 2021, randomized to receive a single dose of either Ad26.COV2.S (n=21,895) or saline placebo (n=21,888)[10]. The median follow-up was 58 days (range 1- 124), 66.5% of subjects were aged 18-59 years, 33.5% were 60 years or over. In the safety population (3,356 vaccine recipients and 3,380 placebo recipients), systemic solicited AEs were more frequent in Ad26.COV2.S (55.2%) than in placebo recipients (35.1%), and in the class of study participants aged 18 to 59 years than in those aged 60 years or over. Headache was the most frequently reported solicited AE (39% vs 23.8% in placebo). Among 7 SAEs that the investigators considered to be related to vaccination, 4 were neurological disorders: two Bell's palsy, one brachial radiculitis, one Guillain–Barré syndrome versus 0 in control (Supplementary Appendix Tables S6 and S7)[10]. One case of Guillain-Barré syndrome and two cases of Bell's palsy in the placebo group, as well as another case of Bell's palsy in the vaccine group, were, however, considered to be unrelated. Moreover, four cases of headache in the vaccine group (vs 2 in control) and 1 syncope (vs 0 in control) were reported as AEs of grade ≥3 (Supplementary Appendix Table S6)[10]. One case of transverse sinus thrombosis with cerebral hemorrhage occurring 21 days after the vaccination in a male of 25 years of age was considered unrelated to vaccination; the patient recovered. Finally, six cases of tinnitus were reported in the vaccine arm and none in the placebo group, while seizures occurred in 4 vaccine recipients and 1 placebo recipient. The causal relationship between these events and the vaccine remains undetermined[10].

Comments: EMA recommendations were updated in April and June 2021 with evolving experience of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria and the Janssen COVID-19 vaccine in people under 60 years of age within three weeks after vaccination, the majority in women[27,28]. On April 23 2021, the FDA recommended resuming the use of the Janssen COVID-19 vaccine in the US after the pause determined by the reports of six cases of a rare and severe type of blood clot following administration[29].

5. Sinovac and Sinopharm inactivated vaccine against COVID-19

Safety, efficacy and immunogenicity data for WHO Sinovac-CoronaVac authorization[19] came from several trials of phase I/II in China[30,31] and ongoing phase III trials in Brazil[32], Turkey, Indonesia and Chile. In the available safety population (n=8,840) who received any dose/schedule of Sinovac, AEs were mild/moderate, and there was no imbalance between vaccine and control group in SAEs, all classified as unrelated/unlikely related to vaccine, or AEs grade 3+[19]. In older subjects, reactogenicity was lower compared to younger adults, while the safety profile was similar. Post-authorization, two neurological SAEs were reported in China (one cerebral hemorrhage and one demyelination) out of over 35.8 million doses[19]. Vaccine efficacy was evaluated to be 51% for symptomatic disease and 100% for severe disease and hospitalization[19]. The WHO authorized Sinopharm BBIBP-CorV COVID-19[18] after assessment of efficacy and safety reported in phase I/II trials in China[33] and an ongoing phase III trial in Bahrain, Egypt, Jordan, and the United Arab Emirates[34]. The available safety population included 16,671 participants who received any dose/schedule of BBIBP-CorV vaccine. Most AEs were mild to moderate, without any imbalance in the number of reported SAEs, AEs of special interest (neurological diseases) or grade 3+ AEs between the BBIBP-CorV and placebo groups. One SAE initially reported as being possibly linked to vaccination was inflammatory demyelination syndrome/acute disseminated encephalomyelitis, later not confirmed. In terms of quality of evidence, the WHO concluded, with a moderate level of confidence, that the risk of SAEs following one or two doses of BBIBP-CorV in adults (age 18-59 years) is low, while for older adults (age ≥60 years) the level of confidence was very low. Vaccine efficacy for symptomatic and hospitalized disease was estimated to be 79% in all age groups combined[18]. No AEs of neurological interest were reported in Sputnik V[20,21] and Covaxin[22] trials.

In summary, neurological AEs were extremely rare in clinical trials of COVID-19 vaccines, and vaccine-induced immune thrombotic thrombocytopenia (VITT) was observed only in a small number of persons receiving AZD1222 and Ad26.COV2.S. However, with mass vaccination, several hundred patients were reported with this syndrome, which is caused by platelet activation and subsequent stimulation of the coagulation system, resulting in thromboembolic complications, as discussed below.

Table 17.2: Neurological adverse events (AEs) in safety populations of trials of COVID-19 vaccines

Vaccine in trials	Randomized population	Safety Population and Safety Time	Headache after dose 1 Vaccine vs placebo/control	Headache after dose 2 Vaccine vs placebo/control	Neurologic SAEs Vaccine vs placebo/control	Neurologic AEs Vaccine vs placebo/control
mRNA-BNT162b[27] Pfizer and BioNTech Phase II/III**7	N= 43,448	N=37,706 n= 18,860 BNT162b2 n= 18,846 placebo July 27-November 14, 2020 median ≥ 2 months after dose 2	42% vs 34% 16-55 yr 25% vs 18% >55 ys	52% vs 24% 16-55 yr 39% vs 14% >55 ys	0	4 Bell's palsy vs 0 *related* sleep disturbances more frequent in vaccine arm
mRNA-127[38] MODERNA Phase III8	N= 30,420	N = 30,351 n= 15,185 mRNA-1273 n= 15,166 placebo July - November 2020 median 63 days after dose 2	35.% vs 29% 18-64 yr 24.5% vs 19% ≥65 yr	66% vs 25% 18-64 yr 46.% vs 17.5% ≥65 yr	16 vs 10 *not related**	3 Bell's palsy vs 1 *related* sleep disorders 30 vs 15 sensory disturbances 20 vs 7
AstraZeneca[9] (AZD1222) Phase I/II/III (4 RCT pooled)[9]	N= 23,848	N=23,745 n= 12,021 AZD1222 n= 11,724 vaccine/placebo April - November 2020 median 3.4 months	54.4% vs 38.1%	32.6% vs 25%	1 transverse myelitis vs 0 *related*§ 7 vs 4§§	1 Bell's palsy vs 1 *related* 1 seizures vs 1 1 peripheral neuropathy and 1 neuritis vs 0
Janssen Vaccine[10] (Johnson &Johnson) Ad26.COV2.S Phase III10	N= 43,783	N=6736 n= 3356 Ad26.COV2.S n= 3380 placebo September 2020-January 2021	39% vs 23.8%	-	2 Bell's palsy, 1 Guillain-Barré syndrome, 1 brachial radiculitis *related* 1 transverse sinus thrombosis *not related*	1 Bell's palsy vs 2 *not related* - 1 Guillain-Barré syndrome in placebo *not related* - 6 tinnitus vs 0 and 4 seizures vs 1 *undetermined*

Sinopharm[31] BBIBP-CorV Phase III interim analysis	N= 40,382	n= 13,459 vaccine 1 n= 13,465 vaccine 2 n= 13,458 control median 77 days (1-121)	12.9% vs 13.1% vs 12.6%		1 Acute disseminated encephalomyelitis, 1 Clinically Isolated Syndrome in vaccine 2 *related*°	
Sinovac# CoronaVac Phase III (submitted)	N= 12,396	n= 8,840 n= 6,195 (vaccine) n= 6,201 (placebo) median 77 days	31.4% vs 32.2%	24.7% vs 24.2%	1 transient ischemic attack *not related*	oral paresthesia 5 vs 1
COVAXIN[22] Bharat Biotech India Phase II trial^^	N= 380	n=190 3 µg n=190 6 µg September 5-12, 2020	1% 1%	1% 1%	0	0
Gam-COVID-Vac[20] (Sputnik V) Phase III^	N= 21,977	N= 12,296 n= 14,964 vaccine n= 4902 placebo September-November 2020	2.9% vs 2.6% in those >60 yr (not stated after which dose)		1 vestibular ataxia, 1 syncope vs 0, 1 Multiple Sclerosis recurrence in placebo *not related*	3 metallic taste vs 0 1 paresthesia vs 1

*3 Serious adverse events (SAEs) of cerebrovascular accident (1 in placebo), 2 SAEs of embolic stroke (none in placebo), and 1 SAE of transient ischemic attack (none in placebo).

** Headache was analyzed in 8,183 participants (reactogenicity subset).

§One case of transverse myelitis 14 days after AZD1222 vaccination was judged to be related (the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination), resulting in temporarily pausing the trial. The other case of transverse myelitis 10 days after AZD1222 vaccination, initially considered to be related, was later judged as pre-existing, but previously unrecognised, multiple sclerosis. The transverse myelitis in control was judged to be unrelated.

§§ Seven cases in vaccine recipients: facial spasm, ischemic stroke, migraine, multiple sclerosis, transverse myelitis (related), presyncope, serotonin syndrome (one each); 4 cases in controls: myelitis, SAE, syncope, transient ischemic attack. All considered unrelated (multiple sclerosis was considered unrelated to study treatment as the MRI showed new and pre-existent brain lesions).

° From Supplementary Appendix Table 8S: in the text it was instead specified that a man aged 30 years was diagnosed with possible demyelinating myelitis after receiving the first dose, but later pathophysiological tests excluded the possibility of multiple sclerosis and identified that the man was heterozygous for very long-chain acyl-CoA dehydrogenase deficiency variant.

Palacios Ricardo et al.[32] Efficacy and safety of a COVID-19 inactivated vaccine in healthcare 2 professionals in Brazil: The PROFISCOV study (submitted) https://dx.doi.org/10.2139/ssrn.3822780

^ In two small, previous open, non-randomized phase I/II trials with two vaccine formulations in 76 volunteers, no SAEs were reported.[21]

^^ A phase III placebo-controlled, double-blind trial is ongoing on 25,800 randomized subjects.

Post-marketing surveillance of neurological complications of COVID-19 vaccines

Several countries have mandatory reporting systems of AEs following immunization used for post-marketing vaccine monitoring and surveillance. While at the population level there are several criteria to establish causality, temporal relationship (the only criterion necessary), strength of association, dose-response relationship, consistency of evidence, specificity, biological plausibility and coherence, at the individual level it is often impossible to achieve certainty about the cause-and-effect link between a reported AE and the vaccine[22]. After considering all other possible explanations, including coincidence, vaccine-quality defect, and error, the conclusions of systematic assessment establish whether the evidence is consistent with the vaccine being a cause, or is inconsistent, or indeterminate.

The US

The Centers for Disease Control and Prevention (CDC) and the FDA use the Vaccine Adverse Event Reporting System (VAERS) to monitor the safety of vaccines licensed for use in the US. According to the last CDC report (June 14 2021), results from VAERS are reassuring as to the safety and effectiveness of COVID-19 vaccines[35]. Anaphylaxis is rare (2-5 people per million vaccinated). After more than 11.7 million doses of the J&J/Janssen COVID-19 vaccine injected, 36 confirmed TTS have been reported (more than half with cerebral venous sinus thrombosis), nearly all in adult women under 50 years of age, and one confirmed case of TTS following mRNA COVID-19 vaccination (Moderna) after more than 310 million doses of mRNA COVID-19 vaccines administered in US. The clinical features of TTS following vaccination with the Janssen COVID-19 vaccine appear to be similar to those being observed following AstraZeneca COVID-19 vaccination in Europe. However, based on available data, there is no an increased risk for TTS after mRNA COVID-19 vaccination. No other neurological AEs of special interest have been reported. Myocarditis and pericarditis after COVID-19 vaccination are

rare. As of June 14 2021, VAERS has received 511 reports of myocarditis or pericarditis (323 confirmed by the CDC and the FDA) among people aged 30 years and under who received a COVID-19 vaccine, most cases being reported after mRNA COVID-19 vaccination (Pfizer-BioNTech or Moderna), particularly in male adolescents and young adults; investigation into the relationship to vaccination is ongoing. From December 14 2020 through June 14 2021, VAERS received 5,343 reports of death (0.0017%) among recipients of COVID-19 vaccines (more than 310 million doses administered in the US), but a review of available clinical information (death certificates, autopsy, medical records) has not established a causal link to COVID-19 vaccines, even if there is a plausible causal relationship between the J&J/Janssen COVID-19 vaccine and TTS, which has led to deaths.

Europe

According to the EMA/EudraVigilance (the system monitoring all suspected AEs to medicines authorized in the European Economic Area [EEA]), as of April 2021, 169 cases of cerebral venous thrombosis, often associated to thrombocytopenia, were reported in the EEA and the UK after the first dose of Vaxzevria vaccination out 34 million of doses injected (4.9 cases per million)[36]. As occurred with the J&J/Janssen COVID-19 vaccine in the US, also AstraZeneca was paused in several European countries in March, to be restarted (in some countries only in persons over 55-60 years of age) when the EMA concluded that the AE had not increased beyond the expected incidence rate[36]. However, the incidence of all cases of TTS seems to be 1/100,000 vaccinated with Vaxzevria (lower in Italy, at around 0.45 cases)[37]. This thrombotic thrombocytopenia, which is immune in origin, seems to be due to the activation of antibodies against platelet factor PF4 and is clinically similar to the autoimmune heparin-induced thrombocytopenia**37**. Similar findings, with more thrombosis and intracerebral hemorrhage, are described after J&J/Janssen COVID19 vaccine with a frequency of presentation comparable to that described for Vaxzevria[38]. The diagnosis of cerebral venous sinus thrombosis (CVST) is suggested by persistent, worsening headache or blurred vision, focal neurological signs, or subacute encephalopathy. Thrombocytopenia is present, brain computed tomography (CT) or magnetic resonance imaging (MRI) detect CVST, PF4 antibody testing is positive. Therapeutic recommendations include intravenous immunoglobulin, oral anticoagulation or anticoagulants other than heparin.

In the European database there are 122 reported cases of myocarditis in Pfizer (Comirnaty) recipients, 16 in the Moderna COVID-19 vaccine, 38 in Vaxzevria) and 0 for the Janssen COVID-19 vaccine[39]. The reported cases of pericarditis were 126 (Comirnaty), 18 (Moderna COVID-19 vaccine), 47 (Vaxzevria) and 1 (Janssen COVID-19 vaccine). The exposure in the EEA for each vaccine was

around 160 million doses for Comirnaty, 19 million doses for Moderna, 40 million for Vaxzevria, and 2 million for Janssen. Most of these cases were mild, resolving within a few days, mainly affecting males under 30 years of age, and after the second dose of vaccination[39]. Six cases of capillary leak syndrome in people who had received Vaxzevria were reported mostly in women within 4 days of vaccination (one of the 3 with history of capillary leak syndrome died)[40].

Overall, cerebral venous thrombosis is the most relevant neurological SAE reported in the post-marketing findings for the two viral vector vaccines, even if its frequency is not considered to be higher than expected in the general population, and both the FDA (J&J/Janssen) and the EMA (J&J/Janssen and Vaxzevria) concluded that the benefits outweigh the risks. However, especially women under 50 years of age should be aware of the rare but increased risk of this adverse event and that there are other COVID-19 vaccine options available for which this risk has not been seen.

There is no evidence at the present time to suggest that any of the vaccines is associated with AEs of neurological interest in any significant numbers. The only consistent neurological AE clearly associated to COVID-19 vaccines in clinical trials is headache, mostly occurring in mRNA vaccines, in younger people, and after the second dose. However, headache is very common after any vaccination (e.g., against Influenza virus and Hepatitis B virus) and probably reflects reactogenicity, with or without other symptoms such as fever and myalgia, and local reactions. Bell's palsy in clinical trials was rare, but investigators and the EMA considered it to be related to mRNA-vaccines, and even if it usually resolved by itself, surveillance is recommended as part of post-marketing procedures. As for influenza, the risk of Guillain-Barré syndrome after COVID-19 is probably higher than the risk after vaccination.

Take-home message

- The most frequent neurological AE associated with COVID-19 vaccines is headache, which is, however, common after any vaccination.
- Other AEs are rare events and are comparable to those of the usual vaccines.
- Occasional reports concerning extremely serious neurological AEs, such as cerebral venous thrombosis, require careful surveillance and the choice of the safest vaccine for a specific class of age and gender.
- Final considerations are limited by the continuing evolution of this unique global vaccination campaign. But it is evident that, despite the fact that extremely serious but very rare AEs are probably attributable to the vaccines, the benefits far outweigh the risks.

References

1. WHO Director-General's opening remarks at the media briefing on COVID19-11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020
2. Walsh EE, Frenck RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. *N Engl J Med*. 2020;383:2439-5240.2450
3. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2- Preliminary report. *N Engl J Med*. 2020;383:1920-1931.
4. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SAR-SCoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med*. 2020;383:2427—2438.
5. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of Ch-AdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2020;396:1979—1993
6. Stephenson KE, Le Gars M, Sadoff J, et al. Immunogenicity of the Ad26.COV2.S vaccine for COVID-19. *JAMA*. 2021;325(15):1535—1544
7. 7. Polack FP, Thomas SJ, Kitchin N, et al., for the C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383:2603-2615.
8. Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416.
9. Voysey M, Clemens SAC, Madhi SA, et al; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397:99-111.
10. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26. COV2.S vaccine against COVID-19. *N Engl J Med*. 2021;384:2187-2201.
11. FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine. December 11, 2020. https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19
12. FDA Takes Additional Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for Second COVID-19 Vaccine. December 18, 2020. https://www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid
13. FDA Issues Emergency Use Authorization for Third COVID-19 Vaccine. February 27, 2021. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine
14. EMA recommends first COVID-19 vaccine for authorisation in the EU. December 21, 2020. https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu
15. EMA recommends COVID-19 Vaccine Moderna for authorisation in the EU. Janu-

ary 6, 2021. https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu

16. EMA recommends COVID-19 Vaccine Janssen for authorisation in the EU. March 11, 2021. https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-janssen-authorisation-eu
17. EMA recommends COVID-19 Vaccine AstraZeneca for authorisation in the EU. January 29, 2021. https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-astrazeneca-authorisation-eu
18. WHO lists additional COVID-19 vaccine for emergency use and issues interim policy recommendations. May 7, 2021. https://www.who.int/news/item/07-05-2021-who-lists-additional-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations
19. WHO validates Sinovac COVID-19 vaccine for emergency use and issues interim policy recommendations. June 1, 2021. https://www.who.int/news/item/01-06-2021-who-validates-sinovac-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations
20. Logunov DY, Dolzhikova IV, Shcheblyakov DV. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet*. 2021;397:671-681.
21. Logunov DY, Dolzhikova IV, Zubkova OV. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. *Lancet*. 2020;396:887-897.
22. Ella R, Reddy S, Jogdand H et al. Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine, BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of immune responses from a phase 1 follow-up report. *Lancet Infect Dis*. 2021;21:637-646.
23. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/
24. Deplanque D, Launay O. Efficacy of COVID-19 vaccines: From clinical trials to real life. *Therapies*. Available at: https://doi.org/10.1016/j.therap.2021.05.004
25. Causality assessment of an adverse event following immunization (AEFI). User manual for the revised WHO clas sification. Geneva: World Health Organization; 2013. Available from: http://www.who.int/vaccine_safety/publications/aevi_manual.pdf
26. EMA COVID-19 vaccine MODERNA safety update. May 11, 2021. https://www.ema.europa.eu/ documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-spikevax-previously-covid-19-vaccine-moderna-11-may-2021_en.pdf
27. COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. April 20, 2021. https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds- possible-link-very-rare-cases- unusual-blood-clots-low-blood
28. EMA raises awareness of clinical care recommendations to manage suspected thrombosis with thrombocytopenia syndrome. July 6, 2021. https://www.ema.euro-

pa.eu/en/news/ema-raises-awareness-clinical-care-recommendations-manage-suspected-thrombosis-thrombocytopenia

29. FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review. April 23, 2021. https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough-safety-review
30. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(2):181-192.
31. Wu Z, Hu Y, Xu M et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(6):803-812.
32. Palacios R, Batista AP, Nascimento de Albuquerque CS, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare 3 professionals in Brazil: The PROFISCOV study (submitted manuscript) https://ssrn.com/abstract=3822780
33. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis*. 2021;21(1):39-51.
34. Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults.A Randomized Clinical Trial. *JAMA*. 2021;326(1):35-45.
35. CDC. Selected Adverse Events reported after COVID-19 vaccination. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html
36. EMA. COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets. March 18, 2021.https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots
37. AIFA. Complicanze tromboemboliche post-vaccinazione anti-COVID-19 con Vaxzevria (ChAdOx1 nCov-19, AstraZeneca) o con COVID-19 Vaccine Janssen (Ad.26. COV2.S, Johnson & Johnson). May 26, 2021. https://www.aifa.gov.it/documents/20142/1289678/Documento_esperti_coagulazione.pdf
38. Hwang J, Lee SB, Lee SW, et al. Comparison of vaccine-induced thrombotic events between ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines. *J Autoimmun*. 2021;122:102681.
39. EMA. COVID-19 vaccines: update on ongoing evaluation of myocarditis and pericarditis. June 11, 2021. https://www.ema.europa.eu/en/news/covid-19-vaccines-update-ongoing-evaluation-myocarditis-pericarditis
40. Vaxzevria: EMA advises against use in people with history of capillary leak syndromeJune 11, 2021. https://www.ema.europa.eu/en/news/vaxzevria-ema-advises-against-use-people-history-capillary-leak-syndrome

Chapter 18. Neuro-COVID in children

Ilaria Viganò*, Chiara Vannicola*, Maria Paola Canevini
*These authors equally contributed to this work

Introduction

Since the first cases identified in December 2019 in Wuhan, China, COVID-19 (COronaVIrus Disease 19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly progressed into a global pandemic. As of 17th May 2021, there have been 162,704,139 confirmed cases of COVID-19 worldwide, including 3,374,052 deaths reported to the World Health Organization (WHO)[1].

Presentations of SARS-CoV-2 vary widely and range from asymptomatic to mild or moderate respiratory symptoms, to severe COVID-19 pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure. Furthermore, many non-respiratory symptoms and manifestations have been reported, including variable long-lasting effects (the post-COVID syndrome or Long COVID)[2,3].

COVID-19 may affect individuals of all ages, but the pediatric population seems to be less susceptible to SARS-CoV-2 infection. Moreover, reports of severe COVID-19 manifestations in children and adolescents are rare. The most common presenting manifestations of COVID-19 in children are non-specific symptoms, such as fever and cough; most children experienced asymptomatic, mild or moderate illness[4,5]. Furthermore, compared to adult populations, children were more likely to have normal leukocyte counts, while lymphopenia or lymphocytosis were infrequent[5]. Currently, few data regarding COVID-19 in the pediatric population are available and there has been no systematic description of the clinical spectrum of the disease in this group.

Although the pulmonary manifestations in COVID-19 are the most common, neurological symptoms are being recognized in an increasing number of patients, especially in severe disease. The first retrospective series published by Mao et al. reported neurological manifestations on 36% of 214 patients hospitalized for COVID-19, including non-specific symptoms such as headache, myalgia, weakness, dizziness and specific neurological signs such as cerebrovascular disease, altered state of consciousness and encephalopathy[6].

Neurological disease in children has already been reported in association with six of the seven human coronaviruses (HCoV), including SARS-CoV-2, while the

seventh, the Middle East respiratory syndrome coronavirus (MERS-CoV), has been described with neurological involvement in adults[7-11]. Neurological manifestations in children with HCoV are relatively rare, therefore there is little information about neurodevelopmental sequelae. However, cases of neurological disease associated with SARS-CoV-2 infections in children are rapidly emerging, suggesting a possible greater neurological involvement in the pediatric population affected by this virus than in other HCoVs. Only a small fraction of children affected by SARS-CoV-2 showed neurological manifestations such as seizures, encephalitis, stroke or neuropathies[12]. In most cases, severe neurological manifestations in the pediatric population appeared to be associated with the presence of Multisystem Inflammatory Syndrome (MIS-C). A review conducted by Chen in 2020 considering 187 children from the six latest reports of MIS-C cases showed that 34% suffered from neurological manifestations[13-19]. Of the 187 children studied, 64 had different neurological symptoms, most of which were headaches, positive meningeal signs (meningism), and altered mental status; taken together, most manifestations represent a central, rather than a peripheral involvement.

Neurological symptoms are thought to be secondary to a combination of different mechanisms, including the direct viral effect on the nervous system, the para- and post-infectious inflammation, and the neurological complications of the systemic effects of COVID-19[20].

Neurological manifestations of COVID-19 in children

Headache

Headache is the most common neurological symptom related to COVID-19 and has been described as one of the presenting symptoms also in children[5,21]. From January 22nd to May 30th 2020, according to case surveillance in the US, headache was reported in 15% of subjects in a cohort of 5,188 children with COVID-19 aged 0-9 years, and in 42% of 12,689 children aged 10-19 years[22]. According to another recent review, headache, together with myalgia and fatigue, were predominant non-specific neurological manifestations, being reported in 16.7% of 3,707 patients aged 18 years[12]. Although headache is frequently reported by patients, this symptom appears to be in most cases non-specific or related to an inflammatory systemic process, fever or migraine exacerbation[23,24]. Headache could be secondary to meningeal irritation, encephalitis and encephalopathy only in a minority of patients. In these cases, headache is only one of a cluster of symptoms indicating an infectious and inflammatory process within the central nervous system (CNS), like seizures, impairment of consciousness, nausea and vomiting, neck stiffness, irritability, and others. Headache is also frequently reported in children with MIS-C, a recently recognized but uncommon Kawasaki syndrome-like hyperinflammatory childhood disorder related to SARS-CoV-2

infection (see below). In a series of 58 hospitalized children from 8 different hospitals in England, headache was the most common symptom in MIS-C affecting 26% of patients[25]. Finally, headache could be one of the symptoms to persist after the resolution of the SARS-CoV-2 infection, also in children[26].

Seizures

Over the past years, betacoronaviruses SARS-CoV and MERS-CoV have been associated with neuropathological alterations and neurological symptoms. The most common neurological manifestations of HCoV infections were seizures; in particular, simple febrile seizures.

Data about a possible neuro-invasiveness of SARS-CoV-2 as well as pathophysiological mechanisms give rise to the hypothesis that the infection could be associated with an increased risk of seizure recurrence or with the development of new onset and acute symptomatic seizures.

Up to now, there have been no important evidence in literature that SARS-CoV-2 infection can cause worsening of the seizure in people with epilepsy. However, it is possible that the infection could favor the onset of seizures triggered by fever. Moreover, a severe disease course and advanced disease stage can result in hypoxic encephalopathy, cerebrovascular events, and the so-called "cytokine storm", which may trigger the development of acute seizures.

Different case reports regarding SARS-CoV-2 infections have suggested a neuro-invasive potential, with occurrence of neurological symptoms such as generalized tonic-clonic seizures, loss of consciousness, headache, and dizziness[27].

Some case series reported the predominance of HCoV-associated simple febrile seizures in children under one year of age[28]. In addition to febrile seizures, some cases of afebrile seizures associated to HCoV were reported. Esper et al. reported new-onset seizures in a patient affected by HCoV-HKU1. Central nervous system infections were ruled out; lumbar puncture, brain magnetic resonance imaging (MRI) were negative[29]. In 2020, Garcia-Howard et al. presented the case of a 3-month-old girl with a mildly symptomatic SARS-CoV-2 infection characterized by 2 days of fever and cough, which developed into two focal motor seizures with impaired awareness. Signs of meningo-encephalitis, other infections or active epilepsy were ruled out, and electroencephalogram and brain MRI were unremarkable. After 3 days, the child presented another afebrile motor seizure, and treatment with levetiracetam was started, with a favorable response. Whole exome sequencing was performed and revealed a pathogenic frameshift mutation in the *PRRT2* gene in both the child and the mother, who had a history of late infantile febrile seizures[30].

Moreover, 4 cases of status epilepticus associated with SARS-CoV-2 infection were described.

Swarz et al. described the case of a healthy 9-year-old child who tested positive for SARS-CoV-2, and who developed an acute-onset focal status

epilepticus. EEG showed a continuous delta slowing throughout the right hemisphere without epileptiform features. Head CT and brain MRI were normal. After the acute event, the patient recovered without reported deficits[31].

Another case of status epilepticus associated to encephalitis in a patient affected by SARS-CoV-2 was reported by McAbee et al. (see below)[32].

Farley et al. described the case of status epilepticus in an 8-year old patient with SARS-CoV-2 infection who remained afebrile throughout the entire course of his illness; the patient had an underlying tic disorder without a previous history of epilepsy[33]. Saeed et al. reported the case of a previously healthy 3-year-old boy with SARS-CoV-2 infection who presented with repeated fever-induced seizure and status epilepticus. Brain CT scan revealed brain edema and 5 days later brain MRI showed intracerebral hemorrhage in the right occipital lobe[34].

In all the cases reported, the patients had a complete recovery without neurological sequelae; however, long-term neurodevelopmental outcome is not yet evaluable due to short follow-up.

Encephalitis

Encephalitis is the inflammation of cerebral parenchyma caused by an infectious agent or aberrant reaction of the immune system against nervous system epitopes. For the diagnosis of infective encephalitis, the evidence of brain inflammation and the detection of the pathogen in cerebrospinal fluid (CSF) are necessary. Table 18.1 reports criteria for the diagnosis of SARS-CoV-2 encephalitis, according to the definition provided in a rapid review by Ellul et al.[20].

Up to now, only a few reports of SARS-CoV-2 infection-associated encephalitis in children are available and virus has not been recovered from CSF in these few cases. McAbee et al. described a previously healthy 11-year-old boy who was admitted to the hospital with status epilepticus. The CSF analysis was compatible with a viral infection and the EEG registered frontal intermittent delta activity. The presence of SARS-CoV-2 was confirmed by nasopharyngeal swab; however, the detection of SARS-CoV-2 in the CSF is not reported. This case did not require specific treatment and the boy had a complete recovery in a few days[32]. Another case, described by Freij et al., was a previously healthy 5-year-old girl, presenting fever and severe headache for 7-10 days, subsequent confusion and seizure, and after another few days, lethargia and asymmetric pupils. Brain MRI showed an extensive meningoencephalitis involving cerebellum and corpus callosum with leptomeningeal enhancement over the surface of the brainstem and into the auditory canal. CSF was suggestive for viral encephalitis but negative for infection. The child died at day 32 of illness. The brain biopsy evidenced the presence of SARS-CoV-2 RNA and *Mycobacterium tuberculosis* complex DNA. In this case, the author hypothesized that the patient was asymptomatically infected with *M. tuberculosis* and the host immune system could not concurrently respond to the SARS-CoV-2 virus[35]. The pathophysiology of SARS-CoV-2-associated encephalitis is still not completely understood, but some mechanisms have been hypothesized. The dysregulation of

the immune system, cell edema secondary to neuroinflammatory injury, immune-mediated neuronal damage due to "cytokine storm" syndrome, and the direct invasion of SARS-CoV-2 to the CNS could all be mechanisms contributing to the encephalitis process[13].

Table 18.1: Diagnostic criteria for encephalitis associated with SARS-CoV-2 infection (Reproduced from [20] with permission)

SARS-CoV-2 meningitis, encephalitis, myelitis, or CNS vasculitis

Confirmed
(1) SARS-CoV-2 detected in CSF or brain tissue or evidence of SARS-CoV-2-specific intrathecal antibody
(2) no other explanatory pathogen or cause found

Probable
(1) SARS-CoV-2 detected in respiratory or other non-CNS sample, or evidence of SARS-CoV-2-specific antibody in serum indicating acute infection
(2) no other explanatory pathogen or cause found

Possible
Patient meets suspected case definition of COVID-19 according to national or WHO guidance on the basis of clinical symptoms and epidemiological risk factors; in the context of known community SARS-CoV-2 transmission, supportive features include the following: the new onset of at least one of cough, fever, muscle aches, loss of smell, or loss of taste; lymphopenia or raised D-dimer level; and radiological evidence of abnormalities consistent with infection or inflammation (eg, ground glass changes)

In conclusion, a surprisingly small number of COVID-19 children develop classic encephalitic symptoms and data demonstrating SARS-CoV-2 in CSF are inconsistent. Clearly, more data are needed to clarify the potential role of SARS-CoV-2 in determining encephalitis.

Stroke and cerebrovascular disease

As regards cerebrovascular involvement, different reports of strokes and other types of cerebrovascular diseases in association with SARS-CoV-2 infections are available, whereas they were not previously described in association with other HCoVs. In Table 18.2 diagnostic criteria for stroke associated to SARS-CoV-2 infection are reported.

Regev et al. reported a case of a 16-year-old boy with unremarkable medical history who, after exposure to a COVID-19 patient, developed fever, sore throat, fatigue, abdominal pain, headache, and nuchal rigidity. After hospitalization, the patient developed septic shock requiring intubation. Diagnostic workup, including CSF and brain MRI documented the presence of a cerebrovascular disease involving

microvascular structures, probably due to an inflammatory process. The patient recovered within 2 weeks after discharge, although muscular weakness persisted[36].

Table 18.2: Diagnostic criteria for stroke associated with SARS-CoV-2 infection
(Reproduced from [20] with permission)

Stroke associated with SARS-CoV-2 infection
Probable association
(1) Either SARS-CoV-2 detected in CSF or other sample, or evidence of SARS-CoV-2-specific antibody in serum indicating acute infection;
(2) no other known traditional cardiovascular risk factors
Possible association
(1) Either SARS-CoV-2 detected in CSF or other sample, or evidence of SARS-CoV-2-specific antibody indicating acute infection;
(2) other traditional cardiovascular risk factors

Schupper et al. described 2 cases of cerebrovascular events in a 2-month-old infant and a 5-year-old child. The first had a medical history of tracheomalacia with tracheostomy and presented with respiratory failure requiring Extra Corporeal Membrane Oxygenation (ECMO). Head CT showed bilateral middle and posterior cerebral artery infarctions with hemorrhagic transformation, and brain MRI documented the presence of evolving hemorrhagic infarctions of bilateral occipito-parietal lobes, left temporal and frontal lobes; EEG showed non-convulsive status epilepticus. At time of publication, the patient was still on mechanical ventilation. The second case was a healthy 5-year-old child who was admitted to hospital after several days of fever, cough, and abdominal pain, with cardiogenic shock and cardiopulmonary failure requiring ECMO. Head CT showed right middle cerebral artery infarction, cerebral edema, and diffuse contralateral subarachnoid hemorrhage. After 5 days on ECMO, the child developed bilateral fixed and dilated pupils followed by loss of brainstem reflexes[37]. A similar case was reported by Kihira et al. describing a healthy 5-year-old child who after 3 days of fever, cough and abdominal pain presented deterioration and cardiogenic shock requiring ECMO; the child died. A large right anterior and middle cerebral artery infarction with subarachnoid hemorrhage in the left hemisphere was documented by head CT[38].

Another case of stroke in a patient with SARS-CoV-2 infection was reported by Tiwari et al. The patient, a 9-year-old child, presented with fever, frontal headache, vomiting and progressive right hemisome weakness that evolved to complete hemiplegia. CT angiography was performed and documented a multifocal smooth stenosis of both intracranial internal carotid arteries, right middle cerebral artery, and segments of the anterior cerebral arteries. The patient partially recovered and was on rehabilitation at time of publication[39]. Furthermore, Freij et al. and Essajee et al. reported

cerebrovascular involvement in 2 patients with concurrence of active *M. tuberculosis* infection and SARS-CoV-2 infection. (See above for the case described by Freij et al[35]).

The case described by Essajee et al. was a healthy two and a half year old girl who presented with an acute onset lethargy, right mydriasis and ptosis, and left-sided hemiparesis. She also had progressively enlarging cervical lymphadenopathy and decreased appetite. Head CT showed pan-hydrocephalus, basal meningeal enhancement and infarction involving the anterior limb of the right internal capsule, lentiform nucleus, and thalamus. Cerebral sinus venous thrombosis was documented.

Both the authors postulated that the hyperinflammatory status caused by the overlapping infections resulted in endothelial damage, which exacerbated coagulopathy and stroke risk[40]. Two more case reports described focal cerebral arteriopathy involving the left middle cerebral artery with acute infarctions of the left insula and basal ganglia in children who tested positive for SARS-CoV-2[41,42]. The most accredited hypothesis up to now, based on the evidence from adult patients, is that cerebrovascular events resulted from the SARS-CoV-2 "cytokine storm" causing inflammation-induced focal vasculitis.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a syndrome characterized by multifocal demyelination and presenting with focal neurological symptoms, typically occurring weeks after an infection. A provisional definition of ADEM related to SARS-CoV-2 infection is shown in Table 18.3.

Table 18.3: Diagnostic criteria for ADEM associated with SARS-CoV-2 infection (Reproduced from [20] with permission)

Acute disseminated encephalomyelitis associated with SARS-CoV-2 infection, Guillain-Barré syndrome, and other acute neuropathies associated with SARS-CoV-2 infection
Probable association
(1) Neurological disease onset within 6 weeks of acute infection
(2) either SARS-CoV-2 RNA detected in any sample or antibody evidence of acute SARS-CoV-2 infection
(3) no evidence of other commonly associated causes
Possible association
(1) Neurological disease onset within 6 weeks of acute infection
(2) either SARS-CoV-2 RNA detected in any sample or antibody evidence of acute SARS-CoV-2 infection
(3) evidence of other commonly associated causes

ADEM has already been reported in association with infections by other HCoVs. In 2004, Ye et al. described the case of a 15-year-old boy who

developed ADEM during HCoV-OC43 infection[43]. De Miranda Henriques-Souza et al. reported the case of a previously healthy 12-year-old female who presented with skin rash lasting 6 days, and headache and fever for 1 day. After 5 days she presented acute, progressive, bilateral, symmetrical motor weakness with inability to stand, walk, or handle objects. On the second day of hospitalization, she developed respiratory failure requiring intubation, quadriparesis, and absence of deep tendon reflexes. CSF analysis was negative for infections but nasopharyngeal swab was positive for SARS-CoV-2; brain MRI revealed a neuroradiological pattern consistent with ADEM.

The patient underwent 5-day therapy with methylprednisolone, which was repeated due to little improvement of her weakness after first pulse therapy. More than two months after the onset, this patient had still not completely recovered and was still unable to sit without support, had persistent spastic quadriparesis with global hyperreflexia, and did not have complete sphincter control[44].

Another recently reported case was a 17-month-old girl who presented with irritability, neck stiffness, right-sided nasolabial fold flattening, left upper extremity rigidity, right upper extremity paresis, lower limb hyper-reflexia, and truncal ataxia. During hospitalization, the patient developed autonomic instability and impairment of consciousness, and was moved to the intensive care unit (ICU). Brain MRI revealed multifocal hyperintense T2 fluid-attenuated inversion recovery signals in subcortical and periventricular white matter. CSF analysis was unrevealing but nasopharyngeal SARS-CoV-2 PCR was positive, as was serum antibody testing. This patient had a complete recovery in 2 months after high-dose methylprednisolone and intravenous immunoglobulin therapy followed by rehabilitation[45]. ADEM has been reported also in a 6-year-old patient with Fisher-Evans syndrome (autoimmune hemolytic anemia, immune thrombocytopenia and/or autoimmune neutropenia), who was given sirolimus and thalidomide. She had positive nasopharyngeal swab for SARS-CoV-2 but no symptoms suggestive of COVID-19. After 10 days, the patient presented a generalized tonic-clonic seizure with spontaneous resolution. A brain MRI showed a pattern consistent with ADEM. The patient received methylprednisolone and had a favorable clinical course[46]. These cases suggest that clinicians should consider ADEM when evaluating a child with encephalopathy and neurological signs together with a recent diagnosis of COVID-19.

Guillain-Barrè syndrome and other neuropathies

Guillain-Barré syndrome (GBS) is an acute polyradiculopathy clinically characterized by rapidly evolving ascending limb weakness, areflexia and sensory symptoms[20]. GBS has already been reported in children with HCoV infections. A case of acute flaccid paralysis was reported by Turgay et al., describing a case of a healthy 3-year-old child who presented with fever and cough, followed, after a few days, by dyspnea, inability to chew, swallow or speak, reduced muscular strength

and absent deep tendon reflexes. The patient developed respiratory failure that required intubation. CSF pressure, glucose, and protein were normal, and blood, urine, and CSF cultures were negative. Electromyography and brain and spine MRI were normal. A nasopharyngeal swab revealed the presence of HCoV-229E and HCoV-OC43 co-infection. Treatment with intravenous immunoglobulin was effective and after 2 weeks the patient could walk with support[47].

Another case of acute flaccid paralysis associated with HCoV-OC43 was reported by Sharma et al. The patient is a 5-year-old healthy male presenting with a left Bell palsy, reduced muscular strength, generalized hypotonia, inability to walk or to raise his arms above the shoulders, dysmetria, ataxia, dysphagia with drooling. CSF showed albumin-cytologic dissociation with no cells, and elevated CSF total protein, elevated albumin index (39.8; reference ≤9) and IgG index (0.89; reference ≤0.66), normal myelin basic protein, no oligoclonal bands. MRI showed brain and spine enhancement of the left bulbar nerve complex and anterior and posterior cervical nerve roots. Clinical and instrumental examinations suggested GBS diagnosis. The patient was treated with non-invasive ventilation for acute respiratory failure, and intravenous immunoglobulin, with a partial recovery after 2 weeks[48]. Khalifa et al. reported a case of GBS associated with SARS-CoV-2 infection in a previously healthy 11-year-old male who, a month after upper respiratory infection and fever, developed acute symmetrical muscular weakness of the lower extremities and loss of deep tendon reflexes, tingling, impaired sensitivity. CSF and brain and spine MRI showing, respectively, albumin-cytologic dissociation and enhancement of the cauda equina nerve roots, in addition to evidence of a demyelinating process at nerve conduction studies, were consistent with a diagnosis of GBS. The patient was treated with intravenous immunoglobulin and after 2 weeks showed improved strength and sensory symptoms[49]. Gaur et al. described the case of a 3-year-old healthy child with asymptomatic SARS-CoV-2 infection, who developed transverse myelitis presenting with progressive extremity weakness resulting in flaccid tetraparesis, areflexia, and impaired sensitivity. Spine MRI showed swelling of cervical spinal cord with a lesion involving most of the transverse spinal cord from the lower medulla to the midthoracic level. CSF studies revealed pleocytosis and mildly elevated proteins[50].

There is no direct evidence of a causative relationship between GBS or other acute flaccid paralysis and SARS-CoV-2 infection but the reports of similar cases and the data available about adult patients can raise the hypothesis that SARS-CoV-2 virus may be a possible trigger.

Other viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV) had previously been implicated in the pathogenesis of GBS. The suggested mechanism is an autoimmune reaction secondary to molecular mimicry between the surface glycoproteins of the offending pathogen and the structures on peripheral nerves causing the antibodies to attack the nerves and cause neurological symptom. It is,

therefore, possible to hypothesize that SARS-CoV-2 could be a trigger for a neurological process as the basis of GBS[51,52].

Furthermore, before the recent pandemic, few cases of GBS secondary to coronavirus infections had been reported, whereas a recent systematic review documented a significant increase in the number of patients with GBS during the COVID-19 pandemic[53].

Table 18.4: Diagnostic criteria for MIS-C associated with SARS-CoV-2 infection according to Centers for Disease Control and Prevention definition

(Reproduced from [55] with permission)

CDC case definition
All 4 criteria must be met:
1. Age <21 years

2. Clinical presentation consistent with MIS-C, including all of the following:
• Fever: Documented fever >38.0°C (100.4°F) for ≥24 hours or Report of subjective fever lasting ≥24 hours
• Laboratory evidence of inflammation, Including, but not limited to, any of the following:
  • Elevated CRP
  • Elevated ESR
  • Elevated fibrinogen
  • Elevated procalcitonin
  • Elevated D-dimer
  • Elevated ferritin
  • Elevated LDH
  • Elevated IL-6 level
  • Neutrophilia
  • Lymphocytopenia
  • Hypoalbuminemia
• Multisystem involvement (2 or more organ systems involved):
  • Cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia)
  • Respiratory (eg, pneumonia, ARDS, pulmonary embolism)
  • Renal (eg, AKI, renal failure)
  • Neurologic (eg, seizure, stroke, aseptic meningitis)
  • Hematologic (eg, coagulopathy)
  • Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding)
  • Dermatologic (eg, erythroderma, mucositis, other rash)
• **Severe illness requiring hospitalization**

No alternative plausible diagnoses
Recent or current SARS-CoV-2 infection or exposure (any of the following): • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Neurological manifestations in Multisystem Inflammatory Syndrome in Children

In contrast to most children with SARS-CoV-2 who develop only mild symptoms which usually do not require medical intervention, in April 2020, a group of clinicians from the UK described 8 previously healthy children presenting with fever, cardiovascular shock, and hyperinflammation[54]. In May 2020, the Centers for Disease Control and Prevention (CDC) defined the criteria for MIS-C and published a health advisory requesting health care practitioners to report suspected MIS-C cases to local, state, and territorial public health authorities. Criteria for MIS-C according to the CDC and the WHO definition are reported in Tables 18.4 and 18.5.

Table 18.5: Diagnostic criteria for MIS-C associated with SARS-CoV-2 infection according to World Health Organization definition[56]

WHO case definition
All 6 criteria must be met:
Age 0 to 19 years
Fever for ≥3 days
Clinical signs of multisystem involvement (at least 2 of the following): • Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) • **Hypotension or shock** • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) • Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
Evidence of SARS-CoV-2 infection. Any of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • Contact with an individual with COVID-19

MIS-C is a Kawasaki-like syndrome with hyperinflammation presenting with acute hypotension and cardiogenic shock. This syndrome is thought to be a post-infection inflammatory phenomenon due to an immune reaction following asymptomatic or pauci-symptomatic COVID-19. Children can develop toxic shock-like symptoms, hypoxia-ischemia, and damage to the heart, kidneys, and other organs[57,58]. Neurological manifestations are frequently described in MIS-C. In New York, 31-47% of affected children reported neurological symptoms like headache, altered mental status, and encephalopathy[19]. A recent systematic review including eight studies reported neurological symptoms in 25-50% of children with MIS-C[59]. A multicenter study on

children with MIS-C in the US described neurological complications such as altered mental status, seizures and encephalitis in 5-11% of cases[57]. Headache was the most common symptom also in patients with MIS-C, affecting 26% of a series of 58 patients[25]. In another series of 27 children with MIS-C, 4 patients developed encephalopathy, headache, dysarthria, dysphagia, weakness, ataxia, and peripheral neuropathy. In 2 patients, lumbar puncture was performed, and CSF was negative for SARS-CoV-2. Three patients showed diffuse slowing at EEG. For all children, brain MRI showed signal abnormalities of the splenium of the corpus callosum[60]. Another series of 21 children from France reported irritability in 57% and "other neurological features" not further specified in 29% of children studied[61]. In a recent case series of inpatients aged <21 years with positive test for SARS-CoV-2 in 61 US hospitals, MIS-C was diagnosed in 36% of patients and in 35% of patients with neurological involvement. Twenty patients with MIS-C who developed life-threatening COVID-19-related neurological conditions had an MIS-C diagnosis. Among these, 8 had severe encephalopathy, 3 had ischemic or hemorrhagic stroke, 6 had acute CNS infection or ADEM, 2 had acute fulminant cerebral edema, and one developed GBS[62]. Patients with neurological manifestations in MIS-C could frequently present with symptoms such as altered mental status or headache, which suggest a CNS infection. However, in the reported cases, no demonstration of SARS-CoV-2 was evident. These data seem to indicate that neurological symptoms of MIS-C could be secondary to a post-infectious immune response. The over-reaction of monocytes, macrophages, and T cells which produces the "cytokine storm" syndrome may contribute to the neuronal damage, further aggravated by the release of interleukin-6 (IL-6)[13]. In conclusion, the impact of SARS-CoV-2 on the developing CNS, the immature immune system, and the neural-immune maturation have to be considered, and further data are needed to understand the pathophysiological characteristics of SARS-CoV-2 neurological involvement in MIS-C.

Conclusions and clinical work-up

Neurological manifestations associated with SARS-CoV-2 infection are rare in children but include a wide variety of central and peripheral insults. Most common symptoms are non-specific (headache, weakness), but severe manifestations such as encephalopathy, seizures, demyelinating disorders, and cerebrovascular events are possible. Furthermore, the pathophysiological mechanism at the basis of neurological manifestations is still under investigation, due to the relatively brief period of observation of the COVID-19 pandemic.

While for unspecific symptoms most cases require no further investigation, when symptoms suggesting a neurological involvement are present, other tests are needed. In particular, clinicians should be guided by signs observed during

the neurological examinations and the symptoms reported by patients themselves. If altered mental status, meningism and neurological signs are detected, the clinical work-up should include brain MRI, EEG, and, if the suspicion of meningoencephalitis is still not clarified, a lumbar puncture with CSF analysis, including SARS-CoV-2 PCR is indicated. If weakness and paresis are present and GBS is suspected, an electromyography with electroneurography should be considered and a CSF examination showing albuminocytologic dissociation could be supportive for the diagnosis.

In conclusion, the diagnostic process should be personalized, based on the diagnostic hypothesis, and addressed by the symptoms reported and signs detected in patients.

Therapeutic recommendation and prognosis

The therapeutic approach in SARS-CoV-2 should follow guidelines for each suspected disorder.

Patients with headache usually benefit from commonly used analgesic drugs like non-steroidal anti-inflammatory drugs (NSAIDs), as no specific treatment options for COVID-19-related headache have been reported. When treating seizures, clinicians should always consider the interactions between anti-seizure medication and drugs used for COVID-19. Caution is needed in particular for carbamazepine, phenytoin, phenobarbital and primidone, enzyme inducers. A list of drug interactions is reported at the web page: https://www.covid19-druginteractions.org.[63]

Clinicians should be guided by conventional inclusion and exclusion criteria for stroke treatment such as systemic fibrinolysis and mechanical thrombectomy, even during SARS-CoV-2 infection.

In addition, the treatment of SARS-CoV-2 infection-related GBS and acute neuropathies does not differ from the conventional treatment, even if performing plasma exchange could present some organizational problems when patients are infectious[64]. According to a recent cohort study reporting on neurological symptoms in SARS-CoV-2 infection in hospitalized children and adolescents in the UK, immunomodulation was used as treatment in 86% of patients with ADEM, 80% of patients with GBS, and in the only patient with limbic encephalitis. Admission to a pediatric ICU admission was necessary in 29% of patients with ADEM, 20% of patients with GBS, and 56% of patients with severe encephalopathy[65].

Prognosis is frequently good but cases with neurological sequelae have been reported.

As regards short-term prognosis, disability was the outcome in 57% of children with ADEM, 40% of patients with GBS, 11% of patients with severe encephalopathy in the previously cited cohort of hospitalized children; in these

groups, no death was reported[65]. Data on long-term outcome of pediatric patients with COVID-19-related neurological involvement are still lacking and should be collected in such a way as to allow effects on cognition and development to be evaluated.

Take home message

- Neurological involvement in SARS-CoV-2 infection in children is rare but has to be considered when symptoms suggesting central or peripheral nervous system disease are present.
- The pathophysiology of neurological diseases in SARS-CoV-2 infection is still not completely clear but probably includes neuroinflammatory injury, a dysregulation of the immune system, immune-mediated neuronal damage due to "cytokine storm" syndrome, and the potential direct invasion of SARS-CoV-2 to the CNS.
- The most common symptom is headache, but cases of encephalopathy, seizures, demyelinating disorders, and cerebrovascular events during SARS-CoV-2 infection in children have been reported.
- Neurological symptoms are more frequent and could be serious in patients with MIS-C.
- Treatment should follow guidelines for each disorder.

References

1. https://covid19.who.int
2. Carfì A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324:603-605.
3. Osuchowski MF, Winkler MS, Skirecki T, et al. COVID-19: Pathophysiology of Acute Disease 1. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet*. 2021;9(6):622-642.
4. Mantovani A, Rinaldi E, Zusi C, et al. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. *Pediatr Res*. 2021;89(4):733-737.
5. Cui X, Zhao Z, Zhang T, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). *J Med Virol*. 2021;93(2):1057-1069.
6. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of hospitalized patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurology*. 2020;77(6):683-690.
7. Desforges M, Favreau DJ, Brison A, et al. *Human coronaviruses: respiratory pathogens revisited as infectious neuroinvasive, neurotropic, and neuro- virulent agents*. In: Neuroviral Infections: RNA Viruses and Retroviruses. Boca Raton, FL: CRC Press; 2013.
8. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92:552e555.
9. Barmore J. 5-year-old with rare complication becomes first Michigan child to die of COVID-19. The Detroit News, April 19, 2020. Accessed: April 30, 2020.
10. Molteni M. What does Covid-19 do to your brain? Available from: www.wired.com, April 15, 2020. Accessed: April 30, 2020.
11. Algahtani H, Subahi A, Shirah B. Neurological complications of Middle East respiratory syndrome coronavirus: a report of two cases and review of the literature. *Case Rep Neurol Med*. 2016;2016.3502683. doi:10.1155/2016/3502683.
12. Panda PK, Sharawat IK, Panda P, et al. Neurological Complications of SARS-CoV-2 Infection in Children: A Systematic Review and Meta-Analysis. *J Trop Pediatr*. 2021;67(3):fmaa070. doi:10.1093/tropej/fmaa070.
13. Chen TH. Neurological involvement associated with COVID-19 infection in children. *J Neurol Sci*. 2020;418:117096.
14. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142:429-436.
15. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis*. 2020;79(8):999-1006.
16. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study, *BMJ*. 2020;369:m2094.

17. Chiotos K, Bassiri H, Behrens EM, et al., Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series. *J Pediatric Infect Dis Soc*. 2020;9(3):393-398.
18. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778.
19. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med*. 2020;383(4):347-358.
20. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol*. 2020;19:767-783.
21. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020;370:m3249.
22. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759.
23. Poncet-Megemont L, Paris,ì P, Tronchere A, et al. High Prevalence of Headaches During Covid-19 Infection: A Retrospective Cohort Study. *Headache J Head Face Pain*. 2020;60(10):2578-2582.
24. Stafstrom CE and Jantzie LL. COVID-19: Neurological Considerations in Neonates and Children. *Children*. 2020;7:133.
25. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA*. 2020;324(3):259-269.
26. Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. *Acta Paediatr*. 2021;110(7):2208-2211.
27. Lau KK, Yu WC, Chu CM, et al. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis*. 2004;10:342-344.
28. Singer TG, Evankovich KD, Fisher K, et al. Coronavirus Infections in the Nervous System of Children: A Scoping Review Making the Case for Long-Term Neurodevelopmental Surveillance. *Pediatr Neurol*. 2021;117:47-63.
29. Esper F, Weibel C, Ferguson D, et al. Coronavirus HKU1 infection in the United States. *Emerg Infect Dis*. 2006;12:775-779.
30. García-Howard M, Herranz-Aguirre M, Moreno-Galarraga L, et al. Case report: benign infantile seizures temporally associated with COVID-19. *Front Pediatr*. 2020;8:507.
31. Swarz JA, Daily S, Niemi E, et al. COVID-19 infection presenting as acute-onset focal status epilepticus. *Pediatr Neurol*. 2020;112:7.
32. McAbee GN, Brosgol Y, Pavlakis S, et al. Encephalitis associated with COVID-19 infection in an 11-year-old child. *Pediatr Neurol*. 2020;109:94.
33. Farley M, Zuberi J. COVID-19 precipitating status epilepticus in a pediatric patient. *Am J Case Rep*. 2020;21:e925776-1-e925776-4.

34. Saeed A, Shorafa E. Status epilepticus as a first presentation of COVID-19 infection in a 3 years old boy; case report and review the literature. *IDCases*. 2020;22:e00942.

35. Freij BJ, Gebara BM, Tariq R, et al. Fatal central nervous system co-infection with SARS-CoV-2 and tuberculosis in a healthy child. *BMC Pediatr*. 2020;20:429.

36. Regev T, Antebi M, Eytan D, et al. Pediatric inflammatory multisystem syndrome with central nervous system involvement and hypocomplementemia following SARS-COV-2 infection. *Pediatr Infect Dis J*. 2020;39:E206-eE207.

37. Schupper AJ, Yaeger KA, Morgenstern PF. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Childs Nerv Syst*. 2020;36:1579e1580.

38. Kihira S, Morgenstern PF, Raynes H, et al. Fatal cerebral infarct in a child with COVID-19. *Pediatr Radiol*. 2020;50:1479e1480.

39. Tiwari L, Shekhar S, Bansal A, et al. COVID-19 associated arterial ischaemic stroke and multisystem inflammatory syndrome in children: a case report. *Lancet Child Adolesc Heal*. 2021;5:88e90.

40. Essajee F, Solomons R, Goussard P, et al. Child with tuberculous meningitis and COVID-19 coinfection complicated by extensive cerebral sinus venous thrombosis. *BMJ Case Rep*. 2020;13:e238597.

41. Gulko E, Overby P, Ali S, et al. Vessel Wall Enhancement and Focal Cerebral Arteriopathy in a Pediatric Patient with Acute Infarct and COVID-19 Infection. *AJNR Am J Neuroradiol*. 2020;41(12):2348-2350.

42. Mirzaee SMM, Gonçalves FG, Mohammadifard M, et al. Focal Cerebral Arteriopathy in a Pediatric Patient with COVID-19. *Radiology*. 2020;297(2):E274-E275.

43. Yeh EA, Collins A, Cohen M, et al. Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. *Pediatrics*. 2004;113:e73ee76.

44. de Miranda Henriques-Souza AM, de Melo ACMG, de Aguiar Coelho Silva Madeiro B, et al. Acute disseminated encephalomyelitis in a COVID-19 pediatric patient. *Neuroradiology*. 2020;63:141e145.

45. McLendon LA, Rao CK, Da Hora CC, et al. Post-COVID-19 Acute Disseminated Encephalomyelitis in a 17-Month-Old. *Pediatrics*. 2021;147(6):e2020049678.

46. Manzo ML, Galati C, Gallo C, et al. ADEM post-Sars-CoV-2 infection in a pediatric patient with Fisher-Evans syndrome. *Neurol Sci*. 2021;12:1-4.

47. Turgay C, Emine T, Ozlem K, et al. A rare cause of acute flaccid paralysis: human coronaviruses. *J Pediatr Neurosci*. 2015;10:280.

48. Sharma K, Tengsupakul S, Sanchez O, et al. Guillain-Barre syndrome with unilateral peripheral facial and bulbar palsy in a child: a case report. *SAGE Open Med Case Rep*. 2019;7:2050313X19838750.

49. Khalifa M, Zakaria F, Ragab Y, et al. Guillain-Barre syndrome associated with severe acute respiratory syndrome coronavirus 2 detection and coronavirus disease 2019 in a child. *J Pediatr Infect Dis Soc*. 2020;9:510e513.

50. Gaur P, Dixon L, Jones B, et al. COVID-19-associated cytotoxic lesions of the corpus callosum. *AJNR Am J Neuroradiol*. 2020;41:1905e1907.
51. Pritchard J. Guillain-Barré syndrome. *Clin Med* (Lond). 2010;10(4):399-401.
52. Yuki N, Hartung H-P. Guillain-Barré Syndrome. *N Engl J Med*. 2012;366(24):2294-2304.
53. Gittermann LMT, Feris SNV, von Oetinger Giacoman A. Relation Between COVID-19 and Guillain-Barré Syndrome in Adults: A Systematic Review. *Neurología* (English Edition) 2020;35(9):646-654.
54. Riphagen S, Gomez X, Gonzalez-Martinez C. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395:1607-1608.
55. Centers for Disease Control and Prevention Health Alert Network (HAN). Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). 2020. Available at: https://emergency.cdc.gov/han/2020/han00432.asp
56. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19: Scientific Brief. 2020. Available at: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
57. 57 Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med*. 2020;383(4):334-346.
58. Nakra NA, Blumberg DA, Herrera-Guerra A, et al. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. *Children*. 2020;7:69.
59. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2: A Systematic Review. *J Pediatr*. 2020;5;226:45-54.e1.
60. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. *JAMA Neurol*. 2020;77(11):1440-1445.
61. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: Prospective observational study. *BMJ*. 2020;369:m2094.
62. LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome. *JAMA Neurol*. 2021;78(5):536-547.
63. https://www.covid19-druginteractions.org
64. Orsucci D, Ienco EC, Nocita G, et al. Neurological features of COVID-19 and their treatment: a review. *Drugs Context*. 2020;9:2020-5-1.
65. Ray STJ, Abdel-Mannan O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. *Lancet Child Adolesc Health*. 2021:S2352-4642(21)00193-0.

Neurology of COVID-19

editor Alberto Priori

The authors will present a comprehensive account of the neurological aspects of SARS-CoV-2 infection. The aim is to provide a practical clinical book which will serve as a guide for clinicians from all specialties involved in the management of COVID-19 patients. The authors share the extensive clinical experience gained in major hospitals in Lombardy, the first European region to face the COVID-19 emergency in 2020. All are recognized international experts in their respective fields and have been involved in the management of COVID-19 cases from the very beginning of the Italian SARS-CoV-2 outbreak. The text begins with a description of pathobiological and pathophysiological aspects related to the involvement of the nervous system, moving on to the discussion of the neurological complications observed in COVID-19 patients; these range from central to peripheral symptoms, and can occur in the acute or post-acute phases of the disease. Further topics are: neuropathology, seizures and EEG, neuroimaging, delirium, encephalomyelitis, stroke, psychopathology and psychiatry, neuropsychology and cognitive impairment, neuromuscular disorders, and the impact of COVID-19 on other pre-existing neurological disorders. In addition, the book will discuss the new developments in teleneurology approaches, which have been a direct response to the ongoing pandemic. Finally, the possible neurological complications of the COVID-19 vaccines and the neurological complications in children will be considered.
Each chapter will present a critical review of the existing literature concerning the specific subject matter, followed by practical clinical recommendations, as well as personal considerations based on the experience gained by each author during the course of the COVID-19 pandemic.

"Neurology of COVID-19" will be an original and innovative reference book for clinicians of all the specialties involved in the management of patients with SARS-CoV-2 infection.

Image cover: graphic reworking of images not subject to copyright

ISBN 979-12-80325-33-4 (print)
ISBN 979-12-80325-35-8 (PDF)
ISBN 979-12-80325-37-2 (EPUB)
DOI 10.54103/milanoup.57