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Two patients with acute meningoencephalitis concomitant with SARS-CoV-2 infection

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Introduction

In December 2019, a cluster of patients with pneumonia of unknown cause led to the identification of a new strain of pandemic coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Since the first SARS-CoV outbreak, human coronaviruses have been known for their neurological tropism [2,3]. Respiratory complications are at the forefront of the clinical presentation of SARS-CoV-2 and neurological involvement remains poorly described and understood. We report here two patients infected with SARS-CoV-2 who presented with neurological symptoms and signs.

Methods

The clinical and ancillary test descriptions were personally retrieved by the authors, who examined the patients. This report was conducted in compliance with the Swiss Federal Act on Research involving Human Beings, which waives ethical approval for case reports of less than five patients. Both patients gave written informed consent for clinical and biological data to be used for this report. Viral/bacterial detection was performed using the FilmArray Meningitis/Encephalitis Panel (BioFire Diagnostics, Salt Lake City, UT, USA) and confirmed by traditional polymerase chain reaction.

Case descriptions

Patient 1

Patient 1 was a 64-year-old woman without psychiatric history, known to have had contact with SARS-CoV-2 (her husband tested positive 15 days before) and presenting for 5 days with flu-like symptoms (mild asthenia, myalgia, cough) without fever, acutely developed psychotic symptoms. She was first admitted to a psychiatric ward, but presented a tonico-clonic seizure motivating her admission to an external hospital. A routine electroencephalogram revealed non-convulsive, focal status epilepticus (abundant bursts of anterior low- to medium-voltage irregular spike and waves superimposed on an irregularly slowed theta background) that was managed with intravenous clonazepam and valproate. She was immediately referred to our center. The patient appeared disoriented, with strong attention deficit, verbal and motor perseverations and bilateral grasping, alternating with psychotic symptoms (hyper-religiosity with mystic delusions, visual hallucinations). There was no neck stiffness or focal signs on neurological examination. Cerebral magnetic resonance imaging was normal, but her lumbar puncture was compatible with viral meningoencephalitis (Table 1) and SARS-CoV-2 was detected in her nasopharyngeal swab. However, neither SARS-CoV-2 nor classic viral/bacterial pathogens were detected in the cerebrospinal fluid (CSF) (Table 1.). Anti-*N*-methyl-D-aspartate antibodies were tested negative in CSF. Treatment by acyclovir was transiently administered until herpes simplex/varicella zoster virus polymerase chain reaction results came back negative. A follow-up electroencephalogram 24 h after admission showed a moderate theta background slowing, without epileptiform features. The patient markedly improved 96 h after admission with resolution of her symptoms.

Patient 2

A 67-year-old woman, already diagnosed with SARS-CoV-2 infection for 17 days with mild respiratory symptoms, presented an intense wake-up headache. A few hours later, she was found drowsy and confused, lying on the floor of her bathroom. She was referred to our hospital. On neurological evaluation, she was disoriented with motor perseverations, bilateral grasping, aggressiveness and left hemianopia and sensory hemineglect; there was no neck stiffness. SARS-CoV-2 pneumonia was diagnosed by a positive nasopharyngeal swab and an ultrasound showing subpleural condensation. Brain magnetic resonance imaging was normal and her lumbar puncture revealed lymphocytic pleocytosis (Table 1). However, CSF SARS-CoV-2 and viral/bacterial pathogen polymerase chain reaction tests were negative (Table 1). The patient transiently received ceftriaxone, amoxicillin and acyclovir. Neurological symptoms resolved within 24 h, except for a mild headache. The patient was discharged 72 h after admission with no symptoms.

Discussion

We report on two patients who developed meningoencephalitis a few days after a diagnosis of SARS-CoV-2 infection. Both had a 'benign' form with only mild respiratory and general symptoms. However, they suddenly developed severe neuropsychological symptoms and one developed a status epilepticus. The CSF

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Table 1 Paraclinal examinations in reported patients

			CSF characteristics							SARS-CoV-2	
	Brain MRI	EEG	Proteins (mg/L)	Glucose ratio (CSF: serum)	Cells (mm^3)	Lymphocytes (%)	Viral pathogens	Bacterial pathogens	Anti-neuronal antibodies	CSF	Nasal swab
Patient 1											
On admission	Normal	Status Epilepticus	466	0.59	17	97	Neg	Neg	Neg	Neg	Pos
Control at 56 h	ND	Normal	399	ND	26	100	Neg	Neg	ND	ND	ND
Patient 2											
On admission	Normal	ND	461	0.62	21	89	Neg	Neg	ND	Neg	Pos
Control at 56 h	ND	ND	485	ND	6	82	Neg[a]	ND	ND	ND	ND

Bacterial pathogens: *Neisseria meningitidis*, *Listeria monocytogenes*, *Streptoccocus pneumoniae*, *Haemophilus influenza*, *Escherichia coli* K1 and *Streptococcus agalactiae*. Viral pathogens: Enterovirus, Herpes Simplex Virus 1, Herpes Simplex Virus 2, Varicella-Zoster, Cytomegalovirus, Human Herpes Virus 6 and Parechovirus. CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; ND, not done; Neg, negative; Pos, positive. [a]Only Herpes Simplex Virus 1 and 2 polymerase chain reactions were performed. Anti-neuronal antibodies: anti-*N*-methyl-D-aspartate receptor, anti-contactin-associated protein-like 2, anti-Leucine-rich glioma-inactivated 1, anti-dipeptidyl-peptidase-like protein 6, anti-gamma aminobutyric acid B receptor, anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, anti-immunoglobulin-like cell adhesion molecule 5, anti-metabotropic glutamate receptor 5 and anti-glycine receptor.

profiles being compatible with viral meningoencephalitis, a large screening for the usual pathogens, including SARS-CoV-2, was performed but was negative. Although proof of a direct involvement of SARS-CoV-2 is missing, we hypothesize that it was responsible for this neurological presentation. Firstly, the usual pathogens that cause viral meningoencephalitis were negative. Second, the neurological picture occurred in the wake of proven SARS-CoV-2 infection. Third, coronaviruses are known for their neurological tropism and for inducing encephalitis. It is of note that CSF detection of coronavirus RNA seems infrequent [3]. A possible mechanism accounting for the encephalitic presentation in these patients may be a para-infectious one, somewhat reminiscent of the association of coronaviruses with acute disseminated encephalomyelitis and (for SARS-CoV-2) Guillain–Barré syndrome [4,5]. Such a mechanism would explain the rapid clinical recovery of both patients and the absence of magnetic resonance imaging lesions, suggesting a limited viral process, contrary to a previous report showing severe encephalitis and viral RNA in the CSF, although, in this case, herpes simplex virus encephalitis was not formally excluded [6].

To conclude, we report the first temporal association between acute SARS-CoV-2 infection and aseptic encephalitis with focal neurological symptoms and signs. Further studies are needed to identify the spectrum of neurological complications of this pandemic outbreak and the underlying pathophysiological mechanisms.

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Disclosure of conflicts of interest

Dr Bernard-Valnet, Dr Pizzarotti, Dr Anichini, Dr Demars, Dr Russo, Dr Schmidhauser, Dr Cerrutti-Sola and Prof. Du Pasquier declare no financial or other conflicts of interest. Prof. Rossetti served as consultant to Marinus Pharmaceutical and reports research support from the Swiss National Science Foundation.

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