

REVIEW

Nervous system-related tropism of SARS-CoV-2 and autoimmunity in COVID-19 infection

Robert Weissert

Department of Neurology, University of Regensburg Hospital, Regensburg, Germany

The effects of SARS-CoV-2 in COVID-19 on the nervous system are incompletely understood. SARS-CoV-2 can infect endothelial cells, neurons, astrocytes, and oligodendrocytes with consequences for the host. There are indications that infection of these CNS-resident cells may result in long-term effects, including emergence of neurodegenerative diseases. Indirect effects of infection with SARS-CoV-2 relate to the induction of autoimmune disease involving molecular mimicry or/and bystander activation of T- and B cells and emergence of autoantibodies against various self-antigens. Data obtained in preclinical models of coronavirus-induced disease gives important clues for the understanding of nervous system-related assault of SARS-CoV-2. The pathophysiology of long-COVID syndrome and post-COVID syndrome in which autoimmunity and immune dysregulation might be the driving forces are still incompletely understood. A better understanding of nervous-system-related immunity in COVID-19 might support the development of therapeutic approaches. In this review, the current understanding of SARS-CoV-2 tropism for the nervous system, the associated immune responses, and diseases are summarized. The data indicates that there is viral tropism of SARS-CoV-2 in the nervous system resulting in various disease conditions. Prevention of SARS-CoV-2 infection by means of vaccination is currently the best strategy for the prevention of subsequent tissue damage involving the nervous system.

Keywords: COVID-19 · Lymphocyte · Nervous system · Post-COVID · SARS-CoV-2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a beta-coronavirus. SARS-CoV-2 is causing coronavirus disease 19 (COVID-19) which emerged at the end of 2019 in Wuhan in China [1, 2]. Since its appearance, it has spread over the globe. COVID-19 is mainly affecting the lungs leading to an atypical pneumonia. Most organs in the body can be affected by COVID-19. SARS-CoV-2 has mutated fast resulting in multiple lineages and sublineages with variations in regional distribution and different degrees of infectivity [3].

The positive ssRNA genome of SARS-CoV-2 encodes 16 non-structural proteins involved in viral replication and four structural

proteins (envelope, spike-glycoprotein, membrane, nucleocapsid) [4]. Angiotensin-converting enzyme 2 (ACE2) is the receptor for uptake of SARS-CoV-2 [5, 6]. Co-factors are heparan sulfates on the cell surface and various additional co-factors for SARS-CoV-2 including neuropilin 1 that may differ also depending on the infected cell type [7–11]. The spike protein is of major importance for interaction with ACE2 and cellular uptake. ACE2 is expressed in many cells of the body and therefore SARS-CoV-2 can infect most organs [12]. SARS-CoV-2 uses the infected cell for the production of virus [13]. Many host factors of relevance have been identified as important for infection by SARS-CoV-2 [11]. Reverse-transcribed SARS-CoV-2 mRNA can integrate into the genome of cultured cells [14]. It can produce chimeric transcripts of the fusion of viral and cellular sequences in human tissue [15]. The SARS-CoV-2-induced presence of the host factor of long interspersed element-1 strongly increases

Correspondence: Dr. Robert Weissert
e-mail: robert.weissert@ukr.de

the efficacy of retrotransposition of SARS-CoV-2 in human tissue [15].

In SARS-CoV-2 infection resulting in COVID-19, there is often affection of the nervous system with impact on the immune system as outlined in this article. Moreover, in post-COVID syndrome, clinical signs of nervous system involvement are observed. So far it is still debated how far SARS-CoV-2 itself is neurotropic. Many effects on the nervous system mediated by SARS-CoV-2 in COVID-19 are related to indirect effects of SARS-CoV-2 infection and SARS-CoV-2-induced autoimmune disease.

Effects of SARS-COV-2 in COVID-19 on the nervous system

SARS-CoV-2 in COVID-19 can affect the nervous system through various mechanisms. The effects of SARS-CoV-2 on the CNS are not just dependent on a putative assault on neurons but in addition on other CNS resident cells like astrocytes, oligodendrocytes, endothelial cells, and microglia. So far it is not completely resolved how far SARS-CoV-2 can infect neurons and which type of neurons are affected since there is no general agreement regarding neurotropism of SARS-CoV-2 [16, 17]. Dysosmia and ageusia have been observed early on in patients with COVID-19 [18]. Sustentacular cells are the major target cell type in the olfactory mucosa that is infected by SARS-CoV-2 [16]. Analysis of post-mortem olfactory sensory neurons from patients with COVID-19 did not show viral infection. Therefore, it has been concluded that SARS-CoV-2 does not appear to be a neurotropic virus. Rather, it has been postulated that transient insufficient support from sustentacular cells triggers olfactory dysfunction in COVID-19, that is, olfactory sensory neurons are affected without getting infected. Viral invasion was not observed due to anatomical barriers at vulnerable interfaces [19]. Olfactory dysfunction in COVID-19 is accompanied by T-cell infiltration with CD4+ and CD8+ positive T-cells expressing IFN- γ and granzyme B [20]. The persistence of olfactory dysfunction is associated with the persistence of T-cells expressing IFN- γ and enrichment of antigen-presenting cells, especially CD207+ dendritic cells [21].

The potential lack of neurotropism has been debated by others who found infection of olfactory bulb sensory neurons [22]. In addition, infection of neurons involved in taste sensing (ageusia) has been reported [23]. It has been shown that human-induced pluripotent stem cell-derived sensory neurons can be infected by SARS-CoV-2 [17]. The infected cells were not capable of producing the virus.

There is evidence that SARS-CoV-2 is neurotropic based on investigations in other parts of the nervous system. Structures and diseases possibly related to direct infection by SARS-CoV-2 in COVID-19 are indicated in Table 1.

Infection with SARS-CoV-2 can lead to endotheliitis that can affect CNS vessels [24, 25]. In endotheliitis, there is accumulation of lymphocytes, neutrophils, and macrophages in endothelial walls. Endotheliitis can have major consequences eventually resulting in ischemic stroke. Also, alternative mechanisms of dam-

age to large and small cerebral vessels by SARS-CoV-2 in COVID-19 have been observed [26]. In the heart, it has been shown that endotheliitis leads to small vessel vasculitis. This can also involve epicardial nerves in COVID-19 with the appearance of an inflammatory neuropathy, possibly resulting in cardiac complications such as myocardial injury and arrhythmias [27]. The main protease (Mpro) of SARS-CoV-2 cleaves NEMO which is a modulator of NF- κ B. This in turn leads to the death of brain endothelial cells in mice [28]. Antibody-mediated cytotoxicity directed against the endothelial cells, which has been observed postmortem in patients with COVID-19, may act as a potential initial triggering event for tissue damage leading to vascular leakage, platelet aggregation, neuroinflammation, and neuronal injury [29].

At biopsy or autopsy, besides hypoxia, CNS microthrombi, thromboembolic disease, inflammation, and hemodynamic-mediated changes were found in COVID-19 [30]. Mainly during the initial emergence of SARS-CoV-2 and COVID-19 due to lack of disease understanding and lack of adequate intensive care respiratory support, reduced oxygenation caused by SARS-CoV-2-induced pneumonia in COVID-19 resulted in severe hypoxia of CNS [31]. Acute hypoxic-ischemic injury led to neuronal loss and presence of apoptotic neurons. This kind of CNS damage is unrelated to direct viral infection of the CNS by SARS-CoV-2 in COVID-19 or indirect effects mediated by the virus-induced immune response within the CNS but a consequence of the strongly reduced oxygenation of erythrocytes in the lung resulting in hypoxia of the CNS.

There is further evidence that SARS-CoV-2 can be present in CNS in COVID-19 [32–35]. In a postmortem study of patients who died of COVID-19, SARS-CoV-2 was found in multiple organs outside the respiratory system including the brain [36]. The degree of infection with SARS-CoV-2 of multiple organs was higher in severe cases of COVID-19. Importantly, in this study, only a low degree of inflammation was observed outside of the respiratory tract. On the other hand, significant neuroinflammation with activation of innate and adaptive immune cells was found in COVID-19 neuropathology [37].

It has been shown that nanotubes provide a route for spreading of SARS-CoV-2 in the CNS [38]. SARS-CoV-2 nucleoprotein is found early in infection in neurons of the myenteric plexus [39]. In this area, ACE2 is highly expressed. In cerebral cortical tissues, NOD-, LRR- and pyrin domain-containing protein 3 is co-localized with ACE2 and viral nucleoprotein [40].

There is preliminary data indicating that SARS-CoV-2 invades the brain and induces molecular and cellular changes as in Alzheimer's disease [41]. There are indications that SARS-CoV-2-derived neurotoxic amyloidogenic peptides may trigger neurological symptoms in COVID-19 [42]. SARS-CoV-2 spike protein may be amyloidogenic [43]. In postmortem brain of rhesus and cynomolgus macaques after pulmonary disease induced with SARS-CoV-2, brain infiltration of T-cells and activated microglia were found [44]. Interestingly, also α -synuclein aggregates were found. Such aggregates are involved in Parkinson's disease. There is an ongoing debate regarding the disease-inducing and modifying roles of SARS-CoV-2 in Parkinson's disease [45].

Table 1. Manifestations of putative direct infection of cells with consequences in the CNS in COVID-19.

Disease manifestation	Affected structure	Involved immune mechanisms	Diagnostics	Available specific treatment
Dysosmia [18]	Olfactory bulb	CD4+, CD8+ T cells, IFN- γ , granzyme B, enrichment CD207+ dendritic cells, and depletion of anti-inflammatory macrophages [20, 21]	C.e., NMR, odor testing	None
Ageusia [18]	Gustatory neurons	CD4+, CD8+ T cells, IFN- γ , granzyme B [20]	C.e., NMR, taste testing	None
Decreased cognitive function [90]	Hippocampus	T cells, activated microglia [33, 91]	C.e., cCT, cNMR, neuropsychological testing	None
Encephalitis [92–94]	Brain parenchyma	T cells, activated microglia [33, 91]	C.e., cCT, cNMR, CSF, EEG	If present, treatment of cerebral edema; treatment of co-infections, steroids, pain management
Meningitis [95, 96]	Meninges	T cells, activated microglia [33, 91]	C.e., cCT, cNMR, CSF	If present, treatment of cerebral edema; treatment of co-infections, steroids, pain management
Headache [94, 97]	Meninges and brain parenchyma	No specific knowledge	C.e., CT, NMR, CSF	If present, treatment of cerebral edema; pain management
Dizziness [1]	Brain parenchyma, occlusive vessel disease	No specific knowledge	C.e., cCT, cNMR, CSF	Antiplatelet therapy, statin
Impaired consciousness [98]	Brain parenchyma, occlusive vessel disease	No specific knowledge	C.e., cCT, cNMR, CSF	If present, treatment of cerebral edema; treatment of infections; if occlusive vessel disease antiplatelet therapy, statin
Epileptic seizures [99, 100]	Brain parenchyma	No specific knowledge	C.e., EEG, cCT, cNMR, CSF	Antiepileptics
Cerebral ischemia [101, 102]	Occlusive vessel disease, thromboembolism	T cells and endothelitis [24]	C.e., cCT, cNMR, ultrasound	Antiplatelet therapy, statin
Cerebral bleeding [25]	Angiitis	T cells and endothelitis [24, 25]	C.e., cCT, cNMR, CSF	Depending on the severity, neurosurgical intervention, pain management
Cerebral venous thrombosis [103]	Changes in blood clotting behavior	No specific knowledge	C.e., cCT, cNMR, CSF	Aspirin or anticoagulation depending on severity, pain management
Posterior reversible encephalopathy [104, 105]	Unknown	No specific knowledge	C.e., cCT, cNMR, CSF, EEG	Antihypertensive, pain management

Abbreviations: c, cerebral; C.e., clinical examination; CSF, cerebro-spinal fluid; CT, computer tomography; EEG, electroencephalography; NMR, nuclear magnetic resonance.

SARS-CoV-2 infected mice with respiratory symptoms had an increased expression of cytokines and chemokines, especially of CCL11 in cerebro-spinal fluid (CSF) leading to an activation of hippocampal microglia [46]. Subsequently, neurogenesis was impaired and there was loss of oligodendrocytes and myelinated axons. Similar findings were seen in patients with respiratory COVID-19.

In a mouse model of neurotropic coronavirus disease induced with mouse hepatitis virus (MHV), surviving oligodendrocytes are long-term infected with MHV for at least 150 days [47]. This infection resulted in cerebral demyelination and the degree of demyelination was associated with increased numbers of infiltrating T cells and the presence of activated microglia and macrophages. MHV-infected oligodendrocytes expressed more major histocompatibility class I (MHC I) molecules on the cell surface compared to non-infected oligodendrocytes. In addition to their potential role in demyelination, such infected oligodendrocytes might also be involved in remyelination.

There are indications that SARS-CoV-2 mainly affects cortical astrocytes in the CNS [48]. Such astrocytes have no or low ACE2 expression. Interestingly, in such astrocytes high levels of CD147 (basigin also known as EEMP inducer) and CD26 (dipeptidyl peptidase-4) are observed which can possibly act as co-receptors for SARS-CoV-2 [49]. Following infection with SARS-CoV-2, downstream cellular stress and glial reactivity were observed. In addition, neuronal infection by SARS-CoV-2 was observed to a much lower degree compared with cortical astrocytes [48].

Taken together, there is much evidence that SARS-CoV-2 is neurotrophic. Not much is known regarding the consequences on the immune system caused by this neurotropism. Possibly, neurotropism differs between different SARS-CoV-2 variants [50].

Indirect effects mediated by SARS-CoV-2 in COVID-19 on the nervous system

In the case of infection with SARS-CoV-2 in COVID-19, a cytokine storm can take place leading to multiple consequences on various organs including the CNS [51]. Inflammasome activation in infected macrophages has been shown to be of paramount importance for driving widespread immune activation and cellular damage [52]. In line with a preceding cytokine storm in severe COVID-19 cases with neurological symptoms is the observation of dedifferentiated monocytes and exhausted CD4⁺ T cells in CSF [53].

There are several neurological symptoms and diseases involving the peripheral or/and CNS that are associated with COVID-19. These include Guillain-Barré syndrome, myasthenia gravis, opsoclonus-myoclonus syndrome, and others as outlined in Table 2. In these diseases, a direct effect of SARS-CoV-2 and subsequent tissue damage is unlikely, and other mechanisms are hypothesized. Such potential mechanisms include activation of the adaptive immune response by molecular mimicry or/and bystander activation. Molecular mimicry means that there may be structural similarity between virus sequences or/and domains and

structures and sequences of the host. These similarities can result in an immune response of T cells and B cells that are not only directed against parts of the virus but also against self-proteins, for example, the nicotinic acetylcholine receptor (nAChR) that is the main autoantigen in myasthenia gravis. In bystander activation, the adaptive immune response triggered by viral infection can cause an activation of an immune response directed against self-antigens that will also result in autoimmune disease.

There is increasing knowledge regarding the structural requirements for induction of autoimmune disease after viral infection with SARS-CoV-2. Preceding infection with SARS-CoV-2 in COVID-19 can lead to broad cellular perturbations in the absence of molecular traces of SARS-CoV-2 in the brain [54]. Especially the choroid plexus, which is involved in T-cell trafficking into the brain, appears to play a pivotal role in these processes. Affected brain regions after COVID-19 seem to be overlapping with neurodegenerative and neuropsychiatric diseases.

In the JHM coronavirus-induced model in the LEW rat, myelin-basic-protein specific T cells were primed by coronavirus that persisted and could be transferred to naïve recipients resulting in CNS disease [55]. In patients with multiple sclerosis T cells that cross-recognize coronavirus sequences of strain 229E and myelin basic protein have been found [56]. Possibly, these findings could be relevant for SARS-CoV-2 mediated nervous system involvement and induction of secondary autoimmunity in COVID-19.

Long-COVID syndrome and post-COVID syndrome

Some patients who had COVID-19 subsequently develop long-COVID syndrome or/and post-COVID syndrome [57–59]. In long-COVID syndrome (time span 4 weeks to three months after COVID-19) it has been found that during this time window, a multitude of symptoms can emerge that are unrelated to the initial manifestations of COVID-19. These often include unspecific neurological symptoms like fatigue, irritability, and mnemonic problems. Also, in post-COVID syndrome (time span three months to years after COVID-19) there is persistence or new emergence of symptoms related to SARS-CoV-2. Long-COVID syndrome as well as post-COVID syndrome are still incompletely understood regarding their pathological, molecular, and immunological basis. Longitudinal effects of SARS-CoV-2 in COVID-19 on the brain in comparison to non-infected individuals were observed in imaging studies with a reduction of grey matter thickness in the orbitofrontal and parahippocampal gyrus [60]. Regions that are functionally connected to the olfactory cortex were affected by morphological changes and a reduction of global brain size was observed. Also, the temporal lobe was involved which is critical for memory formation [60]. The patients often describe neuropsychological deterioration that is named “brain fog” [46]. A typical neurological manifestation during this time window is fatigue with varying degrees. The condition is clinically similar to chronic fatigue syndrome, also named myalgic encephalomyelitis. In chronic fatigue syndrome, there is a strong indication of an energy failure on the cellular level which can result in rapid exhaustion and fatigue.

Table 2. Autoimmune diseases of the nervous system have been reported in the context of COVID-19.

Disease	Disease mechanism	Autoantigen	Diagnostics	Treatment
Myasthenia gravis [106, 107]	Muscular weakness due to antibodies against proteins of the neuromuscular junction	nAChR, MUSK	C.e., determination of autoantibodies, repetitive nerve stimulation	Acetylcholine esterase inhibitors, steroids, plasmapheresis immunosuppressants/immunomodulators
Guillain-Barré-syndrome [108, 109]	Demyelination of peripheral nerves due to activation of the adaptive and innate immune system by viral triggers	Schwann-cell-derived proteins	C.e., neurography, CSF	Plasmapheresis, immunoglobulins
Cranial nerve demyelination [110, 111]	Demyelination of cranial nerves due to activation of the adaptive and innate immune system by viral triggers	Cranial nerve proteins	C.e., neurography, CSF, cNMR	Plasmapheresis, immunoglobulins
Opsoclonus-myoclonus syndrome [112]	Rare neuroimmune disorder with ocular, motor, behavioral, sleep, and language disturbances and ataxia.	Neuronal proteins	C.e., cCT, cNMR, CSF	Steroids, plasmapheresis, immunoglobulins, depletion of B cells
Cerebellar ataxia [113, 114]	Inflammatory disease of the cerebellum with ataxia, vertigo, and visual disturbances	Neuronal proteins	C.e., cCT, cNMR, CSF	Steroids, plasmapheresis, depletion of B cells
Transverse myelitis [115]	Inflammatory disease of the spinal cord with resulting paresis or paralysis (mono, para, tetra), sensory disturbances and bladder dysfunction	Oligodendro-glia- or astrocytic proteins	C.e., sNMR, cNMR, CSF	Steroids, plasmapheresis, depletion of B cells
Limbic encephalitis, autoimmune encephalitis [116, 117]	Encephalitis with autoimmune pathogenesis	Neuronal proteins	C.e., cNMR, CSF, EEG, neuropsychological testing	Steroids, plasmapheresis, immunoglobulins, depletion of B cells
Multiple sclerosis [118]	Autoimmune disease of CNS resulting in inflammation, demyelination, and axonal loss with a multitude of resulting symptoms	MBP, PLP, and other oligodendrocyte-derived proteins	C.e., cNMR, CSF	Steroids, immunomodulatory treatment
Anti-MOG disease [119]	Autoimmune disease of the CNS with lesion development and resulting neurological symptoms	MOG	C.e., cNMR, CSF	Steroids
Acute disseminated encephalomyelitis [32, 120]	Inflammatory disease of the CNS with associated neurological symptoms	MBP, others	C.e., cNMR, CSF	Steroids
Acute hemorrhagic leukoencephalitis, acute necrotizing encephalopathy [121]	Severe inflammatory and hemorrhagic disease of the CNS with high neurological disease burden	Cytokine storm [51]	C.e., cCT, cNMR, CSF	Steroids
Bickerstaff's encephalitis [122]	Inflammatory disease of the brain stem with cranial nerve palsies and ataxia	Glial- and neuronal proteins	C.e., cNMR, neurophysiological studies, CSF	Steroids
Generalized myoclonus [114]	Inflammatory disease affecting neuronal structures with resulting myoclonus	Neuronal proteins	C.e., cCT, cNMR, CSF	Steroids, piracetam

Abbreviations: c, cerebral; C.e., clinical examination; CSF, cerebro-spinal fluid; CT, computer tomography; EEG, electroencephalography; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MUSK, muscle-specific tyrosine kinase; nAChR, nicotinic acetylcholine receptor; NMR, nuclear magnetic resonance; PLP, proteolipid protein; sc, spinal cord.

In addition, there are changes in certain immune cell types that can result in increased susceptibility to infection [61]. Changes in lymphocyte stiffness, monocyte size, neutrophil size and deformability, and heterogeneity of erythrocyte deformation and size were found [62]. Some authors have reported increased mast cell activation in patients with post-COVID syndrome [63].

Many autoantibodies are found in patients with COVID-19 that could be of relevance in long-COVID and post-COVID syndromes [64]. In post-COVID syndrome, antibodies against specific chemokines were omnipresent [65]. Interestingly, the presence of these antibodies was associated with a better disease outcome. Presently, there are no specific markers that allow a laboratory-based diagnosis of post-COVID syndrome. Usually, CSF analysis does not show distinctive features [66, 67]. There are no approved therapeutic options for the treatment of fatigue associated with long-COVID-19 syndrome or post-COVID-19 syndrome. Treatment approaches are mainly based on mild physical endurance training. Currently, much effort is being undertaken to define potentially effective treatments for post-COVID syndrome in clinical trials involving many different treatment modalities [68].

Antigen presentation in CNS in the context of SARS-CoV-2 in COVID-19

The role of antigen presentation of SARS-CoV-2 in COVID-19 in the CNS has not been extensively investigated up to now. Possibly, such investigations would be of value to better understand the effects of SARS-CoV-2 in COVID-19 in the CNS and subsequent immune responses. There is evidence that SARS-CoV-2 infection leads to downregulation of MHC-I in infected cells [69, 70]. Downregulation of MHC-I on infected cells allows viral persistence. This downregulation of MHC-I seems to be mediated by proteins encoded in open reading frames (ORF) of SARS-CoV2, mainly ORF3, ORF7a [70, 71], and ORF8 [69], but also other mechanisms seem to be operative. In ORF8-expressing cells, MHC-I molecules are selectively targeted for lysosomal degradation via autophagy. ORF3a and ORF7a act posttranslationally in the secretory pathway to lower surface MHC-I expression. In one study a mechanism of MHC-I downregulation has been demonstrated that involved STAT1–IRF1–nucleotide-binding oligomerization domain-like receptor family caspase activation and recruitment domain containing 5 [72]. Interestingly, SARS-CoV-2 is capable of immune evasion by spike-dependent targeting of ACE2 on CD8+ T cells and preventing immune synapse formation [73].

Host molecules involved in antigen presentation can have protective roles against the infectivity of SARS-CoV-2. In this respect, it has been shown that CD74 (human leukocytes antigen [HLA]-DR antigens-associated invariant chain) p41 can block the endosomal entry pathway of SARS-CoV-2 [74].

HLA peptidomics were used for the identification of SARS-CoV-2-derived HLA peptides [75]. Several of the SARS-CoV-2 peptides are immunogenic. Many of the SARS-CoV-2 expressed ligands on MHC-I are derived from out-of-frame ORFs [76].

HLA haplotypes and SARS-CoV-2 in COVID-19

There is evidence that HLA haplotypes affect susceptibility to COVID-19 [77]. Severe COVID-19 cases are associated with certain HLA haplotypes [78]. In one specific study, the HLA-B*07:02 allele was associated with an elevated risk of high severity score of COVID-19, whereas the HLA-C*15:02 allele was associated with risk reduction [78]. Depending on the genetic background and SARS-CoV-2 variants, there are indications that the HLA haplotype influences differ [77]. So far, there is no knowledge of the potential influence of HLA haplotypes on neurological manifestations after infection with SARS-CoV-2 in COVID-19.

Interferons type I and SARS-CoV-2 in COVID-19

Autoantibodies against type I interferons are associated with unfavorable outcomes of COVID-19 pneumonia [79]. Especially in older individuals, autoantibodies against type I interferons were observed that were associated with more severe disease and increased mortality in COVID-19 [80]. Inborn errors of type I interferon signatures involving TLR 3-dependent and IRF 7-dependent type I interferon result in the most severe forms of COVID-19 [81]. These findings were not confirmed in another study [82]. No specific knowledge is presently available regarding the influence of type I interferons on nervous system-related outcomes in SARS-CoV-2 in COVID-19.

SARS-CoV-2 and vaccinations

Vaccines against SARS-CoV-2 are of paramount importance for the prevention of COVID-19 or reduction of disease severity in COVID-19. Besides mRNA-based vaccines, adenovirus-based vaccines and protein vaccines have been introduced [83]. Newly emerging subvariants of the omicron variant of SARS-CoV-2 have an increased ability to evade neutralizing antibodies, possibly resulting in lack of efficacy of currently available vaccines [84]. There are several reports of emergence or reactivation of autoimmune disease after vaccination with mRNA-based vaccines against SARS-CoV-2. The development of immune thrombotic thrombocytopenia (ITTP) has been observed mediated by the presence of platelet-activating antibodies against platelet factor 4 (PF4, CXCL4) [85]. Moreover, antineutrophil cytoplasmic antibodies in serum and the associated vasculitis have been reported after vaccination with mRNA-based vaccines [86]. In multiple sclerosis, exacerbations of relapses have been observed after mRNA vaccination against SARS-CoV-2 [87]. There are more reported side effects involving molecular mimicry or/and bystander activation. Importantly, the SARS-CoV-2 mRNA vaccine did not induce long interspersed element-1-mediated reverse transcription and did not lead to integration of the SARS-CoV-2 mRNA vaccine into human tissue [15]. Therefore, the risk of genomic integration in humans of SARS-CoV-2 mRNA vaccines is very low. Taken together, side effects observed after SARS-CoV-2 mRNA vaccination relate to immune-

mediated autoimmune reactions, whereas natural SARS-CoV-2 infection can result in broader tissue pathology.

Vaccination with adenovirus-based vectors has led to unwanted side effects related to immune activation and autoimmunity including ITTP and severe cerebral venous thrombosis [88, 89]. So far, there is not much data available regarding protein-based vaccines and the emergence of autoimmune diseases.

Summary

The most challenging issue relates to the understanding of the long-term consequences of infection with SARS-CoV-2 in COVID-19 on neurological function and disease. Possibly, the long-term effects of preceding viral infection with SARS-CoV-2 will only become evident much later in life. As described above, there are indications of direct and indirect effects of SARS-CoV-2 in COVID-19 on CNS resident cells. Some changes bear similarities to morphological and cellular changes observed in psychiatric and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. To understand whether infection by SARS-CoV-2 can lead to such diseases in the long term, more scientific effort is necessary. Such an effort should especially focus on long-term follow-up including detailed clinical, imaging, molecular, and immunological assessments. Regarding treatment approaches, all data indicates that it would be advantageous to completely clear SARS-CoV-2 from all organs. In this context, vaccination against SARS-CoV-2 also in patients who had COVID-19 is of great importance. Nevertheless, not much is understood about the persistence of genomic information of the SARS-CoV-2 in infected host cells and the consequences due to activation of the immune system. Such immune activation could result in detrimental as well as beneficial outcomes for the host in the long run. In particular induction of autoimmune disease as a long-term consequence of infection with SARS-CoV-2 should not be underestimated and neglected.

It remains to be seen whether new SARS-CoV-2 variants or/and subvariants with an increased tropism for infection of CNS resident cells and possibly detrimental effects such as severe forms of encephalitis will emerge. Presently, virologists and epidemiologists indicate that a scenario with more aggressive and encephalitogenic SARS-CoV-2 variants is highly unlikely since virus variants with a mild disease-inducing capacity, but high infectivity are preferentially selected.

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Abbreviations: ACE2: angiotensin-converting enzyme 2 · COVID-19: coronavirus disease 19 · CSF: cerebro-spinal fluid · HLA: human leukocytes antigen · MHV: mouse hepatitis virus · ORF: open reading frames · SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Full correspondence: Dr. Robert Weissert, Department of Neurology, University of Regensburg Hospital, Universitätsstrasse 84, 93053 Regensburg, Germany
e-mail: robert.weissert@ukr.de

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