Chapter

Neuroimmunology and Neurological Manifestations of COVID-19

Robert Weissert

Abstract

Infection with SARS-CoV-2 is causing coronavirus disease in 2019 (COVID-19). Besides respiratory symptoms due to an attack on the broncho-alveolar system, COVID-19, among others, can be accompanied by neurological symptoms because of the affection of the nervous system. These can be caused by intrusion by SARS-CoV-2 of the central nervous system (CNS) and peripheral nervous system (PNS) and direct infection of local cells. In addition, neurological deterioration mediated by molecular mimicry to virus antigens or bystander activation in the context of immunological anti-virus defense can lead to tissue damage in the CNS and PNS. In addition, cytokine storm caused by SARS-CoV-2 infection in COVID-19 can lead to nervous system related symptoms. Endotheliitis of CNS vessels can lead to vessel occlusion and stroke. COVID-19 can also result in cerebral hemorrhage and sinus thrombosis possibly related to changes in clotting behavior. Vaccination is most important to prevent COVID-19 in the nervous system. There are symptomatic or/and curative therapeutic approaches to combat COVID-19 related nervous system damage that are partly still under study.

Keywords: SARS-CoV-2, COVID-19, CNS, PNS, T cell, B cell, vaccination, treatment, neuroimmunology, molecular mimicry, bystander activation, cytokine storm

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded positive sense ribonucleic acid (ssRNA) virus with an envelope that leads to coronavirus disease 2019 (COVID-19) [1]. COVID-19 has affected millions of people worldwide since its emergence in December 2019 in Wuhan in China. It has caused a worldwide pandemic. Multiple mutated variants of SARS-CoV-2 have appeared with varying infectivity [2, 3]. SARS-CoV-2 has caused major disease burden and death rates worldwide. Due to the threat to individual health and health systems, SARS-CoV-2 and COVID-19 have resulted in a worldwide social and economic crisis. Economically rich Western countries have success in fighting SARS-CoV-2 by vaccination, while this is not true to the same extent for economically weak countries due to a shortage of vaccine supply. In addition, the standard of care for patients with COVID-19 differs dramatically based on the economic wealth of a country [4]. Due to the nature of the pandemic to affect people worldwide, there is a lack of help from rich countries for economically weak countries.

2. Background

SARS-CoV-2 is a beta-coronavirus [5]. The positive ssRNA genome encodes 16 non-structural proteins involved in viral replication. Moreover, four structural proteins are for the envelope, spike-glycoprotein, the membrane, and the nucleocapsid [6]. Angiotensin-converting enzyme 2 (ACE2) is the receptor for uptake of SARS-CoV-2 [7–9]. Co-factors are heparan sulfates on the cell surface [10]. 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. SARS-CoV-2 uses the infected cell for the production of the virus. More receptors and host factors have been described for SARS-CoV-2 cellular entry [11, 12]. Most cells in the body express ACE2 receptors mediating SARS-CoV-2 uptake.

SARS-CoV-2 has the strongest effects on the lung [13, 14]. As a result of infection, SARS-CoV-2 leads to an atypical mainly interstitial pneumonia with patchy infiltrates. In severe cases, the lung can be completely affected resulting in loss of oxygenation. Besides the lung, any tissue can be infected by SARS-CoV-2 and damaged. As written further down and explained for the nervous system, the tissue damage can be a consequence of direct infection with the virus or indirect effects on the tissue due to a dysregulated immune response.

3. Hypoxia and CNS damage

Reduced oxygenation caused by SARS-CoV-2 mediated pneumonia in COVID-19 can lead to severe hypoxia of CNS. In many cases of patients that have died of COVID-19, severe hypoxia of the CNS has been observed [15]. There is an acute hypoxic-ischemic injury with neuronal loss and the presence of apoptotic neurons. This kind of CNS damage is unrelated to direct viral infection of the CNS 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. This reduced oxygenation of erythrocytes results in hypoxia of the CNS. Besides hypoxia, at biopsy or autopsy in CNS microthrombi, thromboembolic disease, inflammation, and to the largest extent hemodynamic mediated changes were found [16].

4. Direct effects of SARS-CoV-2 in CNS

There is evidence that SARS-CoV-2 can be present in CNS [17–19]. There are indications that SARS-CoV-2 can infect many CNS-resident cells [20, 21]. The presence of SARS-CoV-2 in cells is causing cellular dysfunction resulting in a variety of manifestations [22]. For example, infection of olfactory bulb neurons with SARS-CoV-2 will lead to olfactory dysfunction (dysosmia). In addition, infection of neurons involved in taste sensing will lead to the reduction of taste perception (ageusia). Dysosmia and ageusia have been observed early on in patients with COVID-19 [23]. Subsequently, evidence for direct infection of other parts of the CNS has been found (**Table 1**).

5. Vasculature and COVID-19

SARS-CoV-2 infection can lead to endotheliitis [36, 40]. Endotheliitis, caused by SARS-CoV-2 infection also affect CNS vessels. In endotheliitis, there is an

Disease manifestation	Structure	Diagnostics	Treatment
Dysosmia [23, 24]	Olfactory bulb	C.e., NMR, odor testing	None
Ageusia [23, 24]	Gustatory neurons	C.e., NMR, taste testing	None
Decreased cognitive function [25]	Hippocampus	C.e., cCT, cNMR, neuropsychological testing	None
Encephalitis [26]	Brain parenchyma	C.e., cCT, cNMR, CSF, EEG	If present, treatment of cerebral edema; treatment of co-infections
Meningitis [27, 28]	Meninges	C.e., cCT, cNMR, CSF	If present, treatment of cerebral edema; treatment of co-infections
Headache [29]	Meninges and brain parenchyma	C.e., CT, NMR, CSF	If present, treatment of cerebral edema
Dizziness [30]	Brain parenchyma, occlusive vessel disease	C.e., cCT, cNMR, CSF	Antiplatelet therapy, statin
Impaired consciousness [31]	Brain parenchyma, occlusive vessel disease	C.e., cCT, cNMR, CSF	If present, treatment of cerebral edema; treatment of infections; if occlusive vessel disease antiplatelet therapy, statin
Epileptic seizures [32, 33]	Brain parenchyma	C.e., EEG, cCT, cNMR, CSF	Antiepileptics
Cerebral ischemia [34, 35]	Occlusive vessel disease, thromboembolism	C.e., cCT, cNMR, ultrasound	Antiplatelet therapy, statin
Cerebral bleeding [36]	Angiitis	C.e., cCT, cNMR, CSF	Depending on severity, neurosurgical intervention
Cerebral venous thrombosis [37]	Changes in blood clotting behavior	C.e., cCT, cNMR, CSF	Aspirin or anticoagulation depending on severity
Posterior reversible encephalopathy [38, 39]	Unknown	C.e., cCT, cNMR, CSF, EEG	None

c, cerebral; C.e., clinical examination; CNS, central nervous system; CSF, cerebrospinal-fluid; CT, computer tomography; EEG, electroencephalography; NMR, nuclear magnetic resonance.

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

accumulation of lymphocytes, neutrophils, and macrophages in endothelial walls. Endotheliitis can have major consequences eventually resulting in ischemic stroke. Also, alternative mechanisms of damage to large and small cerebral vessels by SARS-CoV-2 in COVID-19 have been observed [41]. In the heart, it has been shown that endotheliitis leads to small vessel vasculitis. This can also involve epicardial nerves in COVID-19 disease with the appearance of an inflammatory neuropathy, possibly resulting in cardiac complications such as myocardial injury and arrhythmias [42].

6. Indirect effects of SARS-CoV-2 in CNS

There are several neurological symptoms and diseases that are associated with COVID-19. These include Guillain-Barré-syndrome (GBS), myasthenia gravis (MG), opsoclonus-myoclonus syndrome (OMS) and others (**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 are molecular mimicry and bystander activation [61, 62]. Molecular mimicry means that there may be the structural similarity between virus sequences or/and domains and structures or/and sequences of the individual [63]. Potentially, these similarities can result in an immune response that is not only directed against parts of the virus but also against self-proteins, for example, the nicotinic acetylcholine receptor (nAChR) that is the autoantigen in myasthenia gravis. In bystander activation, the immune response triggered by a viral infection can cause an activation of an immune response directed against self-antigens that will also result in autoimmune disease. The list of possible autoimmune manifestations due to the affection of SARS-CoV-2 and COVID-19 is growing. This is also the case for autoimmune neurological manifestations (**Table 2**). There is increasing knowledge regarding the structural requirements for induction of autoimmune disease after viral infection with SARS-CoV-2.

Cytokine storm induced by infection with SARS-CoV-2 and COVID-19 can lead to multiple organ damage and potentially induction/boosting of an autoimmune immune response [54].

7. Chronic fatigue syndrome and COVID-19

Some patients that had COVID-19 subsequently develop long-COVID-19 or also named post-COVID-19 [64, 65]. Many of these patients suffer from strong fatigue. The condition is clinically like chronic fatigue syndrome (CFS) also named myalgic encephalomyelitis (ME). In CFS there is a strong indication that there is an energy failure on the cellular level that can result in rapid exhaustion and fatigue. In addition, there are changes in certain immune cell types that can result in increased susceptibility to infection. Changes in lymphocyte stiffness, monocyte size, neutrophil size and deformability, and heterogeneity of erythrocyte deformation and size were found [66]. The exact mechanism of how COVID-19 is resulting in subsequent CFS is not known at present. The diagnosis is mainly based on clinical characteristics with the presence of abnormal fatigue. Presently, there are no specific markers that allow a laboratory-based diagnosis. Usually, CSF analysis does not show distinctive features. There are no approved pharmaceutical options for the treatment of fatigue associated with long-COVID-19 or post-COVID-19. Treatment involves mild physical endurance training.

8. Treatment of COVID-19

Treatment options can be separated according to treatment to counteract viral replication and viral virulence of SARS-CoV-2 and treatment options to counteract and treat organ damage due to consequences of the infection with SARS-CoV-2 (**Table 3**). Remdesivir is a treatment option that counteracts viral replication [67]. This is a drug that has been initially developed for fighting Ebola. It has been shown to be efficacious if given early after infection with SARS-CoV-2. In combination with the Janus-kinase inhibitor baricitinib increased efficacy could be demonstrated [69].

Disease	Disease mechanism	Autoantigen	Diagnostics	Treatment
Myasthenia gravis [43, 44]	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 [45, 46]	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 [47, 48]	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 [49]	Rare neuroimmunological 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 [50, 51]	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 [52]	Inflammatory disease of the myelon with resulting paresis or paralysis (mono, para, tetra), sensory disturbances, and bladder dysfunction	Oligodendroglial- or astrocytic proteins	C.e., sNMR, cNMR, CSF	Steroids, plasmapheresis, depletion of B cells
Limbic encephalitis, autoimmune encephalitis [53, 54]	Encephalitis with autoimmune pathogenesis	Neuronal proteins	C.e., cNMR, CSF, EEG, neuropsychological testing	Steroids, plasmapheresis, immunoglobulins, depletion of B cells
Multiple sclerosis [55]	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 [56]	Autoimmune disease of the CNS with lesion development and resulting neurological symptoms	MOG	C.e., cNMR, CSF	Steroids

Disease	Disease mechanism	Autoantigen	Diagnostics	Treatment
Acute disseminated encephalomyelitis (ADEM) [17, 57]	Inflammatory disease of the CNS with associated neurological symptoms	MBP, others	C.e., cNMR, CSF	Steroids
Acute hemorrhagic leukoencephalitis, acute necrotizing encephalopathy [58]	Severe inflammatory and hemorrhagic disease of the CNS with high neurological disease burden	Cytokine storm [59]	C.e., cCT, cNMR, CSF	Steroids
Bickerstaff's encephalitis [60]	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 [51]	Inflammatory disease affecting neuronal structures with resulting myoclonus	Neuronal proteins	C.e., cCT, cNMR, CSF	Steroids, piracetam

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.

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

Treatment	Approach	Efficacy
Remdesivir [67, 68]	Inhibition of viral replication	Shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection; in combination with baricitinib superior efficacy. Among nonhospitalized patients who were at high risk for COVID-19 progression, a 3-day course of remdesivir in an 87% lower risk of hospitalization or death than placebo.
Baricitinib [69]	Janus-kinase Inhibitor (JAK1 and JAK2)	Mainly in patients receiving oxygen support without invasive mechanical ventilation.
Dexamethasone [70]	Antiinflammatory	Lower 28-day mortality in hospitalized patients among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support; increased mortality compared with usual care in patients not requiring oxygen supplementation.
Tocilizumab [71–73]	anti-IL-6R blockade	Reduces the risk of mechanical ventilation in hospitalized patients with severe COVID-19; improved outcome and survival of COVID-19.
Sarilumab [73]	anti-IL-6R blockade	Improved outcome and survival of COVID-19.
Anakinra [74]	anti-IL-1R blockade	Early increase of soluble urokinase plasminogen activator receptor (suPAR) serum was used as a marker to assess the risk of COVID-19. Early start of treatment with anakinra guided by suPAR levels in patients hospitalized with moderate and severe COVID-19 significantly reduced the risk of worse clinical outcome at day 28 and reduced length of hospital stay compared to placebo.
Regdanvimab [75]	Blockade of spike protein interaction with ACE2	Regdanvimab reduced the risk of hospitalization or death versus placebo in patients with mild-to-moderate COVID-19 symptoms who were considered at high risk of progressing to severe COVID-19 up to day 28.
Casirivimab/Imdevimab [76]	Blockade of spike protein interaction with ACE2	Casirivimab/Imdevimab reduced the risk of COVID-19-related hospitalization or death from any cause, and it resolved symptoms and reduced the SARS-CoV-2 viral load more rapidly than placebo.
Sotrovimab [77]	Neutralisation SARS-CoV-2	The risk of disease progression was reduced among high-risk patients with mild-to-moderate COVID-19 treated with sotrovimab.
Molnupiravir [78]	anti-RNA polymerase activity	The risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19 was reduced in patients treated early with molnupiravir.

Treatment	Approach	Efficacy
Tixagevimab/Cilgavimab [79]	Neutralization of SARS-CoV-2	Preliminary results indicate a decrease in disease severity in COVID-19 patients.
PV-07321332/Ritanovir [79]	Protease Inhibitor of SARS-CoV-2 3-chymotrypsin-like protease	Reduction of risk of hospitalization and death compared to placebo in adults with a high risk of poor outcome of COVID-19

ACE, angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; JAK, janus-kinase; IL-1R, interleukin-1 receptor; IL-6R, interleukin-6 receptor.

Table 3.
Treatment options to counteract viral replication or/and viral virulence or organ damage caused by a viral infection or virus-mediated secondary tissue damage.

Dexamethasone has been shown to have beneficial effects in COVID-19 since it leads to reduction of the host immune response against the virus [70]. This host immune response can lead to catastrophic outcomes for the body. Beneficial effects of dexamethasone are mainly seen in the case of severely ill patients requiring mechanical ventilation. In non-severely affected COVID-19 patients not requiring oxygen supplementation, increased mortality is observed [80]. Tocilizumab an anti-interleukin-6 receptor (IL-6R) directed monoclonal antibody (mAb) has been shown to have some beneficial effects in COVID-19 patients reducing the risk of mechanical assistance [71, 72]. Also, another mAb against IL-6R, Sarilumab, improved the outcome and survival of COVID-19 [73]. Early start of treatment with anakinra a mAb against the interleukin-1 receptor (IL-1R) guided by levels against soluble urokinase plasminogen activator receptor (suPAR) significantly reduced the risk of worse clinical outcome at day 28 and reduced the length of hospital stay compared to placebo in patients hospitalized with moderate and severe COVID-19 [74]. Various mAb directed against the SARS-CoV-2 spike protein have demonstrated beneficial effects in patients with COVID-19 [76, 77, 79]. Malnupavir has anti-RNA polymerase activity and the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19 was reduced in patients treated early with this novel compound [78]. The protease inhibitor PV-07321332/Ritanovir of SARS-COV-2 3-chymotrypsin-like protease resulted in the reduction of risk of hospitalization and death compared to placebo in adults with a high risk of poor outcome of COVID-19 [79]. Much effort is done to identify compounds with beneficial effects in COVID-19 patients including repurposing of drugs from other indications [73, 81]. Importantly, serum from patients recovered from COVID-19 has been used successfully to reduce mortality in patients with active COVID-19 disease [82]. Higher anti-SARS-COV-2 titers of the transfused plasma led to a lower risk of death in non-ventilated patients with COVID-19. So far, besides symptomatic treatments no specific treatments for COVID-19- related neurological conditions have been introduced. Nevertheless, the beneficial effects of treatment on COVID-19 precipitation and severity will also result in reduced neurological disease burden.

9. Vaccination

Vaccination is of paramount importance to counteract the further spreading of SARS-CoV-2 and COVID-19 [83]. The first vaccines were introduced at the end of 2020 [84] and the beginning of 2021 [85–87]. Since then, a major vaccination effort has been undertaken with the fastest vaccination campaigns in Israel and Great Britain. The vaccines also have shown efficacy against mutated variants of SARS-CoV-2 even though breakthrough infections have been observed [88]. Societies

with high numbers of vaccinated individuals have gained better control over the COVID-19 pandemic compared to societies with low vaccination rates. Repetitive vaccination strategies have increased vaccination efficacy and have provided more protection from novel virus variants [89]. Presently as of the end of January 2022, mRNA vaccines and adenovirus vectors with inserts of sequences coding for the spike protein of SARS-CoV-2 and protein-based vaccines have been introduced [84–87, 90, 91]. Vaccination efficacy is much dependent on booster vaccination regimes [89, 92, 93]. All currently approved vaccines are given by intramuscular injection [94]. Muscle cells that take up the mRNA vaccine or the adenovirus-vector-based vaccine are used subsequently to produce SARS-CoV-2- derived spike protein. This protein is recognized as `non-self` by the immune system and a strong T-and B-cell derived immune response is generated. This immune response leads to protection from SARS-CoV-2. The protein-based vaccines lead to the generation of a T- and B-cell response against SARS-CoV-2. There are vaccination-related cases with neurological symptoms [95–97]. In general, vaccination-related side effects were increased in patients with preceding COVID-19 [98].

10. Conclusion

Infection with SARS-CoV-2 resulting in COVID-19 leads to damage of many organs in the body. The nervous system is also often assaulted by the virus and the subsequent immune response. The treatment options are limited. Vaccination to prevent the spread of SARS-CoV-2 and its variants is the most efficacious way to prevent nervous system disease in context with SARS-CoV-2 and COVID-19. Possibly, the insights that are obtained on the worldwide population level by SARS-CoV-2 and COVID-19 will result in a better understanding of the induction of autoimmune disease of the nervous system in general.

Conflict of interest

The author declares no conflict of interest.

Author details

Robert Weissert
Department of Neurology, University of Regensburg, Germany

*Address all correspondence to: robert.weissert@googlemail.com or robert.weissert@ukr.de

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine. 2020;**382**(8):727-733

[2] Abdool Karim SS, de Oliveira T. New SARS-CoV-2 variants—Clinical, public health, and vaccine implications. New England Journal of Medicine. 2021; **384**(19):1866-1868

[3] Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. Nature. 2022 [Online ahead of print]

[4] Oehler RL, Vega VR. Conquering COVID: How global vaccine inequality risks prolonging the pandemic. Open Forum Infectious Diseases. 2021;**8**(10): ofab443

[5] Malik YA. Properties of coronavirus and SARS-CoV-2. Malaysian Journal of Pathology. 2020;**42**(1):3-11

[6] Yao H, Song Y, Chen Y, Wu N, Xu J, Sun C, et al. Molecular architecture of the SARS-CoV-2 virus. Cell. 2020;**183**(3):730-8 e13

[7] Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell. 2020;**181**(4):894-904 e9

[8] Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;**367**(6485):1444-1448

[9] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;**579**(7798):270-273

[10] Clausen TM, Sandoval DR, Spliid CB, Pihl J, Perrett HR, Painter CD, et al. SARS-CoV-2 infection depends on cellular heparan sulfate and ACE2. Cell. 2020;**183**(4):1043-57 e15

[11] Wei J, Alfajaro MM, DeWeirdt PC, Hanna RE, Lu-Culligan WJ, Cai WL, et al. Genome-wide CRISPR screens reveal host factors critical for SARS-CoV-2 infection. Cell. 2021;**184**(1): 76-91 e13

[12] Wang R, Simoneau CR, Kulsuptrakul J, Bouhaddou M, Travisano KA, Hayashi JM, et al. Genetic screens identify host factors for SARS-CoV-2 and common cold coronaviruses. Cell. 2021;**184**(1): 106-19 e14

[13] Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: A descriptive study. Lancet Infectious Diseases. 2020;**20**(4):425-434

[14] Zhang N, Xu X, Zhou LY, Chen G, Li Y, Yin H, et al. Clinical characteristics and chest CT imaging features of critically ill COVID-19 patients. European Radiology. 2020;**30**(11): 6151-6160

[15] Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. New England Journal of Medicine. 2020;**383**(10):989-992

[16] Peiris S, Mesa H, Aysola A, Manivel J, Toledo J, Borges-Sa M, et al. Pathological findings in organs and tissues of patients with COVID-19: A systematic review. PLoS One. 2021;**16**(4):e0250708

[17] Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF. Neuropathology of

COVID-19: A spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. Acta Neuropathology. 2020;**140**(1):1-6

[18] Matschke J, Lutgehetmann M, Hagel C, Sperhake JP, Schroder AS, Edler C, et al. Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. The Lancet Neurology. 2020;**19**(11):919-929

[19] 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

[20] Pajo AT, Espiritu AI, Apor A, Jamora RDG. Neuropathologic findings of patients with COVID-19: A systematic review. Neurological Sciences. 2021;**42**(4):1255-1266

[21] Gagliardi S, Emanuele Poloni T, Pandini C, Garofalo M, Dragoni F, Medici V, et al. Detection of SARS-CoV-2 genome and whole transcriptome sequencing in frontal cortex of COVID-19 patients. Brain, Behavior, and Immunity. 2021;**97**:13-21

[22] Qin Y, Wu J, Chen T, Li J, Zhang G, Wu D, et al. Long-term microstructure and cerebral blood flow changes in patients recovered from COVID-19 without neurological manifestations. Journal of Clinical Investigation. 2021;**131**(8)

[23] Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;**581**(7809):465-469

[24] Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, 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. European Archives of Oto-Rhino-Laryngology. 2020;**277**(8):2251-2261

[25] Alnefeesi Y, Siegel A, Lui LMW, Teopiz KM, Ho RCM, Lee Y, et al. Impact of SARS-CoV-2 infection on cognitive function: A systematic review. Frontiers in Psychiatry. 2020;**11**:621773

[26] Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonghi I, Gazzina S, et al. Steroid-Responsive encephalitis in coronavirus disease 2019. Annals of Neurology. 2020;**88**(2):423-427

[27] Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. International Journal of Infectious Diseases. 2020;**94**:55-58

[28] Khodamoradi Z, Hosseini SA, Gholampoor Saadi MH, Mehrabi Z, Sasani MR, Yaghoubi S. COVID-19 meningitis without pulmonary involvement with positive cerebrospinal fluid PCR. European Journal of Neurology. 2020;**27**(12):2668-2669

[29] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;**395**(10223):497-506

[30] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;**579**(7798):265-269

[31] Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Critical Care. 2020; **24**(1):176

[32] Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A

retrospective multicenter study. Epilepsia. 2020;**61**(6):e49-e53

[33] Mithani F, Poursheykhi M, Ma B, Smith RG, Hsu SH, Gotur D. New-onset seizures in three COVID-19 patients: A case series. Journal of Clinical Neurophysiology. 2021;**38**(2):e5-e10

[34] Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. Journal of Neurology, Neurosurgery, and Psychiatry. 2020;**91**(8):889-891

[35] Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke. 2020; **51**(7):2002-2011

[36] Kirschenbaum D, Imbach LL, Rushing EJ, Frauenknecht KBM, Gascho D, Ineichen BV, et al. Intracerebral endotheliitis and microbleeds are neuropathological features of COVID-19. Neuropathology and Applied Neurobiology. 2021;**47**(3):454-459

[37] Cavalcanti DD, Raz E, Shapiro M, Dehkharghani S, Yaghi S, Lillemoe K, et al. Cerebral venous thrombosis associated with COVID-19. AJNR. American Journal of Neuroradiology. 2020;**41**(8):1370-1376

[38] Kishfy L, Casasola M, Banankhah P, Parvez A, Jan YJ, Shenoy AM, et al. Posterior reversible encephalopathy syndrome (PRES) as a neurological association in severe Covid-19. Journal of the Neurological Sciences. 2020;**414**:116943

[39] Coolen T, Lolli V, Sadeghi N, Rovai A, Trotta N, Taccone FS, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. Neurology. 2020;**95**(14):e2016-e2e27

[40] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;**395**(10234):1417-1418

[41] Keller E, Brandi G, Winklhofer S, Imbach LL, Kirschenbaum D, Frontzek K, et al. Large and small cerebral vessel involvement in severe COVID-19: Detailed clinical workup of a case series. Stroke. 2020;**51**(12): 3719-3722

[42] Maccio U, Zinkernagel AS, Shambat SM, Zeng X, Cathomas G, Ruschitzka F, et al. SARS-CoV-2 leads to a small vessel endotheliitis in the heart. eBioMedicine. 2021;**63**:103182

[43] Huber M, Rogozinski S, Puppe W, Framme C, Hoglinger G, Hufendiek K, et al. Postinfectious onset of Myasthenia Gravis in a COVID-19 patient. Frontiers in Neurology. 2020;**11**:576153

[44] Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia Gravis associated with SARS-CoV-2 infection. Annals of International Medicine. 2020;**173**(12):1027-1028

[45] Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: Causality or coincidence? Lancet Neurology. 2020;**19**(5):383-384

[46] Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barre syndrome associated with SARS-CoV-2. New England Journal of Medicine. 2020;**382**(26):2574-2576

[47] Dinkin M, Gao V, Kahan J, Bobker S, Simonetto M, Wechsler P, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. Neurology. 2020;**95**(5):221-223

[48] Gutierrez-Ortiz C, Mendez-Guerrero A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Manas R, et al. Miller Fisher syndrome and polyneuritis cranialis in

COVID-19. Neurology. 2020;**95**(5): e601-e6e5

[49] Emamikhah M, Babadi M, Mehrabani M, Jalili M, Pouranian M, Daraie P, et al. Opsoclonus-myoclonus syndrome, a post-infectious neurologic complication of COVID-19: Case series and review of literature. Journal of Neurovirology. 2021;**27**(1):26-34

[50] Werner J, Reichen I, Huber M, Abela IA, Weller M, Jelcic I. Subacute cerebellar ataxia following respiratory symptoms of COVID-19: A case report. BMC Infectious Diseases. 2021;**21**(1): 298

[51] Chan JL, Murphy KA, Sarna JR. Myoclonus and cerebellar ataxia associated with COVID-19: A case report and systematic review. Journal of Neurology. 2021;**268**(10):3517-3548

[52] Moreno-Escobar MC, Kataria S, Khan E, Subedi R, Tandon M, Peshwe K, et al. Acute transverse myelitis with dysautonomia following SARS-CoV-2 infection: A case report and review of literature. Journal of Neuroimmunology. 2021;**353**:577523

[53] Pizzanelli C, Milano C, Canovetti S, Tagliaferri E, Turco F, Verdenelli S, et al. Autoimmune limbic encephalitis related to SARS-CoV-2 infection: Case-report and review of the literature. Brain, Behavior, & Immunity-Health. 2021;**12**:100210

[54] Valencia Sanchez C, Theel E, Binnicker M, Toledano M, McKeon A. Autoimmune encephalitis after SARS-CoV-2 infection: Case frequency, findings, and outcomes. Neurology. 2021;**97**(23):e2262-e22e8

[55] Palao M, Fernandez-Diaz E, Gracia-Gil J, Romero-Sanchez CM, Diaz-Maroto I, Segura T. Multiple sclerosis following SARS-CoV-2 infection. Multiple Sclerosis and Related Disorders. 2020;**45**:102377

[56] Jumah M, Rahman F, Figgie M, Prasad A, Zampino A, Fadhil A, et al. COVID-19, HHV6 and MOG antibody: A perfect storm. Journal of Neuroimmunology. 2021;**353**:577521

[57] Shahmirzaei S, Naser MA. Association of COVID-19 and acute disseminated encephalomyelitis (ADEM) in the absence of pulmonary involvement. Autoimmunity Reviews. 2021;**20**(3):102753

[58] Delamarre L, Gollion C, Grouteau G, Rousset D, Jimena G, Roustan J, et al. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. Journal of Neurology, Neurosurgery, and Psychiatry. 2020;**91**(9):1004-1006

[59] Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, et al. Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM consortium position paper. Frontiers in Immunology. 2020;**11**:1648

[60] Llorente Ayuso L, Torres Rubio P, Beijinho do Rosario RF, Giganto Arroyo ML, Sierra-Hidalgo F. Bickerstaff encephalitis after COVID-19. Journal of Neurology. 2020;**268**(6): 2035-2037

[61] Guadarrama-Ortiz P, Choreno-Parra JA, Sanchez-Martinez CM, Pacheco-Sanchez FJ, Rodriguez-Nava AI, Garcia-Quintero G. Neurological aspects of SARS-CoV-2 infection: Mechanisms and manifestations. Frontiers in Neurology. 2020;**11**:1039

[62] Riedhammer C, Weissert R. Antigen presentation, autoantigens, and immune regulation in multiple sclerosis and

other autoimmune diseases. Frontiers in Immunology. 2015;**6**:322

[63] Khamsi R. Rogue antibodies could be driving severe COVID-19. Nature. 2021;**590**(7844):29-31

[64] Yong SJ. Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. Infectious Diseases. 2021;**1-18**

[65] Salamanna F, Veronesi F, Martini L, Landini MP, Fini M. Post-COVID-19 Syndrome: The persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. Frontiers in Medicine. 2021;**8**:653516

[66] Kubankova M, Hohberger B, Hoffmanns J, Furst J, Herrmann M, Guck J, et al. Physical phenotype of blood cells is altered in COVID-19. Biophysics Journal. 2021;**120**(14): 2838-2847

[67] Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the treatment of Covid-19—Preliminary report reply. New England Journal of Medicine. 2020;**383**(10):994

[68] Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. New England Journal of Medicine. 2022;**386**(4):305-315

[69] Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. New England Journal of Medicine. 2021;**384**(9):795-807

[70] Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. New England Journal of Medicine. 2021;**384**(8):693-704

[71] Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. New England Journal of Medicine. 2021;**384**(16):1503-1516

[72] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. New England Journal of Medicine. 2021;**384**(1):20-30

[73] Investigators R-C, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically Ill patients with Covid-19. New England Journal of Medicine. 2021;**384**(16):1491-1502

[74] Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nature Medicine. 2021;**27**(10):1752-1760

[75] Syed YY. Regdanvimab: First approval. Drugs. 2021;**81**(18):2133-2137

[76] Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with covid-19. New England Journal of Medicine. 2021;**385**(23):e81

[77] Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. New England Journal of Medicine. 2021;**385**(21): 1941-1950

[78] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients.

New England Journal of Medicine. 2022;**386**(6):509-520

[79] Garcia-Lledo A, Gomez-Pavon J, Gonzalez Del Castillo J, Hernandez-Sampelayo T, Martin-Delgado MC, Martin Sanchez FJ, et al. Pharmacological treatment of COVID-19: An opinion paper. Revista Española de Quimioterapia. 2021 [Online ahead of print]

[80] Johns M, George S, Taburyanskaya M, Poon YK. A review of the evidence for corticosteroids in COVID-19. Journal of Pharmacy Practice. 2021 897190021998502

[81] Consortium WHOST, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, et al. Repurposed antiviral drugs for Covid-19—Interim WHO solidarity trial results. New England Journal of Medicine. 2021;**384**(6):497-511

[82] Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. New England Journal of Medicine. 2021;**384**(11):1015-1027

[83] Amanat F, Krammer F. SARS-CoV-2 vaccines: Status report. Immunity. 2020;**52**(4):583-589

[84] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New England Journal of Medicine. 2020;**383**(27): 2603-2615

[85] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. New England Journal of Medicine. 2021;**384**(5): 403-416

[86] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. 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**(10269):99-111

[87] Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. New England Journal of Medicine. 2021;**384**(10):2187-2201

[88] Hacisuleyman E, Hale C, Saito Y, Blachere NE, Bergh M, Conlon EG, et al. Vaccine breakthrough infections with SARS-CoV-2 variants. New England Journal of Medicine. 2021;**384**(23): 2212-2218

[89] Sablerolles RSG, Rietdijk WJR, Goorhuis A, Postma DF, Visser LG, Geers D, et al. Immunogenicity and reactogenicity of vaccine boosters after Ad26.COV2.S priming. New England Journal of Medicine. 2022 [Online ahead of print]

[90] Dunkle LM, Kotloff KL, Gay CL, Anez G, Adelglass JM, Barrat Hernandez AQ, et al. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. New England Journal of Medicine. 2022;**386**(6):531-543

[91] Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: A pooled analysis of four randomised trials. Lancet. 2021;**397**(10277):881-891

[92] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. New England Journal of Medicine. 2021;**385**(15):1393-1400

[93] Nemet I, Kliker L, Lustig Y, Zuckerman N, Erster O, Cohen C, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. New England Journal of Medicine. 2022;**386**(5):492-494

[94] Garcia-Montero C, Fraile-Martinez O, Bravo C, Torres-Carranza D, Sanchez-Trujillo L, Gomez-Lahoz AM, et al. An updated review of SARS-CoV-2 vaccines and the importance of effective vaccination programs in pandemic times. Vaccine. 2021;**9**(5)

[95] Perry RJ, Tamborska A, Singh B, Craven B, Marigold R, Arthur-Farraj P, et al. Cerebral venous thrombosis after vaccination against COVID-19 in the UK: A multicentre cohort study. Lancet. 2021;**398**(10306):1147-1156

[96] Schulz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. Annals of Neurology. 2021;**90**(4):627-639

[97] Havla J, Schultz Y, Zimmermann H, Hohlfeld R, Danek A, Kumpfel T. First manifestation of multiple sclerosis after immunization with the Pfizer-BioNTech COVID-19 vaccine. Journal of Neurology. 2022;**269**(1):55-58

[98] Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. New England Journal of Medicine. 2021;**385**(12):1078-1090