Check for updates

European Journal of Immunology

HIGHLIGHTS

Clinical

REVIEW

Autoimmunity and SARS-CoV-2 infection: Unraveling the link in neurological disorders

Daniela Latorre

Institute of Microbiology, ETH Zurich, Zurich, Switzerland

According to the World Health Organization, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already infected more than 400 million people and caused over 5 million deaths globally. The infection is associated with a wide spectrum of clinical manifestations, ranging from no signs of illness to severe pathological complications that go beyond the typical respiratory symptoms. On this note, new-onset neurological and neuropsychiatric syndromes have been increasingly reported in a large fraction of COVID-19 patients, thus potentially representing a significant public health threat. Although the underlying pathophysiological mechanisms remain elusive, a growing body of evidence suggests that SARS-CoV-2 infection may trigger an autoimmune response, which could potentially contribute to the establishment and/or exacerbation of neurological disorders in COVID-19 patients. Shedding light on this aspect is urgently needed for the development of effective therapeutic intervention. This review highlights the current knowledge of the immune responses occurring in Neuro-COVID patients and discusses potential immune-mediated mechanisms by which SARS-CoV-2 infection may trigger neurological complications.

Keywords: autoimmunity, COVID-19, neuro-COVID, neuroimmunology · SARS-CoV-2

Introduction

As the number of COVID-19 cases increases, it is becoming clear that SARS-CoV-2 infection can impact multiple organs in addition to the respiratory system. Since the first description from Wuhan in April 2020 [1], acute or long-term neurological disorders occurring concomitantly or following SARS-CoV-2 infection have been increasingly reported [2–5]. Collectively described with the term Neuro-COVID, they comprise a large spectrum of clinical manifestations ranging from mild symptoms, such as loss of smell and taste, headache, and fatigue, to more severe signs, including encephalitis, stroke, myopathy, and polyneuropathies [6–9]. The diversity in the timing of onset and severity of neurological complications suggests that distinct pathophysiological mechanisms are at interplay in Neuro-COVID patients, including direct viral invasion of neurons, indirect effect of cytokine storm or autoreactive immune responses [10].

Growing evidence suggests that SARS-CoV-2 infection may trigger *de novo* autoimmunity [11], thus potentially contributing to the heterogeneity of symptoms observed in COVID-19 patients, including neurological disorders. While the nervous system was originally considered an immune privileged site, combined observations from human and animal studies have strongly pointed toward an autoimmune origin for numerous diseases affecting the central nervous system (CNS) as well as the peripheral nervous system (PNS), such as multiple sclerosis (MS) and Guillain Barrè Syndrome (GBS) [12]. In addition, autoreactive immune responses have been recently described in other neurodegenerative disorders, namely, Parkinson's and Alzheimer's diseases, whose pathology has long been assumed to be merely due to intrinsic neuronal degeneration [13, 14]. Autoimmunity is also believed to play a role in sleep disorders, epilepsy and neuropsychiatric diseases [12, 15, 16]. Although a clear relationship between certain human neurological disorders and dysregulated immunity seems plausible, understanding how it may influence disease establishment and progression remains mostly elusive.

Correspondence: Daniela Latorre
e-mail: latorred@biol.ethz.ch

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Neurological disorders, such as MS, narcolepsy, and GBS, often have a history of preceding microbial infections [17–21], which are thought to trigger an aberrant immune response through different mechanisms, including molecular mimicry, epitope spreading, and bystander activation [22]. Along this line, several reports have shown that Neuro-COVID manifestations encompass a wide range of rare neurological diseases, such as acute disseminated encephalomyelitis (ADEM), GBS, Miller Fisher syndrome (MFS) and myositis, which have long been suggested to have an autoimmune origin- [6–8]. This evidence has been recently reinforced by a self-controlled case series study that investigated the association between SARS-CoV-2 infection and new-onset neurological disorders in 2 million individuals [9]. Notably, this analysis showed a significantly increased risk of developing GBS, encephalitis, meningitis, and myelitis 28 days after a positive SARS-CoV-2 test [9].

As the number of Neuro-COVID cases is constantly increasing globally, there is an urgent need to understand the underlying cellular and molecular mechanisms to develop effective treatments for this new medical challenge. Shedding light on this issue may also help to decipher a broader spectrum of human neurological diseases that are still poorly understood. In this review, we summarize the available evidence on the immune responses occurring in Neuro-COVID patients and discuss potential immune-mediated processes by which SARS-CoV-2 infection may lead to neurological complications.

Neurodegeneration and SARS-CoV-2 neuronal invasion in Neuro-COVID patients

The presence of neurological manifestations has been related to neuronal loss and pathology in a fraction of Neuro-COVID cases. This is supported by data from magnetic resonance imaging (MRI) and histopathological examination of brain tissue [23, 24] as well as by the detection of markers indicative of neurodegeneration in the blood and cerebrospinal fluid (CSF) of Neuro-COVID patients [25–30]. CSF is a fluid that surrounds the CNS, and its composition reflects the pathophysiological changes of the brain [31]. Thus, its analysis represents an important diagnostic and prognostic tool for neurological disorders [32–34]. CSF levels of matrix metallopeptidase 10 (MMP-10), which is involved in the breakdown of extracellular matrix, have been shown to correlate with the degree of neurological dysfunction in Neuro-COVID patients [25]. Moreover, altered levels of neurofilament light chain (Nfl), a sign of ongoing neuronal disruption, were detected in the CSF or serum of Neuro-COVID patients according to the type and severity of their neurological disorder [26–30, 35]. Interestingly, while serum Nfl levels were elevated across hospitalized Neuro-COVID patients regardless of neurological manifestations, Nfl concentrations in the CSF increased exclusively in patients with CNS inflammatory diseases, namely, ADEM and encephalitis [26]. The levels of Nfl and glial fibrillary acidic protein (GFAP), which is a specific indicator of astrocyte injury, were shown to rise during acute SARS-CoV-2 infection and to remain elevated up to 4 months after infection in a severity-dependent manner [28]. All these observations point to the presence of compartmentalized biomarkers reflecting the existence of neuronal pathology in Neuro-COVID patients, which may represent a potential useful diagnostic tool for accurate clinical classification of neurological disease subtype and severity.

Whether the neuronal disturbances seen in Neuro-COVID patients are caused by the direct viral invasion of neurons or by the indirect effect of systemic inflammation in the absence or presence of an autoreactive immune response is still poorly understood. SARS-CoV-2 was shown to be able to infect the brains of mice overexpressing the human angiotensin converting enzyme-2 (ACE2) receptor, which has been identified as the receptor for SARS-CoV-2 entry into cells, leading to consequent neuronal damage [36]. The same holds true for human brain organoids and *in vitro* models of the blood–brain barrier (BBB) [37–39]. However, studies of brain biopsies and CSF from patients revealed contrasting results. Some case reports detected the presence of SARS-CoV-2 RNA and viral particles in brain tissues from Neuro-COVID patients [24, 36, 40–43], whereas in other studies, SARS-CoV-2 signals were very low or absent [44–49]. A study analyzing brain biopsies from 43 Neuro-COVID patients indicated that despite SARS-CoV-2 being detected in 53% of cases, its presence did not correlate with the severity of neuronal pathology. Pronounced neuroinflammation in the brainstem was commonly observed, whereas neuropathological changes were rather mild [40]. This is in line with other reports showing the existence of microglial activation and T-cell infiltration in brain biopsies from Neuro-COVID patients [41, 45–48, 50].

When identified, SARS-CoV-2 was detected in many areas of the CNS [40, 43, 51], thus suggesting that the virus may reach the brain through different routes, including the olfactory neurons, the endothelial cells of blood vessels or the choroid plexus via the CSF [52]. A recent systematic review estimated that out of 303 Neuro-COVID patients suffering from various neurological disorders, only 17 (6%) of them, all with symptoms localized to the CNS, had a positive PCR result for SARS-CoV-2 in the CSF [53]. Moreover, in a multicenter study including Neuro-COVID patients from 17 different European centers, SARS-CoV-2 was absent in all CSF samples analyzed ($n = 76$) [54]. Overall, although discrepancy in the results may be due to limitations in the sensitivity of the tests used for viral detection, it may also indicate that the appearance of neurological manifestations occurs either after neuronal invasion and virus clearance or as an indirect result of immune-related mechanisms.

Proinflammatory mediators in the CSF of Neuro-COVID patients

Systemic hyperactivation of innate and adaptive immunity accompanied by elevated levels of circulating cytokines, also known as the "cytokine storm," has been largely described in COVID-19 patients and is believed to contribute to disease complications [55–57]. Accordingly, increased systemic levels of various

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

proinflammatory cytokines, such as IL-6 and TNF, have been linked to disease severity and survival in COVID-19 patients [58–60]. Cytokine storms are also known to occur in other coronavirus infections, such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), as well as in sepsis and autoimmunity, and may lead to multiorgan dysfunction and failure if inadequately treated [55, 56]. Neurological manifestations, including confusion, delirium, seizures, and fatigue, have also been associated with cytokine storms, thus suggesting that indeed the excessive systemic amounts of inflammatory molecules observed in COVID-19 patients may affect their nervous system [55]. The recent description in Neuro-COVID patients of a positive correlation between serum levels of brain injury biomarkers and proinflammatory cytokines, such as IL-6 and TNF, supports this hypothesis [28].

Alterations in the concentration of proinflammatory mediators, including chemokines and cytokines, have also been reported in the CSF of Neuro-COVID patients [25, 54, 61–65]. By combining proteomics and cytometric bead array analyses, Remsik et al. performed a comprehensive investigation of soluble factors in CSF and plasma from cancer patients who developed neurological complications after COVID-19 [25]. The results were compared to those obtained from the analysis of non-COVID patients suffering from other neuroinflammatory conditions, including autoimmune encephalitis and chimeric antigen receptor (CAR)-T-cell-associated neurotoxicity syndrome [25]. This work showed a substantial increase in the levels of proinflammatory chemokines and cytokines, including various C-X-C motif chemokine ligand (CXCL) chemokines, IL-6, IL-8, and IFN-β, in the CSF of post-COVID-19 cancer patients. When compared to matched plasma samples from the same patients, the analysis revealed an intrathecal enrichment of IFN-β and IL-8 levels. Additionally, markers of neurodegeneration (i.e., MMP-10) and senescence (i.e., Nfl) were at comparable levels between Neuro-COVID cancer patients and patients with neurotoxicity due to CAR-T-cell therapy, which is recognized to be mainly mediated by inflammatory cytokines [61]. In another study, IL-2, IL-6, CXCL8, and CXCL10 concentrations were found to be augmented in the CSF of Neuro-COVID patients with inflammatory CNS diseases compared to controls suffering from refractory headache after SARS-CoV-2 infection [63]. Interestingly, this inflammatory profile was a unique feature limited to the CSF, as it diverged from the one found in the plasma of the same individuals [63]. Moreover, a recent study revealed that despite displaying high levels of proinflammatory molecules in the CSF, Neuro-COVID patients had less inflammation than patients with other inflammatory neurological disorders [64]. However, in the same study, the levels of specific factors, such as CXCL8, CCL2, and VEGF-A, were increased in patients with severe SARS-CoV-2 infection compared to moderate cases [64]. Elevated concentrations of proinflammatory mediators have also been described in the CSF of a few pediatric cases with acute COVID-19 illness who developed new onset neuropsychiatric symptoms, thus further supporting immune-mediated involvement [65].

Altogether, these data reveal the existence of altered levels of proinflammatory mediators in the CSF as a common feature of Neuro-COVID patients and suggest a potential correlation between neuroinflammation and disease severity. Proinflammatory signals may derive from the periphery as well as from activated innate cells of the CNS, including microglia, astrocytes, and endothelial cells, and may result in increased BBB and blood-CSF barrier (BCSFB) permeability and in the recruitment of other immune cells into the brain parenchyma. Along this line, markers of BCSFB dysfunction, often associated with elevated levels of proinflammatory cytokines in CSF and serum, have been recently described in 58 out of 116 (50%) Neuro-COVID patients without preexisting CNS disorders [54]. Notably, elevated proinflammatory cytokine levels can persist in the CSF for weeks or months after convalescence of the respiratory syndrome [25, 54], thus suggesting that they may also contribute to the prolonged neurological complications that are being increasingly reported in post-COVID-19 patients [66–68].

Immune cell composition in the CSF of Neuro-COVID patients

Immune cell profiling of the CSF by the use of sensitive technologies, such as single-cell RNA sequencing (scRNAseq) and high-dimensional flow cytometry analysis, can provide important insights into distinct pathophysiological processes underlying immune-mediated neurological disorders [34, 69]. Heming et al. employed the scRNAseq approach to investigate the cellular composition in the CSF of a total of eight Neuro-COVID patients as well as of three control groups of patients suffering from neurological disorders not associated with SARS-CoV-2 infection, i.e., idiopathic intracranial hypertension, MS, and viral encephalitis [70]. The analysis revealed the existence of an increased frequency of $CD4^+$ T lymphocytes expressing markers of cytotoxicity and exhaustion as well as of expanded T-cell receptor (TCR) clonotypes in the CSF of Neuro-COVID patients. Moreover, an enrichment of a subset of monocytes displaying increased markers of antigen presentation was identified in the CSF of these patients. Of note, when compared to patients affected by classical viral encephalitis, which is characterized by inflammation due to direct viral invasion of the brain, Neuro-COVID patients showed lower expression of multiple antiviral IFN-associated genes in different immune cell types [70]. This evidence suggests that neurological disorders associated with SARS-CoV-2 infection may be the result of postinfectious immune-mediated mechanisms rather than direct viral infection of neurons. In a parallel work by Song et al., scRNA-seq analysis was performed on matched CSF and peripheral blood samples from Neuro-COVID patients and uninfected healthy individuals [62]. This work revealed the existence of immune-related genes differentially expressed in the CSF but not in the blood of Neuro-COVID patients compared to healthy controls. In particular, an upregulation of genes associated with the IFN signaling pathway and immune cell activation

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

was described in dendritic cells and natural killer (NK) cells from the CSF of these patients. In addition, although the relative proportions of Tcell subsets in the CSF were similar between the two groups of individuals, the study identified increased activation markers in $CD4^+$ and $CD8^+$ T lymphocytes as well as augmented proportions of T helper 1 (Th1) and Th2 subsets in Neuro-COVID patients [62]. TCR repertoire analysis showed the existence of expanded clonotypes, mostly belonging to the $CD4^+$ T-cell subset, in the CSF but not in the blood of Neuro-COVID patients. These expanded TCR clonotypes were unique to each individual and not shared across Neuro-COVID patients [62]. Moreover, the study described different frequencies of distinct B-cell populations in the blood and CSF and detected an enrichment of antibody-secreting B cells in the CSF of Neuro-COVID patients compared to healthy controls [62].

Overall, these observations provide evidence of a compartmentalized CSF immune response ongoing in Neuro-COVID patients, which includes both the innate and adaptive arms of the immune system, thus strongly pointing toward an immune-mediated mechanism underlying neurological manifestations in COVID-19 patients.

Autoreactive immune responses in Neuro-COVID patients

Preexisting autoimmunity, due to genetic defects or autoantibodies disrupting type I IFN immunity, has been shown to contribute to inadequate viral control and to severe clinical complications in a fraction of COVID-19 patients [11, 71–75]. On the other hand, it is becoming increasingly clear that SARS-CoV-2 infection can trigger the *de novo* development of autoantibodies targeting a broad spectrum of autoantigens. Increased titers of anti-nuclear antibodies (ANA), hallmarks of systemic autoimmunity, have been identified in COVID-19 patients compared to healthy controls and seem to correlate with disease severity and systemic inflammation [73, 76–82]. Approximately 50% of hospitalized COVID-19 patients and less than 15% of healthy controls had detectable serum autoantibodies against self-antigens traditionally associated with rare autoimmune diseases, such as autoimmune myositis, systemic erythematous lupus (SLE), and Sjogren's syndrome [73, 81]. In particular, autoantibodies targeting molecules involved in lymphocyte trafficking and functions, including cytokines and chemokines, have been identified in more than 60% of hospitalized COVID-19 patients [72, 73]. These autoantibodies may affect a wide range of immunological processes, thus resulting in exacerbated disease, as confirmed by *in vivo* experiments in a mouse model of SARS-CoV-2 infection [72].

Notably, intrathecal expansion of antibody-secreting plasma cells as well as increased levels of anti-SARS-CoV-2 antibodies have been reported in the CSF of Neuro-COVID patients [35, 62, 83, 84]. Interestingly, these antibodies showed differences in their antigen specificities compared to those found in the plasma of the same individuals [62]. Indeed, CSF-derived antibodies from Neuro-COVID patients exhibited a certain degree of immunoreactivity against self-neural antigens when analyzed by immunostaining of brain tissue, and in some cases, they were able to cross-react with both SARS-CoV-2 spike protein and neural tissue [62, 83]. This evidence indicates that a large proportion of Neuro-COVID patients harbor a humoral immune response in the CSF, which displays compartmentalized features and targets neuronal antigens, thus potentially contributing to new onset neurological symptoms.

Many autoantibodies targeting intracellular and extracellular CNS antigens have also been detected in the serum of COVID-19 patients [28, 54, 72, 85, 86]. Interestingly, antibodies against hypocretin receptor 2 (HCRTR2), which is selectively enriched in the hypothalamus and controls the sleep-wake circuit through HCRT signaling, have been identified and shown to be functional in *in vitro* assays [72]. In addition, anti-myelin-associated glycoprotein (MAG) antibodies, which are frequently associated with peripheral neuropathies, were recently described in 9.6% of Neuro-COVID-19 patients but were absent in healthy controls [28]. Another recent study detected serum anti-myelin antibodies in a fraction of Neuro-COVID-19 patients (6 out of 40) by indirect immunofluorescence of peripheral nerve tissue sections [54]. Furthermore, human monoclonal antibodies isolated from the blood of COVID-19 patients and directed against SARS-CoV-2 proteins were able to cross-react with neural tissue antigens, such as myelin basic protein (MBP), glutamic acid decarboxylase 65 (GAD-65), NFP (neurofilament protein), alpha-synuclein, and synapsin [85, 86]. Of note, antibodies isolated from Neuro-COVID patients displayed a reactivity pattern to brain tissue reminiscent of the binding to surface receptors or ion channels previously described in antibody-mediated encephalitis [83, 86, 87].

Overall, based on all these indications as well as on the widely recognized role of pathogenic autoantibodies in many neurological diseases [87], it is reasonable to speculate that SARS-CoV-2 infection may induce a dysregulated humoral response in a subclass of COVID-19 patients with consequent production of *de novo* autoantibodies that would interfere with physiological neurological functions, thus resulting in Neuro-COVID disorders.

On the other hand, little is known about the existence of autoreactive T lymphocytes in Neuro-COVID patients. As described in the previous section, a clonal expansion of Tcell populations has been found in the CSF of these patients [62, 70], thus indicating a compartmentalized recruitment of potentially pathogenic T cells. However, the antigen specificity of these CSF-infiltrating T cells has yet to be investigated [62, 70]. It is well known that T lymphocytes make up over 80% of CSF cells, but they are not necessarily able to infiltrate the CNS parenchyma under physiological conditions [88]. Indeed, activated T lymphocytes can reach the CSF regardless of their antigen specificity; however, they need to recognize their cognate antigen on resident antigen presenting cells (APCs) to be able to cross into the CNS parenchyma through the glia limitans [89–91]. Nevertheless, the description of markers of neuronal degeneration and brain barrier dysfunction in the CSF of Neuro-COVID patients (described in the previous sections) points to the possibility that expanded T cells may enter the brain parenchyma in an antigen-

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

independent fashion and consequently contribute to neuronal pathology. Overall, whether CSF-infiltrating T cells target SARS-CoV-2 or self-neuronal antigens and whether they can reach the CNS parenchyma are still unclear.

Moreover, while the Tcell response to SARS-CoV-2 has been largely studied and characterized in the blood of COVID-19 patients during the acute and recovery phases of the infection [92], it remains poorly explored in Neuro-COVID patients. A recent study addressed this aspect in patients suffering from long-term neurological sequelae after SARS-CoV-2 infection as well as in convalescent individuals [93]. The measurement of IFN-γ and IL-2 production by peripheral blood mononuclear cells (PBMCs), stimulated *in vitro* with synthetic peptides spanning different SARS-CoV-2 proteins, revealed the existence of peculiar patterns of antigen specificity in long Neuro-COVID patients, showing higher Tcell responses against nucleoprotein rather than spike protein, which was instead the major target in convalescent individuals [93]. These data point to the existence of immunodominant SARS-CoV-2 epitopes preferentially targeted by the Tcell response in Neuro-COVID patients. However, how these findings may relate to the pathophysiological mechanisms underlying Neuro-COVID disorders has yet to be explored.

Potential immune-mediated mechanisms triggered by SARS-CoV-2 infection in Neuro-COVID patients

The body of evidence discussed above indicates that a large fraction of the neurological symptoms seen in Neuro-COVID patients mainly originate from an aberrant immune-mediated response following SARS-CoV-2 infection.

As previously proposed for other infection-associated neurological disorders [94], bystander activation and epitope spreading mechanisms may contribute to the generation of an autoreactive immune response in Neuro-COVID patients (Fig. 1A). The release and spread of neuronal antigens may result from tissue damage caused by direct SARS-CoV-2 infection of the CNS or by the indirect effect of a cytokine storm. In parallel, the robust proinflammatory environment may also lead to hyperactivation of APCs and consequently to the upregulation of costimulatory molecules and antigen presentation capacity [95, 96]. This would result in a simultaneous display of both viral and self-antigens either released by damaged tissue or taken up from cell membranes, which in turn may lead to the activation and expansion of self-reactive T cells. The potential role of bystander activation is also supported by several lines of evidence suggesting that the broad spectrum of autoantibodies observed in COVID-19 patients may result from an extrafollicular B-cell response [72, 81, 97, 98]. Extrafollicular B cells, known as double-negative (DN2) B cells, lack IgD, CD27, CXCR5, and CD21, emerge directly from naïve B lymphocytes and are more prone to generating autoantibodies [99, 100]. Their involvement in the pathophysiology of some neurological diseases, such as anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, has been previously proposed [87]. Notably, DN2 B cells are expanded in the blood of COVID-19 patients compared to uninfected individuals, and their frequency correlates with disease severity and poor clinical outcomes [72, 81, 97, 98]. Together with the description of autoantibodies targeting neuronal antigens in COVID-19 patients [54, 62, 72, 83, 85, 86], these observations indicate that an extrafollicular autoreactive Bcell response may contribute to the establishment or exacerbation of neurological manifestations associated with SARS-CoV-2 infection. In these patients, the differentiation and expansion of autoreactive DN2 B cells may derive from a T-cell-independent activation pathway, in which the simultaneous engagement of Toll-like receptor 7 (TLR7) by the viral single-stranded RNA genome of SARS-CoV-2 and the recognition of self-antigens directly by the Bcell receptor (BCR) on naïve B cells may allow escape from tolerance, which is a mechanism that is believed to occur in other autoimmune disorders, such as systemic erythematous lupus (SLE) [81, 99–101].

Nevertheless, evidence of the existence of SARS-CoV-2 antibodies in the CSF and blood of Neuro-COVID patients, which are able to cross-react with neuronal antigens strongly suggests that molecular mimicry may contribute to disease pathophysiology [62, 83, 85, 86] (Fig. 1B). B and Tcell responses that are cross-reactive between microbial and self-neuronal antigens have been detected and characterized in other infection-associated neurological diseases, such as MS, narcolepsy and GBS [102–105]. Notably, since the initial description of a GBS case in January 2020 in a COVID-19 patient [106], the number of published case reports and observational studies pointing to a potential causal relationship between SARS-CoV-2 infection and peripheral inflammatory neuropathies has grown exponentially [9]. Interestingly, GBS is one among a few examples of an autoimmune neurological disorder in which the role of pathogenic autoantibodies generated by a molecular mimicry mechanism has been described. More than 70% of GBS patients have a history of a preceding bacterial or viral infection that typically occurs approximately 1–2 weeks prior to disease onset and includes *Campylobacter jejuni* in 30–40% of GBS cases [18]. Molecular mimicry between *C. jejuni* lipooligosaccharides and self-gangliosides of the peripheral nerves has been identified and proposed to mediate axonal neuropathy in animal models [107]. However, GBS associated with SARS-CoV-2 infection is often characterized by demyelinating polyneuropathy, and autoantibodies against gangliosides are mostly absent [7, 108], thus supporting the hypothesis that additional immune-mediated mechanisms may be involved in the physiopathology of post-COVID-19 disease. Analysis of sequence homology between 41 human proteins associated with acute and chronic inflammatory neuropathies and SARS-CoV-2 antigens has identified similarities with the human heat shock proteins 90 (HSP90B and HSP90B2) and 60 (HSP60) [109]. However, whether these antigens represent new targets of an ongoing cross-reactive immune response in post-COVID-19 GBS cases has yet to be examined. Moreover, dozens of peptides from SARS-CoV-2 proteins (spike and envelope proteins) with a high sequence identity to human proteins expressed by a broad range of tissues have been described by bioinformatics approaches [109–111]. In addi-

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

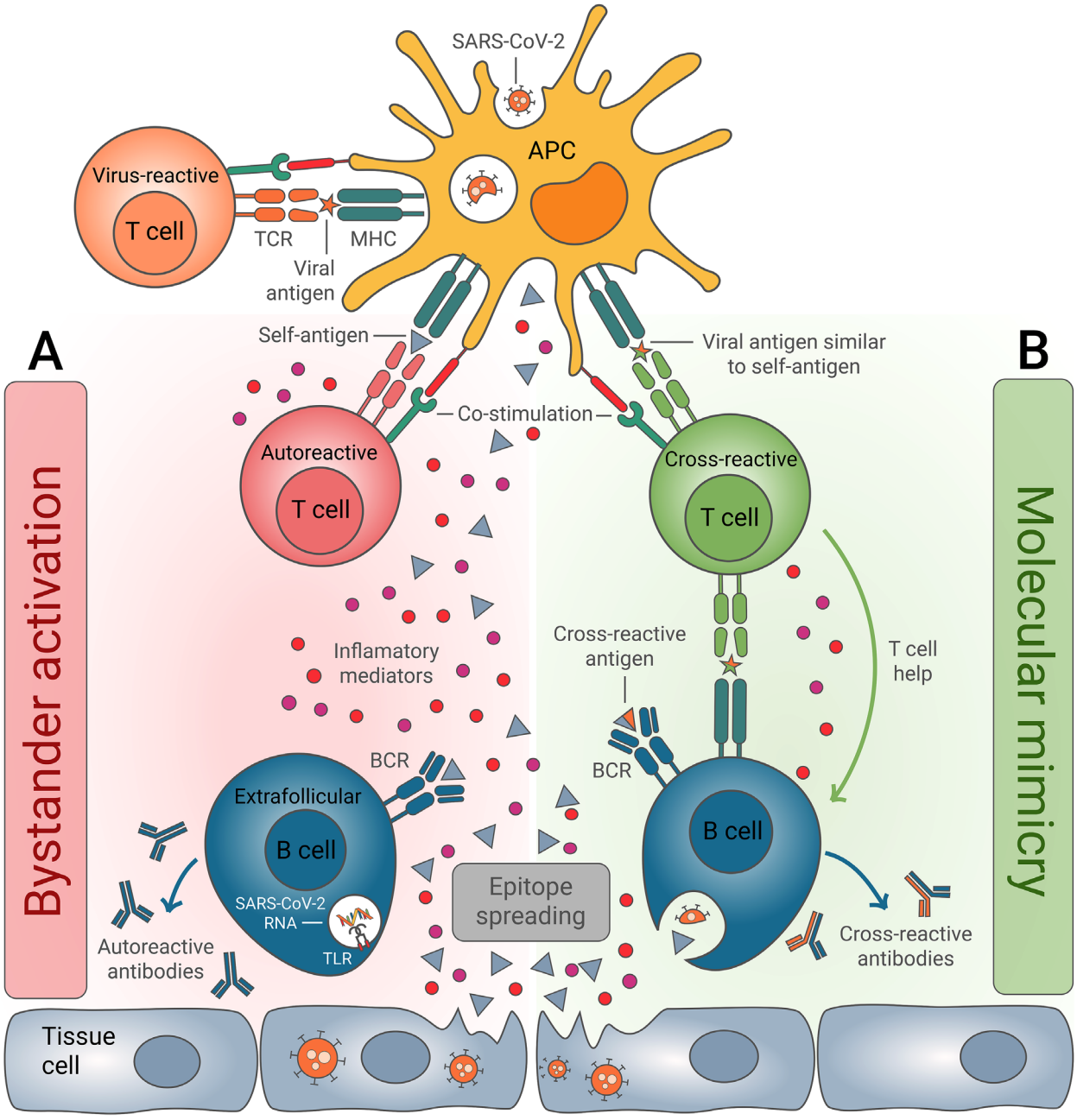

Figure 1. Mechanisms of infection-induced autoimmunity in Neuro-COVID. (A) Release and spreading of self-antigens may result from tissue damage caused by direct SARS-CoV-2 neuronal invasion or by the indirect effect of a proinflammatory environment. Self-antigens can be presented to T cells by activated APCs endowed with increased antigen uptake ability and costimulatory molecule expression, thus facilitating the activation and expansion of autoreactive T cells. In parallel, autoreactive antibodies can be generated in a T-cell-independent fashion by extrafollicular B cells that recognize self-antigens directly on their BCR and are simultaneously activated via SARS-CoV-2 genome sensing through TLR engagement. (B) Recognition of a SARS-CoV-2 antigen that has similarity to a self-antigen can induce activation of autoreactive T cells through a mechanism of molecular mimicry. Similarly, antibodies cross-reactive between SARS-CoV-2 antigens and self-antigens can be generated by virus-specific B cells via a T-cell-dependent mechanism.

tion, other potential targets of autoantibodies may occur when the self- and viral proteins are folded in their native, secondary or tertiary structures. Overall, a combination of molecular mimicry, epitope spreading, and bystander activation mechanisms may contribute to the generation of the aberrant immune response in Neuro-COVID patients.

In conclusion, based on the current knowledge, a potential model of Neuro-COVID immunopathology can be speculated (Fig. 2). Neuroinflammation may be the direct result of SARS-CoV-2 neuronal invasion or the indirect effect of increased systemic and intrathecal levels of proinflammatory mediators. In this scenario, the induction of CNS tissue damage (Fig. 2A)

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

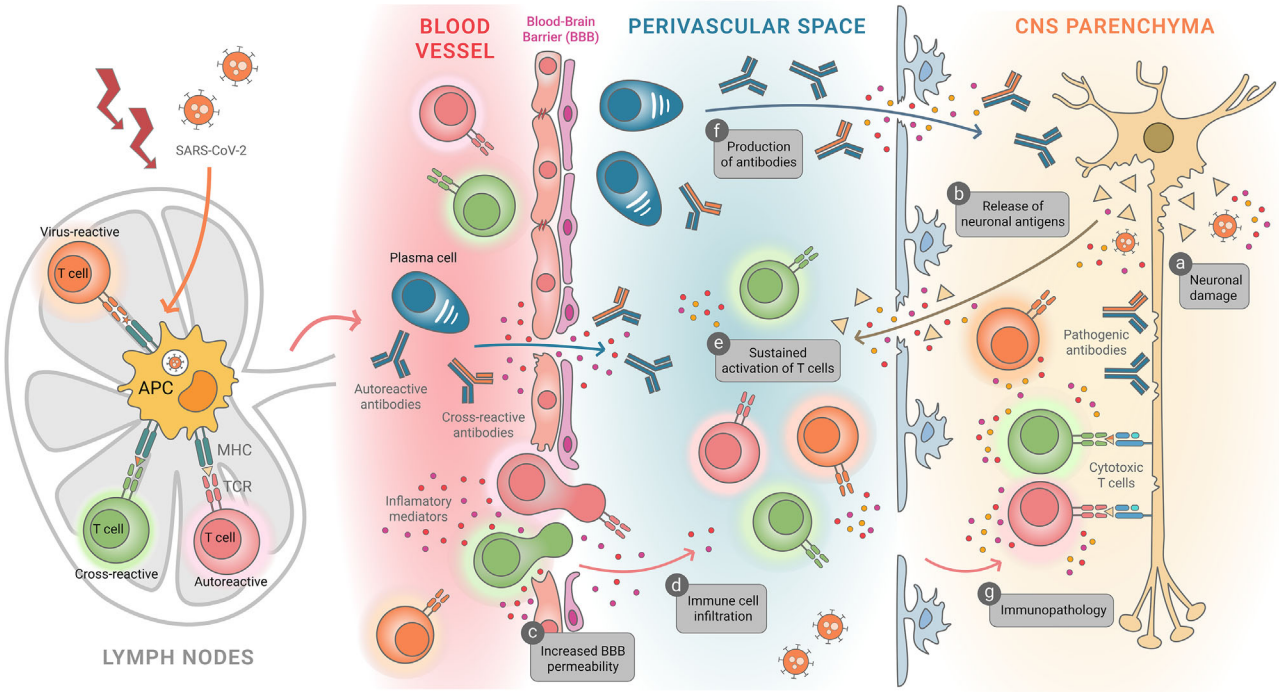

Figure 2. Model of Neuro-COVID immunopathology. Direct SARS-CoV-2 neuronal invasion contributes to the induction of CNS tissue damage (A) with the consequent spread of self-neuronal antigens (B). In parallel, increased systemic levels of proinflammatory mediators affect BBB permeability (C), thus facilitating the recruitment from the blood into the perivascular space of potentially pathogenic soluble molecules, such as autoantibodies and proinflammatory cytokines, as well as immune cells, including autoreactive T lymphocytes, plasma cells and APCs (D). Here, intrathecal clonal expansion and activation of $CD4^+$ and $CD8^+$ Tcell populations may occur (E), and plasma cells may release autoantibodies directly into the CSF (F). In this scenario, pathogenic T lymphocytes and antibodies infiltrate the CNS parenchyma and contribute to disease immunopathology by directly exerting cytotoxic functions and/or indirectly fueling the local inflammatory environment (G).

would consequently lead to the spread of self-neuronal antigens (Fig. 2B), and the impairment of BBB integrity (Fig. 2C) would facilitate the recruitment of disease-mediating soluble factors and immune cells from the blood into the perivascular space, such as autoantibodies, plasma cells, autoreactive T lymphocytes and APCs (Fig. 2D). Clonal expansion and activation of autoreactive $CD4^+$ and $CD8^+$ T-cell populations may be sustained intrathecally [62, 70] (Fig. 2E), and plasma cells may release autoantibodies, which are potentially cross-reactive between SARS-CoV-2 and neuronal antigens, directly into the CSF [62] (Fig. 2F). Altogether, this would result in the infiltration of pathogenic T lymphocytes and antibodies into the CNS parenchyma, which would contribute to the disease immunopathology by directly exerting cytotoxic functions and/or indirectly fueling the local inflammatory environment (Fig. 2G).

Conclusions and future perspectives

Although evidence to date points to the involvement of aberrant immunity in Neuro-COVID patients, further research needs to be performed to better characterize the cellular and molecular players underpinning the large heterogeneity of neurological manifestations affecting COVID-19 patients. In particular, deciphering whether certain neurological disorders develop as parainfectious syndromes due to unspecific exaggerated proinflammatory responses during acute SARS-CoV-2 infection or as an indirect effect of autoimmune responses secondary to the infection would have a major translational impact into clinical applications for the selection of appropriate therapeutic intervention. Notably, long-term clinical manifestations persisting or following acute SARS-CoV-2 infection, which are often referred to as post-acute sequelae of SARS-CoV-2 infection (PASC) or Long Covid syndrome, include many psychiatric and neurological symptoms that are commonly described in other postinfectious syndromes, but whose pathophysiological mechanisms remain elusive [3]. Understanding whether they may be a result of a persistent dysregulated immune response could also open new perspectives in the field of neuroimmunology. To this end, it will be of critical importance to perform comprehensive immunological studies based on rigorous patient stratification according to the type of neurological disorder and with the inclusion of appropriate control groups spanning across diseases and infections, such as COVID-19 patients who do not show any neurological symptoms. In conclusion, the COVID-19 pandemic may represent a unique setting to precisely determine how a viral infection can trigger *de novo* neurological disorders or contribute to the exacerbation of preexisting asymptomatic neurological conditions.

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

Acknowledgments: This work was supported by grants from the Swiss National Science Foundation (PR00P3_185742). The author thanks Lenka Súkeniková and Dr. Anna Mallone for preparation of the original figures accompanying this article and Dr. Antonino Cassotta, Dr. Daniel Hoces Burga, Dr. Maria Cristina Gagliardi, Dr. Anna Mallone, Dr. Laura Pellegrini and Dr. Sinduya Krishnarajah for helpful suggestions.
Open access funding provided by Eidgenossische Technische Hochschule Zurich.

Conflict of interest: The author declares no commercial or financial conflicts of interest.

Data availability statement: Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

References

1 **Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J. et al.**, Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020. **77**: 683–690.

2 **Baig, A. M.**, Counting the neurological cost of COVID-19. *Nat. Rev. Neurol.* 2021.

3 **Spudich, S. and Nath, A.**, Nervous system consequences of COVID-19. *Science* 2022. **375**: 267–269.

4 **Chou, S. H., Beghi, E., Helbok, R., Moro, E., Sampson, J., Altamirano, V., Mainali, S. 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. **4**: e2112131.

5 **Ross Russell, A. L., Hardwick, M., Jeyanantham, A., White, L. M., Deb, S., Burnside, G., Joy, H. M. et al.**, Spectrum, risk factors and outcomes of neurological and psychiatric complications of COVID-19: a UK-wide cross-sectional surveillance study. *Brain Commun.* 2021. **3**: fcab168.

6 **Pezzini, A. and Padovani, A.**, Lifting the mask on neurological manifestations of COVID-19. *Nat. Rev. Neurol.* 2020. **16**: 636–644.

7 **Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., Kneen, R. et al.**, Neurological associations of COVID-19. *Lancet Neurol.* 2020. **19**: 767–783.

8 **Misra, S., Kolappa, K., Prasad, M., Radhakrishnan, D., Thakur, K. T., Solomon, T., Michael, B. D. et al.**, Frequency of neurologic manifestations in COVID-19: a systematic review and meta-analysis. *Neurology* 2021. https://doi.org/10.1212/WNL.0000000000012930

9 **Patone, M., Handunnetthi, L., Saatci, D., Pan, J., Katikireddi, S. V., Razvi, S., Hunt, D. et al.**, Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. *Nat. Med.* 2021. **27**: 2144–2153.

10 **Aschman, T., Mothes, R., Heppner, F. L. and Radbruch, H.**, What SARS-CoV-2 does to our brains. *Immunity* 2022. https://doi.org/10.1016/j.immuni.2022.06.013

11 **Knight, J. S., Caricchio, R., Casanova, J. L., Combes, A. J., Diamond, B., Fox, S. E., Hanauer, D. A. et al.**, The intersection of COVID-19 and autoimmunity. *J. Clin. Invest.* 2021. **131** https://doi.org/10.1172/JCI154886

12 **Nutma, E., Willison, H., Martino, G. and Amor, S.**, Neuroimmunology - the past, present and future. *Clin. Exp. Immunol.* 2019. https://doi.org/10.1111/cei.13279

13 **Lindestam Arlehamn, C. S., Garretti, F., Sulzer, D. and Sette, A.**, Roles for the adaptive immune system in Parkinson's and Alzheimer's diseases. *Curr. Opin. Immunol.* 2019. **59**: 115–120.

14 **Rickenbach, C. and Gericke, C.**, Specificity of adaptive immune responses in central nervous system health, aging and diseases. *Front. Neurosci.* 2022. **15** https://doi.org/10.3389/fnins.2021.806260

15 **Coutinho, E. and Vincent, A.**, Autoimmunity in neuropsychiatric disorders. *Handb. Clin. Neurol.* 2016. **133**: 269–282.

16 **Latorre, D., Federica, S., Bassetti, C. L. A. and Kallweit, U.**, Narcolepsy: a model interaction between immune system, nervous system, and sleep-wake regulation. *Semin. Immunopathol.* 2022. https://doi.org/10.1007/s00281-022-00933-9

17 **Bjornevik, K., Cortese, M., Healy, B. C., Kuhle, J., Mina, M. J., Leng, Y., Elledge, S. J. et al.**, Longitudinal analysis reveals high prevalence of Epstein–Barr virus associated with multiple sclerosis. *Science* 2022. https://doi.org/10.1126/science.abj8222

18 **van den Berg, B., Walgaard, C., Drenthen, J., Fokke, C., Jacobs, B. C. and van Doorn, P. A.**, Guillain–Barre syndrome: pathogenesis, diagnosis, treatment and prognosis. *Nat. Rev. Neurol.* 2014. **10**: 469–482.

19 **Han, F., Lin, L., Warby, S. C., Faraco, J., Li, J., Dong, S. X., An, P. et al.**, Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann. Neurol.* 2011. **70**: 410–417.

20 **Pruss, H.**, Postviral autoimmune encephalitis: manifestations in children and adults. *Curr. Opin. Neurol.* 2017. **30**: 327–333.

21 **Salle, V.**, Coronavirus-induced autoimmunity. *Clin. Immunol.* 2021. **226**: 108694.

22 **Munz, C., Lunemann, J. D., Getts, M. T. and Miller, S. D.**, Antiviral immune responses: triggers of or triggered by autoimmunity? *Nat. Rev. Immunol.* 2009. **9**: 246–258.

23 **Coolen, T., Lolli, V., Sadeghi, N., Rovai, A., Trotta, N., Taccone, F. S., Creteur, J. et al.**, Early postmortem brain MRI findings in COVID-19 nonsurvivors. *Neurology* 2020. **95**: e2016–e2027.

24 **Solomon, I. H., Normandin, E., Bhattacharyya, S., Mukerji, S. S., Keller, K., Ali, A. S., Adams, G.**, et al., Neuropathological Features of Covid-19. *N. Engl. J. Med.* 2020. **383**: 989–992.

25 **Remsik, J., Wilcox, J. A., Babady, N. E., McMillen, T. A., Vachha, B. A., Halpern, N. A., Dhawan, V. et al.**, Inflammatory leptomeningeal cytokines mediate COVID-19 neurologic symptoms in cancer patients. *Cancer Cell* 2021. **39**: 276–283.e3.

26 **Paterson, R. W., Benjamin, L. A., Mehta, P. R., Brown, R. L., Athauda, D., Ashton, N. J., Leckey, C. A.**, et al., Serum and cerebrospinal fluid biomarker profiles in acute SARS-CoV-2-associated neurological syndromes. *Brain Commun.* 2021. **3**: fcab099.

27 **Kanberg, N., Ashton, N. J., Andersson, L. M., Yilmaz, A., Lindh, M., Nilsson, S., Price, R. W. et al.**, Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. *Neurology* 2020. **95**: e1754–e1759.

28 **Needham, E., Ren, A., Digby, R., Outtrim, J., Chatfield, D., Manktelow, A., Newcombe, V.**, et al., Brain injury in COVID-19 is associated with autoinflammation and autoimmunity. *medRxiv* 2021. 2021.12.03.21266112. https://doi.org/10.1101/2021.12.03.21266112 medRxiv

29 **Frontera, J. A., Boutajangout, A., Masurkar, A. V., Betensky, R. A., Ge, Y., Vedvyas, A., Debure, L. et al.**, Elevation of neurodegenerative serum biomarkers among hospitalized COVID-19 patients. *medRxiv* 2021. 2021.09.01.21262985. https://doi.org/10.1101/2021.09.01.21262985 medRxiv

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

30 **De Lorenzo, R., Lore, N. I., Finardi, A., Mandelli, A., Cirillo, D. M., Tresoldi, C., Benedetti, F. et al.**, Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. *J. Neurol.* 2021. **268**: 4436–4442.

31 **Ransohoff, R. M. and Engelhardt, B.**, The anatomical and cellular basis of immune surveillance in the central nervous system. *Nat. Rev. Immunol.* 2012. **12**: 623–635.

32 **Lleo, A., Cavedo, E., Parnetti, L., Vanderstichele, H., Herukka, S. K., Andreasen, N., Ghidoni, R. et al.**, Cerebrospinal fluid biomarkers in trials for Alzheimer and Parkinson diseases. *Nat. Rev. Neurol.* 2015. **11**: 41–55.

33 **Mignot, E., Lammers, G. J., Ripley, B., Okun, M., Nevsimalova, S., Overeem, S., Vankova, J. et al.**, The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch. Neurol.* 2002. **59**: 1553–1562.

34 **Gross, C. C., Schulte-Mecklenbeck, A., Madireddy, L., Pawlitzki, M., Strippel, C., Rauber, S., Kramer, J. et al.**, Classification of neurological diseases using multidimensional CSF analysis. *Brain* 2021. **144**: 2625–2634.

35 **Garcia, M. A., Barreras, P. V., Lewis, A., Pinilla, G., Sokoll, L. J., Kickler, T., Mostafa, H.**, et al., Cerebrospinal fluid in COVID-19 neurological complications: no cytokine storm or neuroinflammation. *medRxiv* 2021. 2021.01.10.20249014. https://doi.org/10.1101/2021.01.10.20249014 medRxiv

36 **Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A. V., Skriabine, S., Lu, P. et al.**, Neuroinvasion of SARS-CoV-2 in human and mouse brain. *J. Exp. Med.* 2021. **218**.

37 **Ramani, A., Muller, L., Ostermann, P. N., Gabriel, E., Abida-Islam, P., Muller-Schiffmann, A., Mariappan, A. et al.**, SARS-CoV-2 targets neurons of 3D human brain organoids. *EMBO J.* 2020. **39**: e106230.

38 **Pellegrini, L., Albecka, A., Mallery, D. L., Kellner, M. J., Paul, D., Carter, A. P., James, L. C. et al.**, SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF barrier in human brain organoids. *Cell Stem Cell* 2020. **27**: 951–961.e5.

39 **Krasemann, S., Haferkamp, U., Pfefferle, S., Woo, M. S., Heinrich, F., Schweizer, M., Appelt-Menzel, A. et al.**, The blood–brain barrier is dysregulated in COVID-19 and serves as a CNS entry route for SARS-CoV-2. *Stem Cell Rep.* 2022. https://doi.org/10.1016/j.stemcr.2021.12.011

40 **Matschke, J., Lutgehetmann, M., Hagel, C., Sperhake, J. P., Schroder, A. S., Edler, C., Mushumba, H. et al.**, Neuropathology of patients with COVID-19 in Germany: a postmortem case series. *Lancet Neurol.* 2020. **19**: 919–929.

41 **Deigendesch, N., Sironi, L., Kutza, M., Wischnewski, S., Fuchs, V., Hench, J., Frank, A. et al.**, Correlates of critical illness-related encephalopathy predominate postmortem COVID-19 neuropathology. *Acta Neuropathol.* 2020. **140**: 583–586.

42 **Puelles, V. G., Lutgehetmann, M., Lindenmeyer, M. T., Sperhake, J. P., Wong, M. N., Allweiss, L., Chilla, S. et al.**, Multiorgan and renal tropism of SARS-CoV-2. *N. Engl. J. Med.* 2020. **383**: 590–592.

43 **Serrano, G. E., Walker, J. E., Arce, R., Glass, M. J., Vargas, D., Sue, L. I., Intorcia, A. J. et al.**, Mapping of SARS-CoV-2 brain invasion and histopathology in COVID-19 disease. *medRxiv* 2021. https://doi.org/10.1101/2021.02.15.21251511 medRxiv

44 **Schaller, T., Hirschbuhl, K., Burkhardt, K., Braun, G., Trepel, M., Markl, B. and Claus, R.**, Postmortem examination of patients with COVID-19. *JAMA* 2020. **323**: 2518–2520.

45 **Thakur, K. T., Miller, E. H., Glendinning, M. D., Al-Dalahmah, O., Banu, M. A., Boehme, A. K., Boubour, A. L. et al.**, COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain* 2021. **144**: 2696–2708.

46 **Yang, A. C., Kern, F., Losada, P. M., Agam, M. R., Maat, C. A., Schmartz, G. P., Fehlmann, T. et al.**, Dysregulation of brain and choroid plexus cell types in severe COVID-19. *Nature* 2021. **595**: 565–571.

47 **Lee, M. H., Perl, D. P., Nair, G., Li, W., Maric, D., Murray, H., Dodd, S. J. et al.**, Microvascular injury in the brains of patients with Covid-19. *N. Engl. J. Med.* 2021. **384**: 481–483.

48 **Fullard, J. F., Lee, H. C., Voloudakis, G., Suo, S., Javidfar, B., Shao, Z., Peter, C. et al.**, Single-nucleus transcriptome analysis of human brain immune response in patients with severe COVID-19. *Genome Med.* 2021. **13**: 118.

49 **Deinhardt-Emmer, S., Wittschieber, D., Sanft, J., Kleemann, S., Elschner, S., Haupt, K. F., Vau, V. et al.**, Early postmortem mapping of SARS-CoV-2 RNA in patients with COVID-19 and the correlation with tissue damage. *Elife* 2021. **10**.

50 **Schwabenland, M., Salie, H., Tanevski, J., Killmer, S., Lago, M. S., Schlaak, A. E., Mayer, L. et al.**, Deep spatial profiling of human COVID-19 brains reveals neuroinflammation with distinct microanatomical microglia-T-cell interactions. *Immunity* 2021. **54**: 1594–1610.e11.

51 **Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., Laue, M. 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**: 168–175.

52 **Butowt, R., Meunier, N., Bryche, B. and von Bartheld, C. S.**, The olfactory nerve is not a likely route to brain infection in COVID-19: a critical review of data from humans and animal models. *Acta Neuropathol.* 2021. **141**: 809–822.

53 **Lewis, A., Frontera, J., Placantonakis, D. G., Lighter, J., Galetta, S., Balcer, L. and Melmed, K. R.**, Cerebrospinal fluid in COVID-19: a systematic review of the literature. *J. Neurol. Sci.* 2021. **421**: 117316.

54 **Jarius, S., Pache, F., Kortvelyessy, P., Jelcic, I., Stettner, M., Franciotta, D., Keller, E.**, et al., Cerebrospinal fluid findings in COVID-19: a multicenter study of 150 lumbar punctures in 127 patients. *J. Neuroinflammation* 2022. **19**: 19.

55 **Fajgenbaum, D. C. and June, C. H.**, Cytokine storm. *N. Engl. J. Med.* 2020. **383**: 2255–2273.

56 **Moore, J. B. and June, C. H.**, Cytokine release syndrome in severe COVID-19. *Science* 2020. **368**: 473–474.

57 **Mangalmurti, N. and Hunter, C. A.**, Cytokine storms: understanding COVID-19. *Immunity* 2020. **53**: 19–25.

58 **Del Valle, D. M., Kim-Schulze, S., Huang, H. H., Beckmann, N. D., Nirenberg, S., Wang, B., Lavin, Y. et al.**, An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat. Med.* 2020. **26**: 1636–1643.

59 **Ling, L., Chen, Z., Lui, G., Wong, C. K., Wong, W. T., Ng, R. W. Y., Tso, E. Y. K. et al.**, Longitudinal cytokine profile in patients with mild to critical COVID-19. *Front. Immunol.* 2021. **12**: 763292.

60 **Kleymenov, D. A., Bykonia, E. N., Popova, L. I., Mazunina, E. P., Gushchin, V. A., Kolobukhina, L. V., Burgasova, O. A. et al.**, A deep look into COVID-19 severity through dynamic changes in Blood Cytokine Levels. *Front. Immunol.* 2021. **12**: 771609.

61 **Belin, C., Devic, P., Ayrignac, X., Dos Santos, A., Paix, A., Sirven-Villaros, L., Simard, C.**, et al., Description of neurotoxicity in a series of patients treated with CAR T-cell therapy. *Sci. Rep.* 2020. **10**: 18997.

62 **Song, E., Bartley, C. M., Chow, R. D., Ngo, T. T., Jiang, R., Zamecnik, C. R., Dandekar, R. et al.**, Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms. *Cell Rep. Med.* 2021. **2**: 100288.

63 **Espindola, O. M., Gomes, Y. C. P., Brandao, C. O., Torres, R. C., Siqueira, M., Soares, C. N., Lima, M. et al.**, Inflammatory cytokine patterns associated

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

with neurological diseases in coronavirus disease 2019. *Ann. Neurol.* 2021. **89**: 1041–1045.

64 **Bernard-Valnet, R., Perriot, S., Canales, M., Pizzarotti, B., Caranzano, L., Castro-Jimenez, M., Epiney, J. B.**, et al., Encephalopathies associated with severe COVID-19 present neurovascular unit alterations without evidence for strong neuroinflammation. *Neurol. Neuroimmunol. Neuroinflamm.* 2021. **8**

65 **Ngo, B., Lapp, S. A., Siegel, B., Patel, V., Hussaini, L., Bora, S., Philbrook, B. et al.**, Cerebrospinal fluid cytokine, chemokine, and SARS-CoV-2 antibody profiles in children with neuropsychiatric symptoms associated with COVID-19. *Mult Scler Relat Disord* 2021. **55**: 103169.

66 **Al-Aly, Z., Xie, Y. and Bowe, B.**, High-dimensional characterization of postacute sequelae of COVID-19. *Nature* 2021. **594**: 259–264.

67 **Taquet, M., Geddes, J. R., Husain, M., Luciano, S. and Harrison, P. J.**, 2021. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. **8**: 416–427.

68 **Groff, D., Sun, A., Ssentongo, A. E., Ba, D. M., Parsons, N., Poudel, G. R., Lekoubou, A. et al.**, Short-term and Long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw. Open* 2021. **4**: e2128568.

69 **Meyer Zu Horste, G., Gross, C. C., Klotz, L., Schwab, N. and Wiendl, H.**, Next-generation neuroimmunology: new technologies to understand central nervous system autoimmunity. *Trends Immunol.* 2020. **41**: 341–354.

70 **Heming, M., Li, X., Rauber, S., Mausberg, A. K., Borsch, A. L., Hartlehnert, M., Singhal, A.**, et al., Neurological manifestations of COVID-19 feature T-cell exhaustion and dedifferentiated monocytes in cerebrospinal fluid. *Immunity* 2021. **54**: 164–175.e6.

71 **Bastard, P., Rosen, L. B., Zhang, Q., Michailidis, E., Hoffmann, H. H., Zhang, Y., Dorgham, K.**, et al., Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020. **370** https://doi.org/10.1126/science.abd4585

72 **Wang, E. Y., Mao, T., Klein, J., Dai, Y., Huck, J. D., Jaycox, J. R., Liu, F.**, et al., Diverse functional autoantibodies in patients with COVID-19. *Nature* 2021. **595**: 283–288.

73 **Chang, S. E., Feng, A., Meng, W., Apostolidis, S. A., Mack, E., Artandi, M., Barman, L.**, et al., New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat. Commun.* 2021. **12**: 5417.

74 **Su, Y., Yuan, D., Chen, D. G., Ng, R. H., Wang, K., Choi, J., Li, S.**, et al., Multiple early factors anticipate postacute COVID-19 sequelae. *Cell* 2022. **185**: 881–895.e20.

75 **Zhang, Q., Bastard, P., Effort, C. H. G., Cobat, A. and Casanova, J. L.**, Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature* 2022. **603**: 587–598.

76 **Gazzaruso, C., Carlo Stella, N., Mariani, G., Nai, C., Coppola, A., Naldani, D. and Gallotti, P.**, High prevalence of antinuclear antibodies and lupus anticoagulant in patients hospitalized for SARS-CoV2 pneumonia. *Clin. Rheumatol.* 2020. **39**: 2095–2097.

77 **Lerma, L. A., Chaudhary, A., Bryan, A., Morishima, C., Wener, M. H. and Fink, S. L.**, Prevalence of autoantibody responses in acute coronavirus disease 2019 (COVID-19). *J. Transl. Autoimmun.* 2020. **3**: 100073.

78 **Pascolini, S., Vannini, A., Deleonardi, G., Ciordinik, M., Sensoli, A., Carletti, I., Veronesi, L. et al.**, COVID-19 and immunological dysregulation: can autoantibodies be useful? *Clin. Transl. Sci.* 2021. **14**: 502–508.

79 **Sacchi, M. C., Tamiazzo, S., Stobbione, P., Agatea, L., De Gaspari, P., Stecca, A., Lauritano, E. C. et al.**, SARS-CoV-2 infection as a trigger of autoimmune response. *Clin. Transl. Sci.* 2021. **14**: 898–907.

80 **Peker, B. O., Sener, A. G. and Kaptan Aydogmus, F.**, Antinuclear antibodies (ANAs) detected by indirect immunofluorescence (IIF) method in acute COVID-19 infection; future roadmap for laboratory diagnosis. *J. Immunol. Methods* 2021. **499**: 113174.

81 **Woodruff, M. C., Ramonell, R. P., Saini, A. S., Haddad, N. S., Anam, F. A., Rudolph, M. E., Bugrovsky, R. et al.**, Relaxed peripheral tolerance drives broad de novo autoreactivity in severe COVID-19. *medRxiv* 2021. https://doi.org/10.1101/2020.10.21.20216192 medRxiv

82 **Taeschler, P., Cervia, C., Zurbuchen, Y., Hasler, S., Pou, C., Tan, Z., Adamo, S. et al.**, Autoantibodies in COVID-19 correlate with anti-viral humoral responses and distinct immune signatures. *medRxiv* 2022. p. 2022.01.08.22268901. https://doi.org/10.1101/2022.01.08.22268901 medRxiv

83 **Franke, C., Ferse, C., Kreye, J., Reincke, S. M., Sanchez-Sendin, E., Rocco, A., Steinbrenner, M. et al.**, High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain Behav. Immun.* 2021. **93**: 415–419.

84 **Alexopoulos, H., Magira, E., Bitzogli, K., Kafasi, N., Vlachoyiannopoulos, P., Tzioufas, A., Kotanidou, A. et al.**, Anti-SARS-CoV-2 antibodies in the CSF, blood–brain barrier dysfunction, and neurological outcome: Studies in 8 stuporous and comatose patients. *Neurol. Neuroimmunol. Neuroinflamm.* 2020. **7** https://doi.org/10.1212/NXI.0000000000000893

85 **Vojdani, A., Vojdani, E. and Kharrazian, D.**, Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. *Front. Immunol.* 2020. **11**: 617089.

86 **Kreye, J., Reincke, S. M., Kornau, H. C., Sanchez-Sendin, E., Corman, V. M., Liu, H., Yuan, M. et al.**, A therapeutic nonself-reactive SARS-CoV-2 antibody protects from lung pathology in a COVID-19 hamster model. *Cell* 2020. **183**: 1058–1069.e19.

87 **Pruss, H.**, Autoantibodies in neurological disease. *Nat. Rev. Immunol.* 2021. **21**: 798–813.

88 **Engelhardt, B. and Ransohoff, R. M.**, The ins and outs of T-lymphocyte trafficking to the CNS: anatomical sites and molecular mechanisms. *Trends Immunol.* 2005. **26**: 485–495.

89 **Engelhardt, B., Vajkoczy, P. and Weller, R. O.**, The movers and shapers in immune privilege of the CNS. *Nat. Immunol.* 2017. **18**: 123–131.

90 **Mapunda, J. A., Tibar, H., Regragui, W. and Engelhardt, B.**, How does the immune system enter the brain? *Front. Immunol.* 2022. **13**. https://doi.org/10.3389/fimmu.2022.805657

91 **Mundt, S., Greter, M., Flugel, A. and Becher, B.**, The CNS immune landscape from the viewpoint of a T cell. *Trends Neurosci.* 2019. **42**: 667–679.

92 **Moss, P.**, The T-cell immune response against SARS-CoV-2. *Nat. Immunol.* 2022. **23**: 186–193.

93 **Visvabharathy, L., Hanson, B., Orban, Z., Lim, P. H., Palacio, N., Jain, R., Liotta, E. M. et al.**, Neuro-COVID long-haulers exhibit broad dysfunction in T-cell memory generation and responses to vaccination. *medRxiv* 2021. https://doi.org/10.1101/2021.08.08.21261763 medRxiv

94 **Geginat, J., Paroni, M., Pagani, M., Galimberti, D., De Francesco, R., Scarpini, E. and Abrignani, S.**, The enigmatic role of viruses in multiple sclerosis: molecular mimicry or disturbed immune surveillance? *Trends Immunol.* 2017. **38**: 498–512.

95 **Merad, M. and Martin, J. C.**, Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat. Rev. Immunol.* 2020. **20**: 355–362.

96 **Chevrier, S., Zurbuchen, Y., Cervia, C., Adamo, S., Raeber, M. E., de Souza, N., Sivapatham, S. et al.**, A distinct innate immune signature marks progression from mild to severe COVID-19. *Cell Rep. Med.* 2021. **2**: 100166.

97 **Woodruff, M. C., Ramonell, R. P., Nguyen, D. C., Cashman, K. S., Saini, A. S., Haddad, N. S., Ley, A. M.**, et al., Extrafollicular B-cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nat. Immunol.* 2020. **21**: 1506–1516.

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH

98 **Castleman, M. J., Stumpf, M. M., Therrien, N. R., Smith, M. J., Lesteberg, K. E., Palmer, B. E., Maloney, J. P. et al.**, SARS-CoV-2 infection relaxes peripheral B-cell tolerance. *J. Exp. Med.* 2022. **219** https://doi.org/10.1084/jem.20212553

99 **Tipton, C. M., Fucile, C. F., Darce, J., Chida, A., Ichikawa, T., Gregoretti, I., Schieferl, S. et al.**, Diversity, cellular origin and autoreactivity of antibody-secreting cell population expansions in acute systemic lupus erythematosus. *Nat. Immunol.* 2015. **16**: 755–765.

100 **Jenks, S. A., Cashman, K. S., Zumaquero, E., Marigorta, U. M., Patel, A. V., Wang, X., Tomar, D. et al.**, Distinct effector B cells induced by unregulated toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. *Immunity* 2018. **49**: 725–739.e6.

101 **Brown, G. J., Cañete, P. F., Wang, H., Medhavy, A., Bones, J., Roco, J. A., He, Y. et al.**, TLR7 gain-of-function genetic variation causes human lupus. *Nature* 2022. https://doi.org/10.1038/s41586-022-04642-z

102 **Yuki, N.**, Ganglioside mimicry and peripheral nerve disease. *Muscle Nerve* 2007. **35**: 691–711.

103 **Luo, G., Ambati, A., Lin, L., Bonvalet, M., Partinen, M., Ji, X., Maecker, H. T. et al.**, Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. *Proc. Natl. Acad. Sci. U. S. A.* 2018. **115**: E12323–E12332.

104 **Greene, M. T., Ercolini, A. M., DeGutes, M. and Miller, S. D.**, Differential induction of experimental autoimmune encephalomyelitis by myelin basic protein molecular mimics in mice humanized for HLA-DR2 and an MBP(85–99)-specific T-cell receptor. *J. Autoimmun.* 2008. **31**: 399–407.

105 **Lanz, T. V., Brewer, R. C., Ho, P. P., Moon, J.-S., Jude, K. M., Fernandez, D., Fernandes, R. A. et al.**, Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. *Nature* 2022. https://doi.org/10.1038/s41586-022-04432-7

106 **Zhao, H., Shen, D., Zhou, H., Liu, J. and Chen, S.**, Guillain–Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* 2020. **19**: 383–384.

107 **Yuki, N. and Hartung, H. P.**, Guillain–Barre syndrome. *N. Engl. J. Med.* 2012. **366**: 2294–2304.

108 **Shoraka, S., Ferreira, M. L. B., Mohebbi, S. R. and Ghaemi, A.**, SARS-CoV-2 Infection and Guillain–Barre syndrome: a review on potential pathogenic mechanisms. *Front. Immunol.* 2021. **12**: 674922.

109 **Lucchese, G. and Floel, A.**, SARS-CoV-2 and Guillain–Barre syndrome: molecular mimicry with human heat shock proteins as potential pathogenic mechanism. *Cell Stress Chaperones* 2020. **25**: 731–735.

110 **Khavinson, V., Terekhov, A., Kormilets, D. and Maryanovich, A.**, Homology between SARS CoV-2 and human proteins. *Sci. Rep.* 2021. **11**: 17199.

111 **Kanduc, D. and Shoenfeld, Y.**, Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. *Immunol. Res.* 2020. **68**: 310–313.

Full correspondence: Daniela Latorre, Institute of Microbiology, ETH Zurich, Switzerland Email: latorred@biol.ethz.ch

Received: 5/3/2022
Revised: 14/5/2022
Accepted: 12/7/2022
Accepted article online: 14/7/2022

© 2022 The Authors. *European Journal of Immunology* published by Wiley-VCH GmbH