Clinical and Pathophysiologic Spectrum of Neuro-COVID

Josef Finsterer¹ • Fulvio A Scorza²

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Abstract
Though the lungs are predominantly affected in SARS-CoV-2-infected patients, extra-pulmonary manifestations can occur. Extra-pulmonary manifestations of the central and peripheral nervous system need to be recognised as they can strongly determine the outcome. This mini-review summarises and discusses previous and recent findings about neuro-COVID. The spectrum of central nervous system disease in COVID-19 patients is much broader than so far anticipated. Peripheral nerves and the skeletal muscle are less predominantly affected. In the vast majority of the cases, there is no direct attack of the virus towards vulnerable structures, which explains why various manifestations of the nervous system manifest favourably to immune suppression or immune modulation. Overall, the pathophysiology and clinical presentation of CNS/PNS involvement in COVID-19 is wider than believed. All patients with COVID-19 should be investigated by the neurologist for primary or secondary involvement of the CNS/PNS in the infection. neuro-COVID responds favourably to immune suppressants or immune modulation.

Keywords SARS-CoV-2 • COVID-19 • Neurological involvement • Side effects • Brain • Central nervous system

Introduction
Since the outbreak of the SARS-CoV-2 pandemic, it becomes increasingly evident that not only the lungs but also other organs may be directly or indirectly affected by the infection (extra-pulmonary involvement) [1]. Organs other than the lungs involved in the infection include the eyes, heart, kidneys, intestines, endocrine organs, skin, vessels, and the nervous system (neuro-COVID) [1]. This mini-review aims at summarising and discussing current knowledge about the clinical presentation and pathophysiology of neuro-COVID.

Results
Neurological disease in SARS-CoV-2-infected patients may not only be due to a direct viral attack towards neurons, glial cells, or components of cerebral vessels or the blood-brain barrier but also secondary due to the immune reaction against the virus, secondary to affection of the lungs, heart, or kidneys, or due to side effects of treatment applied during the acute infection. Additionally, pre-existing neurological disease may become clinically evident or worsen with COVID-19.

Direct affection of the central nervous system (CNS) by the virus is rare and may cause meningitis/encephalitis [2, 3], manifesting as headache, seizures, confusion, ataxia, pyramidal signs, or impaired consciousness (Table 1). Weakness of several studies on the neurological involvement in the infection is that most patients with clinical CNS manifestations did not undergo CNS imaging or investigations of the cerebrospinal fluid (CSF). In case patients undergo a spinal tap, the CSF is often not investigated for virus RNA or negative for the virus. If the CSF would be routinely investigated for virus RNA in COVID-19 patients, the virus would probably be more frequently detected in the CSF. Only with repeated spinal taps would it be possible to assess for how long the virus is present in the CNS after haematogenic or neuronal spread to
### Table 1 Neurological manifestations of COVID-19 according to the pathophysiological background

| CNS/PNS manifestation | Clinical manifestations | Virus RNA in CSF | Reference |
|-----------------------|-------------------------|------------------|-----------|
| **A. Direct viral affection of the CNS/PNS** | | | |
| Meningitis/encephalitis | HA, confusion, CI, ataxia, spasticity, seizures, IC | Yes | [2, 3] |
| Cerebellitis | Vertigo, ataxia | Yes | [4] |
| Olfactory neuropathy | Hyposmia, anosmia | Yes | [5] |
| Gustatory neuropathy | Hypogeusia, ageusia | Yes | [5] |
| **B. CNS/PNS disease secondary to the immune response** | | | |
| AHNE | Seizures, CI | No | [6, 7] |
| Cytokine-release syndrome | Ataxia, tremor, confusion, aphasia, dysautonomia, coma | No | [8, 9] |
| Myoclonus | Myoclonic jerks, tremor | No | [10] |
| ADEM | Weakness, SD, urinary retention, dysarthria, ataxia | No | [11, 12] |
| Limbic encephalitis | Dysarthria, seizures, CI, hallucinations | No | [13] |
| Transverse myelitis | Quadripareisis, SD | No | [7] |
| GBS (polyradiculitis) | ocular/bulbar/facial/limb weakness, SD | No | [7] |
| Mononeuritis | Facial palsy | No | [14] |
| Myositis/dermatomyositis | Myalgia, RL | No | [15, 16] |
| Myasthenia | Fatigability, exercise intolerance, weakness | No | [17] |
| Psychosis | Deletion, disorientation, hallucinations | No | [18] |
| Delirium | Hyperactive, hypoactive | No | [19] |
| Tectocular palsy | Vertical diplopia mydriasis | No | [20] |
| Oculomotor palsy | Unilateral diplopia, strabism | No | [21] |
| Hypoglossal nerve palsy | Dysphagia | No | [22] |
| Cerebral vasculitis | Multifocal ischemic stroke | No | [23] |
| Microbleeds | nm | No | [24] |
| Vasocostriction syndrome | Mental alteration, encephalopathy | No | [25] |
| Optic neuritis | Visual impairment | No | [26] |
| NMO spectrum disorder | Visual impairment, weakness | No | [27] |
| Multiple sclerosis | Visual impairment, weakness, sensory disturbances | No | [28] |
| Trigeminal neuralgia | Facial pain triggered by eating, temperature | No | [29] |
| **C. CNS/PNS complication due to affection of other organs/tissues** | | | |
| Cerebral hypoxia | IC, coma | No | [30] |
| PRES | HA, seizures, IC, visual impairment | No | [31] |
| Ischemic stroke | Hemiparesis, IC | No | [32] |
| Intracerebral bleeding | IC, dilated pupils | No | [33] |
| Sinus venous thrombosis | Hemiparesis, seizures, HA | No | [34] |
| Sleep disorder | Insomnia | No | [35] |
| **D. CNS/PNS disease secondary to COVID-19 treatment** | | | |
| Critical ill neuropathy | Limb weakness | No | [10] |
| Critical ill myopathy | Limb weakness | No | [10] |
| Chloroquine myopathy | Limb weakness | No | [36] |
| Ritonavir myopathy/RL | Limb weakness, myalgia | No | [36] |
| Lopinavir myopathy/RL | Limb weakness, myalgia | No | [36] |
| NMS | Fever, tachycardia, tachypnea, rigidity | No | [37] |
| Rhabdomyolysis | Myalgia, weakness, myoglobinuria | No | [38] |
| Myasthenic syndrome | | No | [39] |
| **E. Neurological disease deteriorating during COVID-19** | | | |
| Myasthenia | Exacerbation of weakness, myasthenic crisis | No | [40] |
| Multiple sclerosis | Optic neuritis, plaque formation | No | [45] |

*ADEM* acute disseminated encephalomyelitis, *AHNE* acute, haemorrhagic, necrotising encephalitis, *CI* cognitive impairment, *HA* headache, *IC* impaired consciousness, *NMS* neuroleptic malignant syndrome, *nr* not reported, *PRES* posterior, reversible encephalopathy syndrome, *RL* rhabdomyolysis, *SD* sensory disturbances
the CNS. Direct affection of the peripheral nervous system (PNS) includes hyposmia or hypogeusia (Table 1).

Neurological disease due to the immune reaction (cytokine storm) against the virus includes myoclonus; acute disseminated encephalomyelitis (ADEM); acute, haemorrhagic, necrotising encephalopathy (AHNE) [6, 41]; cerebral vasculitis; psychosis; delirium; transverse myelitis [7]; cranial nerve palsy; Guillain-Barre syndrome (GBS) [42]; mononeuritis; cytokine release syndrome (CRS) [8]; or myositis [43] (Table 1). GBS is an increasingly recognised complication of COVID-19 and has been reported in at least 62 patients with COVID-19 [42]. Whether myositis in patients with COVID-19 is due to direct attack of the virus or secondary to the immune response remains speculative. In a recent case report about COVID-19 myositis, muscle biopsy showed inflammatory infiltration, but the virus was not found on electron microscopy [43], suggesting that myositis is rather immune-mediated than infectious. A further argument for the immunogenic hypothesis of COVID-19 myositis provided a recent study on 20 patients with dermatomyositis showing that immunogenic epitopes attacked by autologous antibodies have high sequence identity to SARS-CoV-2 proteins [15]. Another neuro-immunologic complication of COVID-19 is transverse myelitis [42, 44]. Accordingly, in none of these patients was the CSF positive for virus RNA [42]. A recently described neuro-immunologic entity in COVID-19 is CRS, clinically manifesting with confusion, coma, tremor, cerebellar ataxia, behavioural alterations, aphasia, pyramidal signs, cranial nerve palsy, dysautonomia, and central hypoventilation [8]. Another novel CNS complication of COVID-19 is myoclonus [10], but it remains speculative if myoclonus is infectious, immune-mediated, post-hypoxic, or due to concomitant renal insufficiency [10].

Additionally, it has to be mentioned that CNS/PNS disease in COVID-19 may secondarily result from affection of the heart or the kidneys (Table 1). Cardiac involvement may be responsible for cardioembolic, ischemic stroke, or ischemic stroke due to hypotension. Furthermore, CNS/PNS disease may be triggered by the anti-viral treatment or mechanical ventilation (Table 1). Drugs used for the treatment of COVID-19 may induce toxic myopathy, critical ill myopathy, critical ill neuropathy, or rhabdomyolysis. Lastly, pre-existing CNS/PNS disease may deteriorate during the acute viral infection (Table 1).

Conclusions

Overall, the pathophysiology and clinical presentation of CNS/PNS involvement in COVID-19 is broader than usually anticipated. All patients with COVID-19 should be investigated by a neurologist for primary or secondary involvement of the CNS/PNS in the infection.

Author Contribution IF: design, literature search, discussion, first draft, and critical comments. SF: literature search, critical comments, and final approval

Data Availability All data are available from the corresponding author.

Declarations We confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate.

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