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REVIEWS

Clinical and Pathophysiologic Spectrum of Neuro-COVID

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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.

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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	Quadriparesis, 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]
Trochlear 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]
Vasoconstriction 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 antiboides 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 hypothyroidism [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 JF: 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.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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