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Minireviews

Guillain Barrè syndrome and myelitis associated with SARS-CoV-2 infection

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ABSTRACT

Despite a likely underestimation due to the many obstacles of the highly infectious, intensive care setting, increasing clinical reports about COVID-19 patients developing acute paralysis for polyradiculoneuritis or myelitis determine additional impact on the disease course and outcome. Different pathogenic mechanisms have been postulated basing on clinical, laboratory and neuroimaging features, and response to treatments. Here we provide an overview with insights built on the available reports. Besides direct viral pathogenicity, a crucial role seems to be represented by immune-mediated mechanisms, supporting and further characterizing the already hypothesized neurotropic potential of SARS-CoV-2 and implying specific treatments. Proper clinical and instrumental depiction of symptomatic cases, as well as screening for their early recognition is advocated.

1. Introduction

The hypothesized SARS-CoV-2 neurotropic potential finds support in the growing body of evidence from medical reports of COVID-19-associated neurological manifestations.[1–5] Neurological symptoms have been reported mostly in patients suffering from severe COVID-19, [1] somehow raising doubts about potentially being determined by the critical illness rather than by SARS-CoV-2 infection, especially for the stroke and encephalopathy cases.[1]

However, acute sensorimotor impairment in COVID-19 patients has also been reported as a consequence of documented peripheral nerve and spinal cord damage, suggesting a more specific neurotropism of the virus.[5–22] Indeed, the association with SARS-CoV-2 infection could be interpreted as "causative" by means of a direct (viral) or a secondary (para- or post-infectious) pathophysiologic pathway, implying substantial differences in prognosis and management.[23]

It is important to note that the incidence of such impairment in COVID-19 patients could have been underestimated, due to the technical difficulties in performing proper neurological examination in the intensive-care setting, but could also have played a major role in determining post-acute functional outcome.

Here we provide a critical overview of clinical features and pathophysiology insights of polyradiculoneuritis and myelitis associated to SARS-CoV-2 infection, in the aim of offering practical suggestions for their early recognition and prompt management.

2. Guillain Barré syndrome

Beyond anosmia and dysgeusia becoming emblematic of COVID-19-related neuropathies probably due to a direct viral attack,[1] the increasing reporting of acute polyradiculoneuritis (or Guillain-Barré syndrome, GBS) cases associated to SARS-CoV-2 infection highlights the existence of a viral-triggered immune-mediated damage to the peripheral nervous system.[5,6]

Previous coronaviruses (SARS-CoV, MERS-CoV, HCV-OC43) infections have been associated with GBS.[24] To date, >30 cases of COVID-19-related GBS have been described (5 of them by our group). [5,6] As finely reviewed by Rahimi,[6] most were classified as AIDP, but all the major subtypes of GBS, including AMAN, AMSAN and Miller-Fisher Syndrome had been observed. About 15% of the reported cases had severe course, leading to neurogenic respiratory failure; follow up data are sparse and, if available, referring to the brief term, thus preventing considerations about efficacy of therapeutic approaches. Diagnoses had been made according to clinical, electrophysiological, cerebrospinal fluid (CSF) and neuroimaging data. SARS-CoV-2 RNA was never detected in the collected CSF samples, whose 80% showed hyperproteinorrachia without pleocytosis.[25] All patients received intravenous immunoglobulins, being plasma exchange uneasily available in the highly contagious intensive care setting. Neurological symptoms began on average after 10–15 days from SARS-CoV-2 infection, with a minimum of 3 and a maximum of 24 days. Notably, in two cases GBS overlapped with COVID-19 infection. Whereas GBS should

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represent a prototypical "post-infectious" condition, the short temporal latency or the actual overlap described in such cases might introduce the possibility of a "*para*-infectious" syndrome mimicking GBS, at least in select cases.[6] Of interest, GBS might be the first manifestation of SARS-CoV-2 infection (as documented by nasopharyngeal swabs) in patients otherwise asymptomatic.[6,26]

It is important to acknowledge that concomitant neuromuscular and respiratory dysfunctions are not easily ascertained in the intensive care unit (ICU) setting, suggesting a potential underestimation of GBS in COVID-19 patients. In addition, GBS should be distinguished from other ICU-related causes of paralysis, such as critical illness neuropathies and neuromyopathies.[27]

Furthermore, the potential coexistence of SARS-CoV-2 infection and GBS, both leading to respiratory failure, should be carefully evaluated as it may further complicate the clinical course and negatively impact prognosis.

3. Acute myelopathies

Besides preclinical evidence of coronaviruses infection resulting in demyelination,[28] upcoming clinical reports of acute inflammatory lesions affecting the CNS[4,29] in COVID-19 patients suggest the occurrence of a potential immune-mediated damage triggered by SARS-CoV-2 infection, likely belonging to the acute disseminated encephalomyelitis (ADEM)-spectrum, however often with an interestingly short latency between infectious and neurological onset. ADEM lesions generally affect the brain to a greater extent than the spinal cord, although post-infectious site-restricted isolated myelitis has already been reported.[30,31]

In COVID-19 patients, spinal cord damage has been observed both in the context of acute disseminated encephalomyelitis and isolated; the latter being preeminently expressed as longitudinal elongated transverse myelitis (LETM), which is known to occur also as *para*-infectious phenomenon.[32,33] To date, limited reports embracing myelopathy in COVID-19 patients are available;[7–22] their features are detailed in Table 1 with a tentative partition in probably para- versus post-infectious conditions, which was made mostly according to the latency and overlap between infectious and neurological course.

As probable examples of *para*-infectious syndromes, a group of Authors from Brescia, Italy,[7] described new-onset, multiple demyelinating lesions in the brain and in the cervico-thoracic spinal cord of a 54 year-old woman with COVID-19 pneumonia, symptomatic for seizures, with complete recovery after high dose intravenous steroids. Zoghi et al, [8] from Tehran, Iran, described a case of encephalomyelitis with LETM after COVID-19 in a 21 year-old man, with slight improvement after plasma exchange treatment. Another cases of isolated LETM has been reported from the United States, affecting a 28 year-old woman soon after mild COVID-19 symptoms, that was treated with steroids with a good clinical response.[9]

Authors from Wuhan, China[10] diagnosed acute myelitis in a male COVID-19 patient presenting with acute paraplegia with sensory impairment and sphincter dysfunction. The diagnosis was based on clinical findings, unfortunately lacking from either spine MRI or CSF analysis data. Another clinically similar case was observed in Ciudad Real, Spain,[11] however with normal spine neuroimaging and CSF features. In both cases, the significant overlap between neurological and systemic infectious symptoms, and the scarce response to treatment with steroids and immunoglobulins may point to a *para*-infectious process. Abdelhady et al[12] and Alketbi et al[13] reported on two male patients who developed flaccid tetraplegia soon after the beginning of COVID-19 symptoms. In both, spine MRI documented LETM featured by a major involvement of the grey matter, suggesting the occurrence of a direct viral damage. In fact, acute flaccid paraplegia can be determined by a number of neurotropic pathogens, namely Enterovirus, West Nile and other Flavivirus,[33,34] causing a direct viral damage of the spinal grey matter, that can be identified through neuroimaging, pathological and neurophysiological studies.[33] The lower motor neuron involvement from the early stage is documented by MRI evidence of lesions (frequently LETM) directly affecting the anterior horn cells, and by electrodiagnostic testing consistent with a motor neuronopathy.[33,34] This kind of anterior myelitis is often labeled as "polio-like viral related syndrome", since its similarity with the classical poliomyelitis. Patients typically develop acute, asymmetric flaccid limb paralysis with generally (but not necessarily) little sensory impairment;[33,34] the most severe forms could present respiratory muscle paralysis, due to the involvement of the lower brainstem through the motor nuclei of the vagus and glossopharyngeal nerves.[33,34]

Cases of post-infectious, isolated myelitis were reported by Authors from Tübingen, Germany,[14] and Sydney, Australia,[15] with remarkable improvement after steroid treatment, and by Authors from Sari, Iran,[16] with notable response to plasma-exchange. Zachariadis et al,[17] from Switzerland, described another case of suspect post-infectious myelitis, although without neuroimaging confirmation and with poorer outcome after treatment with steroids and immunoglobulins.

Besides the temporal relationship between infectious and neurological symptoms, a post-infectious etiology might be supported by the lymphomonocytic prevalence of CSF cells, the disseminated pattern of lesions, and the improvement after immunosuppressive treatment, that are consistent with an immune-mediated, inflammatory damage that should have been reasonably triggered by the previous infection.[30,32]

Notably, three of the reported myelopathies occurring soon after SARS-CoV-2 infection were found to be associated to EMG features compatible with the acute motor axonal neuropathy (AMAN) variant of GBS, highlighting the role of extensive neurophysiological assessments in depicting complex post-infectious neurological syndromes, features by coexisting central and peripheral nerve damage.[20–22]

Our personal experience about acute myelopathies in COVID-19 patients includes: a case of post-infectious multifocal myelitis in a 25 year-old woman, with prompt but incomplete clinical response after high dose intravenous steroids; a case of likely *para*-infectious encephalomyelitis with LETM in a 69 year-old man, with partial response after high dose intravenous steroids followed by intravenous immunoglobulins. Both patients showed no relapses in the mid term follow up (nearly 6 months).[58]

In general, mild to moderate CSF pleocytosis and hyperproteinorrachia were frequently observed, with at least partial resolution at repeated examinations.[7–22] Notwithstanding, a marked CSF pleocytosis has been frequently reported in acute LETM cases, and do not allow differentiating its etiology among inflammatory and infectious causes.[32] Viral RNA was never detected in the CSF samples. The absence of SARS-CoV-2 RNA in the CSF samples does not support a direct role of the virus in the pathogenic process. However, finding viral DNA in the CSF of myelitis patients coincident with virus-associated severe respiratory illness is a rare event.[35] Moreover, in a recent series of COVID-19 patients with CNS symptoms, PCR for SARS-CoV-2 RNA on CSF analysis resulted consistently negative.[36] The failed detection of SARS-CoV-2 RNA could depend on delayed timing of the CSF collection in relation to neuron invasion by the virus, the number of samples inadequate to detect transient viral presence in the CSF, or both.[37–38]

To support the hypothesized pathogenic link between SARS-CoV-2 infection and spinal cord damage, differential diagnoses should be thoroughly excluded, above all systemic and neurological autoimmune disorders (including multiple sclerosis, neuromyelitis optica spectrum disorder, and MOG-IgG encephalomyelitis) and concomitant infection by other neurotropic pathogens.

To date, whether para- and post-infectious myelitis after COVID-19 behave differently from other viral infections is still unknown. Post-infectious demyelination usually undergoes partial or complete resolution at follow up imaging.[39] However, new or persisting lesions have been reported in about 40% of early (<6 months) MRI follow-up of

Table 1
Clinical, laboratory and neuroimaging features in COVID-19 patients with acute myelopathies. *: F-U, follow-up; follow-up evaluation is reported for each symptom within brackets, according to the following coding: P, persisting without substantial improvement; I, improved without full recovery; R, resolved. Follow-up timing is reported in number of weeks after onset. ** the patient's neurological onset occurred 3 weeks after the occurrence of infectious COVID-19 symptoms in her family. # between infectious and neurological symptoms.

	Zanin et al.[7]	Zoghi et al.[8]	Sarma et al.[9]	Zhao et al.[10]	Aguila-Gordo et al.[11]	Abdelhady et al.[12]	Alketbi et al.[13]
Subject	54 y-o F	21 y-o M	28 y-o F	66 y-o M	50 y-o M	52 y-o M	32 y-o M
COVID-19 course	Severe	Moderate	Mild	Severe	Mild	Severe	Moderate
Neurologic onset / symptoms (F-U*, timing)		Sub-acute	Sub-acute	Acute	Sub-acute	Acute	Acute
- Motor d.	N.E.	Tetraplegia (I, 2)	Paraplegia	Flaccid paraplegia (P, 2)	Paraplegia (N.S.)	Flaccid tetraplegia	Flaccid tetraplegia (I, 1)
- Sensory d.	N.E.	Mid-thoracic level (I, 2)	Upper-dorsal level (P, 1)	Mid-thoracic level (N.S.)	Mid-thoracic level (I, N.S.)	N.S.	–
- Sphincter d.	N.E.	Bladder (N.S.)	Bladder	Both (N.S.)	Bladder (N.S.)	N.S.	Bladder (I, 1)
- Other	Seizure, coma (R, 4)	Vomiting (R, 2)	Vomiting	–	–	Exitus after 5 days	–
Latency / Overlap #	"Several days"/Yes	15 days/Yes	1 week/Yes	6 days/Yes	1 day/Yes	3 days/Yes	2 days/Yes
SARS-CoV-2 RT-PCR (in-hospital swab) - Timing after onset:	Positive	Negative	N.P.	Positive	Positive	Positive	Positive
- Infectious	"Several days"	14 days	–	5 days	4 days	3 days	2 days
- Neurological	Simultaneous	4 days	–	Simultaneous	3 days	Simultaneous	Simultaneous
Other COVID-19 supportive tests		IgG+	Previous swab+				
Brain imaging	MRI: Multiple white matter lesions	MRI: Corticospinal and splenial lesions	N.P.	CT: Normal	MRI: Normal	MRI: Normal	N.P.
Spine imaging –	MRI	MRI	MRI	N.P.	MRI	MRI	MRI
N of lesions	Multiple	Single	Single		Normal	Single	Single
-Axial pattern	N.S.	N.S.	N.S.	–	–	Ventral horn grey matter	Grey matter
-Longitudinal extension	Medulla, C2, C3-T6	Cervical LETM	LETM (medulla-conus)	–	–	Thoracic LETM	LETM (cervico-thoraco-lumbar)
-Enhancement	Absent	Absent	Absent	–	–	Absent	Absent
-Hemorrhage	Absent	Absent	Absent	–	–	Absent	Absent
-F-U (timing)	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
CSF findings				N.P.			N.P.
-Cells (n/mmc)	Normal	150 → 250 Ly (3 d)	125 Ly	–	Normal	"Lymphocytosis"	–
-Protein (mg/dl)	Normal	281 → 111 (3 d)	Normal	–	Normal	"Hyperproteinorrachia"	–
-Glucose (mg/dl)	Normal	34	Normal	–	–	–	–
-OCBs	–	Absent	–	–	–	–	–
-SARS-CoV-2 RT-PCR	Negative	Negative	N.P.	–	Negative	Negative	–
Diagnosis	Acute demyelinating encephalomyelitis	Acute demyelinating encephalomyelitis	Acute myelitis	Acute myelitis	Acute myelitis	Acute flaccid myelitis	Acute myelitis
Treatment (dose, duration)							
-Steroids	DEX (20 mg then 10 mg od, each 10 days)	–	M−P (N.S.)	DEX (10 mg od, 10 days)	DEX (N.S.)	+ (N.S.)	M−P (1 g od, 5 days)
-IVIg	–	–	–	IVIg (15 g od, 7 days)	+ (N.S.)	–	–
-P-E	–	5 sessions	2 sessions	–	–	–	–
-Rituximab	–	–	–	–	–	–	–
-Antimicrobials	Antiretroviral (N.S.)	Vancomycin, meropenem, acyclovir (N.S.)	–	Ganciclovir (0.5 g od, 14 days), lopinavir/ritonavir (5 days), moxifloxacin (400 mg od, 6 days), meropenem (1 g bid, 8 days)	Lopinavir/ritonavir (N.S.)	Acyclovir (N.S.)	Acyclovir 750 mg tid (N.S.)
- Other	HCQ (N.S.)	–	–	–	HCQ (N.S.)	–	Enoxaparin 40 mg od

	Munz et al.[14]	Chow et al.[15]	Baghbanian et al.[16]	Zachariadis et al.[17]	Kaur et al.[18]	Sotoca et al.[19]	Maideniuc et al.[20]	Masuccio et al.[21]	Valiuddin et al.[22]

(*continued on next page*)

Table 1 (*continued*)

	Munz et al.[14]	Chow et al.[15]	Baghbanian et al.[16]	Zachariadis et al.[17]	Kaur et al.[18]	Sotoca et al.[19]	Maideniuc et al.[20]	Masuccio et al.[21]	Valiuddin et al.[22]
Subject	60 y-o M	60 y-o M	53 y-o F	63 y-o M	3 y-o F	69 y-o F	61 y-o F	70 y-o F	61 y-o F
COVID-19 course	Moderate	Moderate	Moderate	Moderate	Asymptomatic	Mild	Mild	Mild	Mild
Neurologic onset / symptoms (F-U*, timing)	Acute	Sub-acute	Acute	Sub-acute	Acute	Sub-acute	Sub-acute	Sub-acute	Sub-acute
- Motor d.	Lower limbs (I, 2)	Lower limbs (R, 1)	Distal lower limbs (I, N.S.)	Lower limbs (I, 4)	Four limbs (P, N.S.)	Bilateral hand and lower limbs (I, 4)	Lower limbs (I, 4)	Lower limbs (P, 2)	Lower limbs (P, 4)
- Sensory d.	Mid-thoracic level (I, 2)	Lower limbs (R, 1)	Mid-thoracic level (N.S.)	Mid-thoracic level (P, 4)	–	Bilateral hand and lower limbs (I, 4)	Lower limbs (I, 4)	Four limbs (P, 2)	Mid thoracic level (I, 4)
- Sphincter d.	Bladder (R, 2)	Both (R, 1)	Bladder (R, 1)	Both (P, 4)	–	Both (P)	Both (N.S.)	–	Both (P, 4)
- Other	–	–	–	–	Respiratory failure	–	–	–	–
Latency / Overlap #	> 1 week /No	16 days /No	2 weeks /No	12 days /No	Unidentifiable **	8 days /No	5 days /No	5 days /No	3 days /No
SARS-CoV-2 RT-PCR (in-hospital swab) - Timing after onset:	Negative	Negative	N.P.	Negative	Positive	Positive	Positive	Negative	Positive
- Infectious	>1 week	18 days	–	16 days	–	>1 week	8 days	25 days	7 days
- Neurological	Simultaneous	2 days	–	4 days	Simultaneous	Simultaneous	3 days	10 days	4 days
Other COVID-19 supportive tests	Previous swab+	IgG+>IgA+>IgM+ Previous swab+	Previous swab+	IgM+ IgG +				IgG+	
Brain imaging	MRI: Normal	MRI: Normal	MRI: Normal	MRI: Normal	MRI: Normal	MRI: Normal	MRI: Normal	MRI: Normal	N.P.
Spine imaging –N of lesions	MRI: Multiple	MRI: Single	MRI: Single	MRI: Normal findings	MRI: Single	MRI: Single	MRI: Single	MRI: Single	MRI: Single
-Axial pattern	Transverse	Centromedullary	N.S.	–	Transverse	–	Centromedullary	Posterior columns	Centromedullary
-Longitudinal extension	T3; T9	LETM: T7-T10	LETM: T8-T10	–	LETM: medulla-T7	LETM: medulla-C7	LETM: C1-C7	C7-T1	LETM: C1-C7
-Enhancement	Absent	Absent	N.S.	–	Absent	Patchy	Patchy	Absent	Absent
-Hemorrhage	Absent	Absent	N.S.	–	Patchy (F-U, 5 d)	Absent	Absent	Absent	Absent
-F-U (timing)	Persisting (6 d)	Resolved (10 d)	N.P.	–	Worsened (5 d)	Worsened (7 d)	–	Persisting (5 d)	N.P.
CSF findings									
-Cells (n/mmc)	16 →3 Ly (12 d)	Normal	13 Ly	16 →36 Ly (6 d)	282 RBC, 40N	75 Ly	312 RBC, 3 WBC	Normal	Normal
-Protein (mg/dl)	79.3→73.4 (12 d)	79	Normal	57.3→60 (6 d)	58	283	87	Normal	87→153 (9 d)
-Glucose (mg/dl)	–	Normal	Normal	Normal	–	Normal	73	–	Normal
-OCBs	Absent	–	Absent	Absent	–	Absent	Absent	Mirror pattern	Absent
-SARS-CoV-2 RT-PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	N.P.	Negative
Diagnosis	Post-infectious acute myelitis	Post-infectious acute myelitis	Post-infectious acute myelitis	Post-infectious acute myelitis	Post (?) infectious acute myelitis	Acute necrotizing myelitis	Post-infectious myelitis / AMAN	Post-infectious myelitis / AMAN	Acute myelitis / AMAN
Treatment (dose, duration)									
-Steroids	M–P (100 mg OD, N.S.)	M–P (1 g OD, 3 days)	–	N.S. (N.S., 5 days)	M–P (30 mg/kg, 5 days)	M–P (1 g OD, 5 days, 2 sessions)	M–P (1 g OD, 5 days)	–	M–P 1 g OD for 5 days
-IVIg	–	–	–	(0.4 g/kg, 5 days)	(0.4 g/kg, 5 days)	–	–	+ (N.S.)	–
-P-E	–	–	+ (N.S.)	–	7 sessions	+ (N.S.)	5 sessions	+ (N.S.)	5 sessions
-Rituximab	–	–	–	–	375 mg/m^2	–	–	–	–
-Antimicrobials	–	–	–	–	–	–	–	–	–

Abbreviations: y-o, year-old; F, female; M, male; CNS, central nervous system; Ly, lymphocytes; CSF, cerebrospinal fluid; OCBs, oligoclonal bands; LETM, longitudinal elongated transverse myelitis; N.P., not performed; OD, omne in die; bid, bis in die; M–P, methylprednisolone; P-E, plasma exchange; DEX, dexamethasone; HCQ, hydroxychloroquine; IVIg, intravenous immunoglobulins.

asymptomatic adults with clinically monophasic ADEM.[40] The temporally limited follow-ups that are currently available for the reported COVID-19 associated cases do not allow ruling out neither relapses nor multiphasic course of these neurological syndromes; [30,31,41] prolonging observation will enable a better description of prognosis.

4. Pathophysiology

The exact pathogenesis of COVID-19-related neurological damage is still largely unknown, and many mechanisms might be involved, including direct viral and immune-mediated pathogenicity.[23] The failed detection of the viral RNA in CSF in the majority of tested patients with proven COVID-19 and neurological manifestations does not provide evidence supporting a direct viral invasion.[42,43] On the other hand, the constant finding of CSF markers of inflammation, namely elevated protein levels and/or pleocytosis, supports the occurrence of immune-mediated inflammatory mechanisms.[23,42,43]

The systemic immune dysregulation induced by SARS-CoV-2 infection is likely crucial in determining neurological damage. Typically, as for other neurotropic pathogens, immune-mediated manifestations occur after the acute phase of the infection.[42,43] However, reviewing the details of the clinical course of the encephalomyelitis, myelitis and polyradiculitis cases, most patients experienced neurological symptoms in strict temporal relationship with COVID-19 symptoms, often with overlap, pointing to para- rather than post-infectious syndromes.[43]

GBS is due to an autoimmune reaction that is generally triggered by a viral or bacterial infection in genetically predisposed patients. In response to the antigen, the activation of immune system could result in damaging nerve roots and peripheral nerves because of "molecular mimicry" (the structural similarity between foreign antigen to self-peptides expressed by axons and myelin is thought to lead to a cross-activation of autoreactive lymphocytes).[6] An interesting hypothesis is offered by the presence of sialic acid both in respiratory cell surface glycoproteins (which are known to be involved in the attachment and entry of coronaviruses) and peripheral nerve gangliosides (which are known to be crucial in GBS pathogenesis).[26] In addition, SARS-CoV-2 shares aminoacidic sequences of proven immunologic potential with the human heat shock proteins (HSPs) 90 and 60, which are known to be associated with GBS and other autoimmune diseases.[44] The possibility of a direct nerve invasion by the virus is not supported if considering the absence of the ACE2 receptor,[45] that has been defined as the crucial docking receptor for the virus, in the peripheral nerve. However, cranial polyradiculoneuritis affecting oculomotor, trigeminal, and facial nerve roots could lead to hypothesize also a retrograde axonal transport of the virus through trigeminal nociceptive neuronal receptors in the nasal cavity.[26,45]

Modeling on other coronaviruses' behavior, SARS-CoV-2 probably gains access to the CNS through a direct neuron invasion, via hematic or transolfactory retrograde neuronal route, by linking to the ACE2 receptors in the brain vessels and neurons.[23,45] Other docking receptors (basigin and neuropilin-1) and many proteases have been proposed to facilitate viral cell entry and replication through the blood brain barrier.[42] In this view, another potential entrance to the CNS could be represented by fenestrations of the BBB, particularly common in the hypothalamic region, especially in neurovascular inflammation.[42,46] The hypothalamus plays a pivotal role in systemic immune regulation: the hypothalamic-pituitary-adrenocortical axis is known to be activated by the pro-inflammatory cytokines IL-6, IL-1beta, TNF-alfa that have been found circulating in high titers in severe COVID-19 cases.[42,43,46] The cytokine storm thus contributes to blood brain barrier disruption, CNS invasion,[23,47–50] activation and chemotactic migration of innate and adaptive immune cells resulting in tissue damage.[23,47–50] Increased cytokine levels have been found in the CSF of patients with CNS disorders due to direct viral invasion, such as meningitis and encephalitis.[51] In fact, cytokine and inflammatory cells, namely macrophages and neutrophils, are designated responsible for *para*-infectious CNS immune mediated injury including demyelination.[50,52,53] As abovementioned for the peripheral nervous system, also concerning CNS the molecular mimicry between SARS-CoV-2 and hsp60 has been shown to be recognized by lympho-monocytes of patients affected by demyelinating disease of the CNS.[54] Moreover, viruses can enter the CNS carried by infected immune cells (a phenomenon that has been named "Trojan horse mechanism"), which can also serve as reservoir.[42,55] Indeed, neuropathology studies has produced evidence of demyelination, macrophage infiltration, myelin loss, perivascular "acute disseminated encephalomyelitis-like" appearance in patients with neurological symptoms pointing to CNS involvement.[56]

To date, GBS cases have been invariably treated with intravenous immunoglobulins, in many cases showing poor prognosis.[6] The opportunity to proceed to plasma exchange has been hindered by COVID-19 related clinical and management obstacles.[6] Preliminary evidence have been recently proposed about the role of chloroquine, an antimalarial drug which has been widely but empirically administered and is currently under proper investigations for treating COVID-19. In fact, chloroquine binds with high-affinity sialic acids and GM1 gangliosides, preventing their binding with viral spike that is required for cell infection. These findings could inspire future studies to assess safety and effectiveness of chloroquine in conjunction with intravenous immunoglobulins in COVID-19 related GBS cases.[26,57]

As for myelitis cases, pharmacological immunosuppression was usually associated with improvement of clinical, CSF and neuroimaging features, suggesting immune-mediated mechanisms especially for post-infectious conditions. Though, Kaur et al described an aggressive variant of LETM, extending from the medulla to the midthoracic cord, in a 3 year-old Navajo girl whose nasopharyngeal swab tested positive for SARS-CoV-2 although without reporting any specific infectious symptoms.[18] In that case, despite prompt treatment with high dose intravenous steroids and immunoglobulins, further worsening of clinical conditions and neuroimaging was documented. Subsequent repeated treatment with plasma-exchange and finally rituximab produced a mild improvement.

According to the described reports, adding antimicrobial drugs to immunosuppressive treatments might be beneficial in parainfectious neurological syndromes. In fact, Sotoca et al reported of an acute myelitis in a 69 year-old COVID-19+ woman, who during isolated steroid treatment deteriorated with enlargement and central necrosis of the spinal lesion.[19] However, the use of broad spectrum antibiotics and antivirals to date can only be considered as empirical, in the absence of SARS-CoV-2-specific drugs.

5. Conclusions

Acute paralytic disease occurring in association with COVID-19 can be due to peripheral nerve or spinal cord damage. The incidence can have been underestimated due to disease-related clinical and technical limitations.

According to the limited literature available to date, while post-infectious neurological damage is probably essentially immune-mediated, *para*-infectious neurological syndromes in COVID-19 patients are likely due to a combination of multiple mechanisms, including direct viral pathogenicity but preeminently immune-mediated inflammatory damage, potentially occurring nearly in the same phase of disease.[23,42,43] It is of utmost importance to acknowledge that the temporal relationship between COVID-19 and acute paralytic disease, although suggestive especially after ruling out differential diagnoses, is not sufficient to prove causation and further data are warranted.

To this effect, while ameliorating strategies to limit contagion, further investigations should focus on a thorough characterization of patients by means of complete description of CSF, neurophysiological and neuroimaging features, in order to produce reliable findings and rule out confounders.[43] As it has been already proposed, blood and

CSF samples should be collected longitudinally to study inflammatory biomarkers and the identification of subgroups of patients that may be prone to develop neurological syndromes.[43] Moreover, collecting other biological samples potentially containing detectable SARS-CoV-2 traces, such as nasopharyngeal aspiration and stool, could provide help for understanding whether certain viral strains behave as more neurotropic or immunogenic. A better understanding of the contribution of the systemic immune response and the hypothalamic-pituitary-adrenocortical axis to the pathogenesis of the disease is advocated to identify novel pharmacological approach and lay the groundwork for future clinical trials.[42,43]

CRediT authorship contribution statement

Isabella Canavero: Conceptualization, Data curation, Formal analysis, Validation, Writing - original draft. **Sabrina Ravaglia:** Conceptualization, Data curation, Formal analysis, Validation, Writing - review & editing. **Francesca Valentino:** Conceptualization, Data curation, Formal analysis, Validation, Writing - review & editing. **Giuseppe Micieli:** Conceptualization, Data curation, Formal analysis, Supervision, Validation, Writing - review & editing.

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