Neurological manifestations of coronavirus disease 2019: exploring past to understand present

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Abstract

SARS-CoV-2 infection, resulting in Coronavirus disease 2019 (COVID-19), has significantly affected the entire world. It was labelled a pandemic by World Health Organization. Although it commonly produces respiratory symptoms, neurological features have been described. Neurological manifestations may vary from non-specific symptoms such as headache, dizziness, myalgia and/or fatigue, olfactory or taste dysfunction to specific syndromes including meningitis, stroke, acute transverse myelitis and Guillain-Barre syndrome. This review describes potential pathogenetic mechanisms and neurological manifestations of COVID-19 along with its management. Considering structural and pathogenetic similarity of SARS-CoV-2 with SARS-CoV and MERS viruses, we compared their neurological manifestations and mentioned few features expected in COVID-19 in future. Interestingly, many COVID-19 cases may present with pure neurological manifestations at onset with non-neurological features manifesting few days later and we propose the term "Neuro-COVID syndrome" for such cases. Awareness of neurological manifestations may facilitate its management and improve outcome in such patients.

Keywords Coronavirus · COVID-19 · Neuro-COVID syndrome · neuroinvasion · neurological manifestations · SARS-CoV-2

Abbreviations

ACE2	Angiotensin-converting enzyme 2 receptor
ADEM	Acute disseminated encephalomyelitis
ATM	Acute transverse myelitis
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CoVs	Coronaviruses
CSF	Cerebrospinal fluid
CVST	Cortical venous sinus thrombosis
EEG	Electroencephalography
GBS	Guillain–Barre syndrome
IVIG	Intravenous immunoglobulin
MERS-CoV	Middle East respiratory syndrome coronavirus
MS	Multiple sclerosis
NCS	Nerve conduction study
PRES	Posterior reversible encephalopathy syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2

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Introduction

An outbreak of atypical pneumonia caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was initially reported in December 2019 from Wuhan in China [1]. The resulting disease is now termed as coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a novel beta coronavirus which shares structural and genetic homology to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but is relatively more contagious with a longer incubation period, shorter serial interval, and lower case fatality rate. Its high person-to-person transmissibility resulted in a rapid rise in number of cases, and on March 11, 2020, WHO declared COVID-19 a pandemic with serious health concerns [2]. Owing to a high proportion of cases being asymptomatic or mildly symptomatic, the complete denominator remains unknown. While literature is replete with pulmonary

manifestations of COVID-19, its neurological complications are being increasingly recognized. This review discusses the current state of knowledge about neuropathogenesis and neurological manifestations in COVID-19 along with its management and compares it to SARS-CoV and MERS outbreaks, to obtain further insight into its neuropathogenesis and additional neurological manifestations expected.

Methods

We searched PubMed database from April 1, 2020, to November 15, 2020, for articles published in English from October 1990 to November 15, 2020, along with references from the relevant articles. The search terms used included "Coronavirus," "SARS," "MERS," "COVID-19," "SARS-CoV-2," "SARS-CoV" alone or in combination with "neurology," "neuroinvasion," "meningoencephalitis," "encephalopathy," "stroke," "multiple sclerosis," "acute disseminated encephalomyelitis (ADEM)," "polyneuropathy," "Guillain–Barre syndrome (GBS)," "neuromuscular disorder," and "myopathy."

Pathogenesis

SARS-CoV-2 is an enveloped, non-segmented, single-stranded RNA virus of betacoronaviridae family. While commonly reported human CoV infections cause self-limiting flu-like symptoms, SARS-CoV and MERS-CoV globally infected nearly 10,500 people in past two decades, with case fatality rate of approximately 10% and 36%, respectively [1]. CoVs possess a genomic RNA of 29.9 kilobase pairs in a nucleocapsid core and a phospholipid bilayer with embedded virulent surface proteins including spike (S), hemagglutinin-esterase (HE), membrane (M), and envelope (E) proteins.

The dynamics of SARS-CoV-2 are currently unknown, but a non-human origin like SARS and MERS has been speculated. Various epidemiological studies propose bats its natural zoonotic reservoir. However, intermediate hosts of SARS-CoV-2, fuelling spill-over to humans, remains unknown, with pangolins, livestock, and zoonotic or aquarian animals being the suspected ones [3–5]. Animal-to-human and human-to-human transmission are potential sources of COVID-19 spread with respiratory droplets from coughing and sneezing being the most common mode. The Centers for Disease Control and Prevention, China, suggested an incubation period of 3 to 7 days, with a maximum up to 2 weeks [2].

The SARS-CoV-2, similar to SARS-CoV, uses angiotensin-converting enzyme 2 (ACE2) receptor to enter host cells, although with twenty times higher affinity. ACE2 receptor is ubiquitously expressed and has been detected in adipose tissue, heart, brain, lung, vascular endothelium, liver, and naso-oral mucosa,

thereby making these organs vulnerable [3]. In brain, ACE2 are expressed in neurons, astrocytes, and oligodendrocytes with high concentration found in the motor cortex, posterior cingulate cortex, middle temporal gyrus, sympathetic pathways in brainstem, substantia nigra, ventricles, circumventricular organs, thalamus, and olfactory bulb (Fig. 1) [3, 4]. SARS-CoV-2 uses S1 subunit of spike protein to attach to host's ACE2 receptors and S2 subunit for fusion followed by endocytosis. Once inside the cell, uncoated RNA translates various proteins via sub-genomic RNA, followed by assembly of viral particle buds and release from host cells [3, 4].

In addition to direct cellular invasion, indirect mechanisms like inflammatory response and cytokine storm also contribute to the pathogenesis of SARS-CoV-2. Although both cell-mediated and humoral immunity are essential to contain CoV infections, uncontrolled immune response may often be harmful [3]. SARS-CoV-2 activates both innate and cellular immunities resulting into "cytokine storm" with various pathological effects including increased levels of inflammatory cytokines; activation of T lymphocytes, macrophages, and endothelial cells; and stimulation of complement and coagulation cascade leading to disseminated intravascular coagulation and later multiorgan dysfunction syndrome (MODS) [5].

Detection of neuropathological findings in brain tissue of CoV-infected patients favors their neurotropic and neuroinvasive nature [6, 7]. Several theories have been postulated for the virus entry into nervous system, such as direct entry of the virus through ACE2 receptor, hematogenous spread, and transneuronal spread (Fig. 1). It may infect vascular endothelium and cross blood–brain barrier (BBB) or infect leukocytes that pass through BBB to reach brain tissue, with the latter known as the "Trojan horse mechanism" [4]. Transneuronal spread of virus may occur through transcribrial path from olfactory receptor neurons via olfactory nerve and olfactory bulb to reach hippocampus and nearby brain regions, as shown in animal studies [4, 6]. This hypothesis is supported by orbitofrontal hypometabolism in 18fluoro-2-deoxy-d-glucose (18FDG) positron emission tomography computed tomography (PET-CT) brain scan in a COVID-19-positive patient [8]. Once inside the brain, CoVs could affect brain tissue either by directly damaging the neurons after entering through ACE2 receptors or due to misdirected host immune response in susceptible individuals [3, 4]. Additionally, involvement of other essential organs by SARS-CoV-2 may affect the nervous system indirectly due to resulting hypoxia, blood pressure fluctuations, metabolic and electrolyte imbalances (Fig. 2) [4].

Clinical features

While non-neurological manifestations of COVID-19 illness including fever (77–89%), cough (61–81%), shortness of
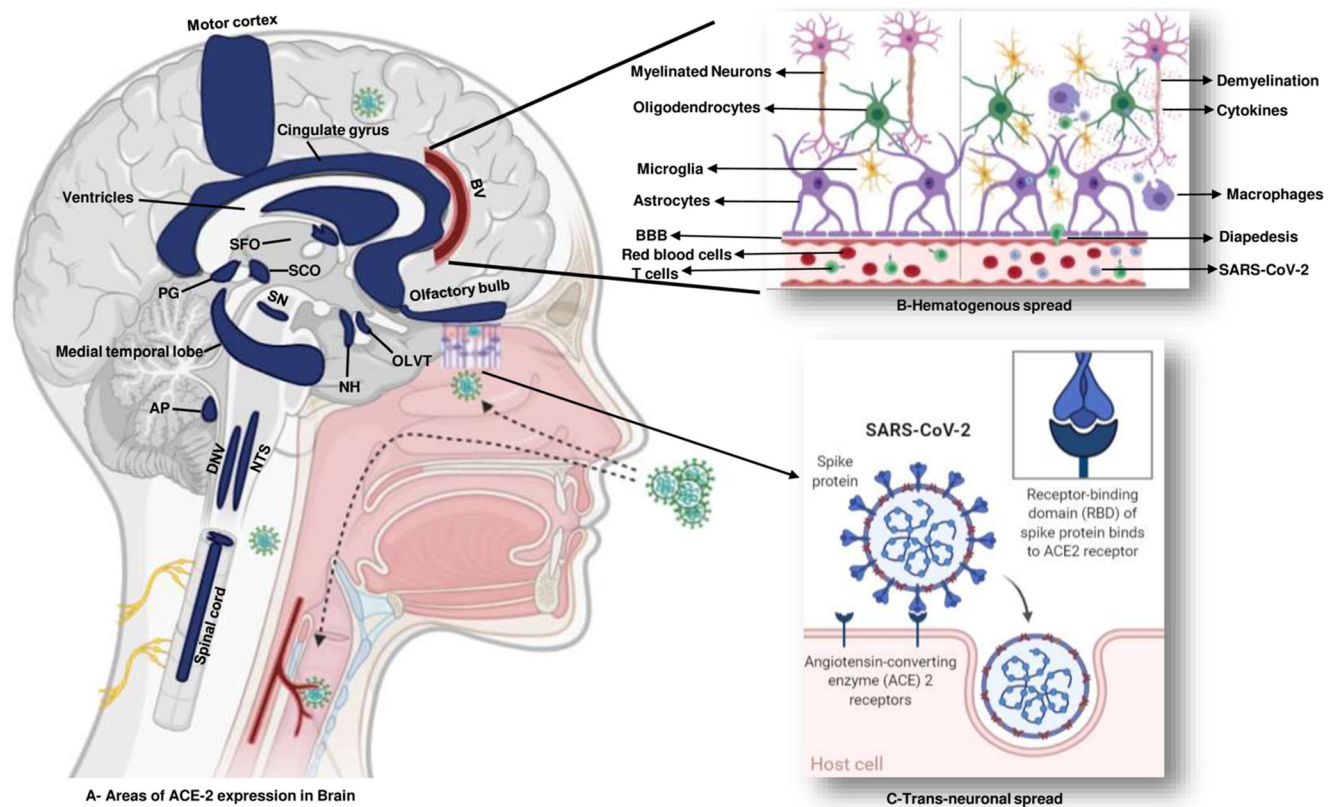
Fig. 1 Schematic diagram depicting high ACE-2-containing brain regions with mechanisms of neuroinvasion by SARS-CoV-2. **a** Brain regions with high ACE-2 expression. **b** Hematogenous spread through blood brain barrier. **c** Transcribial path from olfactory receptor to brain, followed by activation of inflammation. AP area postrema, BV blood vessels, DNV dorsal motor nucleus of vagus, NH neurohypophysis, NTS nucleus tractus solitarius, OLVT organum vasculosum of the lamina terminalis, PG pineal gland, SCO subcommissural organ, SFO subfornical organ, SN substantia nigra

breath (3–26%), sore throat (10%), and gastrointestinal symptoms (5–9%) are commonly reported, more than one third hospitalized COVID-19 cases may have neurological manifestations [1, 9–11]. Neurological features, including myalgia and/or fatigue, dizziness, headache, anosmia, ageusia, and altered mental status, are relatively common in severe disease, elderly population, and in patients with preexisting comorbidities [4, 11, 12]. They may appear due to central and/or peripheral nervous system involvement, either early or later in the course of COVID-19 illness.

CNS involvement

Manifestations of central nervous system (CNS) involvement are reported in up to 25% of COVID-19 cases [11]. While common non-specific symptoms include dizziness, headache, and altered mentation, several CNS syndromes including meningoencephalitis, cerebrovascular events, seizures, and CNS neuro-immunological disorders have also been reported (Table 1).

Dizziness Dizziness is a non-specific symptom encountered in several neurological and non-neurological disorders [5]. It is

the most common neurological feature described in COVID-19, involving up to 17% cases, especially those in ICU due to severe illness [11, 24].

Headache Although most series describe headache in 6–13% of COVID-19 cases [1, 10, 11, 51, 61], it was reported in 82% cases in a French study [62]. Its pathophysiology and character may differ according to phase of COVID-19 illness. While acute headache related to flu-like illness, migraine, and tension-type headache predominate in initial days of illness, headache resulting from hypoxia and systemic inflammation due to cytokine storm may occur later in the course [61]. Headache may also be a sentinel sign in COVID-19-related meningitis and venous sinus thrombosis [24]. A recent cross-sectional study of 130 hospitalized COVID-19 patients revealed that headache was bilateral, of severe intensity with frontal predominance and oppressive quality among three-fourth patients. In 62% patients, headache occurred within 24 h of illness. Nearly all (94%) cases fulfilled ICHD-3 criteria for headache attributed to systemic viral infection. While migrainous phenotype was reported in one-fourth cases, nearly half the cases had tension-type headache [63]. Interestingly, presence of headache in patients with COVID-19 pneumonia
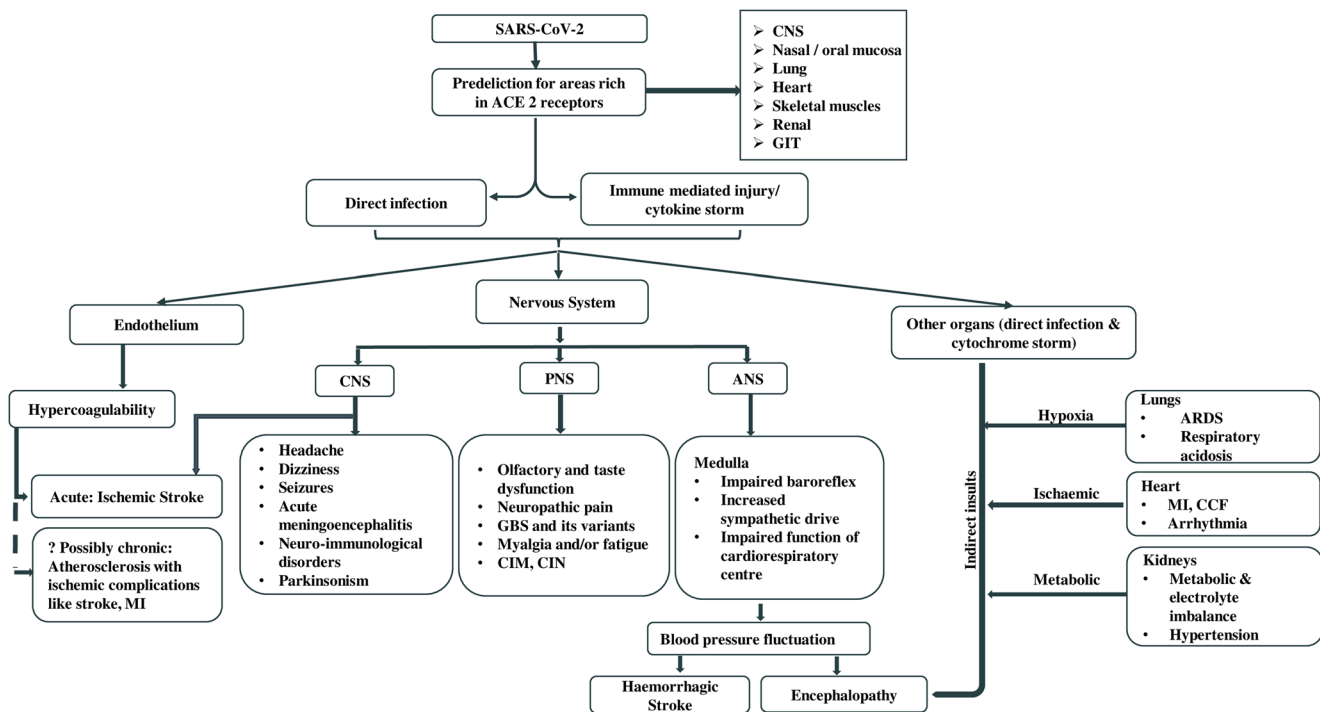
Fig. 2 Possible pathophysiological effects and resulting neurological manifestations of SARS-CoV-2. **S**ARS-CoV-2 can invade and damage susceptible organs expressing ACE2 receptors either by direct infection or immune-mediated mechanism via cytokine storm, leading to manifestations resulting from central, peripheral, and autonomic nervous system involvement. ACE2 angiotensin-converting enzyme 2, ANS autonomic nervous system, ARDS acute respiratory distress syndrome, CCF congestive cardiac failure, CIM critical illness myopathy, CIN critical illness neuropathy, CNS central nervous system, GBS Guillain–Barre syndrome, GIT gastrointestinal tract, MI myocardial infarction, PNS peripheral nervous system

has been associated with a shorter course of non-neurological systemic illness, but disabling headache often persisted [64].

Altered mentation Impairment in the level or content of consciousness may involve up to 9% of hospitalized COVID-19 patients, especially severe cases [11, 21]. Agitation and confusion affect more than two-third cases admitted in ICU and nearly one-third patients can manifest executive dysfunction after discharge [53]. MRI brain in 13 cases with undiagnosed encephalopathy revealed leptomeningeal enhancement in eight (62%), ischemic stroke in three (23%) cases, while bilateral fronto-temporal hypoperfusion in eleven (84%) cases [53]. Various factors contributing to altered mentation in COVID-19 include toxic-metabolic encephalopathy resulting from cytokine storm with systemic hyperinflammation, cerebrovascular events, seizures, para- or postinfectious immune-mediated CNS syndromes and a possible CNS infection by SARS-CoV-2 [11]. In addition, new-onset immune-mediated psychotic symptoms have also been described in COVID-19 cases [65].

Meningitis or meningoencephalitis In 33 meningoencephalitis cases reported in association with SARS-CoV-2 infection, varied manifestations have been described including delirium/altered sensorium (71%), aphasia/dysarthria (53%), headache (34%), seizures/status epilepticus (34%), focal neurological deficits (18%), and myoclonus (9%) with a single patient having parkinsonian syndrome (3%) [18, 21, 49, 62, 66].

Three case reports described more fulminant course of COVID-19-associated encephalitis in patients of acute hemorrhagic necrotizing encephalopathy and rhombencephalitis [18, 20, 21]. Meningeal signs (including nuchal rigidity, Kerning, and Brudzinski signs) along with extensor plantar response were present among all. Commonly reported viral and bacterial screening was negative. While only a single case showed presence of SARS-CoV-2 in cerebrospinal fluid (CSF) [18], three cases had increased anti-S1 IgM antibodies with markedly elevated inflammatory markers in CSF [62], thereby suggesting a role of para-/postinfectious autoimmune response. All cases made good recovery with antiviral with or without immunosuppressants (high-dose methylprednisolone, intravenous immunoglobulins, plasmapheresis).

Cerebrovascular events Ischemic and hemorrhagic arterial stroke, cortical venous sinus thrombosis (CVST), as well as intracranial vasculitis-induced microvascular occlusive disorder have been reported in COVID-19 cases, with ischemic stroke being most common. Of 214 COVID-19 cases in a series, six (2.8%) developed stroke including five ischemic and one hemorrhagic stroke [11]. Another series

Table 1 Neurological features in COVID-19 reported to date, SARS and MERS illnesses. Expected neurological manifestations of COVID-19 are in italics

Neurological features	SARS-CoV	MERS	SARS-CoV2
A. Central nervous system			
1. Infective	• Acute encephalitis [13, 14]	• Acute encephalitis [1] • Bickerstaff encephalitis with GBS [15]	• Acute necrotizing hemorrhagic encephalitis [16, 17] • Viral encephalitis [18–20] • Meningoencephalitis [21] • Rhombencephalitis [22]
2. Vascular	• Ischemic stroke [23]	• Ischemic stroke[1]	• Ischemic stroke with large vessel occlusion [11, 24] • Intracerebral hemorrhage, subarachnoid hemorrhage [25, 26] • CVST [27–29] • PRES [30–33] • Microvascular occlusive disorder [34]
3. Immunological	• ADEM [35] • MS like illness [35–38]	• ADEM[15]	• Post infectious ADEM [38, 39] • Acute transverse myelitis [40–43] • Anti-NMDA encephalitis [44] • Generalized and diaphragmatic myoclonus [45, 46] • Opsoclonus and ocular flutter [47]
4. Extrapyramidal features	• Parkinsonism [48]		• Parkinsonism [49, 50]
5. Miscellaneous (including non-specific features)	• Alzheimer's like dementia [48] • Schizophrenia like illness [48]		• Headache, confusion, dizziness, seizures [1, 5, 10, 11, 24, 51–54] • *Alzheimer and schizophrenia like illness expected in future*
B. Peripheral nervous system			
1. Neuropathy	• CIN [1]	• GBS [15] • CIN [15] • Sensory neuropathy [15]	• Olfactory and taste dysfunction [1, 11, 52, 55–57] • GBS [58] • MFS and polyneuritis cranialis [58] • Facial diplegia [58] • *Sensory neuropathy* • CIN [59]
2. Neuromuscular junction			• Myasthenia gravis [60]
3. Myopathy	• CIM [1]		• Myositis/myalgia [1, 10, 11, 52] • Rhabdomyolysis [1] • CIM [59]

ADEM acute disseminated meningoencephalitis, *CIM* critical illness myopathy, *CIN* critical illness neuropathy, *COVID-19* coronavirus disease 2019, *CVST* cerebral venous sinus thrombosis, *GBS* Guillain–Barre syndrome, *MERS-CoV* Middle East respiratory syndrome coronavirus, *MFS* Miller–Fisher syndrome, *MS* multiple sclerosis, *NMDA* N-methyl-D-aspartate, *PRES* posterior reversible encephalopathy syndrome, *SARS-CoV* severe acute respiratory syndrome coronavirus

of 221 hospitalized COVID-19 cases reported 13 (5.8%) stroke cases including 11 (5%) ischemic and one (0.5%) case each of hemorrhagic stroke and CVST. Stroke commonly affects elderly patients with severe COVID-19 illness along with vascular risk factors including hypertension, diabetes, and prior stroke [11, 24]. Although ischemic stroke usually appears later in the course of COVID-19 illness with a mean duration being 12 days, early occurrence has also been reported. COVID-19-related ischemic stroke often result from large vessel occlusion and may be mutiterritorial [24, 67, 68]. Several cases of COVID-19-associated CVST have been reported. They likely present in the second week of infection with no sex predilection, with headache being the most common symptom followed by focal neurological deficit. Neuroimaging shows non-arterial infarct or hemorrhage [28, 29, 69].

Increased risk of arterial ischemic stroke or CVST in SARS-CoV-2 infection suggests a pro-coagulant state, which may result from either blood flow stasis, especially in critically ill and immobilized patients or due to hypercoagulability and direct endothelial damage via ACE-2 receptors [68]. A highly elevated C-reactive protein (CRP) and D-dimer in COVID-19 patients suggest hyperinflammation and hypercoagulable state, respectively [24]. This in turn stimulates endothelial and mononuclear cells and facilitates tissue factor expression leading to excess free thrombin generation, which results in platelet activation and thrombosis [70]. Thrombocytopenia along with raised CRP and D-dimer in COVID-19-associated stroke cases suggest possibility of underlying virus-associated microangiopathy [71]. Significantly, elevated D-dimer and fibrin degradation product (FDP) along with prolonged PT and APTT on admission suggest poor survival in COVID-19 pneumonia [70]. Elevated antiphospholipid antibodies reported in COVID-19-related ischemic stroke lacks significance due to transient elevation seen in several infections and critically ill patients [67, 72].

ACE2 receptors in circumventricular organ and endothelial cells are essential in modulating cerebral autoregulation, cerebral blood flow, and central autonomic activity. Neuroinvasion of SARS-CoV-2 at these locations may disrupt cerebral autoregulation leading to blood pressure fluctuations resulting in intracerebral and/or subarachnoid hemorrhage reported in COVID-19 cases. Additionally, hyperinflammatory state resulting from cytokine storm along with sympathetic over activity may lead to aneurysm formation and/or trigger its rupture [25, 26].

Extensive intracranial vasculitis resulting in local microthrombosis and micro-hemorrhages has recently been reported in a 68-year-old male patient suffering from SARS-CoV-2, who had persistent impaired sensorium after sedation stoppage. Brain MRI showed multiple areas of restricted diffusion along with scattered hypointensities in SWI sequence. CSF was positive for SARS-CoV-2 RNA. This might have resulted from a systemic pro-coagulant state along with local and systemic inflammation–related endothelium damage and eventual immune-mediated vascular injury [34].

Cerebral autoregulation dysfunction has been implicated in the development of posterior reversible encephalopathy syndrome (PRES), reported in nine COVID19 cases to date, all aged above 60 except a young male of 38. Two-third patients had preexisting hypertension and diabetes. Six patients presented with acute respiratory distress syndrome followed by acute kidney injury (AKI) with rapid elevation of blood pressure preceding PRES. Persistent confusion, lethargy, focal neurological deficits, and seizures despite improvement in other non-neurological parameters helped diagnose PRES. All patients improved with symptomatic management of seizure along with strict control of blood pressure [30–33, 73].

Seizures Seizures and/or status epilepticus (convulsive or non-convulsive) appears likely as SARS-CoV-2 may involve CNS either directly or indirectly related to hypoxia, metabolic and electrolyte imbalances [4]. Few reports describe clinical or electrophysiological evidence of new onset seizures or new-onset refractory status epilepticus (NORSE) in COVID-19 patients [18, 54, 74], but larger studies failed to detect additional risk of acute symptomatic seizures [11, 53]. Breakthrough seizures are commonly reported in epileptic patients developing COVID-19 [4]. Reduced seizure threshold in COVID-19 patients may appear even in absence of overt inflammatory features, resulting in new-onset seizure or status epilepticus or reappearance of well-controlled seizures [30–33, 73, 75].

Generalized, both positive and negative, myoclonus primarily involving craniofacial region and upper extremities have been reported in three COVID-19 cases, lacking evidence of metabolic or hypoxic disturbance, any offending drug or known autoimmune disorders [45]. In addition to being spontaneous, the jerks worsened with voluntary movement and tactile and auditory stimuli with an exaggerated startle response. Available MRI brain and CSF study reports were unremarkable. Based on its character, myoclonus seemed to be of brainstem origin, likely postinfectious or immune-mediated in nature especially when immunomodulation with pulse methylprednisolone and plasma exchange led to significant clinical improvement [37]. Sequential appearance of hyposmia, hypersomnia, and generalized myoclonus in these cases indicate possible transneuronal spread of SARS-CoV-2 through first- and second-order olfactory pathway to involve hypothalamus and brainstem [45].

CNS neuroimmunological disorders Although human CoVs have been implicated in multiple sclerosis (MS) [48], association of SARS-CoV-2 with MS is lacking. MRI brain in a 54-year-old male, presenting with COVID-19 pneumonia and seizures, revealed T2 and FLAIR hyperintense lesions involving bilateral periventricular white matter, corpus-callosum, cervico-medullary junction, and cervico-dorsal spinal cord, lacking diffusion restriction or contrast enhancement. CSF examination failed to detect SARS-CoV-2 or confirm MS. Since demyelinating changes along with virus particles have been detected in autopsied brain tissue in SARS-CoV, a possibility of SARS-CoV-2-related demyelinating pathology can be speculated in this case. SARS-CoV-2 infection–related hyperinflammatory state might cause glial activation and CNS demyelination. Another hypothesis proposes demyelination related to a delayed immune response, after viremia had settled, and hence failure to detect SARS-CoV-2 in CSF [39].

At least four COVID-19-related acute transverse myelitis (ATM) have been reported to date with patients presenting with acute onset symmetrical sensorimotor quadri- or paraparesis with bladder/bowel disturbances. None of these cases manifested features related to cerebrum, optic nerve,

cerebellar pathways, or brainstem involvement. Three of them developed neurological symptoms in the second week of illness, with the fourth case manifesting on the 3rd day of illness [40–43]. MRI study revealed longitudinally extensive transverse myelitis involving the entire length of cord in first two [40], multifocal transverse myelitis in third [42], and brainstem involvement in the fourth case [40]. Although SARS-CoV-2 could not be detected in CSF examination, it revealed lymphocytic pleocytosis with hyperproteinorrhachia in one of the four cases [42]. Relevant autoimmune panel in serum and CSF and serological screening for neurotropic viruses were negative [40, 42, 43]. Considering the onset of myelitis symptoms in the second week of illness along with significant response to immunomodulation, immune-mediated pathology appears likely in these cases [43]. Nevertheless, SARS-CoV-2 directly invading the spinal cord cannot be ruled out, especially when ACE2 receptors have been detected on the surface of spinal cord neurons [76]. A 23-year-old COVID-19 patient with substance abuse disorder, presenting with fever and neuropsychiatric symptoms followed by dysphagia, dyskinesia, hyponatremia, and autonomic dysfunction, showed positive anti-NMDA receptor antibodies and negative SARS-CoV-2 in CSF. Patient showed clinical improvement with high-dose dexamethasone and intravenous immunoglobulin [44].

Movement disorders Probable Parkinson's disease has been reported in a 70-year-old male 2 months following SARS-CoV-2 infection with asymmetrical reduction of 18F-FDOPA uptake in basal ganglia and good response to pramipexole and biperiden. COVID-19-associated immune activation in the olfactory system leading to alpha-synuclein misfolding and development of Parkinsonian features has been speculated in such cases [49, 50]. Reports of COVID-19-associated other movement disorders including ocular flutter, opsoclonus, tremors, myoclonus, and ataxia have also been reported [47, 77, 78]. Most of them manifested in the second or third week of illness, making postinfectious or para-infectious autoimmune phenomenon the likely pathogenesis.

Peripheral nervous system and muscle involvement

PNS involvement has been reported in nearly 10% of COVID-19 patients, with smell and taste impairment being most common [11].

Smell and taste impairment Several series report smell and taste dysfunction in 5–90% COVID-19 cases, with females outnumbering males [1, 11, 52, 55, 57]. They are more commonly reported in European cases as compared to Asian, probably related to genetic variability in distribution and expression of ACE2 receptors or mutation in virus strain. Nearly 80% cases lacking nasal obstruction or discharge report smell impairment. Although olfactory dysfunction in 88% cases appears simultaneously or after clinical onset of COVID-19, it may be the sentinel feature in 12% cases. Although recovery in smell and taste dysfunction may take longer in some cases, near complete resolution has been seen in 25–80% cases within 2 weeks [52, 57]. High prevalence of anosmia and ageusia in absence of nasal obstruction or rhinorrhoea suggest possible sensory neural loss along with trans-nasal transmission, as the underlying cause of the olfactory dysfunction rather than the conductive mechanism seen in most cases of postviral olfactory loss [65, 71, 79].

GBS and cranial neuropathy To date, at least 73 cases of COVID-19-related GBS and its variants have been reported [58]. Flaccid-areflexic weakness (paraparesis/quadriparesis) with/without sensory symptoms was the major clinical form (70%), with 10% cases having features suggestive of Miller–Fisher syndrome (MFS). Other variants reported include facial diplegia (6.8%), polyneuritis cranialis (2.7%), and pharyngeal-cervical-brachial variant (1.3%) [58]. Pupillary sparing oculomotor nerve palsy and isolated ophthalmoplegia involving right abducens have also been reported in two separate cases [80]. Interestingly, early and severe respiratory compromise was observed in one fourth patients, probably related to involvement of brainstem respiratory center [81]. While neurological features in most cases appeared after first week of illness suggestive of postinfectious immune-mediated pathology, a single case showed pure neurological onset favoring a para-infectious autoimmune pathology.

More than four-fifth (81.8%) cases satisfied electrophysiological criteria for AIDP, with AMSAN and AMAN reported in 12.7% and 5.4% cases, respectively. Of 23 patients (31%), who underwent brain and/or spinal cord MRI, contrast enhancement of nerve roots were seen at the level of the brachial plexus in two (8%), lumbosacral plexus in four (17%), cauda equina in four (17%), spinal nerves roots in eight (34%), and cranial nerves (especially third, sixth, seventh, eighth) in five (21%) cases. While CSF SARS-CoV-2 RNA was absent in all tested cases, more than two-third (71%) cases showed albumin-cytological dissociation. A single case of classic sensorimotor GBS along with one of the cases with MFS tested positive for serum anti-GM1 antibodies anti-GD1b, respectively. More than 70% of patients showed a good prognosis, mostly after treatment with intravenous immunoglobulin [58].

Muscle involvement Myalgia and/or fatigue is one of the most common symptoms in COVID-19, reported in 10–74% cases [1, 10, 11, 53]. Skeletal muscle damage with increased serum creatinine kinase levels above 200 U/L had been seen in 11% of hospitalized COVID-19 cases, especially in patients having concurrent liver and renal dysfunction [10]. Rhabdomyolysis has been reported in four COVID-19 cases [1, 82, 83], presenting with weakness, pain, and tenderness in lower limbs. Presence of

ACE2 receptors in skeletal muscle indicate possible direct muscle infection by SARS-CoV-2 but immune-related pathology has also been speculated [5, 11]. Although not reported to date, severe COVID-19 cases requiring prolonged ICU stay may develop critical illness myopathy or neuropathy.

Neuromuscular junction Postinfectious myasthenia gravis associated with SARS-CoV-2 has recently been reported in a 21-year-old female presenting with subacute onset, fluctuating diplopia with unilateral ptosis, developing 4 weeks after COVID-19 infection. Acetylcholine receptor antibodies in serum were elevated, and good clinical recovery occurred following treatment with IVIG and pyridostigmine. The probable molecular mimicry between the SARS-CoV-2 proteins and acetylcholine receptor might have activated the immune response [60].

CIN and CIM In a cohort of 19 critically ill COVID-19 patients manifesting difficulty to wean from mechanical ventilation, nerve conduction study (NCS) and electromyography (EMG) studies revealed presence of critical illness neuropathy (CIN) and critical illness myopathy (CIM) in four and seven cases, respectively. Both CIN and CIM has also been reported in SARS-CoV previously [59].

Interestingly, many COVID-19 cases may present with pure neurological manifestations including headache, dizziness, stroke, GBS, and meningoencephalitis, at the onset of illness with non-neurological features manifesting few days later [11, 21, 38, 58, 81, 84]. Although the current case definition of COVID-19 illness includes a primary respiratory involvement, several cases have been reported with neurological illness being the earliest manifestation of COVID-19. While headache and dizziness are commonly reported at the onset in 26% patients in a series [63], stroke or GBS as the initial manifestation of SARS-CoV-2 infection has also been reported in three cases each [58, 84]. We propose the term "neuro-COVID syndrome" for such cases and physicians must be vigil to facilitate its management and due precautions should be taken to avoid cross-infection. We speculate a possibility of high neurotropism of SARS-CoV-2 as well as predilection of the immune-mediated response to primarily target the central and/or peripheral nervous system and its vascularity, as the plausible reasons for neuro-COVID syndrome. Thus, SARS-CoV-2 infection should be considered in the list of differentials in cases with new-onset unexplained CNS and/or PNS involvement.

Investigations

General investigations to rule out other systemic complications

A neutrophil-lymphocyte ratio (NLR) > 3 has been reported an independent predictor for neurological complications [72].

Serum electrolytes along with renal and liver functions should be tested regularly to detect MODS and rule out metabolic encephalopathy [11]. Derangement in coagulation profile including D-dimer is an independent predictor of systemic vascular complications including stroke [6, 70]. Assays of muscle enzymes including creatinine phophokinase(CPK) and lactate dehydrogenase along with acute phase reactants like serum ferritin and CRP is advisable. While patients with predominant CNS manifestations had lower lymphocyte and platelet counts along with elevated blood urea nitrogen, those with muscle symptoms had significantly high serum CPK (> 200 U/L), neutrophil, CRP, and D-dimer levels with reduced lymphocyte count [11].

Investigations for neurological manifestations

Efforts should be taken to minimize the transmission of SARS-CoV-2 infection in considering investigations requiring shifting patients away from his current ward.

Neuroimaging COVID-19 patients presenting with unexplained altered sensorium, confusion or agitation, focal neurological deficit indicating an acute stroke, meningoencephalitis, and acute myelitis should undergo neuroimaging, preferably MRI of the region of interest. To date, several neuroimaging findings have been reported in COVID-19 patients (Table 2).

CSF To date, CSF RT-PCR or ELISA has detected SARS-CoV-2 in only three COVID-19 cases, who presented with meningoencephalitis, GBS, and brain microvascular occlusive disorders, respectively [18, 34, 86]. Albumino-cytological dissociation in CSF may help diagnose GBS [58]. CSF protein may be elevated in COVID-19-related para- or postinfectious central or peripheral neuroimmunological disorders. Lypmhocytic pleocytosis with elevated CSF protein has been found in COVID-19-related meningoencephalitis [18, 21, 38] and transverse myelitis [40, 42]. However, positive immunological parameters in CSF including IgG index and oligoclonal bands in any COVID-19-related case has not been reported to date.

EEG Various electroencephalography (EEG) findings including focal or diffuse delta-theta slowing, symmetrical or asymmetrical sporadic epileptiform discharges, lateralized periodic discharges with overriding fast activity, generalized sharp waves with spikes, triphasic waves, and repetitive focal rhthmic bursts of nonconvulsive status epilepticus have been reported in COVID-19 patients presenting with altered mental status, delirium, or encephalopathy, and continuous EEG monitoring is advisable in these patients to diagnose NCSE [53, 75, 87].

Table 2 Reported neuroimaging features in COVID-19 cases

Systems involved	Syndromic manifestations	CT brain/PET-CT	MRI
Meninges ± brain parenchyma	• Acute meningoencephalitis [18, 21] • Meningitis/encephalitis [18] • Rhombencephalitis/myelitis [22]		• Leptomeningeal enhancement • T2 hyperintense signal changes in upper pons, limbic lobes, medial thalami and subcortical cerebral white matter • Lateral ventriculitis along with right medial temporal encephalitis • T2 hyperintense lesion in the right inferior cerebellar peduncle, extending to involve a small portion of the upper cord, associated with swelling and microhemorrhages
Cortical and subcortical	• Acute hemorrhagic necrotizing encephalopathy [16, 17] • Hypoxic ischemic encephalopathy [62] • Hypoactive orbitofrontal cortex in anosmia [8]	• Symmetric hypodensities involving bilateral medial thalami • Diffuse swelling of the brain stem. • Hypometabolism of the left orbitofrontal cortex	• Hemorrhagic rim enhancing lesions involving bilateral thalami, medial temporal lobes, and sub-insular regions on post contrast coronal T1-weighted images • T2 and FLAIR hyperintensities with diffusion restriction involving frontal, parietal, temporal, occipital, insular and cingulate gyrus • Right cerebral hemispheric restricted diffusion and cerebral edema and spinal edema • Hyperintensities on T2/FLAIR in splenium • Multiple clusters of lesions in the deep cerebral white matter. Cyst-like areas of varied sizes, some with hemorrhagic foci and peripheral rims of restricted diffusion. • Multifocal and confluent areas of signal change in the cerebral hemispheric, white matter with extensive micro hemorrhages in the subcortical regions • Extensive, confluent, and largely symmetrical areas throughout brainstem, limbic and insular lobes, superficial subcortical white matter and deep gray matter. Clusters of microhemorrhages, restricted diffusion and peripheral rim enhancement • Brain stem swelling with symmetrical hemorrhagic lesions in the brain stem, amygdalae, putamen, and thalamic nuclei • Multifocal confluent lesions in internal and external capsules, splenium and deep white batter of cerebral hemispheres with multiple microhemorrhages and extensive prominent medullary veins. • Components of brachial and lumbosacral plexus showed increased signal and enhancement
Cerebrovascular system	• Ischemic stroke [1, 11, 67] • Intracerebral hemorrhage, subarachnoid hemorrhage [24, 25] • CVST [27, 29, 85] • PRES [30–32, 73]	• Loss of gray-white differentiation at occipital and parietal lobes or hypo dense lobar lesion. • Hyper dense appearance of MCA vessel • SAH centered in the posterior fossa, including the fourth ventricle leading to hydrocephalus • CT angiogram showed right-sided ruptured dissecting posterior-inferior cerebellar artery aneurysm • New bilateral confluent hypodensities in occipital/parieto-occipital/white matter • Patchy lucencies in the bilateral frontoparietal white matter and posterior limb of the left internal capsule • CT angiogram showed a filling defect in the right transverse sinus and jugular bulb suggestive of venous sinus thrombosis	• Cortical microhemorrhages • Absence of normal flow void in right transverse sinus • Occlusion of proximal MCA • Left temporoparietal hemorrhagic venous infarction with left transverse and sigmoid sinus thrombosis • Confluent T2 hyperintensity in the same regions without diffusion restriction or susceptibility hypointensity. • Extensive dural venous sinus thrombosis involving the straight sinus, torcula, left transverse and sigmoid sinus, extending into the jugular vein, as well as right transverse sinus, superior sagittal sinus, and left vein of Labbe.
Brainstem		-	• T2 hyperintensities involving cerebellar peduncles

Table 2 (continued)

Systems involved	Syndromic manifestations	CT brain/PET-CT	MRI
Spinal cord	• Acute rhombencephalitis [22] • Acute transverse myelitis [5, 39, 40, 42]	-	• T2 hyperintensities involving upper cervical and lower dorsal spinal cord • Longitudinally extensive transverse myelitis involving the entire length of the spinal cord
Nerve root	• GBS [58]		• Contrast-enhanced lesions in caudal nerve roots and facial nerve

CT computed tomography, *CVST* cortical venous sinus thrombosis, *GBS* Guillain–Barre syndrome, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging, *FLAIR* fluid-attenuated inversion recovery, *PET-CT* positron emission tomography computed tomography, *PRES* posterior reversible encephalopathy syndrome, *SAH* subarachnoid hemorrhage

NCS and EMG Electrophysiological studies are largely reserved for managing rapidly progressive neuromuscular disorders including GBS [58], myasthenic crisis, inflammatory myopathy, and critical illness neuropathy [59, 88]. NCS in COVID-19-related GBS cases revealed predominant demyelinating involvement in five, axonal in five, and mixed pattern in a single case [58].

Treatment

While more than 80% of COVID-19 cases remain either asymptomatic or develop self-limiting mild features, symptomatic management including oxygen therapy remains the mainstay in managing severe cases. Mechanical ventilation is indicated in respiratory failure refractory to oxygen therapy and hemodynamic support for septic shock [1, 4]. A variety of antiviral medications targeting different steps of viral replication cycle and convalescent plasma are undergoing evaluation [89].

Treatment of COVID-19-related neurological illness

In view of paucity of data regarding management of COVID-19-related neurological manifestations, syndrome-specific therapy along with supportive management employed during pre-COVID-19 time is advocated. Additionally, regular monitoring and manangement of metabolic and electrolyte derangements along with prevention and/or treatment of secondary infections may improve outcome.

Stroke Antiplatelet therapy with aspirin or clopidogrel have been tried in six and anticoagulation with enoxaparin in five ischemic stroke cases, but three cases in former and one in the latter group failed to survive [1]. The interim guidance of the International Society of Thrombosis and Haemostasis (ISTH) proposed a widespread use of prophylactic low molecular weight heparin (LMWH) in all hospitalized COVID-19 patients lacking contraindication (active bleeding and platelet count below 25×10^9/L) [90], and it should be used with caution in ischemic stroke patients in view of possible risk of intracranial hemorrhage or hemorrhagic transformation of acute infarct [67].

Neuroimmunological disorders involving CNS and PNS Use of IVIg may be preferred over plasma exchange as the former aids in managing ARDS by improving passive immunity and modulating immune response [89]. Additionally, plasma exchange procedure carries a substantial risk of cross-infection to healthcare workers. Immunomodulation with oral [40, 41] or intravenous [40, 42] steroids, intravenous immunoglobulin [40], and/or plasma exchange [39] led to remarkable clinical improvement most of COVID-19-related GBS and ATM cases reported to date. Although steroid administration during initial stage of infection may increase viral replication and delay development of adaptive immunity, timed and titrated usage may be safe and beneficial in meningoencephalitis and CNS demyelinating disorders [38, 39].

Seizures

Along with initiation of commonly used antiepileptic drugs (AEDs), management of primary pathology causing seizure is important [74, 75]. Immunomodulation with pulse methylprednisolone and plasma exchange led to significant clinical improvement in generalized myoclonus in three cases, possibly resulting from immune-mediated pathology [45].

Meningitis and/or meningoencephalitis Although lacking concrete evidence, several antivirals including lopinavir-ritonavir and hydroxychloroquine [75] have been tried with some success in COVID-19-related meningitis and/or meningoencephalitis. Symptomatic therapy for raised intracranial pressure including mannitol may improve outcome [66].

Rhabdomyolysis Since aggressive fluid administration may aggravate hypoxia in patients with ARDS, small boluses of intravenous fluid (approximately 250 ml) with monitoring of clinical status and oxygen saturation levels along with serum creatinine and CPK is warranted [82].

Treatment of preexisting chronic neurological illness during COVID-19 pandemic

Patients with chronic neurological conditions especially elderlies; those with comorbid illnesses, including diabetes and chronic heart, lung, liver, or kidney illness; or on immunomodulators may develop severe COVID-19 illness [4]. While data on change in behavior of preexisting chronic neurological illnesses and need to modify their management is lacking, these patients must be followed closely [91]. Management of preexisting chronic stroke, neuroimmunological disorders, Parkinson's disease, epilepsy, migraine, and neuromuscular disorders may remain similar to pre-COVID time. Ongoing immunomodulation should be continued with regular monitoring for drug-related adverse effects, as discontinuation may trigger a relapse [89]. These patients must religiously practice social distancing and hand hygiene to prevent exposure to SARS-CoV-2 [4, 91]. In addition to known offending medications, hydroxychloroquine may worsen myasthenia gravis and should be avoided [4].

Conclusion

COVID-19 may present with a wide spectrum of neurological manifestations. Although neurological manifestations are common in severe cases, a high suspicion should be exercised to diagnose patients with pure neurological presentation ("neuro-COVID syndrome") at onset of COVID-19 illness.

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