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COVID-19

Neuromuscular presentations in patients with COVID-19

Vimal Kumar Paliwal[1] · Ravindra Kumar Garg[2] · Ankit Gupta[1] · Nidhi Tejan[3]

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Abstract

COVID-19 is caused by the coronavirus SARS-CoV-2 that has an affinity for neural tissue. There are reports of encephalitis, encephalopathy, cranial neuropathy, Guillain-Barrè syndrome, and myositis/rhabdomyolysis in patients with COVID-19. In this review, we focused on the neuromuscular manifestations of SARS-CoV-2 infection. We analyzed all published reports on SARS-CoV-2-related peripheral nerve, neuromuscular junction, muscle, and cranial nerve disorders. Olfactory and gustatory dysfunction is now accepted as an early manifestation of COVID-19 infection. Inflammation, edema, and axonal damage of olfactory bulb have been shown in autopsy of patients who died of COVID-19. Olfactory pathway is suggested as a portal of entry of SARS-CoV-2 in the brain. Similar to involvement of olfactory bulb, isolated oculomotor, trochlear and facial nerve has been described. Increasing reports Guillain-Barrè syndrome secondary to COVID-19 are being published. Unlike typical GBS, most of COVID-19-related GBS were elderly, had concomitant pneumonia or ARDS, more prevalent demyelinating neuropathy, and relatively poor outcome. Myalgia is described among the common symptoms of COVID-19 after fever, cough, and sore throat. Duration of myalgia may be related to the severity of COVID-19 disease. Few patients had muscle weakness and elevated creatine kinase along with elevated levels of acute-phase reactants. All these patients with myositis/rhabdomyolysis had severe respiratory complications related to COVID-19. A handful of patients with myasthenia gravis showed exacerbation of their disease after acquiring COVID-19 disease. Most of these patients recovered with either intravenous immunoglobulins or steroids.

Keywords SARS-CoV-2 · COVID-19 · Coronavirus · Anosmia · Ageusia · Guillain-Barrè syndrome · Myositis · Rhabdomyolysis

The COVID-19 pandemic is caused by SARS-CoV-2, a member of the Coronavirinae subfamily. The coronaviruses are classified in four genera: alpha, beta, gamma, and delta coronaviruses [1]. The world has seen three large pandemics in the last 2 decades. The first pandemic originated in Guangdong, China (2002–2003) caused by SARS-CoV-1, and the second pandemic originated in Saudi Arabia (2012), caused by MERS CoV [2–4]. Both pandemics produced severe acute respiratory syndrome (SARS) in thousands of people and produced case fatality rate of 9.6% and 34.4%, respectively [5]. The current pandemic is caused by novel coronavirus named as SARS-CoV-2 that originated in Wuhan, China, in December 2019. As of July 2020, COVID-19 has affected 14.3 million people and produced more than six hundred thousand deaths. All three viruses that produced these three pandemics are beta coronaviruses and share a homologous genomic sequence. The SARS-CoV-2 has a higher affinity for angiotensin-converting enzyme receptor 2 (ACE-2) that is expressed on endothelial cells and neurons. This explains a higher neuro-invasive capacity of SARS-CoV-2 as compared with previous coronaviruses [6].

A number of neurological manifestations of SARS-CoV-2 have been reported. These include encephalitis, acute disseminated encephalomyelitis (ADEM), encephalopathy, steroid-responsive encephalopathy, posterior reversible encephalopathy

✉ Vimal Kumar Paliwal
dr_vimalkpaliwal@rediffmail.com

Ravindra Kumar Garg
garg50@yahoo.com

Ankit Gupta
drankitgupta90@gmail.com

Nidhi Tejan
getnids@gmail.com

[1] Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP 226014, India

[2] Department of Neurology, King George Medical University, Lucknow, UP, India

[3] Department of Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP 226014, India

syndrome (PRES), and meningitis. The neuromuscular manifestations like hyposmia/ageusia, ophthalmoparesis, facial paresis, Guillain-Barré syndrome, symmetrical neuropathy, critical-illness myopathy and neuropathy, myalgia, myositis, and rhabdomyolysis have also been described in patients secondary to COVID-19. In this review, we focused on the neuromuscular manifestation of SARS-CoV-2 infection.

Methods

We analyzed all published reports on COVID-19-associated neuromuscular manifestations. We performed an extensive search of PubMed, Google Scholar, Scopus, and preprint databases (medRxiv and bioRxiv). We identified isolated case reports, case series, and cohort studies. We used search terms, "COVID-19 and Guillain-Barré syndrome, hyposmia, myositis, rhabdomyolysis, neuropathy" and "SARS-CoV-2 and Guillain-Barré syndrome, hyposmia, myositis, rhabdomyolysis, neuropathy". Full-text articles were acquired from journals' websites. We analyzed demographic, clinical, CSF, and neuroimaging characteristics of patients presenting with COVID-19-related peripheral nervous system manifestations. We also discuss the pathogenesis of COVID-19-associated neuropathy and muscle involvement. The last search was done on 2 July 2020.

Search results

We identified 96 studies of COVID-19-related myalgia. After exclusion of descriptive reviews, data in other than English language, and duplicate studies, we selected 13 studies and 2 meta-analysis comprising of 10 and 55 studies, respectively (Table 1) [7–21].

Similarly, we identified 8 case reports (9 patients) with keywords COVID-19 and myositis/rhabdomyolysis (Table 2) [22–29].

Two reports described exacerbation of myasthenia gravis in six patients secondary to COVID-19 infection [30, 31].

We identified 34 reports comprising 39 patients with Guillain-Barrè syndrome and five patients with Miller-Fisher syndrome (Tables 3 and 4) [32–65].

In addition to GBS and MFS, we also included three reports of six patients who developed symmetrical or asymmetrical neuropathy (Table 5) [66–68].

We identified 2 meta-analyses of 24 and 21 studies/case reports respectively that described patients with olfactory/gustatory dysfunction [69, 70]. In addition, we describe 11 studies that evaluated olfactory/gustatory dysfunction in COVID-19 patients (Table 6) [71–81].

We also included 5 reports (6 patients) of isolated cranial neuropathy in COVID-19 patients (Table 6) [82–87].

Myalgia

A meta-analysis of clinical characteristics by Long-quan Li et al. (10 studies, 1995 patients, published between December 2019 and February 2020) showed that prevalence of myalgia was 35.8% (range 11 to 50%). Frequency of other symptoms was fever (88.5%), cough (68.6%), expectoration (28.2%) and dyspnoea (21.9%). Less common symptoms were dizziness, diarrhoea, nausea, and vomiting. They found a fatality rate of 5% and discharge rate of 52% in COVID-19 patients [10]. Another meta-analysis (55 studies, 8697 patients, published between 1 January 2020 and 16 March 2020) showed myalgia in 21.9% COVID-19 patients. Other common symptoms were fever (78.4%), cough (58.3%), fatigue (34%), expectoration (23.7%), anorexia (22.9%), chest tightness (22.9%), and dyspnoea (20.6%). Patients diagnosed before January 31 had higher prevalence of fever and cough. The authors concluded that as the pandemic grew, the prevalence of atypical symptoms increased [15]. In a study of olfactory and gustatory function in COVID-19 patients by Lechien et al., more than 50% patients had myalgia [76]. In a retrospective study by Zhang et al., muscle ache was one of the independent predictors for unimprovement in patients with COVID-19. The other independent predictors were being male, severe COVID-19 condition, expectoration, and decreased albumin at admission [87]. In a cohort of pregnant patients, the frequency of constitutional symptoms of COVID-19 infection was similar to the general population. The study did not find any vertical transmission of COVID-19 infection [88]. In a study comparing the clinical features of SARS-CoV-1 and COVID-19 infection, fever and cough were equally prevalent in both infections but the myalgia and diarrhoea were less common in COVID-19 as compared with SARS-CoV-1 [89]. In a study of 1420 European patients with COVID-19, elderly patients were more likely to have myalgia, fatigue, and fever as compared with younger patients who had higher propensity to acquire symptoms related to ear, nose, and throat [13]. As compared with COVID-19-negative patients, COVID-19-positive patients with respiratory illness reported longer symptom duration (median 7 vs. 3 days), higher prevalence of fever (82% vs. 44%), fatigue (85% vs. 50%), and myalgias (61% vs 27%) [90]. Myalgia persisted at the median time of 23 days of cessation of viral shedding. The other symptoms that persisted at the time of cessation of viral shedding were cough, anosmia, ageusia, and sore throat [91].

Myositis/rhabdomyolysis

Nine patients (age range 16 to 88 years, all males) with COVID-19-related myositis/rhabdomyolysis were reported [22–29]. Eight patients presented with generalized or limb weakness. Myalgias were present in four patients. One patient who did not have muscle weakness presented with myalgia,

Table 1 Studies showing prevalence of myalgia and other presenting symptoms in patients with COVID-19

Author/year	Meta-analysis/study	Prevalence of myalgia (%)	Other presenting symptoms
Huang et al./Feb, 2020 [7]	Study (*N* = 41)	44	Fever 98%, cough 76%, dyspnoea 55%, expectoration 28%, headache 8%, haemoptysis 5%, diarrhoea 3%
Xu et al./Feb, 2020 [8]	Study (*N* = 62)	52	Fever 77%, cough 81%, expectoration 56%, headache 34%, diarrhoea 8%, dypnoea 3%
Liu et al./March, 2020 [9]	Study (*N* = 30 HCW with pneumonia)	70	Cough 83.33%, fever 76.67%, headache 53.33%, GI symptoms 30%, dypnoea 46.67%
Li et al./March, 2020 [10]	Meta-analysis (*N* = 1995)	35.8	Fever 88.5%, cough 68.6%, expectoration 28.2%, Dyspnoea 21.9%, headache 12.1%
Wang et al./Apr, 2020 [11]	Study (*N* = 80, HCW)	23.75	Fever 81.25%, cough 58.75%, fatigue 35%, expectoration 23.75%, diarrhoea 18.75%
Wei et al./Apr, 2020 [12]	Study (*N* = 14, pneumonia)	100	Fever 86%, dry cough 71%
Lechien et al./Apr, 2020 [13]	Study (*N* = 1420)	62.5	Headache 70.3%, anosmia 70.2%, nasal obstruction 67.8%, cough 63.2%, asthenia 63.3%, rhinorrhoea 60.1%, gustatory dysfunction 54.2%, sore throat 52.9%, fever 45.4%
Lai et al./May, 2020 [14]	Study (*N* = 110 HCW)	45.5	Fever 60.9%, cough 56.4%, sore throat 50%
Zhu et al./May, 2020 [15]	Meta-analysis	21.9	Fever 78.4%, cough 58.3%, fatigue 34%, expectoration 23.7%, anorexia 22.9%, chest tightness 22.9%, dyspnoea 20.6%
Lapostolle et al./May 2020 [16]	Study (*N* = 1487)	57	Fever 92.5%, dry cough 94%, headache 55%, asthenia 28%, ageusia 28%, chest pain 21%, hemoptysis 3%
Chen et al./June, 2020 [17]	Study (*N* = 38, fatalities)	15.79	Fever 65.78%, cough 42.10%, dyspnoea 60.52%, chest tightness 26.31%
Korkmaz et al./June, 2020 [18]	Study (*N* = 80, children)	19	Fever (58%), cough (52%)
Reilly et al./June, 2020 [19]	Study (*N* = 14)	67	Dyspnea (77%), fatigue (100%), diarrhoea (67%)
Gaur et al./July, 2020 [20]	Study (*N* = 26)	38.46	Fever (61.54%), sore throat (53.84%), cough (42.3%), dyspnea (23.07%)
Aggarwal et al./July, 2020 [21]	Study (*N* = 32, ARDS)	43.75	Dyspnea (90%), cough (84.4%), fever (68%)

ARDS acute respiratory distress syndrome, *HCW* health care worker

fever, and dyspnoea [26]. One patient presented with repetitive muscle twitching along with tingling and numbness in the legs [28]. Only one patient had cola-coloured urine [29]. Three patients passed red blood cells in the urine. All patients had elevated CPK levels [28, 29]. One patient who presented with cola-coloured urine had most elevated CPK level of 427,656 IU/L. All patients had elevated levels of CRP, LDH, and serum ferritin. Six patients had abnormalities on chest imaging like ground-glass opacities, pneumonia, pleural effusion, or multifocal opacities. Two patients required mechanical ventilation [22, 29]. Five patients improved with conservative management.

In addition to myositis and rhabdomyolysis, there is a report of six COVID-19 patients with critical-illness myopathy. All six patients had acute flaccid quadriparesis. Electrophysiological tests revealed a myopathic pattern. They had mildly elevated creatine kinase and all patients had a good outcome [92]. Cachexia and sarcopenia have also been described in patients affected by COVID-19 [93].

Myasthenia gravis

There are no reports of de-novo occurrence of myasthenia gravis secondary to COVID-19. However, there are two reports of 5 and 1 patients respectively (age range 42–90 years, 4 females) of COVID-19 infection-related exacerbation of the pre-existing myasthenia gravis [30, 31]. Five patients had anti-acetylcholine receptor antibody-positive myasthenia gravis whereas one patient had muscle-specific kinase (MuSK)–positive myasthenia gravis. All patients had exacerbation of myasthenic symptoms after sore throat, fever, cough, and shortness of breath in variable combination. Two patients required mechanical ventilation. Steroids were continued in 4 patients. Two patients received intravenous immunoglobulins. Two patients were taking mycophenolate mofetil that was transiently stopped in view of COVID-19 infection. MMF was resumed in both patients after discharge from the hospital. Five patients improved, and one patient was on mechanical ventilator at the time of publication of the report.

Table 2 Demographic, clinical, and laboratory parameters and outcome of patients with myositis/rhabdomyolysis secondary to COVID-19

Reference/ country	Age/sex	Clinical presentation	Respiratory involvement	Blood parameters	Chest imaging	Neuroimaging	Treatment/outcome
Uysal et al./Turkey [22]	60/M	Myalgia, fatigue	Yes	Raised CK, CRP, LDH, ferritin	B/L ground-glass opacities	NA	HCQ, anti-viral, azithromycin
Valente-Acosta et al./Mexico [23]	71/M	Fever, dyspnea, cough, myalgia, generalized weakness	Yes	CK 8720 U/L, raised myoglobin, creatinine, LDH, IL-6, ferritin	B/L ground-glass opacities	NA	Ventilator, HCQ, anti-viral, tocilizumab
Beydon et al./France [24]	NA	Myalgias, lower limb proximal weakness, fever	No	Raised CPK, CRP, lymphocytopenia	B/L ground-glass opacities	B/L external obturator muscle and quadricipital oedema with contrast enhancement	NA/critical
Suwanwongse et al./USA [25]	88/M	Acute onset B/L thighs pain and weakness, fever, dry cough	No	Raised CPK, LDH	Left pleural effusion	Normal	IV fluids, furosemide, HCQ/improved
Zhang et al./USA [26]	38/M	Fever, dyspnoea, myalgia	Yes	Raised CPK, CRP, LDH	Right upper and middle lobe consolidation	NA	Azithromycin, IV fluids, HCQ, doxycycline/improved
Jin et al./China [27]	60 years M	Fever, cough, pain, and weakness in B/L lower limbs	Yes	Raised CPK, myoglobin, CRP, LDH, leukopenia	B/L ground-glass opacities	NA	Oxygen inhalation, opinavir, moxifloxacin, IV fluids, gamma globulin, plasma transfusion/improved
Chan et al./USA [28]	75 years M	Generalized weakness, reduced appetite	Yes	Elevated CK, AST, ALT, troponin, LDH, CRP, D dimer, ferritin hematuria, normal EKG	Left lower lobe patchy opacity	NA	Antibiotics, hydroxychloroquine/improved
	71 years M	Repetitive leg twitching, generalized weakness, tingling/numbness legs	Yes	Elevated CK, BUN, creatinine, troponin, hematuria, EKG–AF	Multifocal pneumonia	Old lacunar infarct	Antibiotics, hydroxychloroquine, heparin, IV fluids/on mechanical ventilator
Gefen et al./USA [29]	16 years M	Fever, myalgia, shortness of breath, cola-coloured urine, muscle tenderness	No	Elevated CK (427,656 U/L), AST, ALT, procalcitonin, LDH, CRP	NA	NA	IV fluids/improved

AST aspartate amitotransferase, *ALT* alanine transaminase, *AF* atrial fibrillation, *CK* creatine kinase, *CRP* C-reactive protein, *EKG* electrocardiogram, *HCQ* hydroxychloroquine, *LDH* lactate dehydrogenase

Table 3 Clinical, laboratory, treatment, and outcome of COVID-19-related GBS and Miller-Fisher syndrome

References	Age/sex	Preceding illness	Time to GBS	Symptoms/signs	Lab tests	Nerve conduction test	Treatment/outcome
Alberti et al./July 2020 [32]	71/M	Fever	NA	Paraesthesias in all 4 limbs, areflexic flaccid quadriparesis, dyspnoea	Oropharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., CT chest—B/L ground-glass opacities	AIDP	Mechanical ventilation, HCQ, lopinavir, ritonavir, IVIG/died
Farzi et al./June 2020 [33]	41/M	Fever, cough, dyspnea	17 days	Parasthesia, quadreparesis	B/L ground-glass opacities in lungs	AIDP	IVIG/improved
Hutchins KL et al./June 2020 [34]	21/M	Fever, cough, dyspnea, headache, nasal congestion	16 days	Bifacial weakness, facial parasthesia, grade 4/5 power in limbs	Bilateral lung infiltrates, Gadolinium enhancement of bilateral 6th, 7th, and right 3rd cranial nerves	Mixed type sensory motor polyneuropathy	5-cycle plasma exchange/improved
Webb et al./June 2020 [35]	57/M	Cough, headache, myalgia, malaise	7 days	Sensory motor flaccid quadriparesis, areflexia	Left lower lobe consolidation, lymphopenia, raised CRP	Demyelinating neuropathy	Mechanical ventilation, IVIG/improved
Kilinc et al./June 2020 [36]	50/M	Dry cough	4 weeks	Sensory motor quadriparesis, bifacial paralysis	Cranial MRI normal, faecal PCR-positive for SARS-CoV-2	Demyelinating neuropathy	IVIG/improved
Helbok et al./June 2020 [37]	68/M	Dry cough, headache, fatigue, myalgia, fever	14 days	Sensory motor quadriparesis	Raised serum IgG, IgM for SARS-CoV-2, raised ESR, CRP, LDH, fibrinogen, B/L ground-glass opacities in lungs	Demyelinating neuropathy	NIV, plasma exchange/improved
Sancho-Saldaña et al./June 2020 [38]	56/M	Fever, dry cough, dyspnea	15 days	Sensory motor quadriparesis, bifacial paralysis, oropharyngeal weakness	Lobar consolidation in lung, brain stem, and spinal cord leptomeningeal enhancement, CSF-albumin-cytological dissociation	Demyelinating neuropathy	IVIG/improved
Oguz-Akarsu et al./June 2020 [39]	53/F	No preceding infection/-vaccination	NA	Dysarthria due to jaw weakness, predominant lower limb weakness	Ground-glass opacities lung fields, hyperintensity of post-ganglionic roots of brachial lumbar plexuses	Demyelinating neuropathy	HCQ, azithromycin/improved
Lascano et al./June 2020 (3 patients) [40]	NA	Typical COVID-related symptoms	7, 15, and 22 days, respectively	Tetraparesis 2, tetraplegia 1, bifacial paralysis, and bulbar symptom 1	Lumbar root enhancement 1, CSF-albumin-cytological dissociation 2, lymphopenia 2	Demyelinating neuropathy 3	IVIG 3/1 patient discharged, 1 walked with assistance, 1 bed-bound
Chan et al./May 2020 [41]	8/M5	Exposed to relative working in meat-processing plant	20 days after exposure	Bifacial paralysis, no limb weakness	Persistent thrombocytosis, B/L ground-glass opacities in lungs, CSF-albumin-cytological dissociation	Absent blink reflex bilateral, absent F-wave in left tibial nerve	IVIG/some improvement
Riva et al./May 2020 [42]	In sixties	Fever, headache, myalgia, anosmia, ageusia	20 days	Sensory motor quadriparesis, bifacial paralysis, dysarthria, dysphagia	B/L ground-glass opacities lungs, raised acute-phase reactants, SARS-CoV-2 IgG-positive	Demyelinating neuropathy	Mechanical ventilation, IVIG/slow improvement
Zhao et al./May 2020 [43]	61/F	No preceding illness	Not known	Acute paraparesis, areflexic ascending quadriparesis, sensory deficit in hands and feet	CSF-albumin-cells diss. thrombocytopenia, lymphocytopenia, oropharyngeal swab for RT-PCR SARS-CoV-2-positive	AIDP	IVIG, lopinavir, ritonavir, arbidol/recovered
Scheidl et al./May 2020 [44]	54/F	Hypo-osmia, dysgeusia	14 days	Acute areflexic flaccid paraparesis, tingling sensations in all 4 limbs	Oropharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR	AIDP	IVIG/recovered

Table 3 (continued)

References	Age/sex	Preceding illness	Time to GBS	Symptoms/signs	Lab tests	Nerve conduction test	Treatment/outcome
Ottaviani et al./May 2020 [45]	66/F	Fever, cough	10 days	Acute areflexic paraparesis, falls, facial nerve palsy	Nasopharyngeal swab for RT-PCR SARS-CoV-2 positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR, CT chest—B/L ground-glass opacities	Absent F waves, prolonged distal latencies, reduced distal CMAP amplitude, slightly reduced conduction velocities (AIDP)	Mechanical ventilation, IVIG, lopinavir, ritonavir/poor
Caamaño et al./May 2020 [46]	61/M	Fever, cough	10 days	Right facial palsy-LMN followed by left facial palsy, absent blink reflex	Nasopharyngeal swab for RT-PCR SARS-CoV-2 positive, CSF—mildly raised protein, CT chest—B/L pneumonia	Not done	HCQ, lopinavir, ritonavir, prednisolone/minimal improvement
Chan et al./May 2020 [47]	68/M	Fever, URTI	18 days	B/L hands and feet paraesthesia, ataxia, areflexic flaccid paraparesis, B/L facial palsy, dysarthria, dysphagia	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR, CT chest—B/L ground-glass opacities	Not done	Plasmapheresis/progressive improvement
	84/M	Fever	23 days	B/L hands and feet paraesthesias, areflexic flaccid quadriparesis, B/L facial palsy, respiratory failure, dysautonomia	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, elevated GM2 IgM/IgG antibodies, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR, CT chest—B/L ground-glass opacities	Not done	Plasmapheresis, mechanical ventilation, IVIG/residual weakness
Bigaut et al/Sep, May 2020 [48]	48/M	Cough, asthenia, myalgia, anosmia, ageusia	21 days	Flaccid paraparesis, generalized areflexia, lower limb and distal upper limb paresthesia, ataxia, facial palsy	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR, MRI-radiculitis and plexitis on both brachial and lumbar plexus; multiple cranial neuritis (in nerves III, VI, VII, and VIII) CT chest-ground-glass opacities in B/L lung fields	AIDP	IVIG/progressive improvement
	70/F	Anosmia, ageusia, diarrhoea, myalgia	10 days	Flaccid tetraparesis, generalized areflexia, forelimb paresthesia, respiratory failure	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR, CT chest—B/L ground-glass opacities	AIDP	IVIG, NIV/progressive improvement
Assini et al./May 2020 [49]	55/M	Fever, cough, anosmia, ageusia, dyspnoea	20 days	B/L ptosis, dysphagia, dysphonia, B/L masseter weakness, B/L hypoglossal nerve palsy, hyporeflexia in B/L upper and lower limbs	Oropharyngeal swab for RT-PCR SARS-CoV-2-positive, raised ferritin, LDH, lymphocytopenia, CSF-increased IgG/Alb ratio, oligoclonal bands present in CSF and serum	AIDP	Mechanical ventilation, arbidol, lopinavir, ritonavir, IVIG/improved
	60/M		20 days			AMSAN	

Table 3 (continued)

References	Age/sex	Preceding illness	Time to GBS	Symptoms/signs	Lab tests	Nerve conduction test	Treatment/outcome
		Fever, cough, dyspnoea		Acute areflexic paraparesis, autonomic dysfunction	Oropharyngeal swab for RT-PCR SARS-CoV-2-positive, raised ferritin, LDH, lymphocytopenia, CSF-increased IgG/Alb ratio, oligoclonal bands present in CSF and serum, CT chest—interstitial pneumonia		Mechanical ventilation, HCQ, tocilizumab, IVIG/improved
Gigli et al./May 2020 [50]	53/M	Fever, diarrhoea	NA	Parasthesias, ataxia	SARS-CoV-2 IgG/IgM-positive in blood and CSF, CSF-albumin-cell diss., CT chest—B/L ground-glass opacities	AIDP	NA/NA
Arnaud et al./May 2020 [51]	64/M	Fever, cough, dyspnoea, diarrhoea	21 days	Acute areflexic flaccid paraparesis, hypoesthesia	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., CT chest-diffuse GGO with crazy paving appearance	AIDP	Azithromycin, HCQ, IVIG/improved
Rana et al./May 2020 [52]	54/M	Rhinorrhea, odynophagia, fever, chills, night sweats	2 weeks	Quadriparesis, bifacial weakness, mild ophthalmoparesis, difficulty in urination	B/L basal lungs infiltrates/atelectasis	Demyelinating neuropathy	HCQ, azithromycin, oral vancomycin/improving
Su et al./May 2020 [53]	72/M	Diarrhoea, anorexia, chills, no fever	6 days	Ascending sensory motor quadriparesis, dysautonomia, SIADH	CSF-albumin-cytological dissociation, bibasilar atelectasis with consolidation	Demyelinating neuropathy	Mechanical ventilation, antibiotics/persistent weakness
Pfeferkorn et al./May 2020 [54]	51/M	Fever, dry cough, fatigue	14 days	Progressive areflexic flaccid quadriparesis, sensory loss in all extremities, B/L facial and hypoglossal paresis, respiratory failure	Oropharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., CT chest—B/L interstitial infiltrates, MRI spine-contrast enhancement of the spinal nerve roots at all levels of the spine including the cauda equina	AIDP	Mechanical ventilation, IVIG, plasma exchange/poor with residual weakness
Sedaghat Z et al, April, 2020 [55]	65/M	Cough, fever, dyspnoea	14 days	Areflexic ascending quadriparesis, facial diplegia	Oropharyngeal swab RT-PCR SARS-CoV-2-positive, CT chest: consolidations, ground-glass opacities in both lungs	AMSAN	Lopinavir, ritonavir, HCQ, azithromycin, IVIG/improved
Toscano G et al./April 2020 [56]	77/F	Fever, cough, ageusia	7 days	Paresthesia hands/feet areflexic quadriparesis, facial palsy, respiratory failure	Nasopharyngeal swab for RT-PCR SARS-CoV-2 positive, lymphocytopenia, CSF-albumin-cells dissociation, antiganglioside Ab—negative, MRI spine-enhancement of caudal nerve roots, CT chest—interstitial pneumonia	AMSAN, fibrillation potentials on EMG +	2 cycles of IVIG/poor outcome, residual weakness, and dysphagia
	23/M	Fever, pharyngitis	10 days	Lower limb paresthesia, facial diplegia, areflexia, ataxia	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, lymphocytopenia, CSF-albumin-cells	AMSAN, fibrillation potentials on EMG	IVIG/improvement

Table 3 (continued)

References	Age/sex	Preceding illness	Time to GBS	Symptoms/signs	Lab tests	Nerve conduction test	Treatment/outcome
					diss., MRI head-enhancement facial nerves, CT chest—normal		
	55/M	Fever, cough	10 days	Lower limb weakness, paresthesia, neck pain, areflexic quadriparesis, facial palsy, respiratory failure	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, lymphocytopenia, CSF-albumin-cells dissociation, antiganglioside Ab—negative, MRI spine-enhancement of caudal nerve roots, CT chest—interstitial pneumonia	AMAN, fibrillation potentials on EMG +	2 cycles of IVIG/poor outcome, residual weakness
	76/M	Cough, hyposmia	5 days	Lumbar pain and lower limb weakness, areflexic quadriparesis, ataxia	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, lymphocytopenia, CSF—normal, MRI spine and head—normal, CT chest—normal	AIDP, no fibrillation potentials on EMG	IVIG/ poor, mild improvement
	61/M	Cough, ageusia, anosmia	7 days	Lower limb weakness, paresthesia, areflexic paraparesis, facial palsy, respiratory failure	Nasopharyngeal swab for RT-PCR SARS-CoV-2-negative, SARS-CoV-2 IgG-positive lymphocytopenia, CSF—normal, antiganglioside Ab—negative, MRI spine—normal, CT chest—interstitial pneumonia	AIDP, fibrillation potentials on EMG +	IVIG, plasma exchange/poor outcome, ventilator-dependent
Virani et al./April 2020 [57]	54/M	Fever, dry cough	10 days	Numbness and weakness in B/L lower limbs, areflexic quadriparesis	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, MRI spine—normal, CT chest—B/L basilar opacities	Not done	Mechanical ventilation, IVIG, HCQ/improved
Padroni et al./April 2020 [58]	70/F	Fever, dry cough	24 days	Hands and feet paraesthesias, gait difficulties	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cell diss., CT chest—B/L ground-glass opacities	AIDP	Mechanical ventilation, IVIG/poor
Coen et al./April 2020 [59]	70/M	Fatigue, myalgia, dry cough	10 days	Paraesthesias, distal allodynia, urinary retention, constipation, areflexic flaccid paraparesis	Nasopharyngeal swab for RT-PCR SARS-CoV-2 positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR, CT chest—B/L ground-glass opacities	AIDP	IVIG/improved
El Otmani et al./April 2020 [60]	70/F	Fever, dry cough	3 days	Acute flaccoid areflexic quadriparesis	Oropharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., CT chest-ground-glass opacities in the left lung	AMSAN	IVIG, HCQ, azithromycin/improved
Marta-Enguita et al./April 2020 [61]	76/F	Fever, cough	8 days	Lower backache with radiation to B/L lower limbs, progressive areflexic tetraparesis, distal-onset paraesthesia,	Oropharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-NA, CT chest—consolidation	NA	Mechanical ventilation/died

Table 3 (continued)

References	Age/sex	Preceding illness	Time to GBS	Symptoms/signs	Lab tests	Nerve conduction test	Treatment/outcome
				dysphagia, respiratory failure			
Miller-Fisher syndrome							
Reyes-Bueno et al./June 2020 [62]	51/F	Diarrhoea, odynophagia, cough	10 days	Quadriparesis, left lateral rectus palsy, bifacial palsy, dysautonomia	CSF-albumin-cytological dissociation	Demyelinating neuropathy	IVIG/improving
Fernández-Domínguez et al./May 2020 [63]	74/F	Fever, URTI	12–15 days	Progressive gait impairment, areflexia, blurring of vision	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR	Slight F-wave delay in upper limbs	IVIG/improved
Lantos et al./May 2020 [64]	36/M	Fever, chills, myalgia	4 days	Left eyelid drooping, blurry vision, paraesthesia in both legs, left CN 3 palsy, B/L 6th CN palsy, ataxia, hyporeflexia	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, MRI—enlargement with contrast enhancement of left occulomotor nerve	NA	IVIG, HCQ/improved
Gutiérrez-Ortiz et al./April 2020 [65]	50/M	Fever, headache, cough, malaise	5 days	Anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia	Nasopharyngeal swab for RT-PCR SARS-CoV-2 positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR	NA	IVIG/improved
	39/M	Fever, diarrhoea	3 days	Ageusia, B/L abducens palsy, areflexia	Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., negative SARS-CoV-2 RT-PCR	NA	Acetaminophen/improved

AIDP acute inflammatory demyelinating polyneuropathy, *AMAN* acute motor-axonal neuropathy, *AMSAN* acute motor-sensory axonal neuropathy, *CSF* cerebrospinal fluid, *EMG* electromyography, *ESR* erythrocyte sedimentation rate, *HCQ* hydroxychloroquine, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *IVIG* intravenous immunoglobulin, *NA* not available, *RT-PCR* reverse transcriptase polymerase chain reaction, *URTI* upper respiratory tract infection

Table 4 Frequency of various demographic, clinical, and electrophysiological features and good outcome in patients with COVID-19-related GBS

Feature	Frequency
Number	39
Age (data available in 36 patients)	21–85 years, mean = 60.55, median = 61, mode = 70
Males (data available in 35 patients)	26 (74.28%)
Hyposmia/ageusia	6 (15.4%)/7 (17.9%)
Time to onset of GBS (data available in 35patients)	3–28 days, mean = 13.91 days, median = 14, mode = 10
Bifacial paralysis	18 (46.15%)
Other cranial neuropathies	9 (23.07%)
Respiratory involvement	17 (43.58%)
Demyelinating/axonal (data available in 32 patients)	24 (75%)/7 (22%)
Outcome (data available in 38 patients)	GOOD = 25 (65.8%), POOR = 11 (28.9%), DIED = 2 (5.3)

Guillain-Barrè syndrome and Miller-Fisher syndrome

Recently, 39 patients with GBS and 5 patients with MFS secondary to COVID-19 were published. Most of the reports were from China, Italy, and the USA. The demographic profile, frequency of clinical features, electrophysiological features, and good outcome are described in Table 3. GBS and MFS were more frequent in elderly people. Time to onset of GBS/MFS ranged from 3 days to 4 weeks of onset of COVID-19 symptoms. Majority of patients had para-infectious and minority had post-infectious GBS/MFS. Upper respiratory tract symptoms were the usual preceding symptoms. Hyposmia and ageusia were distinctive features seen in COVID-19 patients unlike the typical GBS where these olfactory symptoms are not seen. Most patients had ascending or lower limb areflexic weakness that later on progressed and involved bifacial weakness and other cranial neuropathies. Unlike typical GBS, respiratory failure secondary to lung involvement was common in GBS patients secondary to COVID-19. Majority of patients had severe demyelinating type of neuropathy. CSF-albumin-cytological dissociation was frequently noticed. SARS-CoV-2 RT-PCR was not detected in the CSF of the patients subjected to the test. Most patients with lung pathologies required mechanical ventilation and had a poor outcome in the form of either prolonged ventilatory stay, residual weakness, or death.

Five patients with MFS (age range 36–74 years, 3 males) presented with preceding upper respiratory symptoms (2 patients) and diarrhoea (1 patient). All three patients had gait difficulty, ataxia, and areflexia. One patient had visual blurring and 2 patients had ophthalmoparesis. Two patients had preceding ageusia/hyposmia. Four patients received intravenous immunoglobulin. All five patients improved.

Neuropathy

Three reports of 6 patients with COVID-19-related neuropathy were published [66–68]. Authors claimed that the neuropathy in their patients was different from GBS. Ghiasvand et al. reported a 68-year-old female with symmetrical lower motor neuron quadriparesis after an initial upper respiratory involvement. Due to respiratory involvement, patient died and electrophysiological tests could not be performed [66]. Abdelnour et al. reported a 69-year-old male with lower limb areflexic weakness and gait ataxia without any COVID-19-related preceding symptoms. His RT-PCR from a nasopharyngeal swab was positive for SARS-CoV-2. Electrophysiology tests were not performed. The patient improved spontaneously. In absence of nerve conduction tests, type of neuropathy could not be determined in both cases [67]. Chaumont et al. presented four patients (age range 52 to 72 years, all males), who presented with CNS symptoms along with quadriparesis after or during the weaning stage from the mechanical ventilator [68]. All patients had ARDS secondary to COVID-19 infection, and they developed neurological features after an interval of 12 to 20 days of initial COVID-19 symptoms. All patients had comorbid illnesses like diabetes mellitus in three, hypertension in two, urothelial cancer in one, and obstructive sleep apnoea in one patient. Three patients had evidence of demyelinating polyradiculoneuropathy whereas one patient had denervation in limbs suggestive of axonal neuropathy. One patient had asymmetrical neuropathy whereas the rest of the patients had symmetrical neuropathy. All patients had dysautonomia and action myoclonus, a feature not seen in critical-illness neuropathy.

Table 5 Neuropathy in COVID-19 patients

Reference/ country	Type	Age/ sex	Clinical presentation	Respiratory involvement	Blood parameters/ RT-PCR	Electrophysiology	Neuroimaging	Treatment/outcome
Ghiasvand et al./Iran [66]	Symmetrical polyneuropathy	68/F	Fever, dry cough, myalgia, B/L lower limbs hypotonia with weakness with areflexia	Ground-glass opacities	Raised creatinine, CRP, lymphopenia	Not performed	Normal	Lopinavir/ritonavir, oseltamivir, mechanical ventilation, IV methylprednisolone/died
Abdelnour /UK [67]	Motor neuropathy	69/M	Lower limb weakness, knee/ankle areflexia, gait ataxia, sensory normal	Lower lobe pneumonia	Lymphocytopenia, raised CRP, LDH, ferritin	Not performed	Normal	Spontaneous recovery
Chaumont /France [68]	Encephalopathy with peripheral neuropathy	62/M	Confusion, memory loss, dysphagia, left facial palsy, asymmetrical quadriparesis, lower limb areflexia, upper limb hyperreflexia, action myoclonus, dysautonomia	Mild ARDS	Positive IgM, IgG for SARS-CoV-2, positive RT-PCR nasopharyngeal swab	Demyelinating asymmetric motor polyradiculoneuropathy and moderate axonal sensorimotor neuropathy	Right MCA recent stroke, spine normal	Hydroxychloroquine, azithromycin, IVIg, rehab centre after 36 days, mRS 2
		72/M	Confusion, delusion, hallucinations, memory impairment, dysphagia, slow saccades, quadriparesis, hyperreflexia, dysautonomia	ARDS	Positive IgM, IgG for SARS-CoV-2, positive RT-PCR nasopharyngeal swab	Demyelinating asymmetric motor polyradiculoneuropathy and moderate axonal sensorimotor neuropathy	Normal brain/spine MRI	Hydroxychloroquine, azithromycin, IVIg, rehab center after 50 days, mRS 4
		50/M	Confusion, delusion, hallucinations, memory impairment, dysphagia, slow saccades, quadriparesis, hyperreflexia, dysautonomia	ARDS	Positive IgM, IgG for SARS-CoV-2, positive RT-PCR nasopharyngeal swab	Lower motor neuron involvement, denervation of four limbs	Normal brain/spine MRI	Hydroxychloroquine, azithromycin, IVIg, methyl prednisolone, rehab centre after 76 days, mRS 4
		66/M	Confusion, delusion, hallucinations, memory impairment, dysphagia, slow saccades, quadriparesis, hyperreflexia, dysautonomia	ARDS	Positive IgM, IgG for SARS-CoV-2, positive RT-PCR nasopharyngeal swab	Demyelinating motor polyradiculoneuropathy	Normal brain/spine MRI	Hydroxychloroquine, azithromycin, IVIg, methyl prednisolone, discharged to home after 40 days, mRS 2

ARDS acute respiratory distress syndrome, *CRP* C-reactive protein, *IVIg* intravenous immunoglobulin, *IgM* immunoglobulin M, *IgG* immunoglobulin G, *Mrs* modified Rankin Scale, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging

Table 6 Patients with olfactory/gustatory dysfunction and isolated cranial neuropathy secondary to COVID-19 infection

Type	Reference/country	Age/sex	Clinical presentation	Respiratory involvement	Blood parameters	Chest imaging	Neuroimaging	Treatment/outcome
Olfactory and gustatory dysfunction	Altin et al. COVID-19 cases 81, normal controls 40 [71]	Cases 18–95, controls 18–90	Olfactory complaints Cases—61.7% (50) Controls—none Gustatory dysfunction Cases—27.2% (22)	NA	NA	NA	NA	NA
	Gómez-Iglesias *N* = 909 (online survey) [72]	Mean age 34, females 68.9%	Ageusia (581, 64.1%), hypogeusia (256, 28.2%), dysgeusia (22, 2.4%), anosmia (752 82.8%), hyposmia (142, 15.6%), and dysosmia (8, 0.9%)	NA	NA	NA	NA	NA
	Sayin et al. (telephonic survey) URTI cases (*N* = 128) COVID +VE 64, COVID −VE 64 [73]	Mean 38.63 ± 10.0 8.37.5% males	Impairment of smell/taste COVID +VE 46 (71.9%) COVID −VE 17 (26.6%) hyposmia/parosmia, hypogeusia/dysgeusia more in COVID +VE	NA	NA	NA	NA	NA
	Lee et al./*N* = 1345 (102 COVID +VE, 1243 −VE, sampled 1:3 ratio) [74]	+VE 38, −VE 43 (median)	Anosmia/hyposmia COVID +VE 41.1% COVID −VE 4.2% Dysgeusia/ageusia COVID +VE 46.4% COVID −VE 5.6%	N/A	N/A	N/A	N/A	N/A
	Marchase-Ragona et al. (*N* = 6)/Italy [75]	24–50 years/4F, 2M	Hyposmia and hypogeusia in all, fever and cough in 1 patient, myalgia in 2 patients	No	NA	NA	NA	Conservative/improved
	Lechien et al. (*N* = 417)/Europe [76]	Mean age = 36.9 years/63.1% F	88.8% gustatory dysfunction, 85.6% olfactory dysfunction, others symptoms—fever, cough	No	NA	NA	NA	Paracetamol, NSAIDS, nasal saline irrigation, nasal steroids/favourable
	Luers et al./Germany [77]	Mean age = 38 years/43.1% F	73.6% hyposmia, 69.4% hypogeusia, 50% fever, 75% cough, 62.5% sore throat, 70.8% myalgia, 77.8% headache	No	NA	NA	NA	NA/NA
	Vaira et al./Italy *N* = 345 [78]	Mean age 48.5 years/42.3% Males	Self-reported olfactory/gustatory disturbance 256 (74.2%), combined 79.3%, isolated olfactory 8.6%, isolated gustatory 12.1%	48.4%	NA	NA	NA	Self-reported complete regression for smell (31.3%) and taste (50.4%) at the time of test
	Qui C,et al./multicentre, *n* = 394 [79]	Median age 39 years/57% males	161/394, 41% olfactory/gustatory dysfunction, only olfactory 16%, only gustatory 2%	66%	NA	NA	NA	Olfactory/gustatory function improved in 44%
	Biadsee et al./Israel *n* = 128 [80]	Mean age 36.25	Olfactory dysfunction 67%, anosmia 19.5%, impaired taste 52%, dry mouth	NA	NA	NA	NA	NA

Table 6 (continued)

Type	Reference/country	Age/sex	Clinical presentation	Respiratory involvement	Blood parameters	Chest imaging	Neuroimaging	Treatment/outcome
		years/ males 58	72 patients, facial pain 26%, masticatory muscle pain 11%					
	Kosugi et al./Brazil *n* = 253 (145 COVID-19-positive) [81]	Mean age 36 years/59.1% females	145 COVID-19 patients had sudden olfactory dysfunction	NA	NA	NA	NA	Total recovery 52.6%, COVID-19-positive patients took longer time for recovery as compared with COVID-19-negative (15 days vs. 10 days)
Ophthalmoparesis	Dinkin et al./USA [82]	36/M	Fever, cough, myalgia, left ptosis, diplopia, B/L distal paresthesia, partial left oculomotor palsy, B/L abducens palsies	No	Leukopenia	Normal	T2 hyperintensity and enlargement of left oculomotor nerve with enhancement	IVIG, HCQ/partial improvement
		71/F	Fever, cough, painless diplopia, right abducens palsy	Yes	Lymphopenia	B/L opacities	Enhancement of optic nerve sheaths and posterior tendon capsules	HCQ/improved
	Oliveira/Brazil [83]	69/M	Fever, cough, dyspnea, chest pain, abdominal pain, binocular diplopia, stabbing occipital headache, B/L trochlear nerve palsies	Yes	Raised ESR	B/L	ground-glass opacities	s/o vasculitis of the vertebrobasilar system
IV			methylprednisolone/ improved	Facial palsy	Wan et al./China [84]	65/F	Pain in left mastoid region, left facial drooping	No
Normal	Ground-glass shadows in right lower lung	Normal	Arbidol, ribavirin/improved					
Glossopharyngeal and vagal neuropathy	Aoyagi et al./Japan [85]	70/M	Ageusia, soar throat, cough fever, diarrhoea. 20 days later developed abnormal throat sensation and oropharyngeal dysphagia, absent gag and absent throat sensations	Yes	Elevated TLC and ESR	Ground-glass opacities both lung fields	NA	Mechanical ventilation, antibiotics, anti-viral drugs, dysphagia rehabilitation/improving
Trigeminal neuropathy	de Freitas Ferreira et al./Brazil [86]	39/M	Left orofacial herpes zoster, left trigeminal neuralgia, fatiguability, diarrhoea,	No	Varicella-Zoster IgM-positive, nasopharyngeal swab-positive for SARS-CoV-2	NA	Left trigeminal nerve enhancement	IV acyclovir/improved

ESR erythrocyte sedimentation rate, *HCQ* hydroxychloroquine, *IVIG* intravenous immunoglobulins, *IgM* immunoglobulin M, *NA* not available, *TLC* total leukocyte count

Olfactory and gustatory dysfunction

Olfactory and gustatory dysfunction is accepted as an early symptom of COVID-19 infection. In a review of 24 studies by Mehraeen et al., anosmia, hyposmia, ageusia, and dysgeusia was a presenting feature in majority of the studies [69]. They found anosmia to be the most common olfactory/gustatory symptom. They concluded that SARS-CoV-2 may infect neural and oral tissue and thereby present with olfactory and gustatory symptoms. Another review by Kang et al. (21 studies) had similar observations [70]. They found that the use of intranasal or oral steroids enhanced the recovery of COVID-19-related olfactory/gustatory dysfunction [70]. We found 11 studies that specifically evaluated gustatory and olfactory functions in patients with COVID-19 infection [71–81]. Majority of patients had olfactory/gustatory dysfunction in addition to other symptoms like fever, cough, sore throat, and headache. The presence of olfactory/gustatory symptoms were not related to the severity of disease but related to the duration chemosensitive symptoms [78]. More patients were found to have chemosensitive dysfunction when examined with standard tests as compared with those who self-reported symptoms. By second week, 30 to 50% patients reported regression of olfactory and gustatory symptoms [78].

In an autopsy study of two patients that died of COVID-19 infection (one had anosmia as early feature), authors found inflammation and axonal damage in the olfactory bulb explaining the olfactory symptoms [94]. In both cases, olfactory striae were normal. Other finding was perivascular leukocyte infiltration in the basal ganglia. The olfactory bulb edema has also been demonstrated on cranial MRI of patients with COVID-19 infection [95]. His anosmia and dysgeusia improved by 14 days and olfactory bulb edema also subsided on repeat MRI at 24 days of illness. In a study of 18 COVID-19 patients who underwent Butanol threshold test and smell identification tests, the biopsies of the nasal mucosa revealed CD68 macrophages harbouring SARS-CoV-2 antigen in their stroma [96].

Cranial neuropathy

Various cranial neuropathies are described in patients with COVID-19 infection in relation to encephalopathy/encephalitis or GBS. However, isolated cranial neuropathies have also been described. Dinkin et al. described a 36-year-old male with constitutional symptoms, diplopia secondary to left 3rd, and bilateral 6th nerve palsy [82]. MRI showed hyperintensity on T2-weighted sequence and gadolinium enhancement of left 3rd cranial nerve. He showed partial improvement on intravenous immunoglobulin. Another 71-year-old female presented with painless right 6th cranial nerve palsy. She had gadolinium enhancement of optic nerve sheath. She showed spontaneous improvement in diplopia. Oliveira RMC et al. reported a 69-year-old male with stabbing occipital pain and diplopia secondary to trochlear nerve palsy [83]. He had evidence of vertebrobasilar vasculitis that showed improvement on intravenous methylprednisolone. Another patient reported by Wan et al. had left facial palsy along with pain in left mastoid region. He improved with anti-viral drugs [84]. Glossopharyngeal, vagus, and trigeminal neuropathy (with Herpes Zoster co-infection) have also been described in patients with COVID-19 [85, 86]. All these patients with cranial neuropathies showed lung involvement secondary to COVID-19 infection.

Patho-mechanism of nervous tissue involvement

Neuronal affinity and propagation

ACE 2 is widely expressed on nervous tissue cells like neurons, astrocytes, and oligodendrocytes. Substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb express ACE-2 receptor in high concentrations. In addition, respiratory epithelium, lung parenchyma, vascular endothelium, kidney cells, and intestinal epithelium also express ACE-2 [97, 98]. Virus may gain entry to nervous tissue from vascular endothelial cells. Once inside the nerve cell, SARS-CoV-2 can alter the cellular transport function to facilitate its transmission from one neuron to another [99, 100].

Since SARS-CoV-2 is a respiratory virus, the virus particles have been shown in the CD 68 macrophages in the biopsy of nasal tissues from patients presenting with COVID-19-related olfactory dysfunction [96]. Patients with olfactory dysfunction may have inflammation and edema of olfactory bulb [94, 95]. In animal studies, it has been shown that coronavirus may utilize olfactory pathway to gain entry into central nervous system [101]. Neuronal changes have been detected in hypothalamus and cortex of SARS-CoV victims [102]. Retrograde transmission of the virus from peripheral nerve terminals through nerve synapses with the help of neural proteins dynein and kinesin have also been postulated [98]. SARS-CoV-2 RNA has also been demonstrated in the CSF [98].

Mechanisms of involvement of peripheral nerves

The mechanism of involvement of peripheral nervous system is not fully understood. It is mostly thought to be immune-mediated. In patients with rapid evolution of GBS after the onset of COVID-19 symptoms, direct cytotoxic effects of virus on peripheral nerves is a postulated mechanism. Guillain-Barrè syndrome (GBS) is usually considered an immune-mediated disease of peripheral nerve myelin sheath or

Schwann cells. The glycoproteins on the surface of the virus resemble with glycoconjugates in human nervous tissue [55]. The antibodies formed against the viral surface glycoproteins acts against the glycoconjugates on the neural tissue. This mechanism of nerve injury is famously known as "molecular mimicry". SARS-CoV-2 shares two hexapeptides with human shock proteins 90 and 60. Both these proteins have immunogenic potentials, and they are among the 41 human proteins associated with Guillain-Barrè syndrome and chronic inflammatory demyelinating polyneuropathy [103]. The other neuropathies reported in patients with COVID-19 may also be secondary to immune-mediated mechanisms.

Mechanism of muscle involvement

The mechanism of myositis in COVID-19 infection is not fully understood. Skeletal muscles and other cells in the muscles like satellite cells, leukocytes, fibroblasts, and endothelial cells express ACE-2. Therefore, it is postulated that skeletal muscles are susceptible to direct muscle invasion by SARS-CoV-2 [104]. Animal studies suggest that children are more likely to get affected due to their immature muscle cells [25]. Other possible mechanisms suggested are immune complex deposition in muscles, release of myotoxic cytokines, damage due to homology between viral antigens and human muscle cells, and adsorption of viral protein on muscle membranes leading to expression of viral antigens on myocyte surface. Whether these postulated mechanisms for COVID-19-related myositis are also responsible for myalgia is also not known.

Conclusion

SARS-CoV-2 has a special affinity for the neural tissue. Olfactory and gustatory symptoms are accepted as an early manifestation of COVID-19 infection. Olfactory bulb inflammation and edema with axonal damage in patients with COVID-19 suggest an olfactory route entry of virus to involve the brain and other cranial nerves. The SARS-CoV-2 also involves peripheral nervous system. Myalgia is one of the common early symptoms of the disease. Guillain-Barrè syndrome and Miller-Fisher syndrome are increasingly being described in patients with preceding or concomitant COVID-19 disease. This points towards the involvement of peripheral nerves either by direct infection of nerves or by the mechanism of "molecular mimicry". There are also reports of myositis and rhabdomyositis secondary to COVID-19 disease. Since muscle also expresses ACE-2 receptors, direct muscle involvement by SARS-CoV-2 is postulated in addition to immune-mediated muscle damage.

Availability of data and material (data transparency) All data provided with the manuscript.

Authors' contributions VKP conceived and wrote the manuscript. RKG revised the manuscript. AG and NT wrote tables and collected data.

Compliance with ethical standards

Ethical approval The review does not require ethical clearance.

Conflict of interest The authors declare that they have no conflict of interests.

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