COVID-19 Neuromuscular presentations in patients with COVID-19

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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-Barré 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-Barré 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-Barré syndrome · Myositis · Rhabdomyolysis

The COVID-19 pandemic is caused by SARS-CoV-2, a member of the Coronavirusae 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 infected 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...
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-Barré 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,
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 quadriaparesis. 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 1

| 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%, dyspnoea 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%, dyspnoea 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
| 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 quadricep 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 | Generalised 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 |
| Gefen et al./USA [29] | 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 |

AST aspartate amiotransferase, ALT alanine transaminase, AF atrial fibrillation, CK creatine kinase, CRP C-reactive protein, EKG electrocardiogram, HCQ hydroxychloroquine, LDH lactate dehydrogenase
| 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—BL ground-glass opacities in lungs | AIDP | Mechanical ventilation, IVG-improved |
| Farzi et al./June 2020 [33] | 41/M | Fever, cough, dyspnea | 17 days | Parasthesia, quadriparesis | 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 plexuses and lumbar plexuses | Demyelinating neuropathy | HCQ, IVIG/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/M | Exposed to relative working in meat-processing plant | 20 days after exposure | Bifacial paralysis, no limb weakness | Persistent thrombocytosis, BL ground-glass opacities lungs, CSF-albumin-cytological dissociation | Acute paraparesis, arbovirus, acute-phase reactants, SARS-CoV-2 IgG-positive, CSF-albumin-cytological dissociation 1, CSF lymphocytosis 2 | IVIG, lopinavir, ritonavir, arbidol/recovered |
| Riva et al./May 2020 [42] | 6/F | Fever, headache, myalgia, anosmia, ageusia | 20 days | Sensory motor quadriparesis, dysarthria, dysphagia | CSF-albumin-cytological dissociation 1, CSF lymphocytosis 1 | Acute paraparesis, areflexic ascending quadriparesis, sensory deficit in hands and feet | AIDP |
| Zhao et al./May 2020 [43] | 54/F | Hypo-osmia, dysgeusia | 14 days | Acute multifocal paraparesis, tingling sensations in all 4 limbs | Mechanical ventilation, IVG-improved |

**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                                                                 |
|----------------------------------|---------|------------------|-------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 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 maseter weakness, B/L hypoglosal nerve palsy, hyporeflexia in B/L upper and lower limbs | Nasopharyngeal 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                                                                             |
| References                  | Age/sex | Preceding illness                  | Time to GBS | Symptoms/signs                                      | Lab tests                                                                 | Nerve conduction test                      | Treatment/outcome                                      |
|-----------------------------|---------|-----------------------------------|-------------|----------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------------------|
| 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, 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 ophthalmoplegia, difficulty in urination | CSF-albumin-cytological dissociation, bibasilar atelectasis with consolidation | 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 | Ortopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cells diss., CT chest—B/L interstitial infiltrates, MRI spin-contrast enhancement of the spinal nerve roots at all levels of the spine including the cauda equina | AIDP                                       | Mechanical ventilation, antibiotics/persistent weakness |
| Pfefferkorn 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 | Ortopharyngeal swab for RT-PCR SARS-CoV-2-positive, CT chest—B/L interstitial infiltrates, MRI spin-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, diarrhoea            | 14 days     | Areflexic ascending quadriparesis, facial diplegia | Ortopharyngeal 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                                      |
| References            | Age/sex | Preceding illness      | Time to GBS | Symptoms/signs                                                                 | Lab tests                                                                                           | Nerve conduction test                        | Treatment/outcome                                      |
|-----------------------|---------|------------------------|-------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------|
| Virani et al./April 2020 [57] | 55/M    | Fever, cough           | 10 days     | Lower limb weakness, paresthesia, neck pain, areflexic quadriaparesis, facial palsy, respiratory failure | Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, lymphocytopenia, CSF-albumin-cell 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          |
| Padroni et al./April 2020 [58] | 76/M    | Cough, hyposmia        | 5 days      | Lumbar pain and lower limb weakness, areflexic quadriaparesis, 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                           |
| Coen et al./April 2020 [59] | 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 |
| El Otmani et al./April 2020 [60] | 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 basilar opacities | Not done                                      | Mechanical ventilation, IVIG, HCQ/improved            |
| Marta-Enguita et al./April 2020 [61] | 54/M    | Fever, dry cough       | 10 days     | Numbness and weakness in B/L lower limbs, areflexic quadriaparesis           | 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            |
| El Otmani et al./April 2020 [60] | 70/F    | Fever, dry cough       | 3 days      | Acute flaccid areflexic quadriaparesis                                       | Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-albumin-cell diss., CT chest—B/L ground-glass opacities | AIDP                                          | IVIG/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, | Nasopharyngeal swab for RT-PCR SARS-CoV-2-positive, CSF-NA, CT chest—consolidation | NA                                            | Mechanical ventilation/died                            |
| References                          | Age/sex | Preceding illness                  | Time to GBS | Symptoms/signs                                                                 | Lab tests                                                                 | Nerve conduction test                      | Treatment/outcome                    |
|------------------------------------|---------|-----------------------------------|-------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------|----------------------------------------|
| Miller-Fisher syndrome             |         |                                   |             |                                                                               |                                                                           |                                             |                                        |
| Reyes-Bueno et al./June 2020 [62]  | 51/F    | Diarrhoea, odynophagia, cough      | 10 days     | Quadriplegia, left lateral rectus palsy, bifacial palsy, dysautonomia          | CSF-albumin-cytological dissociation                                      | Demyelinating neuropathy                   | IVIG/improving                         |
| Femández-Dominguez 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 oculomotor 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.
Guillain-Barré 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 ophthalmoplegia. 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. Ghiavand 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 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 35 patients) | 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) |
| 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 MRI normal | Hydroxychloroquine, azithromycin, IV Ig, rehab center 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 | Lower motor neuron involvement, denervation of four limbs | Normal brain/spine MRI | Hydroxychloroquine, azithromycin, IV Ig, methyl prednisolone, 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 | Demyelinating asymmetric motor polyradiculoneuropathy and moderate axonal sensorimotor neuropathy | Lower motor neuron involvement, denervation of four limbs | Normal brain/spine MRI | Hydroxychloroquine, azithromycin, IV Ig, methyl prednisolone, rehab center 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, IV Ig, methyl prednisolone, discharged to home after 40 days, mRS 2 |

ARDS acute respiratory distress syndrome, CRP reactive protein, IV Ig intravenous immunoglobulin, IgM immunoglobulin M, IgG immunoglobulin G, mRS modified Rankin Scale, MCA middle cerebral artery, MRI magnetic resonance imaging
| 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 | — | NA | NA | NA | NA |
| | Gomez-Iglesias N = 909 (online survey) [72] | Mean age 34, females 68.9% | Gustatory dysfunction | — | NA | NA | NA | NA |
| | Sayin et al. (telephonic survey) | Mean 38.63 ± 10.0 8.37.5% males | Impairment of smell/taste | — | NA | NA | NA | NA |
| | URTI cases (N = 128) COVID +VE 64, COVID −VE 64 [73] | +VE 38, −VE 43 (median) Impairment of smell/taste COVID +VE 46 (71.9%) COVID −VE 17 (26.6%) | — | — | — | — | — | — |
| | Lee et al. /N = 1345 (102 COVID +VE, 1243 −VE, sampled 1:3 ratio) [74] | Mean age 36.9 years/63.1% F 24–50 years/4F, 2M 48.8% gustatory dysfunction, 85.6% olfactory dysfunction, others symptoms—fever, cough | Anosmia/hyposmia COVID +VE 41.1% COVID −VE 4.2% Dysgeusia/ageusia COVID +VE 46.4% COVID −VE 5.6% | — | NA | NA | NA | NA |
| | Marchase-Ragona et al. (N = 6)/Italy [75] | Mean age 38 years, 43.1% F 24.5 years/42.3% Males 48.5 years/43.1% F 73.6% hyposmia, 69.4% hyposmia, 50% fever, 75% cough, 62.5% sore throat, 70.8% myalgia, 77.8% headache | — | — | — | — | — | — |
| | Lechien et al. (N = 417)/Europe [76] | Mean age 36.9 years/63.1% F 24–50 years/4F, 2M 48.8% gustatory dysfunction, 85.6% olfactory dysfunction, others symptoms—fever, cough | — | — | — | — | — | — |
| | Luers et al./Germany [77] | Mean age 36.9 years/63.1% F 73.6% hyposmia, 69.4% hyposmia, 50% fever, 75% cough, 62.5% sore throat, 70.8% myalgia, 77.8% headache | — | — | — | — | — | — |
| | Vaira et al./Italy N = 345 [78] | Mean age 48.5 years/42.3% Males 161/394, 41% olfactory/gustatory dysfunction, only olfactory 16%, only gustatory 2% | Self-reported olfactory/gustatory disturbance 256 (74.2%), combined 79.3%, isolated olfactory 8.6%, isolated gustatory 12.1% | — | NA | NA | NA | — |
| | Qui et al./multicentre, n = 394 [79] | Median age 39 years/57% males 161/394, 41% olfactory/gustatory dysfunction, only olfactory 16%, only gustatory 2% | — | — | — | — | — | — |
| | Biadsee et al./Israel n = 128 [80] | Mean age 36.25 3050 | Olfactory dysfunction 67%, anosmia 19.5%, impaired taste 52%, dry mouth | — | NA | NA | NA | — |
### Table 6 (continued)

| Type                  | Reference/country     | Age/sex | Clinical presentation                                                                 | Respiratory involvement | Blood parameters | Chest imaging | Neuroimaging | Treatment/outcome                                                                 |
|-----------------------|-----------------------|---------|---------------------------------------------------------------------------------------|--------------------------|-------------------|---------------|-------------|-----------------------------------------------------------------------------------|
|                      | Kosugi et al./Brazil n = 253 (145 COVID-19-positive) [81] | Mean age 36 years/59.1% females | 72 patients, facial pain 26%, masticatory muscle pain 11% 145 COVID-19 patients had sudden olfactory dysfuncion | 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       | B/L opacities | Enhancement of optic nerve sheaths and posterior tendon capsules s/o vasculitis of the vertebrobasilar system | IVIG, HCQ/partial improvement                                                     |
|                      | 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          | B/L ground-glass opacities | HCQ/improved                                                                  |
|                      |                       | 71/F    | Fever, cough, painless diplopia, right abducens palsy                               | Yes                      | Lymphopenia      | B/L opacities | Enhancement of optic nerve sheaths and posterior tendon capsules s/o vasculitis of the vertebrobasilar system | HCQ/improved                                                                  |
| IV                    |                       | 65/F    | Facial palsy                           | Normal                   | Mechanical ventilation, antibiotics, anti-viral drugs, dysphagia rehabilitation/improving | IV methylprednisolone/ improved | Arbidol, ribavirin/improved | B/L ground-glass opacities | No |
| Normal                | Ground-glass shadows in right lower lung | Normal | Arbidol, ribavirin/improved             |                         | Arbidol, ribavirin/improved | Normal | Ground-glass opacities | Mechanical ventilation, antibiotics, anti-viral drugs, dysphagia rehabilitation/improving | VI acyclovir/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 | B/L          | NA          | Mechanical ventilation, antibiotics, anti-viral drugs, dysphagia rehabilitation/improving | VI acyclovir/improved |
| 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 | VI 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 Mehrraeen 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) 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. In a review of 24 studies by Mehrraeen 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) 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.

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].

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-Barré syndrome (GBS) is usually considered an immune-mediated disease of peripheral nerve myelin sheath or
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 suggests 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-Barré 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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