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REVIEW

Myoclonus and cerebellar ataxia associated with COVID-19: a case report and systematic review

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Abstract

Background Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic in December 2019, neurological manifestations have been recognized as potential complications. Relatively rare movement disorders associated with COVID-19 are increasingly reported in case reports or case series. Here, we present a case and systematic review of myoclonus and cerebellar ataxia associated with COVID-19.

Methods A systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline using the PubMed and Ovid MEDLINE databases, from November 1, 2019 to December 6, 2020.

Results 51 cases of myoclonus or ataxia associated with COVID-19, including our case, were identified from 32 publications. The mean age was 59.6 years, ranging from 26 to 88 years, and 21.6% were female. Myoclonus was multifocal or generalized and had an acute onset, usually within 1 month of COVID-19 symptoms. Myoclonus occurred in isolation (46.7%), or with ataxia (40.0%) or cognitive changes (30.0%). Most cases improved within 2 months, and treatment included anti-epileptic medications or immunotherapy. Ataxia had an acute onset, usually within 1 month of COVID-19 symptoms, but could be an initial symptom. Concurrent neurological symptoms included cognitive changes (45.5%), myoclonus (36.4%), or a Miller Fisher syndrome variant (21.2%). Most cases improved within 2 months, either spontaneously or with immunotherapy.

Conclusions This systematic review highlights myoclonus and ataxia as rare and treatable post-infectious or para-infectious, immune-mediated phenomena associated with COVID-19. The natural history is unknown and future investigation is needed to further characterize these movement disorders and COVID-19.

Keywords Central nervous system · Cortical · Movement disorders · Post-infectious · SARS-CoV-2 · Subcortical

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in December 2019 and the ongoing worldwide pandemic of coronavirus disease 2019 (COVID-19) has now exceeded 65 million cases [1]. Although patients typically present with fever, cough, shortness of breath, myalgia, and fatigue, neurological manifestations involving the central and peripheral nervous system have been reported since the beginning of the pandemic [2]. Commonly described neurological manifestations include impairment of smell and taste, encephalopathy, acute cerebrovascular disease, epilepsy, and Guillain–Barré syndrome (GBS) [2–4]. In context of the large volume of COVID-19 cases, relatively rare post-infectious or para-infectious descriptions of movement disorders, predominately involving acute-onset myoclonus or cerebellar ataxia, are becoming increasingly evident.

Post-infectious or para-infectious myoclonus, characterized by paroxysmal, brief, involuntary contraction of a muscle or group of muscles, can be caused by various viral, bacterial, and parasitic infections [5]. However, myoclonus associated with infection is uncommonly reported in the literature and represent a minority of the numerous causes of myoclonus. Similarly, post-infectious or para-infectious

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cerebellar ataxia is rarely reported in adults [6]. Myoclonus and ataxia can occur together in opsoclonus-myoclonus-ataxia syndrome (OMAS) (or opsoclonus-myoclonus syndrome, OMS), along with opsoclonus, or high-frequency bursts of multidirectional saccades, and cognitive impairment. OMAS is a rare disorder that is thought to be immune-mediated, with primarily para-neoplastic or para-infectious etiologies [6, 7]. Taken together, the ongoing COVID-19 pandemic has enabled the evaluation of myoclonus and ataxia as post-infectious or para-infectious phenomena.

Here, we report a patient with acute-onset myoclonus and cerebellar ataxia associated with COVID-19. A systematic review of the literature was completed to comprehensively summarize cases of myoclonus or ataxia associated with COVID-19, to characterize the clinical presentation, investigations, treatments, and outcomes of these movement disorders and COVID-19, and to discuss potential pathophysiological mechanisms.

Methods

Case report

Written informed consent was obtained from the patient to publish this case report, including the use of video material. The following data were extracted from the patient's chart: patient age and sex, SARS-CoV-2 testing status, COVID-19 disease course, myoclonus and ataxia characteristics, other neurological symptoms and signs, results of investigations, treatments administered for myoclonus and ataxia, and clinical outcome.

Systematic literature review

Cases of myoclonus or ataxia associated with COVID-19 were identified through a systematic review of the literature according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline [8]. The search was completed from November 1, 2019 to December 6, 2020 from the PubMed and Ovid MEDLINE databases using the following keywords: ["COVID" OR "coronavirus" OR "SARS-CoV-2"] AND ["myoclonus" OR "ataxia" OR "tremor"]. The search term "tremor" was used to capture any potentially misclassified movement phenomenology. The search was restricted to publications in peer-reviewed journals in English. Case reports and case series were included if they contained: (1) description of patients with SARS-CoV-2 infection, and (2) description of myoclonus or ataxia. Other publication types were reviewed for data involving novel cases. The references of publications were reviewed to identify additional cases. Publications and cases were excluded if myoclonus or ataxia could be attributed to a non-infectious etiology. For each publication the following data were extracted: patient age and sex, SARS-CoV-2 testing status, COVID-19 disease course, myoclonus and ataxia characteristics, other neurological symptoms and signs, results of investigations, treatments administered for myoclonus and ataxia, and clinical outcome.

Results

Case report

A 44-year-old, right-hand-dominant male of Chinese descent who was otherwise healthy presented with a 4-day history of acute-onset generalized jerky movements, difficulty speaking, difficulty ambulating, and short-term memory impairment. Twelve days before symptom onset, he developed fever, myalgia, cough, fatigue, hyposmia, and hypogeusia, with a positive nasopharyngeal RT-PCR test for SARS-CoV-2. Fever, myalgia, cough, and fatigue resolved before symptom onset. Hyposmia and hypogeusia persisted, but he did not endorse any other neurological symptoms.

Neurological examination demonstrated saccadic intrusions on smooth pursuit, but no ocular flutter or opsoclonus. He had mild rigidity in the upper extremities with activation maneuvers. Spontaneous, action-induced, posture-induced, and tactile stimuli sensitive myoclonus was observed in the face, upper extremities, and lower extremities, without hyperekplexia. He had occasional mild dysarthria, potentially consistent with speech-activated myoclonus. There was dysmetria and dysdiadochokinesia with superimposed action-induced myoclonus in the upper and lower extremities. Myoclonus prevented him from standing independently and he had a wide-based, ataxic gait. The remainder of the neurological examination was normal. During the hospital admission, the patient scored 14/30 on the Montreal Cognitive Assessment (MoCA), with impairment primarily in attention and delayed recall.

Laboratory investigations were unremarkable and repeat nasopharyngeal RT-PCR testing for SARS-CoV-2 was negative. Cerebrospinal fluid (CSF) analysis was unremarkable, including negative RT-PCR testing for SARS-CoV-2. Autoimmune antibody testing was not performed. Computed tomography (CT) of the head and brain magnetic resonance imaging (MRI) with contrast were unremarkable. Electroencephalography (EEG) showed non-specific, generalized background slowing, without electrographic correlates for the patient's ongoing myoclonus. Somatosensory evoked potentials and electromyography (EMG) were not performed.

He was treated with methylprednisolone 1000 mg IV daily for 5 days, from day 6 to 10 after symptom onset, and had some improvement of spontaneous myoclonus over the

5-day course, but action-induced myoclonus and ataxia persisted (ESM Video 1). Action-induced and stimuli sensitive myoclonus were suggestive of a cortical etiology. Consequently, clonazepam was started on day 10 after symptom onset and increased to 0.75 mg PO BID over 3 days, with some improvement. Subsequently, levetiracetam was started on day 14 after symptom onset and increased to 1000 mg PO BID over 2 days. He was discharged from hospital on day 18 after symptom onset. At that time, he had minimal spontaneous myoclonus, mild posture-induced myoclonus, low-amplitude action-induced myoclonus, and the ability to ambulate independently with a slightly wide-based gait. His myoclonus and ataxic gait resolved within 1 week after discharge. At 2 months after symptom onset, he scored 26/30 on the MoCA.

Systematic literature review

A PRISMA flowchart detailing the selection of publications is shown in Fig. 1. The literature search identified 38 publications involving cases of myoclonus or ataxia associated with COVID-19. These consisted of 25 case reports, 11 case series, 1 retrospective study, and 1 review. Six publications (3 case reports, 2 case series, and 1 retrospective study) were excluded, because cases of myoclonus or ataxia could be attributed to a non-infectious etiology. A total of 32 publications were included in the final analysis. Including our case report, there were 51 cases of myoclonus or ataxia associated with COVID-19 identified. Of these, 23.5% (12/51) of cases had myoclonus and ataxia [9–16], 35.3% (18/51) of cases had myoclonus without ataxia [17–23], and 41.2% (21/51) of cases had ataxia without myoclonus [24–40]. Demographic information and COVID-19 characteristics are summarized in Table 1 and neurological features, investigations, treatments, and outcomes are summarized in Table 2.

Overall demographics

Cases of myoclonus or ataxia associated with COVID-19 were reported worldwide. Specifically, cases were reported from the USA ($n=14$), France ($n=13$), Spain ($n=8$), Italy ($n=6$), Belgium, Canada, India, Iran, Japan, Netherlands, New Zealand, Switzerland, and the United Kingdom (each $n=1$). One case had an unclear country of origin. The mean age was 59.6 ± 14.5 (standard deviation, SD) years and the median age was 62.5 years (IQR 50–72), with a minimum

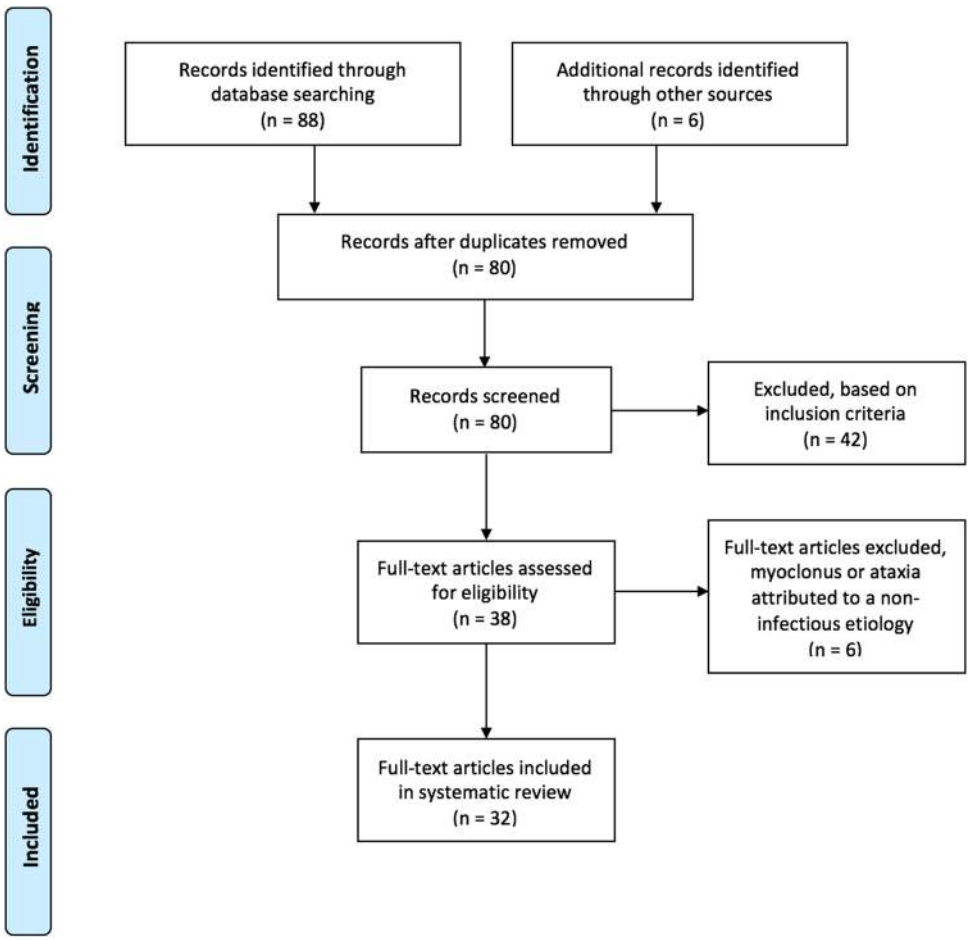

Fig. 1 PRISMA flowchart detailing the selection of publications for this systematic review of myoclonus and ataxia associated with COVID-19

Table 1 Summary of demographic information and COVID-19 characteristics

Publication	Country	Age	Sex	Medical history	COVID-19 symptoms	Mechanical ventilation	CSF SARS-CoV-2 RT-PCR
Cases with myoclonus and ataxia							
Chan et al. (case report)	Canada	44	M	None	Fever, myalgia, cough, fatigue, hyposmia, hypogeusia	No	Negative
Anand et al. [9]	USA	71	M	Not reported	Confusion and gait disturbance at presentation	No	N/A
Chaumont et al. [10]	France	62	M	Hypertension, diabetes mellitus	Fever, cough, ageusea, dyspnea	Yes	Negative
Chaumont et al. [10]	France	72	M	Hypertension, diabetes mellitus, obesity, urothelial carcinoma in remission	Fever, cough, dyspnea	Yes	Negative
Chaumont et al. [10]	France	50	M	Diabetes mellitus	Cough, dyspnea	Yes	Negative
Chaumont et al. [10]	France	66	M	Obstructive sleep apnea	Cough, dyspnea, anosmia, diarrhea	Yes	Negative
Delorme et al. [11]	France	72	M	Not reported	Fever, cough, anosmia	No	Negative
Dijkstra et al. [12]	Belgium	44	M	None	Fever, mild respiratory complaints, anosmia	No	Negative
Grimaldi et al. [13]	France	72	M	Previous transient global amnesia	Arthralgia, sore throat, fever	No	Negative
Sanguinetti and Ramdhani [14]	USA	57	M	Type 2 diabetes mellitus, hypertension, dyslipidemia	Nausea, fever, diarrhea, myalgia	No	N/A
Schellekens et al. [15]	Netherlands	48	M	Asymptomatic HIV	Fever, headache, cough, fatigue	No	Negative
Shah and Desai [16]	India	Middle-aged	M	Not reported	COVID-19 lung infection, details not reported	No	N/A
Cases with myoclonus, without ataxia							
Anand et al. [9]	USA	47	M	Not reported	Headache, odynophagia, cough, fever	Yes	N/A
Anand et al. [9]	USA	28	M	Not reported	Fever, dyspnea, odnynophagia, chest pain, nausea, vomiting, abdominal pain	Yes	N/A
Anand et al. [9]	USA	73	M	Not reported	Cough, generalized weakness	Yes	N/A
Anand et al. [9]	USA	64	M	Not reported	Cough, dyspnea, fever	Yes	N/A
Anand et al. [9]	USA	66	M	Not reported	Cough, dyspnea, fever	Yes	N/A
Anand et al. [9]	USA	72	M	Not reported	Nausea, vomiting, cough	Yes	N/A
Anand et al. [9]	USA	62	M	Not reported	Cough, dyspnea, fever	Yes	N/A
Borroni et al. [17]	Italy	54	F	Hypertension	Fever, cough, dyspnea	No	N/A
Borroni et al. [17]	Italy	80	M	None	Dyspnea, fever, cough	No	Negative
Cuhna et al. [18]	France	67	M	Hypertension, poliomyelitis	ICU admission, no further details	Yes	N/A
Cuhna et al. [18]	France	66	F	Hypertension, nephroangiosclerosis, severe renal insufficiency stage V, hepatitis B healed	ICU admission, no further details	Yes	N/A
Khoo et al. [19]	United Kingdom	65	F	Alzheimer's disease, osteoarthritis, gastroesophageal reflux disease	Cough, fever, myalgia, diarrhea	No	Negative

Table 1 (continued)

Publication	Country	Age	Sex	Medical history	COVID-19 symptoms	Mechanical ventilation	CSF SARS-CoV-2 RT-PCR
Méndez-Guerro et al. [20]	Spain	58	M	Hypertension, dyslipidemia	Cough, fever, nausea, shortness of breath	Yes	N/A
Muccioli et al. [21]	Italy	58	M	Hypertension	Fever, cough, dyspnea	Yes	Negative
Rábano-Suárez et al. [22]	Spain	63	M	Generalized anxiety disorder	Fever, anosmia, shortness of breath	Yes (for management of myoclonus)	N/A
Rábano-Suárez et al. [22]	Spain	88	F	Hypertension, hypothyroidism, non-functioning pituitary adenoma, mild cognitive decline	Anosmia, fever, shortness of breath	No	N/A
Rábano-Suárez et al. [22]	Spain	76	M	None	Fever, malaise, cough, anosmia, ageusia, myalgia	No	N/A
Ros-Castelló et al. [23]	Spain	72	F	Hypertension, asthma	Fever, shortness of breath	Yes	N/A
Cases with ataxia, without myoclonus							
Ashraf and Sajed [24]	USA	26	F	Obesity, post-traumatic stress disorder, depression, asthma	None	No	N/A
Balestrino et al. [25]	Italy	73	M	Hypertension, type 2 diabetes mellitus	Asthenia, gait ataxia, confusion, drowsiness at onset Urinary incontinence, fever, dyspnea	No	N/A
Delorme et al. [11]	France	60	F	Temporal lobe epilepsy (hippocampal sclerosis)	Fever, cough, diarrhea	No	Negative
Diezma-Martín et al. [26]	Spain	70	M	Chronic obstructive pulmonary disease	Fever	No	Negative
Fadakar et al. [27]	Iran	47	M	None	Fatigue, generalized body pain, cough	No	Positive
Fernández-Domínguez et al. [28]	Spain	74	F	Hypertension, follicular lymphoma	Respiratory symptoms, no further details	No	Negative
Gutiérrez-Ortiz et al. [29]	Spain	50	M	Asthma	Cough, malaise, headache, low back pain, fever, anosmia, ageusia	No	Negative
Hayashi et al. [30]	Japan	75	M	Alzheimer's disease	Diarrhea, urinary incontinence, fever	No	N/A
Kopscik et al. [31]	USA	31	M	None	None	No	N/A
Lahiri and Ardila [32]	Unclear	72	M	Not reported	SARS-CoV-2 pneumonia, no further details	Not reported	N/A
Lantos et al. [33]	USA	36	M	Remote strabismus	Fever, chills, myalgia	No	N/A
Lowery et al. [34]	USA	45	M	Dyslipidemia, hypertension, Crohn's disease	Sinus congestion, cough, chest tightness, dyspnea	Yes	N/A
Manganotti et al. [35]	Italy	49	F	Not reported	Fever, cough, dyspnea, hyposmia, ageusia	No	Negative
Manganotti et al. [36]	Italy	50	F	None	Fever, cough, dysgeusia	No	N/A

Table 1 (continued)

Publication	Country	Age	Sex	Medical history	COVID-19 symptoms	Mechanical ventilation	CSF SARS-CoV-2 RT-PCR
Perrin et al. [37]	France	64	M	End-stage renal disease, peritoneal dialysis, diabetes mellitus, hypertension, dyslipidemia, sleep apnea, smoking	Fever, dyspnea, cough, diarrhea, myalgia, headache	No	Negative
Perrin et al. [37]	France	53	F	None	Fever, dyspnea, headache	Yes	Negative
Perrin et al. [37]	France	51	M	None	Fever, dyspnea, anorexia	Yes	Negative
Perrin et al. [37]	France	67	M	Kidney transplantation recipient (C3 glomerulopathy)	Fever, dyspnea, cough, myalgia, headache, anosmia, dysgeusia	No	Negative
Povlow and Auerbach [38]	USA	30	M	None	Nausea, vomiting	No	N/A
Sartoretti et al. [39]	Switzerland	60	M	Hypertension, asthma	Cough, fever	No	N/A
Wright et al. [40]	New Zealand	79	M	Asbestosis, non-disabling stroke, mild cognitive impairment, type 2 diabetes mellitus, hypertension, prostatic hypertrophy	Diarrhea	No	N/A

of 26 years and a maximum of 88 years. There were 11 females (21.6%), with a mean age of 59.7 ± 16.3 (SD) years and median age of 60 years (IQR 51.5–69), and 40 males (78.4%), with a mean age of 59.5 ± 14.1 (SD) years and median age of 63 years (IQR 49–72).

COVID-19 characteristics

All cases reported SARS-CoV-2 infection, with 45 cases reporting positive results from SARS-CoV-2 RT-PCR testing, 2 cases reporting SARS-CoV-2 pneumonia without explicit RT-PCR testing [32, 36], and 2 cases reporting clinical diagnoses of SARS-CoV-2 pneumonia in context of a scarcity of RT-PCR testing [22]. Of the 46 cases that described COVID-19 symptoms, the most common symptoms were fever at 76.1% (35/46), cough at 60.9% (28/46), dyspnea at 47.8% (22/46), hypo/anosmia and/or hypo/ageusia at 26.1% (12/46), myalgia at 17.4% (8/46), diarrhea at 15.2% (7/46), headache at 13.0% (6/46), nausea with or without vomiting at 10.9% (5/46), and fatigue at 10.9% (5/46). Two cases reported odynophagia and two cases reported urinary incontinence. Other symptoms included abdominal pain, anorexia, arthralgia, chest pain, sore throat, low back pain, and sinus congestion, with one case for each. Three cases were asymptomatic for COVID-19 and presented with neurological symptoms [9, 24, 31]. Of the five cases that did not describe specific COVID-19 symptoms, three had respiratory symptoms or SARS-CoV-2 pneumonia without further details [16, 28, 32] and two were admitted to the intensive care unit (ICU) for mechanical ventilation without further details [18]. Overall, 37.3% (19/51) of cases required mechanical ventilation for respiratory management and one case required mechanical ventilation for management of myoclonus.

Myoclonus associated with COVID-19

There were 30 cases of myoclonus [9–23], including our case report, with a mean age of 62.7 ± 12.6 (SD) years and a median age of 65 years (IQR 57–72). All cases described the development of myoclonus after COVID-19 symptoms. In the 21 cases with a clear time of onset for myoclonus, the median latency between COVID-19 symptoms and myoclonus was 13 days (IQR 11–21), with a minimum of 7 days and a maximum of 48 days. All cases, except one case of focal diaphragmatic myoclonus [17], described multifocal or generalized myoclonus, often involving a combination of the face, upper extremities, and lower extremities. Negative myoclonus was reported in four cases [22, 23]. Myoclonus was activated by action in 56.7% (17/30) cases and by sensory stimuli in 46.7% (14/30) of cases. Isolated myoclonus was reported in 46.7% (14/30) of cases. When there were concurrent

Table 2 Summary of neurological features, investigations, treatments, and outcomes

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Cases with myoclonus and ataxia													
Chan et al. (case report)	44	M	12 days	Face, upper extremities, lower extremities	Action, posture, tactile stimuli	12 days	Limbs, gait	Saccadic intrusions, attention and memory impairment	CT: Unremarkable MRI: Unremarkable	EEG: Minor generalized slowing	Methylprednisolone 1000 mg IV daily for 5 days (day 6–10 after symptom onset); clonazepam 0.75 PO BID starting day 10; levetiracetam 1000 mg PO BID starting day 14	Improvement of spontaneous myoclonus after methylprednisolone. Myoclonus improved after clonazepam and levetiracetam. Discharged day 18 after symptom onset, myoclonus and ataxic gait resolved within 1 week after discharge	Post-infectious
Anand et al. 2020 [9]	71	M	Unclear	Generalized	Action	Onset	Gait	Confusion	MRI: Diffuse pachymeningeal enhancement	EEG: Mild diffuse background slowing	Levetiracetam, valproic acid	Myoclonus: Resolved after 14 days Ataxia: Not reported	Myoclonus: Post-infectious, metabolic, hypoxic Ataxia: COVID-19 presentation

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Chaumont et al. 2020 [10]	62	M	Unclear, immediately after extubation	Upper extremities	Posture, action	Unclear, immediately after extubation	Unspecified	Confusion, dysexecutive syndrome, memory deficit, swallowing disorder, left facial palsy, right upper limb and left-sided weakness, lower limb areflexia, upper limb hyperreflexia, dysautonomia	MRI: Small subcortical ischemic stroke in right middle cerebral artery territory	EEG: Global slowing EMG: Demyelinating asymmetric motor polyradiculoneuropathy of limbs and axonal sensorimotor neuropathy of limbs	IVIG 0.4 mg/kg daily for 5 days (day 23–27 after symptom onset)	Myoclonus: Unclear, persisted 3 weeks after discharge Ataxia: Not reported	Post-infectious
Chaumont et al. 2020 [10]	72	M	Unclear, immediately after extubation	Upper extremities	Posture, action	Unclear, immediately after extubation	Unspecified	Confusion, paranoid delusion, visual and auditory hallucinations, frontal syndrome, memory deficit, swallowing disorder, tetraparesis, slowed saccades, generalized hyperreflexia, neurogenic pain, dysautonomia	MRI: Unremarkable	EEG: Global slowing EMG: Demyelinating motor polyradiculoneuropathy and axonal sensorimotor neuropathy of limbs	IVIG 0.4 mg/kg daily for 5 days (day 18–22 after symptom onset)	Myoclonus: Unclear, persisted 3 weeks after discharge Ataxia: Not reported	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Chaumont et al. 2020 [10]	50	M	48 days	Upper extremities	Posture, action	48 days	Unspecified	Confusion, paranoid delusion, frontal syndrome, memory deficit, swallowing disorder, tetraparesis, slowed saccades, generalized hyperreflexia, dysautonomia	MRI: Unremarkable	EEG: Global slowing EMG: Motor denervation of limbs. Normal motor evoked potential amplitude	IVIG 0.4 mg/kg daily for 5 days (day 23–27 after symptom onset)	Myoclonus: Unclear, persisted 3 weeks after discharge Ataxia: Not reported	Post-infectious
Chaumont et al. 2020 [10]	66	M	40 days	Upper extremities	Posture, action	20 days	Unspecified	Confusion, paranoid delusion, visual hallucinations, frontal syndrome, memory deficit, tetraparesis, upper limb hyperreflexia, lower limb areflexia, dysautonomia	MRI: Unremarkable	EEG: Normal EMG: Demyelinating motor polyradiculoneuropathy of limbs	IVIG 0.4 mg/kg daily for 5 days (day 6–10 after symptom onset)	Myoclonus: Unclear, persisted 3 weeks after discharge Ataxia: Not reported	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Delorme et al. 2020 [11]	72	M	15 days	Upper extremities	None	15 days	Unspecified	Psychomotor agitation, cognitive and behavioural frontal lobe syndrome	MRI: Unremarkable FDG-PET: Bilateral prefrontal and left parieto-temporal hypometabolism, cerebellar vermis hypermetabolism	EEG: Normal	IVIG 2 g/kg	Myoclonus and ataxia: Resolved	Post-infectious
Dijkstra et al. 2020 [12]	44	M	2 weeks	Face, speech, arms, trunk	Action, tactile stimuli, auditory stimuli	2 weeks	Limbs, gait	Saccadic intrusions, ocular flutter, attention and memory deficits, perseveration, impulsivity, anxiety, hypervigilance, insomnia	MRI: Unremarkable	N/A	Methylprednisolone 1000 mg IV daily for 5 days (day 7–11 after symptom onset); IVIG 0.4 g/kg daily for 3 days (day 15–17 after symptom onset)	Myoclonus and ataxia: Slow response to methylprednisolone, resolved within 2 months	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Grimaldi et al. 2020 [13]	72	M	17 days	Proximal limbs	Action, stimuli	17 days	Limbs	Dysarthria	MRI: Unremarkable FDG-PET: Putamen and cerebellum hypermetabolism, diffuse cortical hypometabolism	EEG: Diffuse background slowing	IVIG 0.4 g/kg daily for 5 days (day 6–10 after symptom onset); methylprednisolone 1000 mg IV daily for 5 days (day 13–17 after symptom onset)	Myoclonus and ataxia: No response to IVIG; cessation of myoclonus and upper limb dysmetria by day 20 after symptom onset	Post-infectious
Sanguinetti and Ramdhani 2020 [14]	57	M	Unclear, at least 5 days	Upper extremities, lower extremities	Action	Unclear, at least 5 days	Gait	Opsoclonus	MRI: Unremarkable	N/A	Clonazepam; IVIG 0.4 g/kg daily for 5 days; methylprednisolone 40 mg BID	Myoclonus and ataxia: Improved over hospitalization	Post-infectious
Schellekens et al. 2020 [15]	48	M	13 days	Face, trunk, limbs	Posture, action	13 days	Limbs, gait	Saccadic intrusions, hypermetric saccades	MRI: Unremarkable	N/A	Levetiracetam	Myoclonus: Resolved within days of starting levetiracetam Ataxia: Improved by 49 days after symptom onset	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Shah and Desai 2020 [16]	Middle-aged	M	Unclear, at least 3 weeks	Unspecified	None	Unclear, at least 3 weeks	Speech, limbs, trunk, gait	Opsoclonus	MRI: Unremarkable	N/A	Methylprednisolone 1000 mg IV daily, valproate 20 mg/kg/day, clonazepam 2 mg/day, levetiracetam 2000 mg/day	Myoclonus and ataxia: Resolved in 1 week after treatment	Post-infectious
Cases with myoclonus, without ataxia													
Anand et al. 2020 [9]	47	M	8 days	Generalized	Stimuli			None	CT: No acute	N/A	Ketamine, dexmedetomidine	Resolved after 2 days	Post-infectious, metabolic, medication, hypoxic
Anand et al. 2020 [9]	28	M	8 days	Generalized	Stimuli			None	CT: No acute	N/A	Lorazepam, midazolam, dexmedetomidine	Resolved after 1 day	Post-infectious, metabolic, medication, hypoxic
Anand et al. 2020 [9]	73	M	10 days	Torso, upper extremities	Stimuli			None	CT: No acute	N/A	Levetiracetam	Resolved after 2 days	Post-infectious, metabolic, medication, hypoxic
Anand et al. 2020 [9]	64	M	11 days	Upper extremities	Stimuli			None	MRI: Equivocal right temporal T2 hyperintensity	N/A	Dexmedetomidine	Resolved after 1 day	Post-infectious, metabolic, medication, hypoxic
Anand et al. 2020 [9]	66	M	12 days	Upper extremities, face	None			None	CT: No acute	N/A	Dexmedetomidine	Resolved after 2 days	Post-infectious, metabolic, medication, hypoxic

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Anand et al. 2020 [9]	72	M	16 days	Generalized	Stimuli			None	CT: No acute	EEG: Muscle artifact	Valproic acid, levetiracetam, lorazepam, dexmedetomidine	Improved myoclonus, though reintubated	Post-infectious, metabolic, medication, hypoxic
Anand et al. 2020 [9]	62	M	12 days	Generalized	Stimuli			None	N/A	EEG: Generalized dysfunction, occasional low-amplitude sharp transients, myogenic activity	Valproic acid, primidone, clonazepam, lorazepam	Improved starting at least 10 days after symptom onset	Post-infectious, metabolic, medication, hypoxic
Borroni et al. 2020 [17]	54	F	Within 2 weeks	Diaphragm, left limbs	Posture			None	MRI: Unremarkable	EEG: Normal EMG: Rhythmic and synchronous contractions of diaphragm at 3 Hz with abdominal contractions	Clonazepam 0.5 mg TID	Significant benefit of clonazepam	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Borroni et al. 2020 [17]	80	M	23 days	Diaphragm	None			None	CT: No acute	EEG: Lateralized periodic discharges synchronous and asynchronous with diaphragmatic myoclonus	Levetiracetam 1000 mg BID	Resolved after 3 days of levetiracetam, with improvement of EEG features	Post-infectious
Cuhna et al. 2020 [18]	67	M	Unclear, after ICU discharge	Extremities	None			Mild right hemiparesis	MRI: Corpus callosum microbleeds DaTScan: Normal	EMG: Myoclonus with 24–44 ms duration and post-myoclonic inhibition 36–86 ms. Duration consistent with cortical–subcortical myoclonus	Not reported	Not reported	Post-infectious, metabolic, hypoxic

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Cuhna et al. 2020 [18]	66	F	Unclear, after ICU discharge	Upper extremities	Posture, action			Critical illness myopathy	MRI: Deep and peripheral microbleeds DaTScan: Normal	EMG: Myoclonus with 70–94 ms duration and long loop C-reflex with 50 ms latency. Duration consistent with cortical-subcortical myoclonus, long loop C-reflex consistent with cortical myoclonus	Not reported	Not reported	Post-infectious, metabolic, hypoxic
Khoo et al. 2020 [19]	65	F	7 days	Face, tongue, upper extremities, lower extremities	Tactile stimuli, visual stimuli, auditory stimuli			Confusion, ocular flutter, convergence spasm with miosis, expressive aphasia, perseveration, echopraxia, visual hallucinations	MRI: Unremarkable	N/A	Levetiracetam 750 mg BID and clonazepam 0.25 mg BID; methylprednisolone 1000 mg IV daily for 3 days (day 14–16 after symptom onset), then prednisone 1 mg/kg PO daily	Partially improved after levetiracetam and clonazepam. Progressively improved after corticosteroids, discharged 10 days after	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Méndez-Guerro et al. 2020 [20]	58	M	34 days	Upper extremities	Action			Postural tremor upper extremities, decreased consciousness, opsoclonus, upgaze restriction, round the house vertical saccades, impaired smooth pursuit, tetraparesis, right-sided hypokinetic-rigid syndrome, hypomimia, decreased blinking, glabellar tap	CT/CTA: Unremarkable MRI: Normal DaTSPECT: Bilateral decrease in presynaptic dopamine uptake in putamen	EEG: Unremarkable EMG: 7 Hz rest tremor (completed after myoclonus resolved)	None	Spontaneously resolved	Post-infectious
Muccioli et al. 2020 [21]	58	M	At least 23 days	Multifocal	Action, tactile stimuli			None	MRI: Cerebral small-vessel disease	EEG: Unremarkable EMG: Myoclonus with 140–220 ms duration. Duration consistent with subcortical myoclonus	Clonazepam and levetiracetam	Marked improvement within 5 days of starting treatment	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Rábano-Suárez et al. 2020 [22]	63	M	9 days	Face, limbs (positive, negative)	None			None	CT: Unremarkable MRI: Unremarkable	EEG: Mild diffuse slowing	Propofol; levetiracetam, valproic acid, clonazepam; methylprednisolone 1000 mg IV daily for 5 days; plasmapheresis, 5 treatments	No improvement with levetiracetam, valproic acid, clonazemam. Slight improvement with methylprednisolone. Improvement after plasmapheresis	Post-infectious
Rábano-Suárez et al. 2020 [22]	88	F	3 weeks	Face, limbs (positive, negative)	Action, tactile stimuli, auditory stimuli			None	CT: Unremarkable	EEG: Mild diffuse slowing	Methylprednisolone 250 mg IV for 3 days	Resolved after methylprednisolone	Post-infectious
Rábano-Suárez et al. 2020 [22]	76	M	11 days	Face, limbs (positive, negative)	Action, tactile stimuli, auditory stimuli			None	CT: Unremarkable MRI: Unremarkable	EEG: Mild diffuse slowing	Clonazepam and levetiracetam; methylprednisolone 250 mg IV for 3 days	No improvement with clonazepam or levetiracetam. Spontaneous progressive improvement, 2 weeks after methylprednisolone	Post-infectious

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Ros-Castelló et al. 2020 [23]	72	F	35 days	Upper extremities (positive), lower extremities (negative)	Action, tactile stimuli, auditory stimuli			None	MRI: Cortical and brainstem ischemic lesions	N/A	Clonazepam	Almost resolved after 2 days of clonazepam	Hypoxic
Cases with ataxia, without myoclonus													
Ashraf and Sajed 2020 [24]	26	F				Onset	Right limb, gait	Headache, vomiting, right numbness and tingling, right weakness, dysarthria	CTA: Unremarkable MRI: Acute right cerebellar and cerebellar peduncle infarct MRA: Narrowing of right superior cerebellar artery	N/A	Aspirin, clopidogrel, statin	Not reported	Ischemic stroke

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Balestrino et al. 2020 [25]	73	M				Onset	Gait	Confusion, drowsiness	CT: Unremarkable	EEG: Sporadic, focal polymorph delta in anterior-frontal left, sporadic spikes without epileptic correlate in fronto-temporal lobe, predominately left	No specific neurological treatment. Treatment with lopinavir/ritonavir, chloroquine, steroids, levofloxacin	Resolved within 6 weeks	COVID-19 presentation
Delorme et al. 2020 [11]	60	F				Onset	Limbs, gait	Psychomotor agitation, anxiety, depressed mood, dysexecutive syndrome, dysarthria, nysgtagmus	MRI: Right mesial sclerosis (known) FDG-PET: Hypometabolism in bilateral orbito-frontal cortices, hypermetabolism in bilateral striatum and cerebellar vermis	EEG: Normal	Pulse corticosteroids 2 mg/kg daily for 3 days	Resolved within a few days of starting corticosteroids	COVID-19 presentation

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Diezma-Martín et al. 2020 [26]	70	M				17 days	Ataxia/tremor of voice, upper extremities, lower extremities, gait	Orthostatic tremor	MRI: Unremarkable	N/A	Clonazepam	Slight improvement with clonazepam. Improved slowly in month after discharge	Post-infectious
Fadakar et al. 2020 [27]	47	M				3 days	Limbs, gait, trunk	Vertigo, headache, dysarthria, hypermetric saccades, saccadic pursuit, loss of optokinetic nystagmus, impaired vestibular suppression response, end-gaze rotational nystagmus	MRI: FLAIR hyperintensities in bilateral cerebellar hemispheres and vermis, cerebellar cortical meningeal enhancement	N/A	No specific neurological treatment. Treatment with lopinavir/ritonavir 400/100 mg BID for 14 days	Marked improvement, within 14 days of treatment start, continuing to 1 month	Para-infectious, acute cerebellitis
Fernández-Domínguez et al. 2020 [28]	74	F				12–15 days	Gait	Lower extremity areflexia	MRI: Unremarkable	EMG: Slight F-wave delay in upper limbs	IVIG 20 g daily for 5 days	Improvement after IVIG	Miller Fisher syndrome variant

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Gutiérrez-Ortiz et al. 2020 [29]	50	M				3 days	Gait	Right internuclear ophthalmoplegia, right oculomotor nerve palsy, perioral paresthesia, generalized areflexia	CT: Unremarkable	N/A	IVIG 0.4 g/kg daily for 5 days (day 5–9 after symptom onset)	Resolved within 2 weeks after IVIG	Miller Fisher syndrome variant
Hayashi et al. 2020 [30]	75	M				Onset	Limbs, gait	None	MRI: Diffusion restriction in the splenium of corpus callosum	N/A	No specific neurological treatment	Resolved 2 days after onset	COVID-19 presentation
Kopscik et al. 2020 [31]	31	M				Onset	Limbs, gait	Bilateral cranial nerve VI palsy, vertical nystagmus, left cranial nerve VII palsy, left cranial nerve XII dysfunction, numbness, upper and lower extremities, lower extremity areflexia	MRI: Unremarkable	N/A	IVIG	Improvement and return of patellar reflexes after IVIG	Miller Fisher syndrome
Lahiri and Ardila 2020 [32]	72	M				Onset	Unspecified	Encephalopathy	N/A	N/A	Not reported	Not reported	COVID-19 presentation

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Lantos et al. 2020 [33]	36	M				4 days	Gait	Partial left cranial nerve III palsy, decreased sensation in lower extremities, areflexia	MRI: Enlargement and enhancement of left cranial nerve III	N/A	IVIG	Improvement after IVIG	Miller Fisher syndrome variant
Lowery et al. 2020 [34]	45	M				2 weeks	Gait	Left facial and bilateral lower extremity numbness, dysgeusia, dysphagia, quadriparesis, bilateral ptosis, cranial nerve III, IV, and VI weakness, generalized areflexia	MRI: Unremarkable	N/A	IVIG 0.4 g/kg daily (day 1 of ICU admission, then days 6–8)	Improvement, noted 5.5 months after diagnosis	Miller Fisher syndrome, Guillain-Barré syndrome overlap
Manganotti et al. 2020 [35]	49	F				14 days	Limbs	Bilateral ophthalmoplegia, generalized areflexia, right face hypoesthesia, mild right facial deficit	MRI: Unremarkable	EMG: Increased distal latency for facial nerve recorded from orbicularis oris and decreased amplitude on right	IVIG 0.4 g/kg daily for 5 days	Improvement after IVIG	Miller Fisher syndrome variant

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Manganotti et al. [36]	50	F				16 days	Gait, left upper extremity	Opthalmoplegia, generalized areflexia, lower facial deficits, left face hypoesthesia	MRI: Unremarkable	N/A	IVIG 0.4 g/kg daily for 5 days	Resolved, 7 days after IVIG start	Miller Fisher syndrome variant
Perrin et al. [37]	64	M				13 days	Unspecified	Confusion, agitation, tremor, aphasia, apraxia, pyramidal syndrome, coma, dysautonomia	MRI: FLAIR and DWI white matter hyperintensities in middle cerebellar peduncles, persistent cytotoxic edema on posterior left frontal lobe	EEG: Global and diffuse slowing EEG2: Bilateral delta organized in bursts or predominant opposite bifrontal diversions with bilateral theta	Dexamethasone for 5 days; IVIG for 5 days	Improvement with dexamethasone, then relapse, then rapid improvement with IVIG	Parainfectious, cytokine release syndrome
Perrin et al. [37]	53	F				Unclear, immediately after extubation	Unspecified	Confusion, agitation, tremor, aphasia, behavioural alterations, cognitive disturbances	MRI: Unremarkable	EEG: Normal	No specific neurological treatment	Spontaneous and gradual improvement, 7 days after symptom onset	Parainfectious, cytokine release syndrome

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Perrin et al. [37]	51	M				Unclear, immediately after extubation	Unspecified	Confusion, agitation, tremor, pyramidal syndrome, behavioural alterations, cognitive disturbances	MRI: FLAIR hyperintensities and microhemorrhages in splenium of corpus callosum	N/A	No specific neurological treatment	Spontaneous and gradual improvement	Para-infectious, cytokine release syndrome
Perrin et al. [37]	67	M				11 days	Unspecified	Decreased visual acuity, cranial nerve VI palsy, behavioural alterations, pyramidal syndrome	MRI: Unremarkable	N/A	Methylprednisolone 500 mg daily for 3 days	Rapid improvement with methylprednisolone	Para-infectious, cytokine release syndrome
Povlow and Auerbach [38]	30	M				Onset	Limbs, gait	Dysarthria, direction-changing nystagmus horizontally	CTA: Unremarkable MRI: Unremarkable MRA: Unremarkable	N/A	No specific neurological treatment	Some improvement by hospital day 10	COVID-19 presentation

Table 2 (continued)

Publication	Age	Sex	Myoclonus			Cerebellar ataxia		Other neurological features	Brain Imaging	Electrophysiology	Treatment	Outcome	Proposed etiology
			Latency	Distribution	Activation	Latency	Distribution						
Sartoretti et al. [39]	60	M				17 days	Unspecified	Vertigo, headache, nystagmus	CT: Hyperdense right vertebral artery CTA: Right vertebral artery and posterior infereior cerebellar artery (PICA) occlusion MRI: Susceptibility weighted, long-segment vessel occlusion with blooming artifact in right vertebral artery and PICA. Diffusion restriction in cerebellar hemispheres and vermis	N/A	Aspirin, atorvastatin	Not reported	Ischemic stroke
Wright et al. 2020 [40]	79	M				8 days	Trunk, gait	Confusion, agitation, ocular flutter, opsoclonus	MRI: Unremarkable	N/A	None	Opsoclonus resolved 17 days after onset	Post-infectious

neurological features, the most common were ataxia at 40% (12/30), cognitive or psychiatric changes at 30.0% (9/30), or opsoclonus or ocular flutter at 16.7% (5/30). Demyelinating or axonal neuropathy was reported in 13.3% (4/30) of cases, myopathy in 3.3% (1/30) of cases, hypokinetic-rigid syndrome in 3.3% (1/30) of cases, and right middle cerebral artery (MCA) territory stroke in 3.3% (1/30) of cases, all cases that were admitted to the ICU. Notably, 53.3% (16/30) of cases required mechanical ventilation and an ICU admission at some point during their disease course for respiratory management. One case was mechanically ventilated for management of myoclonus with propofol sedation [22].

Anti-neuronal antibody testing was reported in ten cases, with negative results in nine cases (Table 3). One case found autoantibodies directed against Purkinje cells, striatal neurons, and hippocampal neurons [13]. All cases, except one, had brain imaging with CT or MRI. CT was reported in 11 cases, without any remarkable findings. MRI was reported in 22 cases and was generally unremarkable. However, one case found diffuse pachymeningeal enhancement [9], one case found corpus callosum microbleeds [18], one case found deep and peripheral microbleeds [18], and one case found cortical and brainstem ischemic lesions [23]. Fluorodeoxyglucose positron emission tomograph (FDG-PET) was reported in two cases, with bilateral cortical hypometabolism and cerebellar hypermetabolism in both cases [11, 13]. One case also had bilateral putamen hypermetabolism [13]. Dopamine transporter single-photon emission computed tomography (DaT-SPECT) was reported in three cases, with two cases reporting normal findings [18] and one case finding bilateral decrease in dopamine uptake in the putamen in context of hypokinetic-rigid syndrome [20].

With regard to electrophysiology, 17 cases reported EEG and 9 cases reported EMG. One case found lateralized period discharges on EEG that were synchronous and asynchronous with diaphragmatic myoclonus [17], although EEG in the remainder of cases did not find electrographic correlates for myoclonus. EMG in three cases suggested a cortical, subcortical, or cortical–subcortical physiologic classification for multifocal myoclonus [18, 21]. With regard to etiology, 62.5% (10/16) of ICU cases acknowledged multiple contributions to symptomatic myoclonus, including metabolic abnormalities such as hypoglycemia, hyponatremia, uremia, and renal failure, hypoxia, medications, and a post-infectious process [9, 18]. One ICU case identified cortical and brainstem ischemic lesions on MRI and attributed myoclonus to hypoxia secondary to COVID-19 [23]. Nonetheless, 4 ICU cases and the 14 non-ICU cases of myoclonus were thought to be post-infectious, in the absence of another identified secondary etiology. CSF was tested for SARS-CoV-2 in 12 cases and all were negative.

Treatment strategies were variable across cases and consisted of symptomatic treatment with anti-epileptic medications and immunotherapy directed at a post-infectious, immune-mediated etiology. Of the 28 cases that reported on treatment, 32.1% (9/28) used anti-epileptic medications alone, 28.6% (8/28) used immunotherapy alone, and 21.4% (6/28) used anti-epileptic medications and immunotherapy. Of the remaining cases, four cases in ICU treated myoclonus with sedatives, including midazolam, lorazepam, ketamine, and dexmedetomidine [9] and one case did not use treatment [20].

Anti-epileptic medications included levetiracetam in 11 cases, clonazepam in 10 cases, valproic acid in 5 cases, and primidone in 1 case. Levetiracetam and clonazepam were used as monotherapy or with other anti-epileptic medications, whereas valproic acid and primidone were used with other anti-epileptic medications. After anti-epileptic medications were started, myoclonus improved in 11 cases, partially improved in 2 cases, and had no response in 2 cases. Improvement was associated with levetiracetam, clonazepam, valproic acid, and primidone. Myoclonus resolved within days of starting anti-epileptic monotherapy with either levetiracetam or clonazepam in five cases [9, 15, 17, 23]. However, other cases used multiple anti-epileptic medications or anti-epileptic medications in combination with immunotherapy. Immunotherapies included methylprednisolone in nine cases, intravenous immunoglobulin (IVIG) in eight cases, and plasma exchange in one case. After methylprednisolone, myoclonus improved in six cases and partially improved in three cases, whereas after IVIG, myoclonus improved in three cases and had no response in five cases. Monotherapy with methylprednisolone resolved myoclonus in one case, whereas monotherapy with IVIG resolved myoclonus in one case and had no response in four cases. Often, cases used multiple immunotherapies in sequence or in combination with anti-epileptics. The case that initially required propofol sedation to manage myoclonus did not respond to anti-epileptic medications, partially improved with methylprednisolone, and ultimately improved with plasma exchange [22].

Overall, 80% (24/30) of cases reported improvement or resolution of myoclonus. One case had myoclonus that spontaneously resolved within days, but subsequently developed hypokinetic-rigid syndrome [20]. The duration of myoclonus varied from 1 day to 2 months. There were four cases that had persisting myoclonus at the time of report [10] and two cases that did not report outcomes.

Ataxia associated with COVID-19

There were 33 cases of ataxia [9–16, 24–40], including our case report, with a mean age of 56.9 ± 14.6 (SD) years and a median age of 58.5 years (IQR 47.75–71.25). Three

Table 3 Cases with anti-neuronal antibody testing

Publication	Age	Sex	Sample	Antibodies tested	Results
Cases with myoclonus and ataxia					
Delorme et al. [11]	72	M	Serum and CSF	Unspecified	Negative
Dijkstra et al. [12]	44	M	Serum and CSF	Intracellular: ANNA-1/Hu, ANNA-2/Ri, GAD65 Surface: AMPA-R, CASPR2, $GABA_BR$, LGI1, NMDA-R	Negative
Grimaldi et al. [13]	72	M	Serum and CSF	Nerve tissue immunostaining; onconeural and membrane antigens, unspecified	Autoantibodies directed against Purkinje cells, striatal neurons, and hippocampal neurons. Onconeural and membrane antigens negative
Schellekens et al. [15]	48	M	Serum and CSF	Serum: VGKC CSF: Paraneoplastic, unspecified	Negative
Shah and Desai [16]	Middle-aged	M	Unspecified	Intracellular: Amphiphysin, ANNA-1/Hu, ANNA-2/Ri, GAD, Ma2	Negative
Cases with myoclonus, without ataxia					
Khoo et al. [19]	65	F	Serum and CSF	Intracellular: GAD Surface: CASPR2, DPPX, Gly-R, LGI1, NMDA-R	Negative
Méndez-Guerro et al. [20]	58	M	Serum and CSF	Intracellular: Amphiphysin, ANNA-1/Hu, ANNA-2/Ri, CV2, GAD65, Ma1, Ma2, PCA1/Yo, SOX1 Surface: AMPA-R1, AMPA-R1, CASPR-2, DPPX, $GABA_BR$, IgLON5, LGI1, NMDA-R	Negative
Muccioli et al. [21]	58	M	Serum	Intracellular and surface, unspecified	Negative
Rábano-Suárez et al. [22]	63	M	Serum and CSF	Intracellular: Amphiphysin, ANNA-1/Hu, ANNA-2/Ri, CV2, GAD65, Ma1, Ma2, PCA1/Yo, SOX1 Surface: AMPA-R1, AMPA-R2, CASPR2, DPPX, $GABA_BR$, LGI1, NMDA-R	Negative
Rábano-Suárez et al. [22]	76	M	Serum	Intracellular: Amphiphysin, ANNA-1/Hu, ANNA-2/Ri, CV2, GAD65, Ma1, Ma2, PCA1/Yo, SOX1 Surface: AMPA-R1, AMPA-R2, CASPR2, DPPX, $GABA_BR$, LGI1, NMDA-R	Negative
Cases with ataxia, without myoclonus					
Delorme et al. [11]	60	F	Serum and CSF	Unspecified	Negative
Diezma-Martín et al. [26]	70	M	Serum	Onconeuronal, unspecified	Negative
Fadakar et al. [27]	47	M	Serum and CSF	Intracellular: AGNA, ANNA-1/Hu, ANNA-2/Ri, CV2, GAD, Ma2, PCA1/Yo, PCA2, SOX1, Tr/DNER, Zic4 Surface: CASPR2, LGI1, mGluR1, NMDA-R	Negative
Perrin et al. [37]	64	M	CSF	Unspecified	Negative
Perrin et al. [37]	53	F	CSF	Unspecified	Negative
Perrin et al. [37]	51	M	CSF	Unspecified	Negative
Perrin et al. [37]	67	M	CSF	Unspecified	Negative
Povlow and Auerbach [38]	30	M	Serum	Intracellular: GAD	Negative

AGNA anti-glial nuclear antibody, *AMPA-R* alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *ANNA* anti-neuronal nuclear antibody, *CASPR2* contactin-associated protein 2, *DNER* delta/notch-like epidermal growth factor-related receptor, *DPPX* dipeptidyl-peptidase-like protein 6, *$GABA_BR$* gamma-aminobutyric acid type B receptor, *GAD* glutamic acid decarboxylase, *GAD65* glutamic acid decarboxylase 65 kDa isoform, *GlyR* glycine receptor, *LGI1* leucine-rich glioma inactivated 1, *mGluR1* metabotropic glutamate receptor 1, *NMDA-R N*-methyl-D-aspartic acid receptor, *PCA* Purkinje cell cytoplasmic antibody, *VGKC* voltage-gated potassium channel, *Zic4* zinc-finger protein 4

cases were asymptomatic for COVID-19 and presented with ataxia and other neurological symptoms [9, 24, 31]. Other cases either developed ataxia concurrently with or after COVID-19 symptoms. In the 23 cases with a clear time of onset for ataxia, the median latency between COVID-19 symptoms and ataxia was 13 days (IQR 3–15.5), with five

cases with concurrent ataxia and COVID-19 symptom onset and a maximum latency of 48 days. All cases except one [30] had concurrent neurological features. The most common were cognitive or psychiatric changes at 45.5% (15/33), myoclonus at 36.4% (12/33), ophthalmoplegia at 21.2% (7/33), areflexia without hyperreflexia at 21.2% (7/33), sensory changes at 18.2% (6/33), opsoclonus or ocular flutter at 12.1% (4/33), tremor at 12.1% (4/33), nystagmus at 9.1% (3/33), and pyramidal syndrome at 9.1% (3/33). Headache concurrent with neurological features, rather than COVID-19 symptoms, occurred in two cases of ischemic stroke [24, 39] and one case of acute cerebellitis [27]. Four cases of demyelinating or axonal neuropathy and one case of right MCA territory stroke in the context of ICU were included in the myoclonus group above. Overall, 21.2% (7/33) of cases required mechanical ventilation and an ICU admission at some point during their disease course for respiratory management. One of these cases was mechanically ventilated for respiratory failure secondary to Miller Fisher syndrome-GBS overlap syndrome [34].

Anti-neuronal antibody testing was reported in 13 cases, including 5 cases described in the myoclonus group above, with negative results in all cases except for the case with autoantibodies against Purkinje cells, striatal neurons, and hippocampal neurons (Table 3) [13]. All cases, except one, had brain imaging with CT or MRI. CT was reported in six cases, with one case finding a right vertebral artery and posterior inferior cerebellar artery occlusion [39]. MRI was reported in 30 cases and 8 cases had findings that could relate their neurological presentations. Cerebellar infarcts were found in two cases [24, 39]. One case found fluid attenuated inversion recovery (FLAIR) hyperintensities in the cerebellar hemispheres and vermis and cerebellar leptomeningeal enhancement [27] and one case found FLAIR and diffusion-weighted imaging (DWI) hyperintensities involving the white matter of the middle cerebellar peduncles [37]. One case found diffusion restriction [30] and one case found microhemorrhages [37] involving the splenium of the corpus callosum. One case found enlargement and enhancement of the left oculomotor nerve [33]. FDG-PET was reported in three cases, including the two cases described in the myoclonus group above. The additional case also had bilateral cortical hypometabolism and cerebellar hypermetabolism, along with striatal hypermetabolism [11].

With regard to electrophysiology, 12 cases reported EEG and 6 cases reported EMG, with 8 and 4 cases respectively included in the myoclonus group above. In general, the EEGs were normal or showed nonspecific generalized slowing. EMG in two cases supported a diagnosis of Miller Fisher syndrome variant [28, 35]. With regard to etiology, all cases of ataxia were thought to be associated with COVID-19 or related sequelae. Ataxia was a presenting symptom of COVID-19 in 18.2% (6/33) of cases. Ataxia associated with a variant of Miller Fisher syndrome secondary to COVID-19 occurred in 21.2% (7/33) of cases. Ataxia was acute onset in 6.1% (2/33) of cases and due to cerebellar infarcts that were thought to be secondary to COVID-19-related endothelial inflammation or hypercoagulability. The remaining 54.5% (18/33) of cases were thought to be post-infectious or para-infectious, in the absence of another identified etiology. CSF was tested for SARS-CoV-2 in 19 cases and positive in one case with acute cerebellitis [27].

Treatment strategies were guided by the cause of ataxia. In the 12 cases of myoclonus and ataxia, where cognitive impairment was often also a feature, treatment consisted of anti-epileptic medications alone in two cases, immunotherapy in six cases, or both in three cases. Improvement or resolution of ataxia was reported within 2 months in seven of these cases. Outcomes for ataxia were not reported in the other five cases. The seven cases of ataxia associated with a variant of Miller Fisher syndrome all improved after treatment with IVIG. The two cases of ataxia associated with cerebellar infarct were treated with antiplatelet and statin therapy and did not report outcomes. Three cases of post-infectious or para-infectious ataxia improved after treatment with methylprednisolone, dexamethasone, or IVIG, and one case reported slight improvement after treatment with clonazepam alone. Interestingly, seven cases of post-infectious or para-infectious ataxia improved within 6 weeks without any specific neurological treatment. One case did not report treatment or outcomes.

Discussion

Although COVID-19 is primarily a respiratory disease, neurological manifestations such as encephalopathy, acute cerebrovascular disease, epilepsy, and GBS are recognized as potential complications [2–4]. As COVID-19 continues to spread worldwide, relatively rare neurological phenomena associated with SARS-CoV-2 infection are increasingly reported. In this systematic review, we examine the clinical features and potential pathophysiological mechanisms of myoclonus and ataxia associated with COVID-19.

In the sample described here, myoclonus associated with COVID-19 was multifocal or generalized and had an acute onset, usually within 1 month of COVID-19 symptoms. Myoclonus severity varied widely from being manageable in an outpatient setting to requiring hospitalization. In most cases, myoclonus either occurred in isolation or concurrently with ataxia. Limited electrophysiology suggested cortical, subcortical, or cortical–subcortical physiological mechanisms [18, 21]. Metabolic abnormalities, medications, and hypoxia during the course of COVID-19 may contribute to myoclonus, especially in the ICU, but the majority of cases were thought to be post-infectious and immune-mediated.

Consequently, treatments consisted of symptomatic management with antiepileptic medications and immunotherapy with corticosteroids, IVIG, or plasma exchange. Myoclonus typically improved or resolved within 2 months and a self-limited course could not be excluded.

Similar to myoclonus, ataxia associated with COVID-19 had an acute onset. However, ataxia generally occurred earlier and was sometimes a presenting symptom of COVID-19. Cases of ataxia were hospitalized, but compared to cases of myoclonus, their disease course less frequently involved the ICU. Ataxia was almost always accompanied by other neurological features, with cognitive or psychiatric changes, myoclonus, or a variant of Miller Fisher syndrome being the most common. All cases were thought to be associated with post-infectious or para-infectious sequelae of COVID-19. Ataxia typically improved or resolved within 2 months and notably, several cases improved without any specific neurological treatment.

When myoclonus and ataxia occurred together, there were cases with cognitive impairment [9–12] and cases with opsoclonus or ocular flutter [12, 14, 16]. In addition, there were cases of myoclonus without ataxia [19, 20] and a case of ataxia without myoclonus [40] that had opsoclonus or ocular flutter. Based on proposed criteria, a diagnosis of OMAS is made when at least three of four features are present: (1) opsoclonus, (2) myoclonus or ataxia, (3) behavioural change or sleep disturbance, and (4) tumorous conditions or the presence of anti-neuronal antibodies [7, 41]. Although only one case met criteria with ataxia, behavioural change, and opsoclonus [40], cases often had two of the four features. Consequently, myoclonus and ataxia associated with COVID-19 may be on the spectrum of OMAS. OMAS has been associated with infections such as human immunodeficiency virus [42], Epstein–Barr virus [43], cytomegalovirus [44], human herpesvirus 6 [45], enterovirus 71 [46], hepatitis C [47], West Nile virus [48], *Mycoplasma pneumoniae* [49], *Streptococcus* [50], *Borrelia burgdorferi* [51], and *Salmonella enterica* [52]. The pathophysiology of myoclonus and ataxia associated with COVID-19 is unclear, but a similar mechanism to OMAS may be possible.

An immune-mediated mechanism has been implicated in OMAS, with the most convincing evidence arising from its response to immunotherapies such as corticosteroids, adrenocorticotropic hormone, and IVIG [7]. In a minority of cases of paraneoplastic and nonparaneoplastic OMAS, neuronal and cell surface antibodies have been identified, including autoantibodies directed against Purkinje cells [7, 53, 54]. Dysfunctional Purkinje cells may lead to abnormal disinhibition of the deep cerebellar nuclei and consequently hyperexcitation of cortical motor and non-motor areas [7]. Alternatively, dysfunction in saccade circuits, cerebellar circuits, and motor circuits as a result of brainstem hyperexcitability may be responsible for generating opsoclonus, ataxia, and myoclonus respectively [7]. Taken together, a post-infectious, antibody-mediated process involving similar anatomical areas may also contribute to myoclonus and ataxia associated with COVID-19, particularly if COVID-19 symptoms resolved prior to the onset of myoclonus or ataxia.

Although autoimmune and paraneoplastic antibody panels were generally negative, a case of myoclonus and ataxia had serum and CSF autoantibodies directed against Purkinje cells, striatal neurons, and hippocampal neurons [13]. Myoclonus, ataxia, and autoantibodies against Purkinje cells and striatal neurons coincided with cerebellar and striatal hypermetabolism on FDG-PET [13] and a similar metabolic pattern was found in other cases [11]. Cerebellar hypermetabolism has also been reported with infectious encephalitis [55], paraneoplastic cerebellar degeneration [56], and OMAS [57], and may be related to an inflammatory or immune-mediated process. Overall, the cerebellum is preferentially targeted by autoimmune processes [58] and may be a neuroanatomical hub for post-infectious neurological symptoms associated with COVID-19. Beyond ataxia, cognitive impairment is associated with cerebellar cognitive affective syndrome [59] and cerebellar dysfunction has been implicated in the pathogenesis of cortical myoclonus [60]. Cortical, subcortical, or cortical-subcortical myoclonus associated with COVID-19 [18, 21] would be consistent with involvement of the cerebellum, brainstem, or striatum as localizations for a post-infectious process causing myoclonus and ataxia.

Several cases of ataxia attributed to a variant of Miller Fisher syndrome provide further support for an antibody-mediated mechanism. Miller Fisher syndrome is a subtype of GBS characterized by prominent ataxia, thought to be a cerebellar-like sensory ataxia caused by dysfunction in spinocerebellar afferents [60], ophthalmoplegia, and areflexia. Generally, GBS is post-infectious and thought to be caused by molecular mimicry between infectious and nervous system antigens [61]. Specifically, Miller Fisher syndrome has a strong association with anti-ganglioside Q1b (anti-GQ1b) antibodies [60, 61], which were found in two cases of ataxia associated with COVID-19 [31, 34]. Miller Fisher syndrome and GBS associated with COVID-19 indicate that molecular mimicry between SARS-CoV-2 and the nervous system may play a role in pathogenesis. Interestingly, some cases of GBS associated with COVID-19 had concurrent neurological and COVID-19 symptoms [62] and suggest that distinct but overlapping para-infectious and post-infectious mechanisms may be contributory.

A para-infectious, inflammatory process affecting the cerebellum, brainstem, and striatum may also contribute to myoclonus or ataxia associated with COVID-19. SARS-CoV-2 infection is associated with increased levels of pro-inflammatory cytokines and systemic inflammation, including cytokine storm or cytokine release syndrome, is thought

to underlie multiple organ failure [63, 64]. Indeed, several cases of myoclonus, ataxia, and myoclonus and ataxia had increased serum or CSF levels of interleukin-6, a key pro-inflammatory cytokine [11, 21, 37]. Some of these cases also had increased levels of SB100 protein, an astroglial marker that indicates increased blood–brain barrier permeability [37]. Blood–brain barrier dysfunction associated with inflammation may lead to central nervous system edema, activation of microglia, and a secondary neuroinflammatory response [37]. Brain MRI findings with COVID-19 involving the cerebellar white matter [37] or splenium of the corpus callosum [30, 37] are likely secondary to a neuroinflammatory response and consistent with those described with the influenza virus [65]. Nonetheless, brain MRI is often normal with influenza-associated encephalitis [65] and this likely also applies to COVID-19 in the para-infectious or post-infectious stage.

Since the beginning of the pandemic, it has been hypothesized that SARS-CoV-2 may act directly on the nervous system to cause neurological symptoms. The angiotensin converting enzyme 2 (ACE2) receptor is used by SARS-CoV-2 to enter human cells [66] and is found in endothelium and smooth muscle in the brain [67]. Neuroinvasive potential is also a common feature of other human coronaviruses (HCoVs), including SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), HCoV-229E, and HCoV-OC43 [66]. SARS-CoV-2 was detected in the CSF of one case of ataxia [27], but this could be explained by blood–brain barrier dysfunction from acute cerebellitis. The absence of SARS-CoV-2 in the CSF in all other cases does not support neuroinvasion as a mechanism for myoclonus or ataxia.

Given the likely para-infectious and post-infectious mechanisms associated with COVID-19, myoclonus and ataxia may be self-limited, particularly as systemic inflammation resolves. Some cases spontaneously resolved, and most cases improved or resolved with treatment over time. However, the natural history of myoclonus and ataxia associated with COVID-19 and chronic complications of neurological involvement remain unknown. Myoclonus and ataxia are often debilitating, and treatment is warranted. Clonazepam or levetiracetam, alone or in combination, has been used to successfully alleviate myoclonus associated with COVID-19 and is consistent with potential cortical, subcortical, or cortical-subcortical mechanisms. For myoclonus and ataxia, immunotherapy with methylprednisolone or IVIG may accelerate recovery. Plasma exchange may be considered in cases that are refractory to methylprednisolone and IVIG.

The ongoing COVID-19 pandemic enabled this systematic review to include a relatively large number of post-infectious or para-infectious myoclonus and ataxia cases attributable to a single infection. Overall, the cases summarized in this review are likely an underestimate of the total number of COVID-19 cases that have developed myoclonus or ataxia. The severity of SARS-CoV-2 infection ranges from being asymptomatic to critically ill and patients with COVID-19 and its complications are managed across outpatient, inpatient, and intensive care settings. The severity of myoclonus and ataxia is also variable, and patients with minor and tolerable symptoms may not present to medical attention. Of note, many cases of myoclonus were observed in the ICU or required hospitalization for management. Consequently, there is ascertainment bias in the literature towards patients who are hospitalized. Nonetheless, myoclonus and ataxia associated with COVID-19 are likely rare post-infectious or para-infectious phenomena, similar to myoclonus and ataxia associated with other infections. As more cases and case series of myoclonus and ataxia are reported, future investigation will be required to further elucidate the relationship between these movement disorders and COVID-19.

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Compliance with ethical standards

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