Movement Disorders
CLINICAL PRACTICE
REVIEW

De Novo Movement Disorders and COVID-19: Exploring the Interface

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Abstract: Background: Neurological manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being widely documented. However, movement disorders in the setting of 2019 coronavirus infectious disease (COVID-19) have been a strikingly less discussed topic.
Objectives: To summarize available pieces of evidence documenting de novo movement disorders in COVID-19.
Methods: We used the existing PRISMA consensus statement. Data were collected from PubMed, EMBASE, Web of Science, and Scopus databases up to the 29th January, 2021, using pre-specified searching strategies.
Results: Twenty-two articles were selected for the qualitative synthesis. Among these, a total of 52 patients with de novo movement disorders were reported. Most of these had myoclonus, ataxia, tremor or a combination of these, while three had parkinsonism and one a functional disorder. In general, they were managed successfully by intravenous immunoglobulin or steroids. Some cases, primarily with myoclonus, could be ascribed to medication exposures, metabolic disturbances or severe hypoxia, meanwhile others to a post-or para-infectious immune-mediated mechanism. SARS-CoV-2 could also invade the central nervous system, through vascular or retrograde axonal pathways, and cause movement disorders by two primary mechanisms. Firstly, through the downregulation of angiotensin-converting enzyme 2 receptors, resulting in the imbalance of dopamine and norepinephrine; and secondly, the virus could cause cellular vacuolation, demyelination and gliosis, leading to encephalitis and associated movement disorders.
Conclusion: De novo movement disorders are scantly reported in COVID-19. The links between SARS-CoV-2 and movement disorders are not yet established. However, we should closely monitor COVID-19 survivors for the possibility of post-COVID movement disorders.

Neurological manifestations of a predominantly respiratory pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are being widely documented.[1] These may include mild headache, hyposmia/anosmia, hypogeusia/ageusia, ischemic stroke, intracerebral hemorrhage, encephalitis, alterations in circadian rhythm, cognitive impairment, increased seizure frequency, myopathy, and Guillain-Barré syndrome variants, among others[1–5]; as such, the infection may affect almost all parts of the neural axis.[1] However, movement disorders preceded by coronavirus disease of 2019 (COVID-19) have been a strikingly less discussed topic.

Infectious diseases are among the most common causes of neurological disability worldwide. A series of movement disorders can develop in isolation (i.e., direct neurovirulence) due to encephalopathy, or as part of a broader neurological dysfunction (i.e., indirect neurovirulence).[6] On most occasions, infection-related movement disorders are the result of an active immune-mediated process affecting the neural substrates through

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molecular mimicry and host susceptibility.[6, 7] In some instances, this immunological mimicry may result in the development of targeted antibodies against cell surface dopaminergic receptors in the basal ganglia.[8, 9] Similarly, anti-neuronal antibodies directed against the cerebellar fastigial nucleus and omnipause neurons in the brainstem may give rise to an opsoclonus-myoclonus syndrome, as reported in several infectious diseases.[10, 11]

Japanese encephalitis (JE) is one of the viral diseases with a major spectrum of movement disorders among its clinical manifestations.[12] In this infection, there is structural damage involving the thalamus, brainstem and basal ganglia, resulting in damage to the cortico-basal ganglia-thalamocortical loop with resultant movement disorders.[12] Norepinephrine and dopamine have important roles in movement disorders associated with JE.[13] Indeed, low levels of catecholamines in JE-associated movement disorders compared to Parkinson's disease and other extrapyramidal symptoms have been reported and may be due to severe structural damage to the thalamus, basal ganglia and brainstem.[13] Analogous pathophysiological mechanisms are believed to be a feature of other flavivirus infections.[14, 15] Similarly, anti-basal ganglia antibodies targeted against large striatal neurons have been reported in infantile bilateral striatal necrosis after recent respiratory tract infection with Streptococcus spp, manifesting as dystonic movements.[16] In a significant number of cases, common herpetic encephalitis and JE have produced anti-N-methyl-d-aspartate receptor antibodies, resulting in diffuse encephalopathies and movement disorders.[17, 18] Over the years, human immunodeficiency virus (HIV) infection has been associated with a multitude of movement disorders due to either direct or secondary damage to the basal ganglia or its connections (aberrant immunological response), or as a result of drug therapy.[19] Parkinsonism as a complication of viral infections is well documented and has been associated with influenza, JE, enterovirus, Epstein–Barr, western equine encephalitis, dengue, hepatitis E, measles, herpes simplex, HIV, coxsackie and many other viruses.[15, 20–28] Further, acute post-infectious anti-neuronal antibody-mediated cerebellar ataxia is seen in numerous cases following viral encephalitis in children.[29]

The influenza pandemic of 1918 is famous for the post-infectious complication known as encephalitis lethargica,[30, 31] characterized by a myriad of abnormal movements, i.e., post-encephalitic parkinsonism, tremor, dystonia, chorea, myoclonus, and oculo-masticatorymyorhythmias.[32] Encephalitis and encephalopathies in COVID-19 are being reported commonly,[1] but surprisingly, reports of movement disorders are scant.[33] During a time in which the medical literature is witnessing a deluge of COVID-19 related papers, those that report COVID-19 induced movement disorders are meager.

The purpose of this review was to summarize available pieces of evidence documenting de novo movement disorders in COVID-19 patients. Indeed, the movement disorders that have been reported in those patients who have suffered from COVID-19 rather than on the people already living with diagnosed or undiagnosed movement disorders. We also analyzed several putative pathological mechanisms of development of movement disorders in SARS-CoV-2 infection and finally, assessed why there is a scarcity of de novo movement disorders.

Methods

Search Strategy

We searched through the PubMed, Embase, Web of Science, and Scopus databases with the following keywords (["Parkinsonism" OR "Ataxia" OR "myoclonus" OR "tremor" OR "dystonia" OR "chorea" OR "movement disorders"] AND ["SARS-CoV-2" OR "COVID-19"]), up to 29th January 2021. The articles were imported into the Rayyan QCRI software.[34] We also hand-searched additional COVID-19 specific articles using the reference list of the selected studies and relevant journal websites from 2019 to the current date for literature inclusion. To decrease publication bias, we invigilated the references of all studies potentially missed in the electrical search. Content experts also searched the gray literature of any relevant articles.

Study Selection Criteria

All peer-reviewed studies, including cohort, case–control studies, and case reports, which met the pre-specified inclusion and exclusion criteria, were included in this study.

Inclusion Criteria

Our inclusion criteria were as follows: (1) studies reporting COVID-19 associated movement disorders; (2) studies reporting of management and outcome of the cases; and (3) studies approved by an Ethics Committee or Institutional Review Board, along with mandatory written informed consent before inclusion. Only studies that were published in English were considered. Accordingly, we excluded the studies with the following criteria: (1) prior history of movement disorder; (2) insufficient data and, subsequently, failure to contact the authors; (3) non-clinical research, animal studies and reviews; and (4) duplicate publications. The references of the original articles and reviews identified were manually searched further for any article that has been missed out.

Exclusion Criteria

We excluded studies if COVID-19 had not been confirmed and those written in languages other than English. We also excluded review papers, viewpoints, commentaries, and studies where information related to neurological manifestations or movement disorders was not reported.

Study Selection and Evidence Synthesis

The titles and abstracts were studied by two reviewers independently, and selected studies underwent full-text review. For the studies that were included for this review, the following information was extracted: demographics, disease semiology, time to diagnosis, clinical history, diagnostic methods employed, including neuroimaging, therapy, final outcome, cerebrospinal fluid

(CSF) study, and autoimmune encephalitis panel. The extracted information was qualitatively synthesized. Because the number of studies and patients were limited, quantitative synthesis was not carried out.

Statistical Analysis

Qualitative data were expressed in percentages. Unit discordance among the variables was resolved by converting the variables to a standard unit of measurement. A P value <0.05 was considered statistically significant, but it could not be calculated due to insufficient data. A meta-analysis was planned to analyze the association of the demographic findings, symptoms, biochemical and neuroimaging parameters and outcomes, but was later omitted due to lack of sufficient data.

Ethics

This is a review of published literature on de novo movement disorders in COVID-19 and did not involve any human or animal subjects. Hence, approval from an Ethics Committee was not applicable.

Results

The selection process carried out according to the Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) consensus statement is shown in Figure 1. The published cases are summarized in Table 1.[35–56] Twenty-two articles were finally selected for the qualitative synthesis. Among these, a total of 52 patients with de novo movement disorders were reported. Most of these had myoclonus, ataxia, tremor or a combination of these, while three had parkinsonism and one a functional disorder. Cases of post-infectious generalized myoclonus were firstly reported by Khoo et al.[35] and Rábano-Suárez et al.[44] Anand et al.[38] in their case series, from three different centers, reported eight cases of myoclonus associated with SARS-CoV-2 infection; the cases had variable backgrounds, comorbidities and outcomes.[38] Seven of these eight patients had significant metabolic disturbances, hypoxemia and medication exposure, which may have contributed to the development of myoclonus.[38] Seven cases of opsoclonus-myoclonus syndrome, presumably para-infectious, were described by Emamikhah et al.,[56] who inferred that COVID-19 was probably the initial trigger infection. Six of these cases also had voice tremors.[56] Authors of all the four manuscripts concluded that myoclonus was probably secondary to immune-mediated brain injury.[35, 38, 44, 56]

Diezma-Martín et al.[43] reported a case of tremor and ataxia in a 70-year-old man following COVID-19. A similar case of gait ataxia was described by Balestrino et al.[45] in an aged patient with multiple comorbidities. Chaumont et al.[47] reported four cases of severe COVID-19 in male patients aged 50–70 years after weaning of mechanical ventilation and extubation. Among a myriad of neurological manifestations, the patients had upper limb myoclonus, which persisted 3 weeks after discharge and an immunoglobulin regimen.[47] Méndez-Guerrero et al.[46] reported a case of opsoclonus-myoclonus complex in a 58-year-old man with an asymmetric hypokinetic-rigid syndrome, in whom there was asymmetrically decreased presynaptic dopamine uptake in the putamen on I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (I-FP-CIT) dopamine transporter single photon emission computed tomography (DAT-SPECT). Schellekens et al.[48] reported the case of a 48-year-old man with a history of asymptomatic HIV infection who had a partially reverted picture of myoclonus-ataxia in the setting of COVID-19. Paterson et al.[49] described a total of 43 COVID-19 patients with neurological manifestations, among which seven had post-COVID-19 ataxia. Intriguingly, lower limb tremors were observed in a SARS-CoV-2 infected woman, which could neither be traced to neurological impairment on examination nor an infectious or hormonal etiology on serum testing. The authors categorized it as a "functional movement disorder threatening existential continuum".[50]

In general, the patients were managed successfully by intravenous immunoglobulin or steroids. In a few patients, a multimodal approach was employed. In the case of Cohen et al.[39] the symptoms persisted even after treatment with steroids, pramipexole, and biperidine. Clonazepam was used alone or in combination with other drugs in multiple patients where the condition improved.[35, 38, 43, 44, 52, 53, 55, 56] In four cases, the patients improved without any specific treatment.[42, 45, 46] The positive effect of immunotherapy in many of the patients points towards that the pathogenetic mechanisms for the development of some movement disorders, following SARS-CoV-2 infection, may be mediated by aberrant immune-mediated injury.

Discussion

During this ongoing pandemic, a plethora of neurological manifestations in COVID-19 affecting both the central and the peripheral nervous systems are being reported.[1] However, surprisingly, data regarding movement disorders are scarce. Movement disorders in COVID-19 might be an under-recognized neurological complication. Thus, in the present review, we have only found 52 patients with de novo movement disorders.

Regarding the pathophysiology of movement disorders in COVID-19 as a whole, there are currently three possible explanations. Firstly, many cases, mainly those with myoclonus, could be ascribed to drugs, metabolic disturbances, or simply severe hypoxia.[44] Further, cases of autoimmune encephalitis with subacute cerebellar syndrome and myoclonus, triggered by SARS-CoV-2 infection, have just started to surface,[51] as are therapy-related complications, such as opsoclonus-myoclonus in COVID-19 therapy-induced serotonin syndrome.[42] Secondly, a post- or para-infectious immune-mediated mechanism somehow related to the inflammatory phase of COVID-19. In this sense, there are many reports in the literature of myoclonus or parkinsonism presenting shortly after the onset of infection.[15, 20–28, 57]

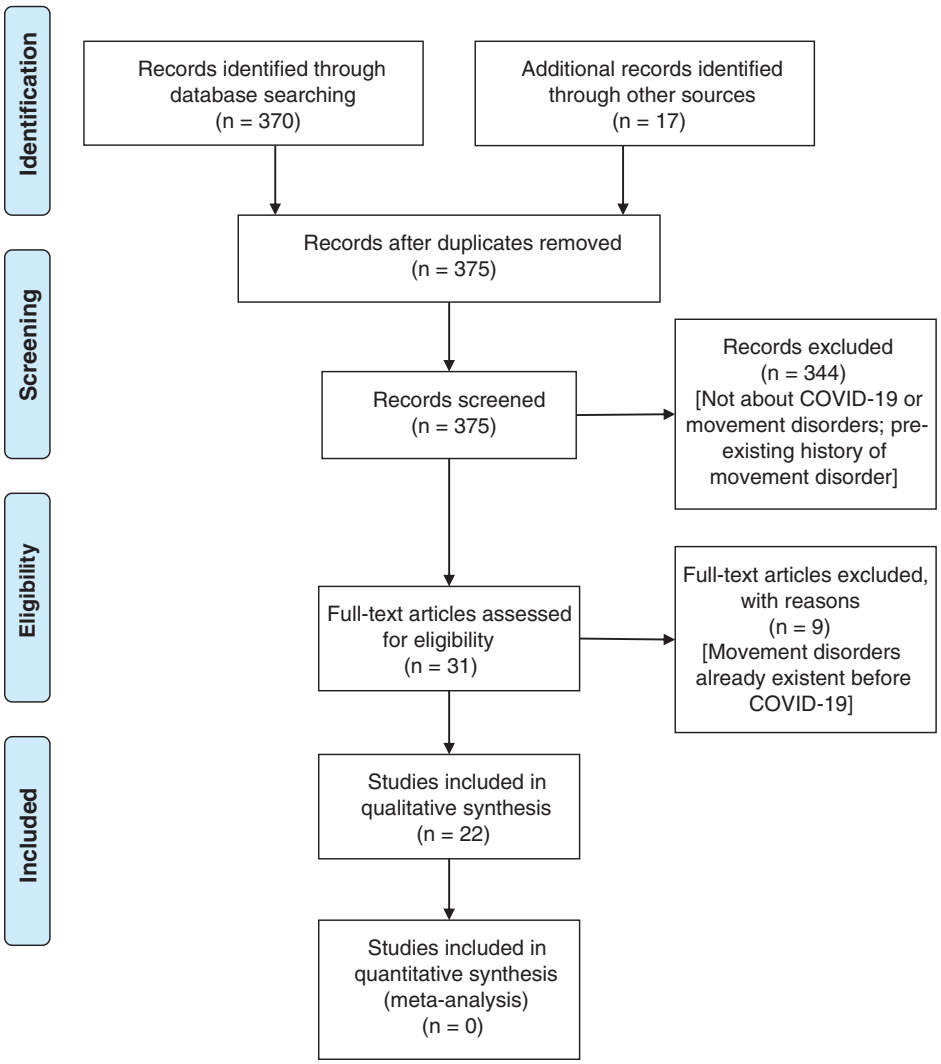

FIG. 1. PRISMA 2009 flow diagram.

Finally, the neuroinvasive potential of SARS-CoV in humans is well known.[58, 59] Notably, SARS-CoV,[60] as well as the H1N1 influenza virus,[61] when they are inoculated intranasally, could spread through a transneuronal route to first- and second-order structures connected with the olfactory bulb. SARS-CoV-2 is present in some COVID-19 patients in their cerebrospinal fluid.[1] This agrees with previous studies that have found antibodies to coronaviruses in the cerebrospinal fluid of patients with Parkinson's disease,[62] suggesting the potential of SARS-CoV-2 for causing parkinsonism. Interestingly, striatal dopaminergic neurons, microglia, and astrocytes of basal ganglia bear angiotensin-converting enzyme 2 (ACE-2), the receptor for SARS-CoV-2,[63, 64] which would create a pathway for the entry of this virus, affecting these structures.[65]

The fact that hyposmia is one of the most prevalent symptoms of COVID-19 [66] and that the olfactory system is early affected in alpha-synucleinopathies might be an intriguing coincidence.[67] However, it is notable that recent studies indicate that α-synuclein may participate in the innate immune response to any viral infection.[68] Sadasivan et al.[69] demonstrated that multiple hits by H1N1 infection and exposure to environmental toxins simultaneously may damage the dopaminergic neurons in substantia nigra to a greater extent than a single hit by any single agent. This potentially keeps alive the threat of development of post-COVID-19 parkinsonism as a delayed and long-term debility as it was in the pandemic of 1918.[70–72]

The basal ganglia is involved in cases of encephalitis following infection with respiratory pathogens.[73] Fishman et al.[74] demonstrated that the murine coronavirus has neurotropic potential and particular predilection towards the involvement of the basal ganglia, resulting in extra- and intra-cellular vacuolation, neuronal loss, chronic demyelination and gliosis. As suggested,[74] a virus

TABLE 1 Clinical and radiological spectrum of COVID-19 associated de novo movement disorders

Author(s)	Age (y)/sex	Type of movement disorder(s)	Neuromaging/ Electroencephalogram (EEG)	Therapy for movement disorder	Outcome	Time to movement disorder onset	CSF PCR for SARS-CoV-2	Autoimmune encephalitis panel
Khoo et al.[35]	65 / Woman	Generalized myoclonus, ocular flutter, ocular-facial-synkinesis, convergence spasm and acquired hyperekplexia	Normal / Normal EEG	Levetiracetam, clonazepam and corticosteroids	Improvement	Seven days	Negative	Negative
Lechien et al.[36]	28 / Woman	Inspiratory and expiratory paradoxical movement of the vocal folds	Not performed	Speech therapy	Recovery after four months	Seven weeks	Not performed	Not performed
Dijkstra et al.[37]	44 / Man	Generalized, stimulus-sensitive myoclonus, transient ocular flutter and cerebellar ataxia	Normal / Not available	Intravenous corticosteroids and immunoglobulins	Full recovery after two months	Two weeks	Negative	Negative
Anand et al.[38]	Multicenter case series (eight patients)	Myoclonus (mostly stimulus sensitive; in one case it was spontaneous)	Normal in most cases/EEG was performed in most cases ranging from background slowing, transient bifrontal sharp waves to generalized dysfunction	Levetiracetam, clonazepam, valproate, dexmedetomidine (most cases), ketamine, lorazepam and primidone	One patient died. In five cases, myoclonus completely resolved while in three cases, it persisted for 10 days or longer.	Variable	Negative	Not performed
Cohen et al.[39]	45 / Man	Asymmetric (right>left) tremor in legs, increased urinary frequency, micrography, hypomimia, bradykinesia and cogwheel rigidity	Normal brain magnetic resonance imaging. Positron emission tomography (PET) scan showed decreased ^{18}F-FDOPA uptake in both putamina, more apparent on the left side. Additionally, mild decreased uptake in the left caudate was also suspected / Normal EEG	Corticosteroids, pramipexole and biperidin	Persistence of symptoms	Three to four weeks	Negative	Negative
Faber et al.[40]	35 / Woman	Generalized and asymmetric (right>left) bradykinesia, cogwheel rigidity, stooped posture, reduced arm swing, enbloc turning, and decreased stride length.	Normal magnetic resonance imaging and PET scans; decreased dopamine transporter (DAT) density on the left putamen (more evident in the mid-putamen, different from the posterior involvement usual of idiopathic Parkinson's disease)/ EEG not available	Levodopa/benserazide	Significant improvement with anti-parkinsonian drugs	Two to four weeks	Negative	Negative

(Continues)

TABLE 1 *Continued*

Author(s)	Age (y)/sex	Type of movement disorder(s)	Neuromaging/ Electroencephalogram (EEG)	Therapy for movement disorder	Outcome	Time to movement disorder onset	CSF PCR for SARS-CoV-2	Autoimmune encephalitis panel
Cuhna P et al.[41]	Case series (five patients)	Upper limbs postural and action-tremor in four patients; one of them had also irregular orthostatic tremor, another one bilateral upper limbs jerky/ myoclonic abnormal movements at rest and during posture and action	Magnetic resonance imaging in four patients showed microbleeds and a bilateral frontotemporal hypoperfusion in one patient. Neuromelanin-sensitive magnetic resonance imaging showed dorsal-nigral hyperintensity bilaterally in all, but one. 123I-FP-CIT single photon emission computed tomography performed in four patients was normal / not performed	None	Not performed	Two to five weeks	Not performed	Not performed
Mas Serrano et al.[42]	Case series (two patients)	Myoclonus (multi-focal) and ocular clonus	Normal neuroimaging in both cases/EEG showed diffuse encephalopathy in both cases	None	Improvement to baseline	One to two weeks	Not performed	Not performed
Diezma-Martín et al.[43]	70 / M	Tremor and ataxia	Normal / Not performed	Clonazepam	Improved after one moth of discharge	Two to five weeks	Negative	Negative
Rábano-Suárez et al.[44]	Case series (three patients)	Stimulus sensitive generalized myoclonus	Normal / EEG showed diffuse background slowing	Dexmedetomidine, clonazepam, valproate, levetiracetam, propofol, corticosteroids and plasmapheresis	Improved	Two weeks	Negative	Negative
Balestrino et al.[45]	73 / Man	Ataxia	Normal / EEG showed reactive, unstable, symmetrical background alpha activity in posterior regions; sporadic, low-voltage, focal polymorph delta elements in the anterior-frontal left cortex and sporadic spikes without clear epileptic correlate in the frontotemporal lobe, predominantly on the left	None	Improved after several weeks	One to two weeks	Not performed	Not performed
Méndez-Guerrero et al.[46]	57 / Man	Myoclonus, tremor, parkinsonism and vertical ocular movement abnormalities	DAT- single photon emission computed tomography showed bilateral decrease in presynaptic dopamine uptake asymmetrically involving both putamina / EEG showed diffuse mild and reactive slowing	No specific therapy	Improved to baseline within three weeks	40 days	Negative	Negative

(Continues)

TABLE 1 *Continued*

Author(s)	Age (y)/sex	Type of movement disorder(s)	Neuromaging/ Electroencephalogram (EEG)	Therapy for movement disorder	Outcome	Time to movement disorder onset	CSF PCR for SARS-CoV-2	Autoimmune encephalitis panel
Chaumont et al.[47]	Case series (four patients)	Upper limbs myoclonus	Normal MRI except recent stroke in case 1 / EEG showed global slowing in patients 1, 2, and 3; and normal in patient 4	Intravenous immunoglobulins and methylprednisolone	Some improvement	Variable	Negative	Not performed
Schellekens et al.[48]	48/Man	Myoclonus and cerebellar ataxia	Normal / EEG was not performed	Levetiracetam	Improved	Variable	Negative	Not performed
Paterson et al.[49]	Case series (seven patients)	Ataxia and bilateral intention tremor in one patient	Normal in five; multiple large lesions in periventricular white matter of both cerebral hemispheres in one and mild to moderate small vessel disease in another one / EEG was not performed	Intravenous immunoglobulin and corticosteroids	Four cases recovered incompletely an three completely	Variable	Negative in four and not performed in three	Not performed in four; matched oligoclonal bands in serum in two; and negative in one
Piscitelli et al.[50]	39/Woman	Lower limbs tremor and ataxia	Normal magnetic resonance imaging/EEG was not performed	Benzodiazepines	No improvement	11 days	Not performed	Not performed
Grimaldi et al.[51]	72/Woman	Cerebellar syndrome and myoclonus	^{18}F-FDG-PET showed diffuse cortical hypometabolism, associated with putaminal and cerebellum hypermetabolism / EEG showed symmetric bilateral background slowing	Intravenous corticosteroids	Rapid improvement	12 days	Negative	High titers of autoantibodies directed against nuclei of Purkinje cells, as well as to striatal and hippocampal neurons were detected
Borroni B et al.[52]	Two cases (54 / Woman and 80 / Man)	Diaphragmatic myoclonus	Normal / EEG was normal in case 1 and lateralized periodic discharges synchronous and asynchronous with the diaphragmatic myoclonic movements in case 2	Clonazepam in case 1 and levetiracetam in case 2	Improvement	Two weeks in case 1 and one month in case 2	Negative	Not performed
Shah et al.[53]	Middle aged male	Opsoclonus, cortical myoclonus, symmetric cerebellar ataxia of speech, limbs, trunk and gait	Normal / Not available	Corticosteroids, levetiracetam, valproate and clonazepam	Improvement	Three weeks	Negative	Negative
Muccioli et al.[54]	58 / Man	Subcortical myoclonus	Chronic small vessel disease / Normal EEG	Corticosteroids, levetiracetam and clonazepam	Improvement	12 days	Negative	Negative

(Continues)

TABLE 1 *Continued*

Author(s)	Age (y)/sex	Type of movement disorder(s)	Neuromaging/ Electroencephalogram (EEG)	Therapy for movement disorder	Outcome	Time to movement disorder onset	CSF PCR for SARS-CoV-2	Autoimmune encephalitis panel
Ros-Castelló et al.[55]	72 / Woman	Myoclonus	Cortical and brainstem small vessel disease / Normal EEG	Clonazepam	Improvement	Five days	Not performed	Not performed
Emamikhah et al.[56]	Case series (seven patients)	Opsoclonus-myoclonus syndrome and voice tremor	Normal (in one, it was not performed) / EEG was normal in one patient and not performed in the rest	Levetiracetam, valproate, clonazepam, intravenous immunoglobulins and dexamethasone	Recovery (partial for three patients; complete for two patients); one lost to follow-up; and one under treatment	Variable	Negative for two and not performed for rest	Negative for one and not performed for the rest

capable of causing both encephalitis and persistent infection in several species may be related to post-encephalitic parkinsonism. A study by Haddadi et al.[75] regarding a case of SARS-CoV-2 associated hemorrhagic encephalitis involving the basal ganglia bilaterally, further supports the affinity of coronaviruses by these structures. A cross-sectional, retrospective, observational study by Chougar et al.[76] revealed two distinct patterns of brain parenchymal involvement in SARS-CoV-2 infection, including white matter enhancing lesions and basal ganglia abnormalities. Similarly, SARS-CoV-2 infection has been associated with immune-mediated acute hemorrhagic encephalopathy involving brainstem and thalami[77] as well as with vasculopathic or demyelinating processes involving bilateral putamina.[78]

Recently, both ACE-2 and transmembrane serine protease 2 (TMPRSS2) have been found to be expressed in human corneal epithelium, suggesting that ocular surface cells could also be a potential viral entry point.[79] SARS-CoV-2 could invade the central nervous system, through vascular or retrograde axonal pathways, and infect the striatal neurons (Fig. 2).[80] From here onwards, there might be two primary mechanisms through which the virus may cause movement disorders (Fig. 2). Firstly, the downregulation of ACE-2 receptors could result in an imbalance of neurotransmitter levels,[81] primarily dopamine and norepinephrine (Fig. 2), leading to dopamine deficiency. Secondly, the virus could cause cellular vacuolation, demyelination, and gliosis, leading to encephalitis and associated movement disorders (Fig. 2).

Movement disorders are now sparse among COVID-19 patients (Fig. 3). In most cases of neurological complications associated with SARS-CoV-2 infection, the neural substrates for movement disorders are spared; in fact, pure cortical, cortico-subcortical interface and deep white matter involvement predominates, as evidenced by various imaging-based studies.[76, 82–85] Furthermore, movement disorders following an infectious-autoimmune process typically develop after a period of weeks to months. Hence, there remains a possibility that expected parenchymal changes in the brain are just waiting to reach a threshold level to manifest as delayed movement disorders.[41] On the other hand, the differential distribution of ACE-2 receptors and its ancillary protein co-regulators among several brain cell types may be the cause of more strokes and fewer movement disorders.[86] Finally, human coronavirus can lie dormant in the leukocytes for a long period and may manifest as delayed or persistent central nervous system infection, later giving rise to movement disorders.[87] Indeed, immune dysregulation brought about by SARS-CoV-2 infection[88] may lead to neurodegeneration[89] and potentially neurodegenerative movement disorders might manifest later. Notwithstanding, movement disorders are being increasingly documented because of the higher reporting frequency of COVID-19 cases worldwide.

There are some limitations in the current review. Given the notable asymmetry between the total number of affected cases and reported cases of de novo movement disorders in COVID-19, it can be assumed that cases are currently under-reported. The current review is based on a small number of cases, even after an extensive search of available literature. Examination

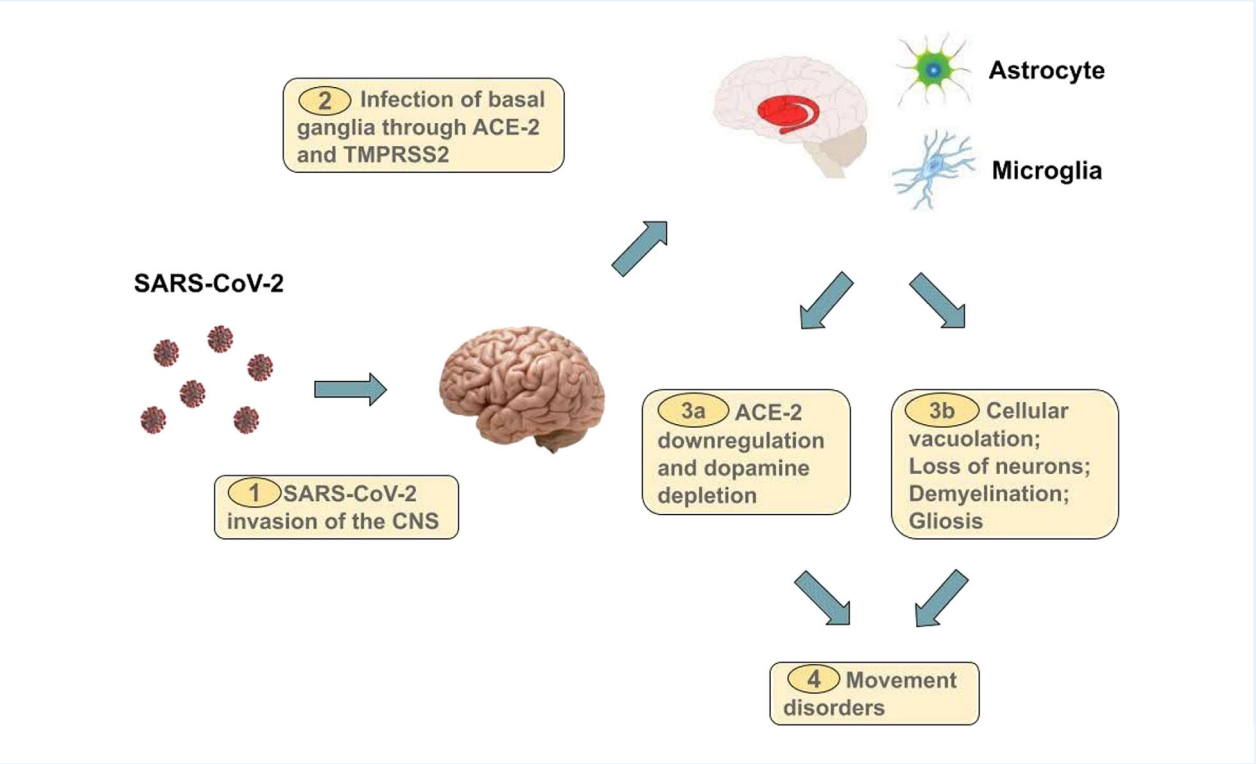

FIG. 2. Proposed pathogenic pathway for the development of de novo movement disorders in COVID-19.

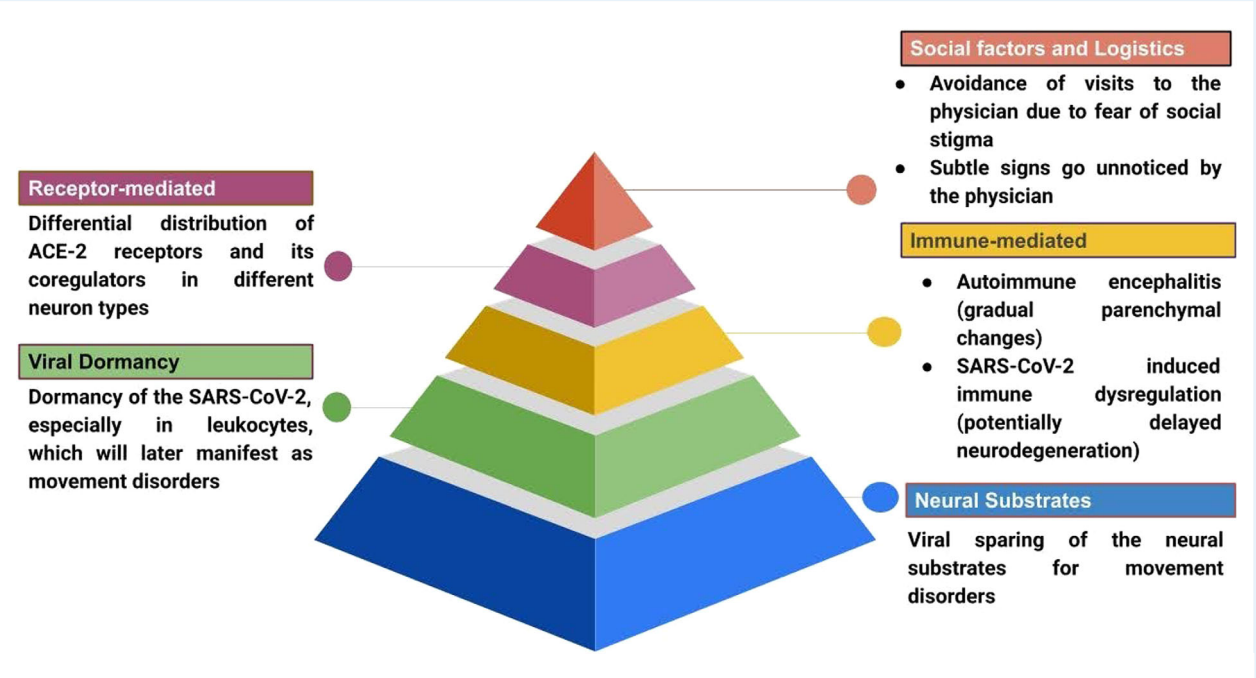

FIG. 3. Possible factors responsible for the scarcity of reports of movement disorders in COVID-19.

performed on in-hospital patients wearing masks, mostly by videoconferencing, may perhaps explain the limited description of these conditions. Also, several of the available reports do not describe the timeline of events in an organized manner, making interpretation difficult. Laboratory, electroencephalography and neuroimaging features have also not been mentioned in detail in a few of the cases. In addition, there is considerable heterogeneity in the available data that may be considered a hindrance in advanced analysis. Finally, we have not included non-English articles. Despite these shortcomings, the present organized review will act as a preliminary guide for clinicians while dealing with movement disorders that appear in the setting of COVID-19.

In closing, only a few case reports have been published describing mainly patients suffering from myoclonus, parkinsonism, tremor, and ataxia. Some cases, mainly those with myoclonus, could be ascribed to medication exposures, metabolic disturbances, or by severe hypoxia, and others, to a post- or para-infectious immune-mediated mechanism somehow related to the inflammatory phase of COVID-19. SARS-CoV-2 could also invade the central nervous system through vascular or retrograde axonal pathways and cause movement disorders. Finally, although SARS-CoV-2 may cause neurodegeneration, leading to movement disorders, this link is not yet established. However, we should closely monitor COVID-19 survivors for the possibility of post-COVID movement disorders. For now, we must patiently and vigilantly wait for time to unravel whether "post-COVID movement disorder" will be an additional entity to add to the spectrum of movement disorders.

Author Roles

(1) Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

R.G.: 1A, 1B, 1C, 2A
U.B.: 2A, 2B
D.R.: 1B, 1C, 2B
A.P.: 1C, 2B
D.L.: 1C, 2B
B.K.R.: 1C, 2B
J.B.L.: 1A, 1B, 1C, 2B

Disclosures

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