INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, 2019-nCoV) emerged in December 2019 and spread into a worldwide pandemic. More than 260 million people worldwide have been verifiably infected with Sars-CoV-2 (as of December 2021), with more than 5.2 million deaths. The number of human coronavirus disease 2019 (COVID-19) cases continues to rise as countries roll out their vaccine programs.

There is a broad range of clinical presentations of COVID-19, including neurological manifestations [1]. It is estimated that 10%–30% of COVID-19 patients develop neurological symptoms in the acute phase, which may be the presenting sign. Neurological manifestations of COVID-19 include cerebrovascular disorders, including ischemic stroke and macro/microhemorrhages, encephalopathies and (meningo-)encephalitis, para-/postinfectious immune-mediated complications such as Guillain-Barré syndrome, movement disorders, and neuropsychiatric complications [2–4]. In parallel to the
diagnosed with both COVID-19 and a movement disorder, including
neurodegenerative disease that may manifest with a movement disorder, termed long COVID. Second, we discuss the general impact produced by the pandemic (i.e., restrictions, lockdown, preventive measures) on patients with a pre-existing movement disorder with regard to quality of life and access to care. Third, we review relevant implications of this relationship for health care provision.

METHODS

We searched the literature using PubMed and medRxiv, the preprint server for health sciences, to identify relevant articles published until August 2021. To select a preliminary list of articles, we used the combinations of terms movement disorder, parkinsonism/Parkinson’s disease, dystonia, chorea, tics, myoclonus, functional disorder, Sars-CoV-2, COVID-19, and COVID-19 vaccine/vaccination, with a focus on studies that yielded clinical descriptions. Further articles were identified by cross-referencing. We selected studies reporting patients diagnosed with both COVID-19 and a movement disorder, including single case reports and case series. Overall, 1335 hits were identified; 1231 papers did not satisfy inclusion criteria or did not provide sufficient information. The final list included 104 articles published in peer-reviewed journals. For side effects related to the vaccination, we searched the EudraVigilance database as outlined below.

RESULTS

Movement disorders: From manifestations of acute COVID-19 to long-term sequelae

Movement disorders appear to be overall rare in COVID-19 compared to pulmonary, cardiovascular, or psychiatric disease [5]. Nonetheless, there is an increasing body of literature reporting movement disorders in the context of COVID-19, which may occur during the acute phase or as potential long-term consequences (long COVID). The clinical phenotype includes both hypo- and hyperkinetic movement disorders, which will be reviewed in the following sections.

COVID-19 and myoclonus

Of all movement disorders, myoclonus is the most frequently reported manifestation with onset in the acute phase. More than 50 cases have been described in the literature as single cases or in small case series (for recent review also see Chan et al. [6]). Myoclonus mostly manifests as spontaneous or action-induced, multifocal or generalized, positive (and rarely negative) myoclonus, affecting axial or proximal limb muscles, face, and tongue [7,8]. Diaphragmatic involvement has also been described (causing disabling shortness of breath, despite the complete recovery of previous respiratory symptoms) [9]. The jerks are often (but not always [10,11]) sensitive to stimuli (e.g., touch or sound), in the absence of cortical discharges at electroencephalographic (EEG) jerk-locked back-averaging. The long duration of myoclonic bursts on electrophysiological workup are consistent with a subcortical or cortical generator. Severity ranges from mild (i.e., manageable in an outpatient setting) to severe (i.e., requiring hospitalization).

Although myoclonus may occur in isolation [12], it is frequently accompanied by other brainstem signs such as hyperekplexia and opsoclonus as well as cerebellar signs (e.g., ataxia, saccadic intrusions, hypermetric saccades, ocular flutter on eye movement assessment), which may also be the presenting sign [11,13,14]. Beyond this, cognitive or psychiatric changes, demyelinating or axonal neuropathy (in distinction to critical illness-related neuropathy [15]), myopathy, an akinetic rigid syndrome, and autonomic involvement [16] have been described.

Notably, onset is usually delayed by 1 week (up to 4 weeks) with respect to the initial Sars-CoV-2 infection. Cerebrospinal fluid (CSF) and antibody testing are typically normal. Autoantibodies directed against Purkinje cells, striatal neurons, and hippocampal neurons were detected in one case [17]. Variable lesions in anatomical correlation were reported on neuroimaging, including single cases with microbleeds [18], ischaemic lesions [19] or diffuse pachymeningeal enhancement [20]; however, imaging was normal in most cases. EEG may show nonspecific slowing in the absence of electrographic correlates for the myoclonus.

Different hypotheses as to the pathogenesis of COVID-19-associated myoclonus have been proposed. These include (1) anoxic brain injury [19] (Lance–Adams syndrome), subsequent to pulmonary breathing restrictions or stroke (however, in view of normal imaging, an anoxic aetiology seems unlikely in most of the cases reported), (2) direct viral central nervous system invasion (however, the absence of Sars-CoV-2 in the CSF in most cases does not support the presence of direct viral infection [6]), (3) cytokine-mediated neuroinflammation with brainstem involvement, or (4) adverse drug reaction (e.g., provocation by propofol or opioids like fentanyl, in line with previously reported cases [21,22]; serotonin syndrome induced by lopinavir/ritonavir [23]). Many authors favour (5) a postinfectious immune-mediated pathophysiology; in line with the latter, myoclonus may also occur with other viral infections, with concomitant encephalopathy/encephalitis or as isolated postinfectious myoclonus.

In approximately 80% of reported cases, myoclonus improved or subsided within days to 2 months. This occurred spontaneously or...
after treatment with immunotherapies (e.g., corticosteroids, intravenous immunoglobulin, or plasma exchange) or symptomatic agents (i.e., with antiepileptic drugs). Notably, some of the latter drugs may be more effective in cortical myoclonus rather than subcortical or spinal myoclonus, which may point toward the anatomical location of the generator [24]. Metabolic abnormalities, such as hypoglycaemia, hyponatraemia, or those secondary to liver and renal failure, that may also precipitate myoclonus in the setting of COVID-19 should be targeted specifically.

COVID-19 and parkinsonism

Newly developed parkinsonism in acute COVID-19

Notably, ACE2 is expressed in high levels in midbrain dopamine neurons, which may make these cells vulnerable to COVID-19-associated pathology [25–27]. This link is supported by the notion that infections with corona viruses, including Sars-CoV-2, in mice show strong tropism for the basal ganglia, particularly the subthalamic nucleus and neighbouring region, compared to other brain regions [28,29].

Several patients have developed an acute akinetic rigid syndrome following a Sars-CoV-2 infection [11,30,31]. They presented with parkinsonism with loss of spontaneous movement, mixed postural and resting tremor, frontal release signs, and eye movement abnormalities (e.g., impairment of smooth pursuit and vertical saccades), with onset approximately 1 month after the initial infection following a transient episode of decreased consciousness, which lasted several hours. Asymmetrically reduced presynaptic dopamine uptake on [123I]-iофлupане dopamine transporter single photon emission computed tomography (SPECT) was demonstrated, whereas structural brain imaging was reported as normal [11]. Cardiac autonomic denervation was not detected on [123I]-metaiodobenzylguanidine myocardial SPECT [11].

Sars-CoV-2 triggering neurodegenerative parkinsonism: A manifestation of neurological long COVID

COVID-19 survivors may not fully recover but be left with long-term residual symptoms (e.g., long haulers, defined as persons who experience symptoms for >28 days after the diagnosis of the Sars-CoV-2 infection). The importance of this issue is reflected by the recently created new International Classification of Diseases, 10th Revision, Clinical Modification codes for COVID-19-associated disorders including U09.91 for post-COVID-19 disorders.

Thirty-four percent of 236,379 survivors of COVID-19 received a neurological or psychiatric diagnosis in the 6 months after their COVID-19 diagnosis [5].

Among others, in view of Spanish flu and the subsequent wave of encephalitis lethargica in the 1920s, there is concern that COVID-19 may precipitate a neurodegenerative process leading to the development of parkinsonism or a neurodegenerative disorder [26,32–36] in the middle or long term. However, the clinical evidence on this specific aspect is still limited. In one study, the number of patients with parkinsonism diagnosed within 6 months after COVID-19 was reported to be relatively low (0.46% of patients who had encephalopathy) [37]. The hypothesis is, nevertheless, supported by animal studies. In a study of rhesus macaques infected with Sars-CoV-2, Lewy bodies were detected in the brain of all these primates, emphasizing the virus’s capability to induce neuropathology in a nonhuman primate model [38]. Although no viral RNA was detected in the macaque brain samples, the authors reported evidence of neuroinflammation. This appears intriguingly in line with the “hit-and-run” hypothesis formulated when no viral material could be isolated from archival samples of patients who had suffered from encephalitis lethargica and postencephalitic parkinsonism after the Spanish flu [39,40]. Instead, the neurotropic virus may have triggered an autoimmune reaction, leading to brain damage and making it more susceptible (“priming”) to later neurotoxic processes (“second hit”). In other words, the “hit-and-run” mechanism may explain how an offending viral agent, which is no longer present, may cause a long-lasting immune response in the brain that persists for many years after the initial insult has resolved. These secondary sequelae may manifest years after the original insult as long-term complications [41,42]. With older age and the inability to control chronic, low-grade, subclinical inflammation, there may be increased susceptibility to develop neurodegenerative changes (“inflammaging” or “immunosenescence”) [43]. The clinical phenotype may be partly explained by the belief that midbrain dopamine neurons are particularly susceptible to systemic inflammation [44]. Likewise, the “dual hit” hypothesis has been proposed for other viruses, including H1N1 and H5N1 influenza viruses. For herpes simplex HSV-1 (region U4222-36) and Epstein–Barr virus (EBV) [45] (repeat region in latent membrane protein 1 encoded by EBV), structural similarities with α-synuclein (αsyn100–114; C-terminal region) may be an important early step in the pathophysiological cascade (molecular mimicry) [46]. Structural similarities between protein components of Sars-CoV-2 and α-synuclein have not yet been identified.

Another link between COVID-19 and parkinsonism is the olfactory deficit, which is one of the most common neurological symptoms of acute COVID-19. It is well documented that olfactory problems are a characteristic sign of Parkinson disease (PD), affecting up to 90% of patients. It has also been demonstrated that the reduced sense of smell is often present from the earliest phases of PD (prodromal/premotor stage) and may thus be a warning sign that someone may subsequently develop PD motor symptoms. In larger case series of COVID-19 patients, a reduced sense of smell was present in 44%–87% [33,47–49]. Genetic variability and the mutation rate within the receptor binding domain of the virus’s spike protein influence the prevalence of olfactory disorders in different populations [47]. Remarkably, there are reports of young COVID-19 patients who were overall only mildly affected clinically (manifesting an olfactory disorder as the leading symptom) [50], but in whom brain involvement could be demonstrated morphologically on brain imaging. This once
more suggests that the brain is an important place of manifestation of COVID-19, and those mild acute symptoms may be accompanied by subclinical changes that may harbor a long-term risk.

A likely route of viral invasion is through the nose and the olfactory bulb (peripheral mechanisms of anosmia by affecting olfactory receptor cells and sustentacular cells in the olfactory epithelium), from where it may reach higher brain regions including the brainstem by transsynaptic transfer, bypassing the blood–brain barrier (central mechanism of anosmia) and leading to COVID-19-related olfactory deficits [1,3,34]. Sars-CoV-2-mediated neuronal inflammation of the olfactory bulb and a reduction of the neural stem cell population, which is involved in renewing olfactory receptor neurons (ORNs) in the olfactory epithelium, have been hypothesized [51]. Similarly, failure to replenish degenerating ORNs in the olfactory epithelium is seen in PD underlying anosmia and may thus be a shared mechanism. Although most people recover from COVID-19-induced olfactory deficits, in 10%–20% of patients olfactory dysfunction is still present months after disease onset, suggesting that-based on the current figures—as many as 20–40 million people globally may currently continue to suffer from olfactory disorders after their COVID-19 illness.

Another similarity between COVID-19 and PD is the involvement of the gastrointestinal tract, which affects 12%–60% of COVID-19 patients in the initial phase [52,53] and persists in 3% and 79% as a long COVID symptom [54]. In PD, gastrointestinal symptoms such as constipation are very common and may precede motor onset by decades [55], with the gut–brain axis potentially playing an important role in the pathogenesis of PD [56].

Cognitive decline is another common feature of PD and several atypical parkinsonian syndromes. There is growing evidence suggesting that cognitive deterioration might represent a possible long-term outcome manifestation of a COVID-19 infection. In a study that enrolled 236,379 COVID-19 survivors, almost 5% of patients older than 65 years had received a new diagnosis of dementia within 6 months after the infection, which was significantly more than after influenza or other respiratory tract infections [5]. This supports previous data from the same authors suggesting an association between COVID-19 and dementia [37]. Remarkably, a large-scale cross-sectional online study of almost 85,000 participants [32] revealed that the degree of decline in global cognitive performance in patients with a history of severe COVID-19 was equivalent to the loss of 10 years on average compared to matched controls.

Younger patients may also be affected by long-lasting cognitive symptoms, as shown in a study in middle-aged adults (mean age = 42.2 years) following mild to moderate COVID-19. Seventy-eight percent of them reported sustained cognitive deficits and performed worse in a telephone cognitive screening compared to age-matched healthy controls [57]. Thus, even those recovering from mild COVID-19 were shown to perform worse cognitively compared to non-COVID controls [32]. In summary, cognitive abnormalities appear to be common at 3-month follow-up, and the frontal cortex has been discussed as one of the main anatomical regions involved [58].

COVID-19 and other hyperkinetic disorders

Chorea is a rare manifestation of COVID-19. Hassan et al. [59] recently described a 58-year-old male who presented with fever, respiratory complaints, and generalized chorea. His lung X-ray was highly suspicious for a Sars-CoV-2 infection; the virus was detected in the CSF, which was otherwise unremarkable (i.e., no oligoclonal bands, negative autoimmune markers). Brain magnetic resonance imaging demonstrated mild periventricular ischemic changes without evidence of gross neuronal injury. Oral umifenovir, procyclidine, risperidone, and amantadine sulphate led to gradual improvement [59].

Children with COVID-19 may also display choreiform movements, affecting two among 27 children (7.4%) in a prospective UK cohort study of children and adolescents hospitalized with COVID-19 [60].

Cognitive deterioration might represent a possible long-term outcome manifestation of a COVID-19 infection. In a study that enrolled 236,379 COVID-19 survivors, almost 5% of patients older than 65 years had received a new diagnosis of dementia within 6 months after the infection, which was significantly more than after influenza or other respiratory tract infections [5]. This supports previous data from the same authors suggesting an association between COVID-19 and dementia [37]. Remarkably, a large-scale cross-sectional online study of almost 85,000 participants [32] revealed that the degree of decline in global cognitive performance in patients with a history of severe COVID-19 was equivalent to the loss of 10 years on average compared to matched controls.

Younger patients may also be affected by long-lasting cognitive symptoms, as shown in a study in middle-aged adults (mean age = 42.2 years) following mild to moderate COVID-19. Seventy-eight percent of them reported sustained cognitive deficits and performed worse in a telephone cognitive screening compared to age-matched healthy controls [57]. Thus, even those recovering from mild COVID-19 were shown to perform worse cognitively compared to non-COVID controls [32]. In summary, cognitive abnormalities appear to be common at 3-month follow-up, and the frontal cortex has been discussed as one of the main anatomical regions involved [58].

COVID-19 and functional movement disorders

A number of case series have documented a relevant increase in the incidence of functional movement disorders since the beginning of the pandemic. At one large tertiary care movement disorders clinic in the United States, the number of newly referred patients who received a diagnosis of functional movement disorders has increased by 60.1% (90.1% in the paediatric cohort and 50.9% in the adult cohort) [62]. At the same time, several clinicians and researchers have witnessed a striking, “epidemic” increase in the incidence of first-ever, acute onset tic-like behaviours, mainly functional in nature, presumably related to pandemic-related social restrictions, changes in frequency and modality of routine social and academic activities, specific social media exposures related to tics and tic-like behaviours, and pandemic-related stress and anxiety levels in vulnerable adolescents and young adults [61]. Similar observations were made by different clinicians and researchers across Canada, the United States, Europe, and Australia [61–67]. These young patients exhibit an unusually rapid onset of complex movements and vocalizations, in some cases reflecting shared exposure to social media triggers, and high prevalence of comorbid anxiety and depressive disorders. A combination of psychoeducation and cognitive behavioural therapy with special emphasis on the identification and management of the antecedents and consequences of these
behaviours has been proposed as urgent treatment of choice, but more data are required to appraise response on a large scale [63,68].

A case of functional tremor starting after a positive test for Sars-CoV-2 (performed 2 weeks after a febrile illness) was recently reported [69]. The patient, a 39-year-old nurse, demonstrated tremor with variable frequency and amplitude affecting her legs and abnormal movements while sitting (e.g., twisting movements), walking, and at rest (e.g., jerky movements in supine position), receiving a definitive diagnosis of a complex functional movement disorder.

Impact of COVID-19 on pre-existing movement disorder syndromes

Impact of the pandemic on patients with parkinsonian disorders

In addition to the reports of newly developed movement disorders, the pandemic has had a negative impact on the clinical status, access to health care, and overall well-being of patients with pre-existing movement disorders. Most studies demonstrating this have focused on PD, but findings likely equally apply to other movement disorders. These direct and indirect effects, which reach across multiple domains, are shown in Figure 1.

PD patients reported negative effects on their motor status, mental health with increased stress and depression [70], and physical activity compared with their prelockdown state [71,72]. Access to PD medication was globally affected by the pandemic due to slowed delivery systems, or, in some settings, limited access to dispensaries based on an International Parkinson and Movement Disorder Society (MDS)-wide survey [73]. Similarly, elective surgical procedures may have been delayed [73]. This resulted in deterioration of patients’ symptomatic control.

There is no evidence that PD patients may be particularly prone to developing symptomatic COVID-19 beyond the finding that PD primarily affects the elderly who, by age, are the most vulnerable to severe COVID-19. Based on the current knowledge and similar to other categories of patients with a chronically progressive illness, the risk for individual PD patients to contract a COVID-19 infection is predominantly dependent on their living environment, for example, whether the patient lives in a nursing home or long-term care facility, and number of social contacts. Notably, studies found that, similar to the non-PD population, a substantial proportion of infected PD patients remain asymptomatic [74]. Some studies reported an often mild clinical course with low to nil [74,75] mortality, whereas others observed mortality rates of 20% [76,77].

Once infected, Sars-CoV-2-positive PD patients may experience worsening of their motor (e.g., bradykinesia, tremor, motor fluctuations) or nonmotor symptoms (e.g., increased urinary urge/incontinence, diarrhoea, orthostatic hypotension, cognitive impairment, and psychosis) requiring adjustment of therapy [74]. Older age, longer disease duration with use of advanced therapies, and concomitant dementia and hypertension have been found to predict poor COVID-19 outcome in PD patients [76,78]. Pre-existing dysphagia predisposes PD patients (but similarly patients with other movement disorders with swallowing impairment, e.g., Huntington disease) to aspiration and aspiration pneumonia. This may be aggravated by prescribed or over-the-counter drugs used to manage COVID-19 symptoms, for example, drugs for cough or influenzalike symptoms. Pre-existing respiratory restrictions (e.g., due to rigidity, dystonia, or bradykinesia of chest wall muscles) or abnormal posturing of the trunk (e.g., due to camptocormia) may lead to additional challenges during intubation. Intensive care unit care also necessitates adjustment of therapies with regard to the dose and the route of administration. Further treatment implications are discussed below.

Impact of the pandemic on patients with dystonia and hemifacial spasm

A study on the overall effect of the pandemic on patients with pre-existing dystonia found that the majority of patients noted worsening of symptoms (65%) [79], approximately one third of patients reported stable symptoms, and <5% noted improvement of dystonia. Forty-two percent of patients felt that dystonia management had, at some point, been inadequate to their clinical need. Appointments for botulinum toxin injections were frequently delayed, which led to worsening of mood and patients’ perception of care. Interestingly, in another study, 11% of patients reported improvement related to wearing masks, which served as a sensory trick for their dystonia [80]. Notably, for most of these cases, this information was based on self-report only, without assessment by a physician. Unsurprisingly, patients with hemifacial spasm reported that wearing masks reduced the stigmatization of their facial movement disorder.

Impact of the pandemic on patients with tic disorders

An increase in tic symptoms in some children and adolescents with a pre-existing diagnosis of tic disorders has been reported. To elaborate, 48%–67% of individuals with Tourette syndrome developed worsening of the overall clinical condition [81,82]. This is compared to an improvement reported by 8% and 20.5%, and no variation observed by 7% of cases in one and 44% in another study [81,82]. Most worsened symptoms included tics, hyperactivity, rage attacks, obsessions/compulsions, and anxiety, often across multiple domains [81].

Impact of the pandemic on patients with functional disorders

A survey in patients with pre-existing functional movement disorders revealed that most (54%) noted no change of their disorder, whereas one third reported worsening [83].
Implications for treatment

As shown in Table 1, there are several facets of how the pandemic has impacted the treatment of patients with movement disorders. Most studies have predictably focused on PD.

As outlined above, access to medication has been restricted due to the closing of routine clinical space, faltering delivery systems, or, in some settings, the inability to access dispensaries or pay for medication based on an MDS survey [73], with a higher frequency of affected patients in lower-income compared to higher-income countries. Similarly, routine clinical visits and elective surgical procedures, such as deep brain stimulation (DBS) surgery, and nonurgent infusion therapies, for example, levodopa/carbidopa intestinal gel and apomorphine pumps, may have been delayed [73]. An important weakness of this study is the low response rate, with only 350 respondents, mostly doctors, out of 10,000 contacted, which may be source of a selection bias.

Sars-CoV-2 infection, COVID-19, and the restrictions imposed by the pandemic (i.e., lack of physical activity or mood changes in the context of social distancing) may lead to worsening of motor symptoms and require an adjustment or additional medication. In some cases, drugs administered to treat COVID-19-related symptoms may trigger or aggravate movement disorders. For example, over-the-counter cough and cold medications used to treat mild COVID-19 symptoms are available as combination products, which may contain antihistamines (e.g., diphenhydramine and dimenhydrinate), which have anticholinergic properties and can worsen constipation, confusion, as well as urinary symptoms in PD patients or other complex movement disorder syndromes [84]. Doctors and pharmacists should inform patients about such effects.

### Table 1
Impacts of the COVID-19 pandemic on treatment for patients with Parkinson disease and other movement disorders

| Impact                                                |
|-------------------------------------------------------|
| 1. Restricted access to medication, advice of health care professionals, or rehabilitation programmes |
| 2. Need to adjust drug regimen, e.g., when COVID-19 leads to change (e.g., worsening) of symptoms |
| 3. Worsening of movement disorder symptoms by COVID-19 medication |
| 4. Difficulty of administering drugs (e.g., during ICU care with ventilation) |
| 5. Pharmacological interference of medications used for COVID-19 symptoms with drugs used for the movement disorder |

Abbreviation: ICU, intensive care unit.

### FIGURE 1
Impact of the COVID-19 pandemic on movement disorder patients. ICU, intensive care unit; MD, movement disorders
When patients become hospitalized, pre-existing dysphagia or intubation tubes can hamper oral administration of drugs. This scenario is not COVID-19 specific. One easy, cost-effective, and efficient solution is to convert to liquid solutions to be administered via a nasogastric tube or, alternatively, switch to alternative routes of administration, for example, using a transdermal patch or apomorphine pump [85].

Dangerous drug combinations may occur when COVID-19 medication is added to some medications used to treat PD. For example, the combination of monoamine oxidase (MAO) B inhibitors (like rasagiline, selegiline, and safinamide) and over-the-counter antitussive pharmaceutical preparations containing dextromethorphan, nasal decongestants containing pseudoephedrine, phenylephrine, or phenylpropanolamine, or some of the analgesic opioid receptor agonists (such as methadone, propoxyphene, tramadol, and meperidine, which modestly inhibit serotonin reuptake) may enhance serotonin toxicity and trigger a serotonin syndrome [84,86]. Similarly, the combination of MAO inhibitors and decongestants may lead to severe hypertensive outcomes in the case of increased alpha agonist effects of the decongestants [84].

**PD drugs to treat COVID-19?**

Amantadine is one of the standard medications for the management of PD. It was originally used as an antiviral drug based on its activity against influenza A viruses. Later, an antiviral activity of amantadine against SARS-CoV-1 was demonstrated [87]. By analogy, a positive effect on Sars-CoV-2 was reasoned, and small observational studies suggest a positive clinical effect of amantadine on COVID-19 [88-90]. Basic science data support this notion [87,91,92]. Amantadine inhibits Sars-CoV-2 cell entry [87] and some authors proposed its topical administration by inhalation or intranasal instillation, as it may result in a sufficient amantadine concentration in the airway epithelium without high systemic exposure. However, there are no sufficient clinical data yet to support effectiveness and safety of this medication for the treatment of Sars-CoV-2 infection [91].

**Movement disorders as an adverse event of the COVID-19 vaccination**

Large databases have been established to systematically detect adverse drug reactions. Based on the European database, EudraVigilance [93], the number of reported movement disorders that occurred as a side effect after COVID-19 vaccines is low (Table 2), occurring with a remarkably low frequency of 0.00002-0.0002 depending on the product used. The vaccine by AstraZeneca was 10 times more likely to be associated with the development of new onset movement disorders compared to the other products. For all vaccines, tremor was by far the most frequently reported side effect (Table 2).

Detailed reports on movement disorders side effects are scarce. Recently, Erro et al. [94] reported two patients with PD (a 61-year-old with an 11-year history of PD and a 79-year-old with a 5-year history of PD) who developed prominent dyskinesia after receiving the BNT162b2 (Pfizer/BioNTech) mRNA vaccine. Motor symptoms were well controlled previously. Dyskinesia occurred within 6 h after (the first dose) and on the day after (the second dose) the vaccination. In the latter case, dyskinesia was accompanied by fever and confusion. Reduction of her daily anti-PD drug dose and fever medication led to disappearance of the dyskinesia. The authors hypothesize that the systemic inflammatory response triggered by the vaccination may have led to increased permeability of the blood–brain barrier and subsequent drug availability, causing severe dyskinesia.

The occurrence of transient akathisia following after the second dose of the Pfizer/BioNTech COVID-19 vaccine was observed in a 36-year-old Hispanic woman with a past medical history of atopic dermatitis and allergic rhinitis. Onset was 12 h after the injection, when she developed an urge to move described as “restless body syndrome.” Five hours later, she developed low-grade fever, myalgias, and nausea. The restless movements ceased spontaneously. The authors discuss similarities to reports of dopaminergic-responsive parkinsonism after tetanus and measles vaccinations, with disputed causal relationships [95-97].

**Efficacy of vaccines for movement disorder patients**

There are currently no studies that have systematically, specifically looked at the efficacy and safety of COVID-19 vaccines for persons with movement disorders [98]. Experience will grow as more movement disorder patients are vaccinated worldwide. Overall, there are no specific concerns as to why patients with movement disorders should not be vaccinated. On the contrary, COVID-19 vaccination has been explicitly recommended by the MDS, and specific information updates can be found on the MDS website (https://www.movementdisorders.org/COVID-19-Pandemic-MDS.htm).

**Continuity of care and use of telemedicine**

The pandemic has made continuity of care more challenging. Outpatient appointments have been cancelled or postponed by patients or care facilities to reduce the risk of infection. Some have reported an increasing request of telehealth services [99], whereas others have observed that patients were not willing to participate in telehealth services [100]. Potential explanations for the latter may include socioeconomic barriers and caregiving structure [100]. It also has to be kept in mind that invasive treatment is excluded from any telehealth monitoring or follow-up options [101]. In particular for management of DBS patients, teleneuropsychological pre-DBS evaluation and remote monitoring of DBS settings have been implemented by some centres [102].

In response, there has had to be a rapid reorganization of health care systems. Among others, this has boosted the application and acceptance of telemedicine [103], a term that encompasses a broad range of health care tools, including video-conferencing,
smartphone health care applications, body-worn sensors, and smart homes equipped with sensors [104].

Some have criticized the “progressivism” by which telemedicine has been implemented [105], given that the medical examination remains the cornerstone of practice and is restricted in a non-face-to-face consultation. In particular, the assessment of balance and gait remains suboptimally standardized for remote evaluations. This is in line with the findings that the majority of patients chose a face-to-face consultation [106], mainly because of lack of trust on virtual assessment and the opportunity to go outdoors during the lockdown [106]. Other disadvantages include concerns about data protection and device-related issues (e.g., access to technology, webcam quality, high-speed internet connection). The growing complexity of frequently changing laws and regulations surrounding telemedicine practice and reimbursement pose always new challenges for users. Nevertheless, other authors foresee that the overall benefits of this approach will render telemedicine progressively part of neurological clinical practice. Further information and practical advice are

| Supplier | Pfizer/BioNTech | Moderna | AstraZeneca | Janssen |
|----------|-----------------|---------|-------------|---------|
| Name of vaccine | TOZINAMERAN | CX-024414, Spikevax | CHADOX1 NCOV-19, Vakzevera | AD26.COV2.S |
| Total doses administered in EU/EEA | 477,960,508 | 66,735,671 | 68,846,754 | 18,051,866 |
| Total number of reported side effects in EU/EEA | 592,779 | 161,667 | 413,987 | 38,686 |
| Total number of reported movement disorders (sum of rows below) | 8259 | 2895 | 13,067 | 627 |
| Frequency of movement disorders among all doses administered | 0.00002 | 0.00004 | 0.0002 | 0.00003 |
| Movement disorders (not specified) | 1081 | 263 | 395 | 58 |
| Parkinsonism | 23 | 2 | 16 | 0 |
| Parkinson disease | 55 | 39 | 30 | 4 |
| MSA | 1 | 0 | 0 | 0 |
| PSP | 3 | 1 | 0 | 0 |
| Cogwheel rigidity | 1 | 1 | 0 | 0 |
| Parkinsonian rest tremor | 1 | 0 | 1 | 0 |
| akinesia/bradykinesia/hypokinesia | 608 | 210 | 49 | 61 |
| Hyposmia | 95 | 24 | 40 | 0 |
| Tremor | 5293 | 1912 | 11,580 | 399 |
| Rest tremor | 13 | 9 | 11 | 0 |
| Action tremor | 3 | 2 | 6 | 0 |
| Essential tremor | 11 | 4 | 5 | 0 |
| Postural tremor | 3 | 2 | 1 | 0 |
| Dyskinesia | 415 | 209 | 214 | 44 |
| Dystonia | 53 | 23 | 30 | 7 |
| Myoclonus | 157 | 44 | 76 | 7 |
| Chorea | 18 | 6 | 0 | 1 |
| Ballism | 5 | 0 | 2 | 0 |
| Tardive dyskinesia | 9 | 6 | 1 | 0 |
| Akathisia | 15 | 5 | 22 | 3 |
| Restless legs syndrome | 255 | 70 | 473 | 28 |
| Orthostatic tremor | 1 | 0 | 0 | 0 |
| Ataxia | 140 | 63 | 115 | 15 |

Note: The terms in the first column were taken from the database in the original wording. We appreciate that these partly overlap or may be imprecise (which may be due to non-movement disorder experts submitting the information to the database). Nonetheless, we chose not to combine them, as this may lead to false reclassification, that is, not all types of action tremor are essential tremor, et cetera.

Abbreviations: EEA, European Economic Area; EU, European Union; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

aSource: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab; accessed 1 December 2021.

bSource: EudraVigilance, https://www.adreports.eu/en/search_subst.html [93], accessed 1 December, 2021.
CONCLUDING REMARKS

The pandemic has had negative consequences for the health care of individuals and entire nations, the economy, and social coexistence. As outlined above, PD and other movement disorders face challenges that go beyond the burden of unaffected individuals. Movement disorders may also newly develop because of the viral infection, in particular in patients with acute or subacute onset myoclonus. With time, studies will provide robust data about when and in what manner long COVID may manifest.

The disturbances of the interwoven global links became clear when supply chains broke off, which affected goods, commodities, and standard drugs. It is impressive how quickly scientists and the industry reacted and presented improved symptomatic care and a highly efficient vaccine, albeit in combat with newly emerging resistant variants of concern. The health care system also quickly adjusted by establishing digital solutions to allow continuity of care. This may be a turning point for future developments and the way patients and carers interact.

Despite this growing insight into the virus, COVID-19 clinical presentations and outcomes, the pathophysiology of disease and treatment, and the effects of the pandemic in general, numerous questions remain unanswered. For example, to date neuropathological findings in COVID-19 survivors are largely unstudied. Studies determining causes and mechanisms underlying long-term manifestations are also clearly required [107]. In addition, long-term surveillance programmes are needed to uncover causal links.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

None of the authors has any conflict of interest related to this article.

AUTHOR CONTRIBUTIONS

Susanne A. Schneider: Conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), writing—original draft (lead). Anita Hennig: Data curation (supporting), writing—review & editing (supporting). Davide Martino: Formal analysis (supporting), methodology (supporting), writing—review & editing (supporting).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were derived from public domain resources as referenced. They are available from the corresponding author upon reasonable request.

ORCID

Susanne A. Schneider https://orcid.org/0000-0001-7283-1995
Davide Martino https://orcid.org/0000-0002-2217-0487

REFERENCES

1. Karuppan MKM, Devadoss D, Nair M, Chand HS, Lakshmanan MK. SARS-CoV-2 infection in the central and peripheral nervous system-associated morbidities and their potential mechanism. Mol Neurobiol. 2021;58(6):2465-2480.
2. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020;143:3104-3120.
3. Mao L, Jin H, Wang M, et al. Neurological manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683-690.
4. Maury A, Lyoubi A, Peiffer-Smadja N, de Broucker T, Meppiel E. Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: a narrative review for clinicians. Rev Neurol (Paris). 2021;177:51-64.
5. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021;8:416-427.
6. Chan JL, Murphy KA, Sarna JR. Myoclonus and cerebellar ataxia associated with COVID-19: a case report and systematic review. J Neurol. 2021;268(10):3517-3548.
7. Muccioni L, Rondelli F, Ferri L, Rossini G, Cortelli P, Guarino M. Subcortical myoclonus in COVID-19: comprehensive evaluation of a patient. Mov Disord Clin Pract. 2020;7:971-973.
8. Rabano-Suarez P, Bermejo-Guerrero L, Mendez-Guerrero A, et al. Generalized myoclonus in COVID-19. Neurology. 2020;95:e767-e772.
9. Borroni B, Gazzina S, Dono F, et al. Diaphragmatic myoclonus due to SARS-CoV-2 infection. Neurol Sci. 2021;41:3471-3474.
10. Schellekens MMI, Bleeker-Rovers CP, Keurlings PAJ, Mummery CJ, Bloem BR. Reversible Myoclonus-Ataxia as a postinfectious manifestation of COVID-19. Mov Disord Clin Pract. 2020;7:977-979.
11. Mendez-Guerrero A, Laespada-Garcia MI, Gomez-Grande A, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. Neurology. 2020;95:e2109-e2118.
12. Eli Omtani H, Moutouakil F, Ouazzani M, Mjahed K. Isolated generalized myoclonus immune-mediated by SARS-CoV-2: an illustrative videotaped case. Neurol Sci. 2021;42(8):3411-3413.
13. Dijkstra F, Van den Bossche T, Willekens B, Cras P, Crosiers D. Myoclonus and cerebellar ataxia following Coronavirus disease 2019 (COVID-19). Mov Disord Clin Pract. 2020;7:974-976.
14. Shah PB, Desai SD. Opsoclonus myoclonus ataxia syndrome in the setting of COVID-19 infection. Neurology. 2021;96:33.
15. Chaumont H, San-Galli A, Martino F, et al. Mixed central and peripheral nervous system disorders in severe SARS-CoV-2 infection. J Neurol. 2020;267:3121-3127.
16. Zimmermann KM, Harmel J, Wojtecki L. CORE-myoclonus syndrome: a proposed neurological initial manifestation of COVID-19. Mov Disord Clin Pract. 2021;8:637-638.
17. Grimaldi S, Lagarde S, Harle JR, Bourcrait J, Guerdj E. Autoimmune encephalitis concomitant with SARS-CoV-2 infection: insight from (18)F-FDG PET imaging and neuronal autoantibodies. J Neurol. 2020;61:1726-1729.
18. Cuhna P, Herlin B, Vassilev K, et al. Myoclonus and cerebellar ataxia following Coronavirus disease 2019. Mov Disord Clin Pract. 2020;7:974-976.
19. Shah PB, Desai SD. Opsoclonus myoclonus ataxia syndrome in the setting of COVID-19 infection. Neurology. 2021;96:33.
20. Chaumont H, San-Galli A, Martino F, et al. Mixed central and peripheral nervous system disorders in severe SARS-CoV-2 infection. J Neurol. 2020;267:3121-3127.
21. Zimmermann KM, Harmel J, Wojtecki L. CORE-myoclonus syndrome: a proposed neurological initial manifestation of COVID-19. Mov Disord Clin Pract. 2021;8:637-638.
22. Grimaldi S, Lagarde S, Harle JR, Bourcrait J, Guerdj E. Autoimmune encephalitis concomitant with SARS-CoV-2 infection: insight from (18)F-FDG PET imaging and neuronal autoantibodies. J Neurol. 2020;61:1726-1729.
23. Cuhna P, Herlin B, Vassilev K, et al. Myoclonus and cerebellar ataxia following Coronavirus disease 2019. Mov Disord Clin Pract. 2020;7:974-976.
24. Anand P, Zakaria A, Benameur K, et al. Myoclonus in patients with coronavirus disease 2019: a multicenter case series. Crit Care Med. 2020;48:1664-1669.
25. Han PK, Arnold R, Bond G, Janson D, Abu-Elmagd K. Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. J Pain Symptom Manage. 2002;23:66-72.
66. Olvera C, Stebbins GT, Goetz CG, Kompoliti K. TikTok tics: a pandemic within a pandemic. Mov Disord Clin Pract. 2021;8:1200-1205 (published online).

67. Muller-Vahl KR, Pisanenko A, Jakubovski E, Fremer C. Stop that! It’s not Tourette’s but a new type of mass sociogenic illness. Brain. 2021;awab316. 10.1093/brain/awab316.

68. McGuire JF, Bennett SM, Conelea CA, et al. Distinguishing and managing acute-onset complex Tic-like behaviors in adolescence. J Am Acad Child Adolesc Psychiatry. 2021;60(12):1445-1447.

69. Piscitelli D, Perin C, Tremolizzo L, Peroni F, Cerri CG, Cornaggia CM. Functional movement disorders in a patient with COVID-19. Neurol Sci. 2020;41:2343-2344.

70. Prasad S, Holla VV, Neeraja K, et al. Parkinson’s disease and COVID-19: perceptions and implications in patients and caregivers. Mov Disord. 2020;35:912-914.

71. Shalash A, Roushdy T, Essam M, et al. Mental health, physical activity, and quality of life in Parkinson’s disease during COVID-19 pandemic. Mov Disord. 2020;35:1097-1099.

72. Leavy B, Hagstromer M, Conradsson DM, Franzen E. Physical activity and perceived health in people with Parkinson disease during the first wave of Covid-19 pandemic: a cross-sectional study from Sweden. J Neurol Phys Ther. 2021;45(4):266-272.

73. Cheong JL, Goh ZHK, Marras C, et al. The impact of COVID-19 on access to Parkinson’s disease medication. Mov Disord. 2020;35:2129-2133.

74. Buccafusca M, Micali C, Autunno M, Versace AG, Nunnari G, Musumeci O. Favourable course in a cohort of Parkinson’s disease patients infected by SARS-CoV-2: a single-centre experience. NeuroSci. 2021;42:811-816.

75. Cilia R, Bonvegna S, Straccia G, et al. Effects of COVID-19 on Parkinson’s disease clinical features: a community-based case-control study. Mov. Disord. 2020;35:1287-1292.

76. Fasano A, Elia AE, Dallocchio C, et al. Predictors of COVID-19 outcome in Parkinson’s disease. Parkinsonism Relat Disord. 2020;78:134-137.

77. Fasano A, Cereda E, Barichella M, et al. COVID-19 in Parkinson’s disease patients living in Lombardy, Italy. Mov Disord. 2020;35:1089-1093.

78. Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson’s disease patients affected by COVID-19. Mov Disord. 2020;35:905-908.

79. Delgado C, Parees I, Kurtis MM. Patients’ perspective of dystonia symptoms during the SARS-CoV-2 pandemic. Mov. Disord. 2021;36(7):1485-1486.

80. Erbguth F, Lange R. Sensory trick effect in craniofacial dystonia as one of the possible impacts of wearing face masks during the COVID-19 pandemic. NeuroRx Res Pract. 2021;3:24.

81. Conte G, Baglioni V, Valente F, Chiarotti F, Cardona F. Adverse mental health impact of the COVID-19 lockdown in individuals with Tourette syndrome in Italy: an online survey. Front Psychiatry. 2020;11:583744.

82. Mataix-Cols D, Ringberg H, Fernandez de la Cruz L. Perceived worsening of Tics in adult patients with Tourette syndrome after the COVID-19 outbreak. Mov Disord Clin Pract. 2020;7:725-726.

83. Delgado C, Parees I, Jimenez-Huete A, Kurtis MM. Impact of the coronavirus disease 2019 pandemic on functional movement disorders: lessons from a specialized clinic. Mov Disord. 2020;35:1723-1724.

84. Elbeddini A, To A, Tayefehchamani Y, Wen C. Potential impact and challenges associated with Parkinson’s disease patient care amidst the COVID-19 global pandemic. J Clin Mov Disord. 2020;7:7.

85. Garg D, Dhamija RK. The challenge of managing Parkinson’s disease patients during the COVID-19 pandemic. Ann Indian Acad Neurol. 2020;23:S24-S27.

86. Chen JJ. Pharmacologic safety concerns in Parkinson’s disease: facts and insights. Int J Neurosci. 2011;121(Suppl 2):45-52.

87. Zhao MM, Yang WL, Yang FY, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct Target Ther. 2021;6:134.

88. Grieb P, Swiatkiewicz M, Prus K, Rejdak K. Amantadine for COVID-19. J Clin Pharmacol. 2021;61:412-413.

89. Artusi CA, Romagnolo A, Letta C, et al. COVID-19 and Parkinson’s disease: what do we know so far? J Parkinsons Dis. 2021;11(2):445-454.

90. Aranda-Abreau GE, Aranda-Martinez JD, Araujo R. Use of amantadine in a patient with SARS-CoV-2. J Med Virol. 2021;93:110-111.

91. Fink K, Nitsche A, Neumann M, Grossegesse M, Eisele KH, Dahnys W. Amantadine inhibits SARS-CoV-2 in vitro. Viruses. 2021;13:539.

92. Li Z, Yang L. Underlying mechanisms and candidate drugs for COVID-19 based on the connectivity map database. Front Genet. 2020;11:558557.

93. EudraVigilance European database of suspected adverse drug reactions. www.adrereports.eu [online]. Accessed December 1, 2021.

94. Erro R, Buononimo AR, Barone P, Pellecchia MT. Severe dyskinesia after administration of SARS-CoV2 mRNA vaccine in Parkinson’s disease. Mov. Disord. 2021;36:2219.

95. Reijneveld JC, Taphoorn MJ, Hoogenraad TU, van Gijn J. Severe but transient Parkinsonism after tetanus vaccination. J Neural Neurosurg Psychiatry. 1997;63:258.

96. Alves RS, Barbosa ER, Scaff M. Postvaccinal Parkinsonism. Mov. Disord. 1992;7:178-180.

97. Fenichel GM. Postvaccinal parkinsonism. Mov. Disord. 1993;8:253.

98. Bloem BR, Trenkwalder C, Sanchez-Ferro A, et al. COVID-19 vaccination for persons with Parkinson’s disease: light at the end of the tunnel? J Parkinsons Dis. 2021;11:3-8.

99. Zhang C, Zhu K, Lin Z, et al. Utility of deep brain stimulation telemedicine for patients with movement disorders during the COVID-19 outbreak in China. Neuromodulation. 2021;24:337-342.

100. Pfalzer AC, Hale LM, Huitz E, et al. Healthcare delivery and Huntington’s disease during the time of COVID-19. J Huntingtons Dis. 2021;10:313-322.

101. Erro R, Scannapieco S, Russo M, Picillo M, Barone P. Impact of COVID-19 on neurological patients attending a botulinum toxin service. Neurol Sci. 2021;42:433-435.

102. Chen Y, Hao H, Chen H, Li L. The study on a telemedicine interaction mode for deep brain stimulation postoperative follow-up. Annu Int Conf IEEE Eng Med Biol Soc. 2015;2015:186-189.

103. Miele G, Straccia G, Moccia M, et al. Telemedicine in Parkinson’s disease: how to ensure patient needs and continuity of care at the time of COVID-19 pandemic. Telemed J E Health. 2020;26:1533-1536.

104. Group MTS Telemedicine in your movement disorders practice - a step-by-step guide. [online]. Accessed April 8, 2021.

105. Mulroy E, Menozzi E, Lees AJ, Lynch T, Lang AE, Bhatia KP. Reply to: “A new day: the role of telemedicine in reshaping care for persons with movement disorders”. Mov. Disord. 2020;35:1903-1904.

106. Li WS, Heng DL, Chia TH, Lim EC, Tan EK. High outpatient attendance during COVID-19 lockdown when patients were given the option to return. Mov. Disord. 2020;35:2137-2138.

107. Fiscarò F, Di Napoli M, Liberto A, et al. Neurological sequelae in patients with COVID-19: a histopathological perspective. Int J Environ Res Public Health. 2021;18:1415.

How to cite this article: Schneider SA, Hennig A, Martino D. Relationship between COVID-19 and movement disorders: A narrative review. Eur J Neurol. 2022;29:1243-1253. doi:10.1111/ene.15217