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LEADING TOPIC

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Incidence and characteristics of post-COVID-19 parkinsonism and dyskinesia related to COVID-19 vaccines

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ABSTRACT

Background. Coronavirus disease 2019 (COVID-19) is an infectious disease mainly affecting the respiratory system; however, a significant prevalence of neurological symptoms has been noted.

Objectives. To investigate the incidence and characteristics of post-COVID-19 parkinsonism and to study dyskinesia related to COVID-19 vaccines.

Material and methods. The MEDLINE, PubMed, Scopus, and Web of Science databases were searched for all manuscripts relevant to post-COVID-19 parkinsonism and dyskinesia related to COVID-19 vaccines. Subsequently, we extracted and analysed data from the manuscripts in a structured manner.

Results. We found 24 patients with post-COVID-19 parkinsonism, with a mean onset age of 58 years after a mean of 30 days from the COVID-19 onset. Akinetic-rigid (n = 11) and mixed (n = 6) subtypes were the most common. Asymmetry was present in 13/15 patients. Brain MRI was unremarkable in 11/19, whereas dopaminergic system imaging was abnormal in 8/8 patients. Responsiveness to dopaminergic treatment was observed in 12/15 patients. Four patients improved after immunomodulatory therapy. Comorbidities were present in 9/24, encephalopathy symptoms in 11/24, and loss of smell in 9/13 patients. Most patients (n = 14) suffered serious COVID-19-related complications and three were treated with haloperidol. Parkinsonism improved (n = 5) or resolved (n = 4) during the follow-up.

Five patients, with a mean age of 52, developed dyskinesia at a mean of 25 hours after receiving the COVID-19 mRNA vaccines. One patient had a history of neuropsychiatric symptoms and developed functional dyskinesia of the tongue. Four patients had a previous history of Parkinson's Disease (PD) with a mean duration of 10 years and developed dyskinesia and dystonia, which resolved (n = 2) or improved (n = 2) during the follow-up.

Conclusions. Post-COVID-19 parkinsonism is a very rare complication, and it is likely that this is an umbrella syndrome that includes many different etiologies. Dyskinesia due to COVID-19 vaccines is exceedingly rare and probably has the same pathophysiological basis as in other conditions with exacerbation of PD symptoms.

Key words: SARS-CoV-2, Parkinson's Disease, levodopa, dopaminergic, vaccination, dystonia

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Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel strain of coronavirus that causes coronavirus disease 2019 (COVID-19), an infectious disease mainly affecting the respiratory system [1, 2]. The first case of COVID-19 was confirmed in Wuhan, China, on 8 December, 2019 [1]. The subsequent outbreak of pneumonia that spread across the globe led to the declaration of a pandemic by the World Health Organisation in March 2020.

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Apart from respiratory symptoms, many patients affected by COVID-19 have presented symptoms and signs suggestive of central (dizziness, headache, altered consciousness, stroke, ataxia, seizure) and peripheral (disorders of smell and taste, vision impairment, neuralgia) nervous system involvement [3, 4]. Furthermore, considering the 1918 flu pandemic with post-encephalitic parkinsonism and the particularly high prevalence of neurological symptoms in COVID-19, concerns have arisen regarding a future increase in the prevalence of parkinsonism and other neurodegenerative disorders [2, 5, 6].

By early December 2022, three years after the index case of COVID-19, more than 640 million cases had been confirmed, and almost 13 billion vaccines administered [24]. The literature on COVID-19, its short- and long-term complications, and the safety of COVID-19 vaccines, continues to grow [7]. As most papers reporting neurological complications in detail are case reports, we felt there was a strong need to review and analyse them collectively in order to draw more meaningful conclusions.

This paper adds to the growing body of knowledge on the capability of COVID-19 to cause parkinsonism by reviewing and summarising all of the published cases of post-COVID-19 parkinsonism. In addition, we investigated any possible relationship between COVID-19 vaccines and dyskinesia.

Material and methods

We searched the MEDLINE, PubMed, Scopus, and Web of Science databases for all manuscripts in English published up to the end of November, 2022 reporting parkinsonism due to COVID-19 or dyskinesia related to COVID-19 vaccination. We used the following search terms: 'parkinsonism' and 'SARS-CoV-2'; 'parkinsonism' and 'COVID', 'dyskinesia' and 'SARS-CoV-2'; 'dyskinesia' and 'COVID'; and 'dyskinesia' and 'vaccine'. Subsequently, we screened the titles and abstracts to check that they were pertinent to the review topic. In addition, we searched the reference lists of the relevant articles and websites to verify the comprehensiveness of the bibliography. Next, we extracted the data from the full-text manuscripts in a structured manner. In the patients with parkinsonism due to COVID-19, we collected data on sex, age, comorbidities, COVID-19 pneumonia severity according to the National Institutes of Health guidelines [8], loss of smell, symptoms of encephalopathy, other COVID-19 complications, the timespan between parkinsonism onset and first COVID-19 symptoms, the subtype of parkinsonism [9, 10], asymmetry of parkinsonism, brain magnetic resonance imaging (MRI) findings, dopaminergic system imaging, by 6-^{18}F-fluoro-L-dopa (^{18}F-FDOPA) positron emission tomography (PET) or ^{123}I-ioflupane (DaTscan) single-photon emission computerised tomography (SPECT), responsiveness to levodopa or other dopaminergic medications, application of immunomodulatory therapy and response to thereof, follow-up time, and outcomes. In the patients with dyskinesia related to COVID-19 vaccination, we retrieved data on sex, age, comorbidities, presentation of dyskinesia, number and type of vaccine, time of symptoms onset since vaccination, concomitant symptoms, brain MRI findings, management, follow-up time and outcomes.

Results

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram is presented in Figure 1.

Our search identified 468 records in MEDLINE, 1,846 in PubMed, 637 in Scopus and 255 in Web of Science. After removing duplicates (n = 2,359), this yielded 1,796 papers. Next, we screened the papers and removed 1,775 that were not relevant to the subject of this review. We did not identify any other relevant study via citation or website searching. Finally, we retrieved and reviewed the data from the remaining 21 manuscripts, including 18 papers reporting parkinsonism due to COVID-19 and three on dyskinesia following COVID-19 vaccination.

Parkinsonism related to COVID-19 [11–28]

A summary of the data retrieved on patients with parkinsonism due to COVID-19 is set out in Table 1. The material is heterogenous, and the presented information refers to the number of patients who underwent a specific procedure (e.g. neuroimaging).

A total of 24 patients (nine females, 13 males, and two sex not reported) developed parkinsonism related to COVID-19. The mean age of parkinsonism onset was 58 years (range 31–75) after a mean of 30 days (range 0–120) from the first COVID-19 symptoms. The most common parkinsonism subtype was akinetic-rigid (n = 11), followed by mixed (n = 6). Asymmetry was present in 13/15 patients with sufficient data. Brain MRI was unremarkable in 11/19 patients. Dopamine transporter single-photon emission computerised tomography (DaTscan-SPECT) (n = 7) and ^{1}-F-fluorodopa positron emission tomography (^{1}-F-FDOPA PET) (n = 1) were abnormal in 8/8 patients, and asymmetry was noted in 7/8 cases. Responsiveness to levodopa was observed in 11/15 patients (good in 10 and moderate in one), with a mean daily dose of 400mg (range 220-600). Additionally, one patient responded well to a small dose of pramipexole (0.375 mg/day). Lack of response to dopaminergic therapy was noted only in two patients on levodopa (daily doses of 300 mg and 450 mg), and in another one on a small dose of apomorphine (2 mg/day).

Twelve patients were treated with immunomodulatory therapy, including steroids (n = 9), intravenous immunoglobulins (n = 3), and convalescent plasma (n = 2). Most patients did not benefit from the immunomodulatory treatment (n = 7), although improvement was noted in four.

In the whole group, mean follow-up was 160 days (range 6–360), during which parkinsonism resolved in four and

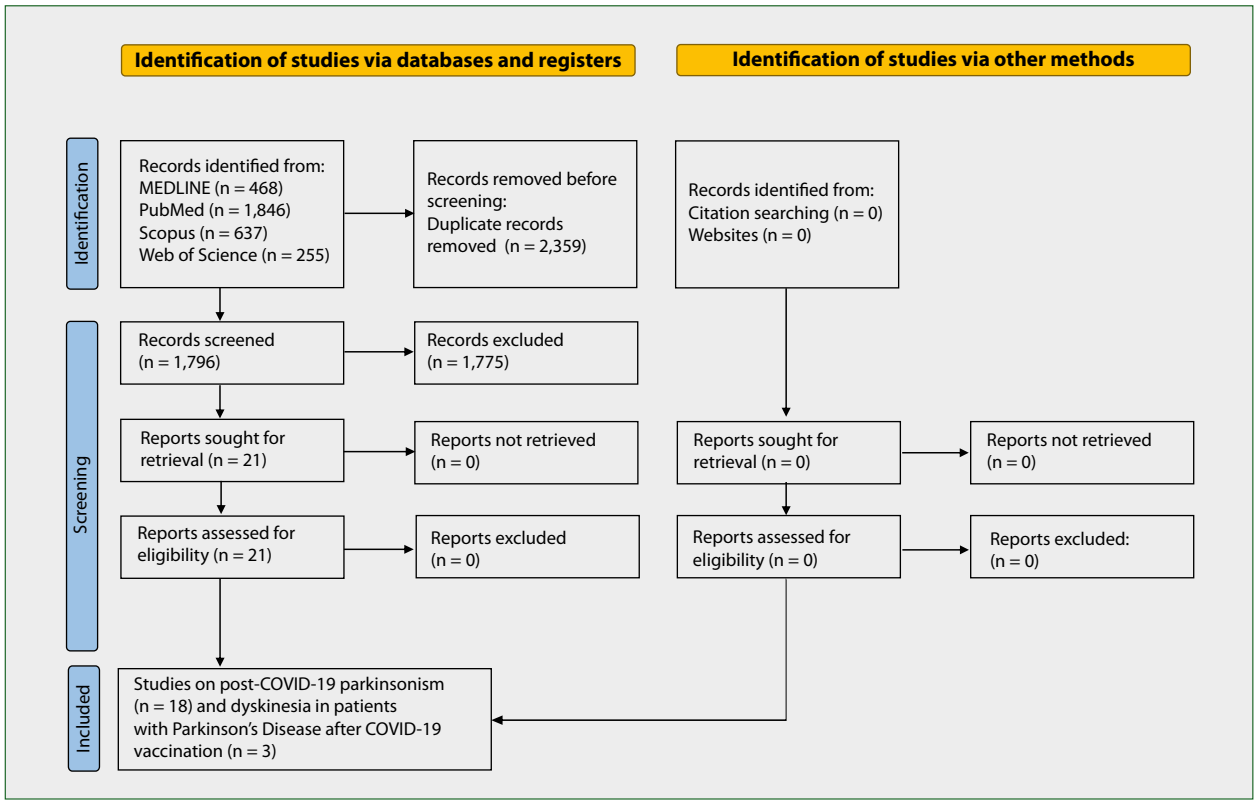

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases, registers, and other sources From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

improved in five of the 15 patients with follow-up outcomes data.

Comorbidities were present in 9/24 patients, the most common being cardiovascular disease (n = 7), whereas 10 patients had an unremarkable history, and in five data was not reported. COVID-19 pneumonia severity was ascertained as mild in seven, moderate in five, severe in six, and critical in five patients. Encephalopathy symptoms were present in 11, not reported in three, and absent in 10 patients. Loss of smell was noted in nine patients, whereas four patients had normal smell, and in 11 patients ability to smell information was not provided.

Most patients (n = 14) suffered from complications in the acute phase of COVID-19, the most common being acute kidney injury (n = 5), mental problems (n = 4), and coagulation disorders (n = 3). However, individual patients developed other serious complications, including extrapontine osmotic demyelination syndrome, severe encephalitis with coma, and others. In addition, three patients were treated with haloperidol; however, only in one case was the time and dose provided (total 28mg over five days), and in another one approximate duration of treatment was noted (three months). In addition, one patient treated with haloperidol had DaTscan-SPECT performed, which showed asymmetrically reduced striatal activity.

Dyskinesia related to COVID-19 vaccination [29–31]

The data on dyskinesia due to COVID-19 vaccination is set out in Table 2. Five patients (three females, two males) with a mean age of 52 years (range 20–79) developed dyskinesia at a mean of 25 hours (range 6–72) after receiving the mRNA COVID-19 vaccine. Besides dyskinesia, other symptoms, including fatigue, fever, and insomnia, were observed in three of them.

The first patient was a female in her early 20s with a one-year history of depression, anxiety, and insomnia, who developed tongue dyskinesia three days after receiving her first COVID-19 mRNA vaccine. Her brain MRI was normal, and extensive diagnostic work-up was unrevealing. She was diagnosed with functional dyskinesia of the tongue, and during the 11-month follow-up, her involuntary movements became more tremor-like, combining irregular tongue tremor and jerks. The other four patients (two females and two males) had a previous history of Parkinson's Disease (PD) with a mean duration of 10 years (range 5–13); however, they did not develop troublesome dyskinesia and indeed only occasionally displayed slight dyskinesia. In addition, one patient was treated with subthalamic deep brain stimulation (DBS-STN), and another one with a levodopa/carbidopa intestinal gel

Table 1. Summary of data retrieved on patients with parkinsonism due to COVID-19

Number	Paper	Sex	Age (years)	Comorbidities	COVID-19 pneumonia severity	Loss of smell	Symptoms of encephalopathy	Other COVID-19 complications	Timespan between parkinsonism onset and first COVID-19 symptoms (days)
1	Ghosh et al. (2021)	F	65	Diabetes mellitus	Severe	N/R	Yes	Severe osmotic demyelination syndrome with hyperglycaemic hyper-osmolar state	11
2	Maramattom et al. (2021)	M	75	None	Mild	N/R	Yes	Severe COVID-19 encephalitis with coma	3
3	Rao et al. (2021)	M	72	None	Severe	Yes	No	Acute kidney injury, peripheral thrombophlebitis	14
4	Rao et al. (2021)	M	66	Diabetes mellitus, Cardiovascular disease, Seizures	Severe	N/R	No	Acute kidney injury	21
5	Rao et al. (2021)	M	74	None	Moderate	N/R	No	Acute kidney injury	21
6	Fearon et al. (2021)	M	46	N/R	Critical	N/R	N/R	Acute kidney injury, disseminated intravascular coagulation	N/R
7	Morassi et al. (2021)	F	70	Cardiovascular disease, Depression (trazodone, fluoxetine, benzodiazepines)	Severe	No	Yes	Delirium controlled with haloperidol; seizures	31
8	Morassi et al. (2021)	F	73	Cardiovascular disease, Depression with psychotic symptoms (olanzapine, amisulpride)	Mild	No	Yes	Aspiration pneumonia, infected bedsores	0
9	Ong et al. (2021)	M	31	None	Severe	N/R	Yes	Delirium controlled with haloperidol	15
10	Akilli et al. (2021)	M	72	Diabetes mellitus, Cardiovascular disease	Critical	N/R	Yes	Acute respiratory distress syndrome	2
11	Makhoul &Jankovic (2021)	F	64	N/R	Mild	Yes	No	N/R	5
12	Cohen at al. (2020)	M	45	Cardiovascular disease, Asthma	Moderate	Yes	No	None	18
13	Faber et al. (2020)	F	35	None	Mild	Yes	No	None	10
14	Mendez-Guerrero et al. (2020)	M	58	Cardiovascular disease	Critical	Yes	Yes	Acute respiratory distress syndrome	38
15	Tiraboschi et al. (2020)	F	40	Obesity	Critical	Yes	Yes	Delirium, generalised tonic-clonic seizures, stereotypical paroxysmal lower-limb and choreiform upper limb movements treated with haloperidol	57
16	Roy et al. (2021)	M	60	Cardiovascular disease, Diabetes mellitus	Critical	N/R	Yes	Septic shock, ventricular tachycardia, acute renal failure requiring haemodialysis, COVID-induced coagulopathy	8
17	Cavallieri et al. (2021)	M	67	None	Moderate	Yes	No	None	120
18	Cavallieri et al. (2021)	M	45	None	Mild	Yes	No	None	90
19	Ayele et al. (2021)	F	35	None	Moderate	Yes	Yes	Fluctuating mentation and abnormal behaviour, fever, and visual hallucination	10
20	Pilotto et al. (2020)	M	73	N/R	N/R	N/R	Yes	N/R	0
21	Rass et al.	N/R	N/R	N/R	Severe	N/R	N/R	N/R	N/R
22	Rass et al.	N/R	N/R	N/R	Moderate	N/R	N/R	N/R	N/R
23	Beckers et al. (2022)	F	50	None	Mild	No	No	None	N/R
24	Beckers et al. (2022)	F	50	None	Mild	No	No	None	N/R

F — female; M — male; N/R — not reported →

Table 1. cont. Summary of data retrieved on patients with parkinsonism due to COVID-19

Number	Subtype of parkinsonism	Asymmetry of parkinsonism	Brain MRI findings	Dopaminergic system imaging	Levodopa responsiveness (dose in mg/day)	Immunomodulatory herapy	Effect of immunomodulatory therapy on neurological deficits	Time of follow-up (days)	Follow-up outcome
1	Akinetic-rigid	No	Abnormal (osmotic demyelination syndrome with predominant basal ganglia)	N/R	Good response (500 mg)	Steroids before development of neurological symptoms	Deterioration	120	Significant improvement
2	Akinetic-rigid	N/R	N/R	N/R	No response (300 mg/day)	Steroids	None	210	Significant improvement
3	Gait difficulty	N/R	N/R	N/R	Good response (220 mg/day)	Steroids	None	120	Resolution of symptoms
4	Akinetic-rigid	Yes	Unremarkable	N/R	Good response	Steroids	None	30	Significant improvement
5	Mixed	N/R	Unremarkable	N/R	Good response	N/R	N/R	150	Significant improvement
6	Mixed	Yes	Bilateral lesions in basal ganglia	N/R	Unresponsive (450 mg/day)	N/R	N/R	360	Severe parkinsonism unresponsive to L-Dopa
7	Akinetic-rigid	Yes	*De novo* slight ventricular enlargement	Abnormal, left side more affected	Moderate response (400 mg/day)	Steroids, intravenous immunoglobulins	None	270	Gait difficulty, cognitive decline
8	Akinetic-rigid	N/R	Unremarkable	N/R	Good response (400 mg/day)	Steroids, intravenous immunoglobulins	None	30	Death
9	Akinetic-rigid	No	Abnormal (bilateral thalamic and pontine lesions)	N/R	N/R	Steroids	Improvement	6	Resolution of symptoms
10	Akinetic-rigid	No	Unremarkable	N/R	N/R	Convalescent plasma treatment	Improvement	60	Resolution of symptoms
11	Tremor-dominant	Yes	N/R	Abnormal, right side affected	N/R	N/R	N/R	N/R	N/R
12	Akinetic-rigid	Yes	Unremarkable	Abnormal, left more side affected	Good response (pramipexole, 0.375 mg)	Steroids	None	N/R	N/R
13	Akinetic-rigid	Yes	Unremarkable	Abnormal, left side affected	Good response (600 mg/day)	N/R	N/R	N/R	N/R
14	Mixed	Yes	Unremarkable	Abnormal, left side affected	No response (apomorphine, 2 mg)	N/R	N/R	53	Partial improvement
15	Mixed	Yes	Unremarkable	N/R	N/R	Intravenous immunoglobulins	Improvement, however simultaneous withdrawal of haloperidol	143	Resolution of symptoms
16	Akinetic-rigid	N/R	Basal ganglia and corona radiata stroke	N/R	Good response (300 mg/day)	Convalescent plasma treatment	N/R	120	Partial improvement
17	Tremor-dominant	Yes	Mild white matter hyperintensities	Abnormal bilaterally	N/R	N/R	N/R	N/R	N/R
18	Tremor-dominant	Yes	Unremarkable	Abnormal bilaterally	N/R	N/R	N/R	N/R	N/R
19	Mixed	Yes	Symmetrical non-enhancing, T1 isointense, T2 and FLAIR hyperintense lesions with no diffusion restriction in both pallidal regions	N/R	Good response (375 mg/day)	Steroids	Improvement	N/R	Significant improvement
20	N/R	N/R	T2 frontal hyperintensities	N/R	N/R	N/R	N/R	N/R	Severe neurological deficit
21	N/R	N/R	N/R	N/R	N/R	N/R	N/R	360	Persistence of parkinsonism
22	N/R	N/R	N/R	N/R	N/R	N/R	N/R	360	Persistence of parkinsonism
23	Akinetic-rigid	Yes	Unremarkable	Abnormal	Good response	No	Not applicable	N/R	N/R
24	Mixed	Yes	Unremarkable	Not performed	Good response	No	Not applicable	N/R	N/R

F — female; M — male; N/R — not reported

Table 2. Summary of data retrieved on patients with dyskinesia related to COVID-19 mRNA vaccine

Number	Paper	Sex	Age (years)	Comorbidities	Presentation	Number and type of vaccine	Time of symptoms onset since vaccination (hours)	Concomitant symptoms	Brain MRI	Management	Time of follow-up (days)	Follow-up outcome
1	Demartini et al. (2022)	F	20	One year history of depression, anxiety and insomnia	Functional involuntary movements of tongue (tremor-like dyskinesia)	First dose mRNA COVID-19 vaccine	72	Tiredness and fatigue	Normal	N/R	330	Deterioration
2	Erro et al. (2021)	F	61	Parkinson's Disease for 11 years and no dyskinesia	Severe generalised dyskinesia and/or confusion	First dose mRNA COVID-19 vaccine	6	None	N/R	Reduction of levodopa dose	21	Remained without dyskinesia with wearing off
3	Erro et al. (2021)	F	79	Parkinson's Disease for 5 years with occasional slight peak of dose dyskinesia	Severe dyskinesia	First dose mRNA COVID-19 vaccine	24	Fever, confusion, delusions	N/R	Paracetamol and reduction of levodopa dose	14	Mild confusion and dyskinesia more severe than before vaccination
4	Imbalzano et al. (2022)	M	46	Parkinson's Disease for 9 years, treated with subthalamic deep brain stimulation	Left foot dystonia	Third (booster) dose mRNA COVID-19 vaccine	12	Low back pain, insomnia	N/R	Increasing DBS-STN parameters and adding additional levodopa dose	5	Resolution of symptoms and restoration of previous therapeutic regimen
5	Imbalzano et al. (2022)	M	55	Parkinson's Disease for 13 years, treated with levodopa carbidopa intestinal gel (LCIG) infusion	Severe dyskinesia	Third (booster) dose mRNA COVID-19 vaccine	12	None	N/R	Reduction of LCIG dose with partial improvement	5	Almost complete resolution of dyskinesia and restoration of previous therapeutic regimen

F — female; M — male; N/R — not reported

infusion. Two developed symptoms after receiving their first COVID-19 vaccine, whereas the other two only presented involuntary movements after the third (booster) dose. Three of these patients developed severe post-vaccination dyskinesia that was managed by a reduction in the levodopa dose. One patient manifested left foot dystonia that was alleviated by increasing the levodopa dose and the DBS-STN parameters. During mean follow-up of 11 days (range 5–21) the symptoms spontaneously improved in all four patients; however, only two could return to their original treatment regimen.

Discussion

The age at onset in post-COVID parkinsonism was similar to that in sporadic PD [32]. Asymmetry of parkinsonism was present in the majority of patients. Although this is not limited to sporadic PD or secondary parkinsonism, it occurs more often in the former [32]. An akinetic-rigid subtype of parkinsonism was the most common in the present review, and has also been reported to be the most frequent phenotype of sporadic PD [32]. The prevalence of other subtypes is challenging to compare, as most previous papers on sporadic PD used different and inconsistent classification systems [10].

Responsiveness to levodopa, one of the supportive features of sporadic PD [33], was also present in most patients with post-COVID parkinsonism. Among the three non-responders to dopaminergic medications, one received a small dose of apomorphine (equal to 20 mg of levodopa), another underwent severe COVID-19 encephalitis with coma, and the third suffered from disseminated intravascular coagulation and had severe lesions in the basal ganglia (oedema with small haemorrhagic foci). The dopaminergic system imaging (DaTscan-SPECT) was performed only in the first case and showed bilaterally reduced asymmetric nigrostriatal uptake. It is tempting to believe that the first case had sporadic PD and was just undertreated; however, his symptoms significantly improved during the follow-up without any PD-specific treatment, which supports the secondary aetiology of parkinsonism in this patient [21]. Brain MRI was unremarkable, whereas dopamine system imaging was abnormal and asymmetric in most patients in whom the dopaminergic system was evaluated, which may suggest sporadic PD as opposed to secondary or atypical parkinsonism. In eight patients, various abnormalities were evidenced by MRI. Interestingly, four responded to levodopa, comprising one with extrapontine osmotic demyelination syndrome, one with ventricular enlargement, one with basal ganglia stroke, and one with bilateral pallidal lesions. Moreover, five of the 11 patients with signs of encephalopathy had levodopa-responsive parkinsonism. This reminds us that forms of parkinsonism other than sporadic PD may also, albeit usually with poorer outcomes, respond to levodopa [34]. As the follow-up in these patients was short, it will be very interesting to see if their response changes over the long term.

Parkinsonism partially improved or resolved in more than half of the affected patients. In some cases, the improvement was spontaneous, whereas it was attributed to the immunomodulatory treatment or dopaminergic therapy in others. However, as the group was small and diverse, we did not identify any factors associated with better or worse outcomes. Although immunomodulatory therapy was used in half of the patients with post-COVID parkinsonism, only four benefitted from the treatment. Due to the different clinical settings, administration time, and type of therapy used, it is challenging for us to compare the effects of the therapy. This difficulty in evaluating the role of immunomodulatory treatment in managing post-COVID-19 parkinsonism is illustrated by the case of a 40-year-old female who suffered from critical COVID-19 pneumonia, followed by agitation, confusion, generalised-clonic seizures, and choreiform limb movements [22]. She received intravenous immunoglobulin therapy and started haloperidol. Over the following days she improved, but parkinsonism was noted. After approximately two months, the treatment with intravenous immunoglobulins was repeated, and she simultaneously tapered down haloperidol. Subsequently, she recovered completely within a few weeks [22]. However, the curative treatment (i.e. either immunomodulation or the withdrawal of a potentially offending drug or a combination of the two), is impossible to ascertain. Parkinsonism may be related to neuroleptic treatment.

Many patients afflicted with COVID have received amantadine, which was initially introduced as an antiviral drug in 1966. In recent decades, it was mainly used in PD due to its potential to increase dopamine and block NMDA receptors. It was initially suggested that it might be beneficial in COVID [35, 36]; however, a recent study on a large group of 552 patients did not confirm this observation [37]. Although there was no sufficient information available in the literature to analyse the impact of amantadine use on post-COVID parkinsonism, a causal relationship would be interesting to explore.

The heterogeneity of clinical presentation and follow-up outcomes of post-COVID-19 parkinsonism is probably related to different pathophysiological mechanisms, or a combination thereof. Similar to other coronaviruses, SARS-CoV-2 seems to have a tropism for the central nervous system [2, 38, 39]. Previous studies have shown that it may enter the brain through infiltration of the olfactory mucosa and spread through the olfactory projections via axonal transport [38]. Angiotensin-converting enzyme-2 (ACE-2) is the main cell entry receptor for SARS-CoV-2 [2, 38, 39]. The receptor is expressed in glia and neurons, particularly in the brainstem, cerebral cortex, hypothalamus, substantia nigra, and basal ganglia [2, 37, 38]. High expression of the ACE2 receptor in the dopaminergic neurons may explain the predilection of SARS-CoV-2 to affect these brain regions [38]. The inflammatory reaction and hypoxic-ischaemic damage in the central nervous system, rather than direct viral load, have been postulated as pathogenic mechanisms [38]. Moreover, it has been suggested

that expression of DOPA decarboxylase (DDC), an enzyme playing a crucial role in dopamine and serotonin synthesis, is functionally linked with ACE-2 expression, and that the systemic failure observed in some COVID-19 patients may be due to the disruption of the dopamine synthetic pathway [40]. The ACE-2 receptor is also highly expressed in intestinal epithelial cells [38, 40]. The infiltration and inflammation of intestinal mucosa may alter microflora and disturb the gut-brain axis [39]. As alterations of intestinal microbiome and gut inflammation have been linked to PD, this may be another mechanism involved in the development of post-COVID-19 parkinsonism [39]. Intraneuronal deposition of alpha-synuclein is the pathological hallmark of PD. Laboratory tests have shown that SARS-CoV-2 nucleocapsid protein can boost alpha-synuclein aggregation [41]. However, the alpha-synuclein levels in cerebrospinal fluid and blood of patients with COVID-19 and neurological symptoms did not differ from those with COVID-19 and no neurological manifestations or from healthy controls [38]. The ACE-2 receptor is also expressed in the vascular endothelium of the brain [38].

Therefore, SARS-CoV-2 may infiltrate the endothelial cells causing vasculitis and blood-brain barrier disruption [2, 38]. This mechanism may explain the high incidence of ischaemic and haemorrhagic brain injury in patients with COVID-19 [38]. Besides vascular damage, infiltration of the endothelium may open yet another route for SARS-CoV-2 invasion, being responsible for the presence of SARS-CoV-2 in brain regions that do not receive projections from olfactory nerves [2, 38].

Finally, the 'unmasking' of underlying latent PD by COVID-19 cannot be excluded [28]. Exacerbation of motor symptoms in patients with sporadic PD, short-lived or permanent, has been reported in infections (ranging from severe systemic infections to mild urinary tract infections), surgery, trauma, and psychological stress [28, 42]. The last of these is frequently reported as a precipitatory factor by many patients with sporadic PD [28]. It has been postulated that alteration of dopamine pathways by proinflammatory mediators, changes in intestinal microflora, stress hormones, and triggering of striatal glia-mediated inflammation may be the involved mechanisms [28, 42]. Individual genetic architecture impacts upon the risk of developing PD [10, 43]. As many genetic variants cause or increase the chances of developing PD, carriers thereof may be more susceptible to develop parkinsonism after COVID-19.

Hence, as many patients with post-COVID-19 parkinsonism display features of sporadic PD (i.e. similar age at onset, asymmetry, and response to levodopa), we speculate that in some cases, most likely those with a pre-existing genetic or other susceptibility to developing PD, COVID-19 can overtax their compensatory mechanisms and unmask PD. We suggest performing a brain MRI study and DaTscan-SPECT in all cases of post-covid parkinsonism [44].

The only patient who developed dyskinesia due to the COVID-19 vaccine and who had no history of PD was diagnosed with a functional movement disorder (FMD) [29]. Previous studies showed that 75% of patients diagnosed with FMD are females; they commonly have a history of pre-existing neuropsychiatric symptoms (particularly anxiety and depression), and many of them report precipitatory factors in the form of medical procedures or stressful life events [45, 46]. Therefore, in this case, the functional aetiology of the symptoms was attributed to the patient's expectations, beliefs, individual psychological profile, and predispositions [29].

The other four patients who developed dyskinesia and dystonia following the COVID-19 vaccine were at the advanced stage of PD, in which dyskinesia, dystonia, and motor fluctuations are expected to occur [47]. The precise mechanism by which the COVID-19 mRNA vaccine could trigger dyskinesia in PD is unknown; however, stimulation of the immune system and the resultant systemic inflammatory response may be one possible explanation [30, 31]. Furthermore, besides the mechanisms mentioned above involved in worsening PD symptoms, inflammatory cytokines may also increase the permeability of the blood-brain barrier, and thus increase the delivery of dopaminergic medication to the brain, which would explain the frequent worsening of dyskinesia during infections in patients with PD [30, 31]. However, given that more than 5 billion people worldwide have received at least two doses of COVID-19 vaccines and that only five cases with associated dyskinesia have been reported, the relationship between the two is close to chance levels, and simple coincidence cannot be excluded.

Conclusions

Despite initial concerns about a surge of post-COVID-19 parkinsonism, so far it remains a very rare complication. Most likely, post-COVID-19 parkinsonism is an umbrella syndrome that includes many different aetiologies. However, as the time elapsed and thus the follow-up since the index case of COVID-19 is still short, more observation time is needed to ascertain the relationship between COVID-19 and parkinsonism. In 1918 after the flu pandemic, post-encephalitic parkinsonism developed several years after recovery. In addition, it seems that dyskinesia due to COVID-19 vaccines is exceedingly rare and probably has the same pathophysiological basis as dyskinesia in other conditions with exacerbation of PD symptoms.

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