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LETTER TO THE EDITORS

COVID-19 and Parkinson's disease: a casual association or a possible second hit in neurodegeneration?

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Dear Sirs,

A 67-year-old man was admitted to the Emergency Department because of the acute onset of dyspnea, fever, anosmia and ageusia. Chest CT showed bilateral interstitial pneumonia and nasopharyngeal swab was positive for SARS-CoV-2. Due to worsening of his respiratory function, he was immediately treated with tocilizumab with subsequent symptoms improvement and hospital discharge after 5 days. Four months later, he was seen in the neurology outpatient clinic because of new progressive impaired finger dexterity and mild resting tremor at the right hand, and nightmares characterized by vocal sounds and limbs' movements. Before COVID-19 infection, no Parkinson's Disease (PD) prodromal symptoms were ever noted by the patient and his family. Neurological examination (NE) showed mild resting tremor in the right hand, slight bilateral bradykinesia and rigidity, and reduction of right arm swing during gait (MDS-UPDRS-III: 12/132). Brain MRI showed mild microvascular changes (Fig. 1A) whereas single-photon emission computed tomography (SPECT) with Ioflupane I123 injection (DaTscan™) showed a mild bilateral reduction in presynaptic dopaminergic uptake (Fig. 1B). A diagnosis of probable PD was made [1]. An extensive genetic testing for mutations in common hotspots of the leucine-rich repeat kinase 2 (LRRK2) gene and full gene sequencing of glucocerebrosidase (GBA) variants revealed the presence of an heterozygous variant in the GBA gene (NM_000157.3:c.1223C > T-p.(Thr408Met); [T369M]).

A 45-year-old previously healthy male was seen at the outpatient neurological clinic with the chief complaint of resting tremor at the left leg since approximately 1 month. Four months earlier, he presented with fever, anosmia and ageusia that lasted for 20 days. He was diagnosed with mild COVID-19 infection after a positive nasopharyngeal swab for SARS-CoV-2. NE revealed mild resting tremor at his left leg and slight bradykinesia at his left hand (MDS-UPDRS-III: 4/132). Brain MRI was unremarkable (Fig. 1C) but SPECT DaTscan™ revealed decreased dopamine transporter density in both putamens (Fig. 1D). A diagnosis of probable PD was made [1]. The medical history was negative for PD prodromal symptoms. An extensive genetic testing for mutations in 68 genes related to PD revealed the presence of a heterozygous variant in the PRKN gene (chr6:162683546–162683807NM_004562; exons:3).

A few cases of parkinsonism linked to COVID-19 infection have been reported so far [2–4]. Onset was acute or subacute in all of them (10–32 days after COVID-19 diagnosis) raising the possibility of a post- or para-infectious parkinsonian syndrome [2–5]. However, the presence of decreased DaTscan™ uptake in all of the reported cases, which would be unlikely to occur within a short period of time, supports a possible conversion from prodromal to symptomatic PD promoted by the COVID-19 infection

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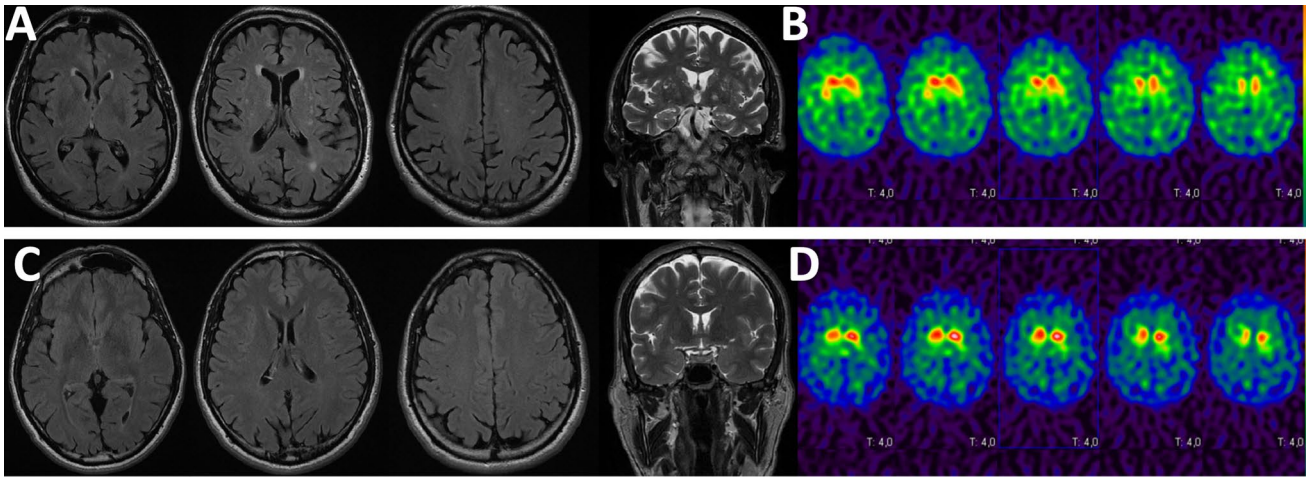

Fig. 1 Patient 1: Axial Fluid Attenuated Inversion Recovery (FLAIR) brain MRI sequences show the presence of mild white matter hyperintensities of presumed vascular origin in the centrum semiovale and external capsule bilaterally; T2-weighted coronal sequence shows the presence of enlarged perivascular spaces in the basal ganglia bilaterally (**A**). Single-photon emission computed tomography (SPECT) with Ioflupane I123 injection (DaTscan™) shows a mild bilateral reduction in presynaptic dopaminergic uptake (**B**). Patient 2: FLAIR brain MRI and T2-weighted coronal sequences do not show any abnormalities (**C**). SPECT with Ioflupane I123 injection (DaTscan™) reveals a decreased dopamine transporter density in both putamens (**D**)

[4]. Our cases can fit with this hypothesis considering both the genetic findings and the relative short period of time between COVID-19 infection and the pathological DaTscan™. Indeed, both our patients presented with a genetic susceptibility to PD given by the heterozygous variants in the GBA and PRKN gene. However, no prodromal symptoms were reported before the COVID-19 infection so that both patients could have been considered as asymptomatic carriers of heterozygous GBA and PRKN variants. Although the role of single variants in the PRKN gene is still controversial, some authors have suggested an association with an increased risk of PD [6]; while variants in the GBA gene are a well-known genetic risk factor for PD. Therefore, in our patients, the COVID-19 infection could have acted as an infectious second hit, like the "double hit" hypothesis of PD [7], unmasking an underlying preclinical PD linked to a genetic predisposition [2]. In conclusion, our cases suggest that COVID-19 may act as an environmental trigger in the development of PD in genetically predisposed asymptomatic carriers.

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Availability of data and materials (data transparency) The authors have full access to all of the data.

Declarations

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Ethics approval Not applicable.

Consent for publication All the patients provided written informed consent for publication.

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