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Parkinson's disease in a patient with multiple sclerosis and heterozygous glucocerebrosidase gene mutation

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ABSTRACT

More than 30 patients with multiple sclerosis (MS) and Parkinson's disease (PD) have been reported so far. Theories on the co-occurrence of MS and PD range from coincidental to causal. There has been only one report of MS in young onset PD in a patient heterozygous for *Parkin* mutation. We report a patient with MS who developed signs typical for PD and was found to be heterozygous mutation carrier in the gene for glucocerebrosidase (*GBA1*), a well-known risk factor for PD.

More than 30 patients with multiple sclerosis (MS) and Parkinson's disease (PD) have been reported in the recent literature [1]. Theories on the co-occurrence of MS and PD range from coincidental to causal. There has been only one report of MS in early onset PD in a patient, heterozygous for *Parkin* mutation [2]. We report a patient with MS who developed signs typical for PD. The patient was found to be a heterozygous glucocerebrosidase (*GBA1*) gene mutation carrier, a well-known risk factor for PD and a cause of Gaucher disease (GD) in homozygous patients.

A 52 year-old nurse with uneventful family history for neurological diseases was diagnosed with MS in 2016. The neurological examination revealed discrete right-sided hemiparesis. Five years ago, she suffered transient right leg numbness and gait difficulties, a probable unrecognized MS episode. The oligloclonal bands were positive in the cerebrospinal fluid. Brain MRI (Fig. 1a) showed lesions typical for MS. At diagnosis, Expanded Disability Scale score (EDSS) was 1 and was started on teriflunomid. In 2017, she had a further relapse with weakness and numbness of the right leg and tremor of the right arm. After treatment with intravenous methylprednisolone (iv-MP), her symptoms subsided, except for the right arm tremor. She was switched to fingolimod, but the same year she suffered similar relapse with weakness and numbness of the right limbs. Again, iv-MP led to symptomatic improvement, but the tremor sustained. No active lesions were seen on repeated brain MRI. At this point, the EDSS score was 3.5. She was switched to natalizumab, but despite the change in immunomodulatory therapy, the tremor got worse. She also complained of increasing stiffness of the right limbs and slowness of gait. This time the neurological examination revealed clear signs of parkinsonism - she was hypomimic, with resting and postural tremor of the right arm and asymmetric bradykinesia and rigidity more pronounced in the right extremities. Moreover, there was a clear response to levodopa. A dopamine transporter single photon emission computerized tomography (DaTSCAN) (Fig. 1c) showed signs of presynaptic dopaminergic deficiency more pronounced in the left striatum. She was diagnosed with PD. Slow release ropinirole was introduced, later followed by levodopa, after which tremor, rigidity, and bradykinesia improved. Genetic analysis (New Generation Exon Sequencing), ordered due to relatively young age of the patient, revealed a heterozygous mutation (c.1289C > T, P391L) in the *GBA1* gene.

To the best of our knowledge, this is the first report of co-occurrence of MS and *GBA1*-associated PD. Our patient was initially diagnosed with MS and later developed PD, similarly to some previously reported cases [1]. An opposite sequence of events (PD followed by MS) has been observed before [2]. PD symptoms were not immediately recognized as such, due to the relatively rare co-occurrence of the diseases, relatively young age of the patient and the common appearance of PD-like signs in MS, such as tremor. There were no lesions at or near the basal ganglia arguing against direct,

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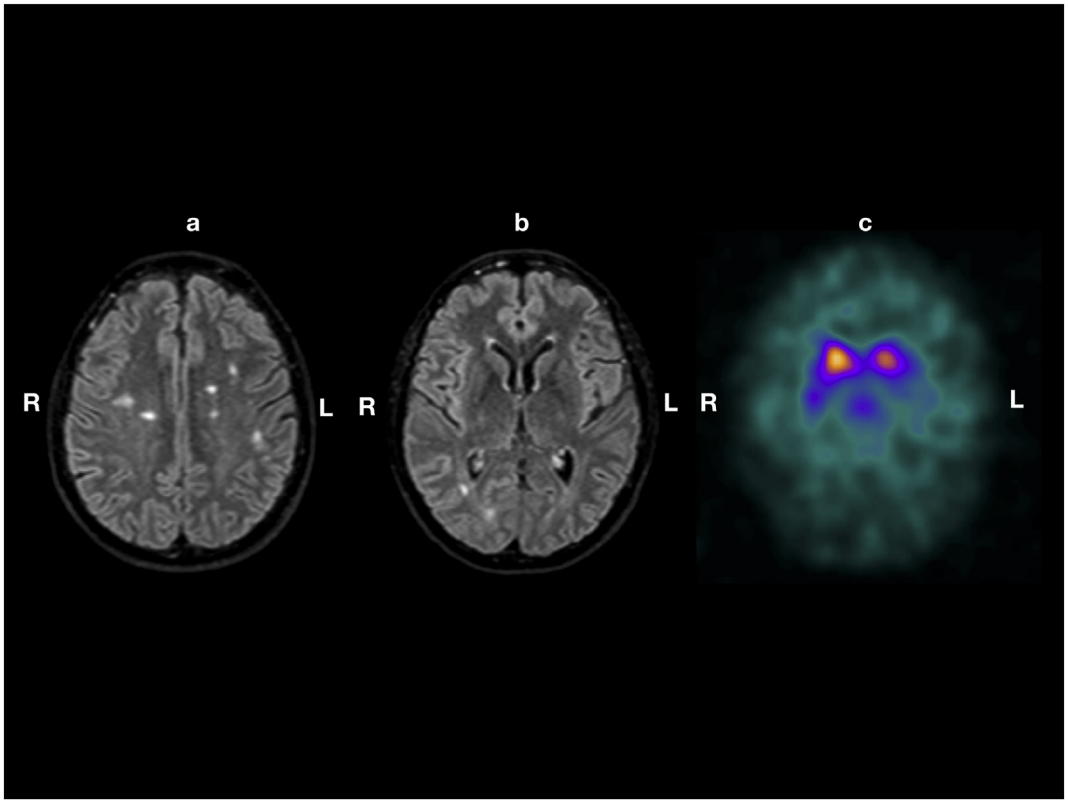

Fig. 1. T1 MRI sequences of the MRI of the brain at two different levels (a and b), showing a typical distribution of the white matter demyelination lesions (a), with no visible lesions of the basal ganglia. The DaTSCAN (c) showed a clear evidence of bilateral presynaptic dopaminergic deficiency more pronounced on the left side. L = left, R = right.

symptomatic link between parkinsonism and MS plaques. She was found to carry c.1289C > T (P391L) *GBA1* gene mutation, already described in a PD patients [3]. This mutation is much rarer than the most common *GBA1* mutation, c1448T > C (L444P), associated with PD. Unlike L444P that shows some, albeit lower glucocerebrosidase activity, P391L mutation shows no enzymatic activity [4]. It is well known that *GBA1* mutations are a major risk factor for PD development. The possible mechanism by which heterozygous *GBA1* mutations could predispose to the development of PD in MS patients is not clear, but it might affect alpha-synuclein clearance in the brain. Besides coincidental occurrence of *GBA1* positive PD in MS patients, it might be that inflammatory process characteristic for MS can trigger development of parkinsonism in heterozygous carriers of *GBA1* mutation. It has also been suggested that strategic micro lesions in substantia nigra and its connected structures may cause parkinsonism in MS [1]. In addition, one may not exclude the incriminating role of immunomodulatory therapy. Conversely, neurodegeneration underlying PD, which presumably starts 10 to 15 years before motor symptoms appear, may be associated with vulnerability to MS. Recently, a patient diagnosed with type three GD has been reported to develop motor neuron disease, suggesting that *GBA1* mutations and glycosphingolipid accumulation might be associated with neurodegenerative diseases other than PD [5]. Further studies are needed to elucidate the association between MS and (*GBA1* positive) PD.

Declaration of competing interest

Nothing to report.

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