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Letter to the Editor

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The unexpected finding of CNS autoantibodies in GBA1 mutation carriers with atypical parkinsonism

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To the Editor:

Although mutations in the beta-glucocerebrosidase gene (GBA1) are the most important risk factor for developing Parkinson disease (PD) and Lewy body dementia (1), very few reports have linked atypical parkinsonism to GBA1 pathogenic variants (2, 3); moreover, little is known about their pathogenic role in these cases. We report the cases of 2 unrelated subjects with atypical parkinsonism carrying the GBA1 L444P mutation (c.1448 T>C; p.Leu483Pro) who also tested positive for anti-basal ganglia antibodies (ABGAs) and anti-AMPA-glutamate receptor3 (anti-GluR3) antibodies. Genetic analyses were performed by next-generation sequencing (NGS) on genomic DNA extracted from venous blood. The gene panel included the following genes: *APP, ATP13A2, ATP7B, CHMP2B, DCTN1, DNAJC6, FBXO7, FUS, GBA1, GCH1, GRN, LRRK2, MAPT, PARK7, PINK1, PLA2G6, POLG, PRKN, PRNP, PSEN1, PSEN2, RAB39B, SYNJ1, SNCA, TARDBP, TREM2, TWNK, UBQLN2, VCP,* and *VPS35*.

The first case was a 51-year-old woman with a 1-month history of falls, bradykinesia, and rigidity with negative family history. She presented with severe akinetic-rigid parkinsonism associated with mild involuntary movements of the right limbs, limitation of upward conjugate gaze, and postural instability, without dysautonomia or psychiatric disorder. Her cognitive assessment showed mild deficiency on attentive functions. Levodopa administration (1000 mg qd) showed a poor response (UPDRS-III OFF state 56, ON state 51). The brain MRI revealed atrophy of the posterior putamen (L>R) in T2-weighted sequences. Dopamine transporter (DAT)-SPECT demonstrated reduced specific binding ratio values in bilateral putamen (L>R) compared to healthy subjects; 18F-Fluorodeoxyglucose PET (FDG–PET) showed markedly reduced uptake in the right putamen and moderately reduced uptake in the left putamen. Due to the rapidly worsening course, a cerebrospinal fluid (CSF) analysis was performed with normal results. Suspecting a possible autoimmune encephalitis, a steroid bolus therapy was attempted without benefit. Autoimmune screening carried out by Western immunoblotting (Fig. 1), revealed the presence in both serum and CSF of ABGAs and anti-GluR3 antibodies. Finally, genetic analysis (whole-exome sequencing) identified the GBA1 L444P mutation in the heterozygous state. No other candidate pathogenic variants associated with PD, Alzheimer disease, or frontotemporal dementia genes were identified. Immunotherapy with intravenous immunoglobulin (400 mg/kg daily for 5 days) produced mild improvement of the symptoms.

The second patient was a 66-year-old woman with asymmetric extrapyramidal syndrome started at age 63 years with rigidity and bradykinesia of the left arm, and progressive worsening because of falls and postural instability. Her medical history revealed a previous diagnosis of breast cancer with negative oncologic follow-up, and hypertension. Parkinsonism was found in her grandmother's records. The neurological examination disclosed severe rigidity and bradykinesia of the left limbs, associated with dystonic postures, limitation of upward conjugate gaze, and a marche à petit pas. No significant improvement with Levodopa (800 mg daily) was observed (UPDRS-III OFF state 53, ON state 48). Her brain MRI revealed putaminal atrophy and T2 and SWI hypointensity of the posterolateral part of both putamina, together with mild

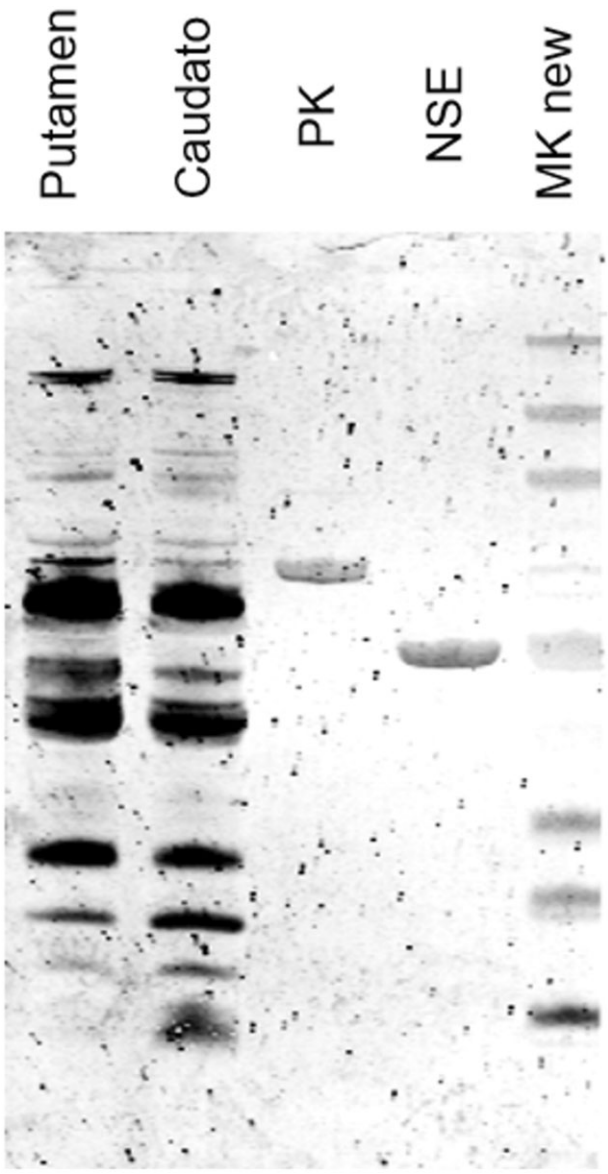

Figure 1. Western blot patient 1. The antigens used were protein extracts from caudate and putamen nuclei and recombinant proteins (pyruvate kinase [PK], 60 KDa) and neuronal enolase [NSE], 40 KDa). The test is considered positive when there is detection of a signal corresponding to the specific recombinant proteins.

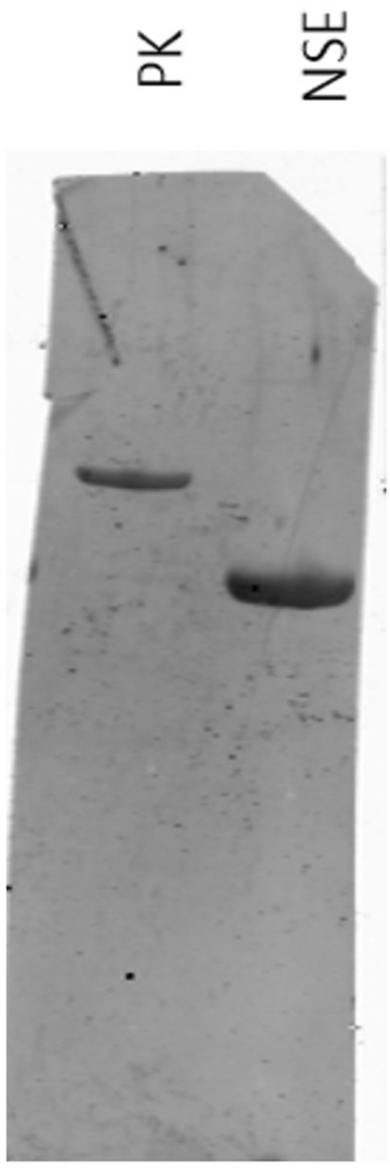

Figure 2. Western blot patient 2.

mesencephalic atrophy. (DAT)-SPECT demonstrated reduced specific binding ratio values in bilateral putamen (R>L). The FDG–PET showed a reduction of the uptake in both putamina (R>L). CSF analysis showed a slight reduction of beta-amyloid levels. An autoimmune panel showed positivity of anti-GluR3 and ABGAs antibodies on both serum and CSF, detected also in this case by Western immunoblotting (Fig. 2). She underwent genetic analysis (NGS gene panel) resulting identification of heterozygous carrier of the GBA1 L444P variant. A therapeutic attempt with plasma exchange was performed without relevant improvement. Neither of the 2 patients had a history of infections, autoimmune diseases, or neuropsychiatric disturbances.

To our knowledge, these are the first 2 documented cases of patients with parkinsonism carrying a GBA1 variant (L444P) and displaying ABGAs and anti GluR3 antibodies. Having detected these autoantibodies, we speculate that an inflammatory/autoimmune process could have contributed at some point to a broader neurodegenerative process than that of typical PD, involving also basal ganglia, and leading to an atypical phenotype. Indeed, a severe akinetic rigid phenotype was unresponsive to levodopa and there was evidence of putaminal degeneration supporting the diagnosis of atypical parkinsonism. A recent study revealed that the L444P mutation could be responsible for an earlier onset of PD, PD-MCI and PDD (4), as seen in our first case, but to date, very few cases of atypical parkinsonism were found to carry GBA1 mutations. However, ABGAs, anti-GluR3 or other antibodies have not been tested in any of these cases. Although a medical history of the reported clinical cases is not strongly suggestive for any autoimmune disease (slow evolution, no seizure, or psychiatric

disorders), there was a mild response to immunotherapy in the first patient treated with immunoglobulin. Interestingly, activation of the innate and adaptive immune cells was recently reported in Gaucher disease, the lysosomal storage disorder caused by biallelic GBA1 mutations (5). In line with this observation, the finding of autoantibodies against CNS antigens may also imply a role of immune activation in the monoallelic GBA1 carriers.

ABGAs are antibodies reacting against extracellular dopamine-2 receptor, essential to regulate the dopaminergic neurotransmission (6). Most of the patients with movement disorders and ABGAs described present with a hyperkinetic phenotype and younger onset (6). Nevertheless, a few cases of akinetic–rigid disorders have also been reported. However, so far, detection of ABGAs is non-specific because is possible to detect them in various unrelated neurological diseases. Moreover, the sensitivity and specificity of ABGAs vary depending on the technical protocol used (7); and they have also been detected in Brain Bank human samples of caudate, putamen, and globus pallidus from participants without any evidence of neurological disease (7). With respect to GluR3 antibodies, we know that they are directed against glutamate receptors and are present in patients with different types of epilepsy, underpinning also forms of "autoimmune epilepsy"; however, their pathogenic role is still unclear. In humans, antiAMPA-GluR3 antibodies have been mainly reported in patients with seizures, Rasmussen encephalitis, schizophrenia, and bipolar disorder. In the light of these data, we speculate that there may be a role for autoimmunity as an additional factor accelerating and/or broadening the neurodegenerative process in patients carrying a GBA1 mutation. Knowing that more evidence is needed, this intriguing hypothesis should stimulate confirmatory studies in larger cohorts of patients with atypical parkinsonism or PD carrying pathogenic variants of GBA1 to evaluate the possible pathogenic role of ABGAs, anti-GluR3, and other autoantibodies.

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The authors report no conflicts of interest.

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