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Levodopa responsive asymmetric Parkinson's disease as clinical presentation of progranulin gene mutation: a case report

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Introduction: Mutations in the progranulin gene (GRN) are one of the major causes of autosomal dominant frontotemporal dementia (FTD). In this setting parkinsonism can develop over the course of FTD or may rarely be the presenting feature of the disease, mimicking idiopathic Parkinson's disease (PD) or atypical parkinsonism.

Case presentation: A 53 years-old man with a family history of PD (both parents and one paternal uncle) and dementia (one paternal uncle) came to our attention for rest tremor, bradykinesia, and rigidity in the right hand. Neurological examination confirmed the presence of a right-sided hemiparkinsonism. Brain-MRI was normal while DaTscan revealed bilateral reduction in presynaptic dopaminergic uptake. A diagnosis of PD was made and ropinirole was introduced with good motor response, followed two-year later by carbidopa/levodopa. Four years after diagnosis, the patient developed motor complication in the form of wearing-off episodes and peak-dose dyskinesia. In the following year cognitive decline appeared together with sleep disturbances, delusions, hallucinations and axial features. A new brain-MRI was repeated showing mild cortical diffuse atrophy, while cerebral 18F-FDG PET study showed bilateral hypometabolism involving frontal, parietal, and occipital cortices, precuneus, posterior cingulate cortex and basal ganglia. Neuropsychological assessment showed severe cognitive impairment involving mainly executive functions, attention, and visuospatial functions. A diagnosis of dementia associated with PD was made. Interestingly, a NGS screening of mutations in PD and dementia genes revealed a pathogenic monoallelic variant in the GRN gene p.R110X (class 1 ACMG).

Conclusions: This case underlying the phenotypic variability of GRN mutations that may rarely resemble an asymmetric levodopa-responsive idiopathic PD. Considering that clinical trials with recombinant monoclonal antibody against the GRN regulatory protein sortilin are ongoing, it appears extremely relevant to test for the presence of GRN mutations PD patients with early cognitive decline and a strong positive family history for PD or dementia.