Early visual memory deficits
A neuropsychological marker of GBA mutations in PD?

Among nonmotor symptoms of Parkinson disease (PD), cognitive impairment substantially reduces patients’ daily living activities and quality of life. The risk factors are still poorly known: some demographic and clinical variables (older age, longer disease duration, severity of parkinsonian motor symptoms) are positively associated with cognitive decline and dementia in PD; abnormal accumulation of $\alpha$-synuclein in Lewy bodies plays a pathogenic role. Heterozygous glucocerebrosidase (GBA) gene mutations are also strong risk factors for synucleinopathies, including PD (accounting for 4%–5% of sporadic cases) and dementia with Lewy bodies (DLB). There is also evidence that GBA mutations increase the neocortical accumulation of Lewy bodies leading to more frequent and more severe cognitive impairment as compared to patients with PD without mutations. Patients with PD with GBA mutations may also show more severe neuropsychiatric symptoms (anxiety, sleep and eating disorders, depression, apathy) as compared to patients with sporadic PD without GBA mutations. Spread of Lewy body pathology to limbic and visual associative cortical areas is probably related to the occurrence of neuropsychiatric features observed in DLB.

In this issue of Neurology®, Alcalay et al. compared 2 groups of patients with PD with early age at onset (<51 years) matched for age and disease duration, who were carriers of 4 heterozygous mutations in the GBA gene (N370S, L444P, 84GG, R496H: 26 patients) or noncarriers of any known genetic mutation (39 patients). The results showed that GBA mutation carriers were more likely to receive a diagnosis of mild cognitive impairment or dementia and performed worse than noncarrier patients on the Mini-Mental State Examination and on tasks assessing visual memory and visuospatial abilities. These data suggest that mutations in the GBA gene may be an independent risk factor for cognitive impairment in patients with PD. The study is of interest for 2 reasons. First, patients with PD were assessed by a relatively extensive neuropsychological test battery, whereas in a previous study in patients with GBA mutations, cognitive assessment was carried out only by the Montreal Cognitive Assessment. Second, results indicated that some specific cognitive domains (most remarkably, visual memory deficits) were selectively affected in GBA mutation carriers. Since prominent deficits of visual memory are not features of PD or DLB, the findings by Alcalay and coworkers support the hypothesis that a neuropsychological pattern with prominent early deficits of visual memory may provide a clinical marker to identify patients carrying GBA mutations.

The study by Alcalay et al. has some methodologic limitations. Since only the most common GBA mutations were genotyped in these patients with PD, carriers of untested GBA mutations could have been inadvertently misclassified as noncarriers. Furthermore, the neuropsychological test battery used in the study did not include tasks specifically assessing executive functions, such as problem-solving and set-shifting (for example, the Wisconsin Card Sorting Test), which are critically impaired in PD, often in early disease stages. In addition, some neuropsychiatric features that are considered more prevalent in GBA mutation carriers (e.g., depression, apathy, sleep and anxiety disturbances) were not evaluated. Finally, each patient with PD underwent a single complete neuropsychological assessment and the study did not address the rate of progression of cognitive impairment.

Early identification of GBA carriers may facilitate the implementation of specific treatment strategies, including those introduced for Gaucher disease. In keeping with the human data reported by Alcalay et al., it has been recently shown that mutated mice carrying a single-point heterozygous mutation in the GBA gene display memory deficits and a progressive accumulation of $\alpha$-synuclein/ubiquitin aggregates in hippocampal neurons. Injection of adeno-associated viral vectors expressing human GBA into...
the hippocampi of these mutated mice yielded an improvement of memory deficits and the reduction of aggregates. This reinforces the hope for a possible genetic treatment in patients with PD carrying GBA mutations. Extensive GBA testing is expensive and has a low yield in sporadic PD cases. The identification of specific neuropsychological features, such as visual memory deficits suggesting a possible GBA carrier status, may allow identifying patients with PD at increased risk to be addressed to GBA genetic testing. Patients with PD carrying GBA mutations might benefit from specific treatments, including early-stage gene therapy.

**DISCLOSURE**

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

**REFERENCES**