Early visual memory deficits

A neuropsychological marker of *GBA* mutations in PD?

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Neurology® 2012;78:1372–1373

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[1]; abnormal accumulation of α-synuclein in Lewy bodies plays a pathogenic role.[2] Heterozygous glucocerebrosidase (*GBA*) gene mutations are also strong risk factors for synucleopathies, including PD (accounting for 4%–5% of sporadic cases)[3] and dementia with Lewy bodies (DLB).[4] There is also evidence that *GBA* mutations increase the neocortical accumulation of Lewy bodies[5] leading to more frequent and more severe cognitive impairment[5,6] 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.[6] Spread of Lewy body pathology to limbic and visual associative cortical areas is probably related to the occurrence of neuropsychiatric features observed in DLB.[7]

In this issue of *Neurology*®, Alcalay et al.[8] 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.[6] 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.[8] 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[6]) 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.[9] In keeping with the human data reported by Alcalay et al.,[8] 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 α-synuclein/ubiquitin aggregates in hippocampal neurons.[10] Injection of adeno-associated viral vectors expressing human GBA into

See page 1434

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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.**

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