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Predicting parkinsonism: New opportunities from Gaucher disease

Grisel Lopez and **Ellen Sidransky***
Section of Molecular Neurogenetics, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

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The diagnosis of Parkinson disease has evolved over time to include aspects not originally emphasized when it was first described [1]. Olfactory dysfunction, neuropsychiatric symptoms, sleep disorders and autonomic dysfunction such as orthostatic hypotension and constipation are now recognized as part of the clinical spectrum seen by physicians or reported by patients affected with Parkinson disease [2]. This non-motor/pre-motor period is consistent with a hypothesis of progressive involvement of specific nervous system structures [3], although these features currently cannot be used to identify at-risk individuals with great accuracy. While advances in our understanding of Parkinson disease have prompted inclusion of this disorder in the differential diagnosis of seemingly unrelated symptoms, the diagnosis is still based on the presence of certain motor features that on their own are not diagnostic but, when taken together, significantly increase the probability of accurate identification. Technological advances in the field of genetics have expanded our understanding of pathological mechanisms contributing to the death of neurons in these particular anatomical structures.

As we advance our understanding of possible disease mechanisms, the development of new therapies to decrease the rate of progression or halt the disease process altogether becomes more likely. It is thus imperative to develop the means to identify individuals at highest risk for the development of parkinsonian manifestations so that neuroprotective therapies can be targeted to those who need them most.

Mutations in *glucocerebrosidase* (*GBA1*), the gene mutated in Gaucher disease, are now widely recognized to be an important and common genetic risk factor for Parkinson disease and Dementia with Lewy Bodies [4]. Examining large cohorts of patients with Parkinson disease and dementia with Lewy bodies, the odds ratios for carrying a *GBA1* mutation were found to be greater than 5 and greater than 8, respectively [5,6]. Conversely, patients with

*Corresponding author at: Section on Molecular Neurogenetics, Medical Genetics Branch, NHGRI, National Institutes of Health, Building 35, Room 1A213, 35 Convent Drive, MSC 3708, Bethesda, MD 20892-3708, USA. Fax: +1 301 402 6438.: sidranse@mail.nih.gov (E. Sidransky).

Gaucher disease and *GBA1* mutation carriers have an increased risk of developing these neurodegenerative disorders, although the vast majority of such individuals do not develop parkinsonian features. This genetic association provides an at-risk population that could be followed longitudinally in order to distinguish early manifestations of parkinsonism. Such cohorts can facilitate the identification of early diagnostic features, the discovery of novel biomarkers, and the development of interventions and/or new therapeutic strategies.

The paper by McNeill et al. [7] that appears in this issue is one attempt to presymptomatically identify subjects likely to develop Parkinson disease through the use of optical coherence tomography. Since it has been reported that in early Parkinson disease the retinal ganglion cell layer may demonstrate thinning [8], the authors evaluated eleven adult patients with type 1 Gaucher disease, three *GBA1* mutation carriers and seven healthy controls for evidence of retinal ganglion changes. They identified four patients with retinal thinning who also had other non-motor/pre-motor signs of Parkinson disease such as hyposmia and memory disturbances, as well as one patient with motor symptoms. These signs were not observed in the remainder of the subjects, who also had no sign of retinal thinning. Based on this pilot study, the authors suggest that optical coherence tomography may be useful in the early identification of patients likely to develop Parkinson disease.

One limitation of the study is the small sample size. The study also lacked a group of patients with known Parkinson disease who are *GBA1* mutation carriers to serve as an additional control group. Moreover, one of the patients with “potential clinical markers of neurodegeneration” could be considered parkinsonian under certain diagnostic criteria, since rest tremor and rigidity were observed. It will be essential to follow both those with and without “potential clinical markers of neurodegeneration” over time to determine whether progression to Parkinson disease occurs in the future, and whether the development of Parkinsonian features correlates with the presence or absence of retinal ganglion thinning. The identification of subjects that lack both retinal findings and parkinsonism may also prove to be important, potentially enabling us to identify factors that are protective in this at-risk population.

Even with these significant limitations, the authors should be commended for their efforts to investigate potential new clinical bio-markers to identify at-risk individuals. There is no question that additional evaluations like optical coherence tomography are sorely needed for future natural history and interventional studies. Such non-invasive tools can provide objective standards to assist clinicians in detecting those at most risk, and can be used in combination with clinical signs and symptoms to render a more accurate diagnosis.

Previous studies have identified other clinical markers currently used in movement disorders clinics or investigated in Parkinson disease research centers around the world, including hyperechogenicity of the substantia nigra using transcranial sonography [9], olfactory testing [10], acoustic analysis [11], and cerebrospinal fluid analysis [12]. Some of these tests, like optical coherence tomography or transcranial sonography, require specific expertise and equipment and may have suboptimal specificity. However, taken together they move us a step closer toward the accurate identification of individuals who are very early in the process of neurodegeneration that otherwise would not be recognized. Functional imaging studies,

including positron emission tomography (PET), are also used as clinical biomarkers that may represent disease activity.

PET imaging was recently explored as a tool to identify early Parkinson disease manifestations in patients with Gaucher disease and their carrier relatives by studying brain dopamine synthesis and resting regional cerebral blood flow (rCBF) in 107 subjects (38 women, 69 men) [13]. Using voxel-based methods, the sporadic Parkinson disease group and the Gaucher disease/Parkinson disease group showed similar striatal dopamine loss that was greater in the caudal striatum, with less reduction in the caudate. However, rCBF studies showed differences between these two groups. Patients with both Gaucher disease and Parkinson disease showed decreased rCBF in the lateral parieto-occipital association cortex and precuneus bilaterally. This decrease in rCBF had a pattern suggestive of diffuse Lewy body disease and parallels the increased frequency of cognitive complaints reported by patients with *GBA*-associated parkinsonism. This technique offers another means to probe the role of *GBA1* mutations in the neurobiology of Parkinson disease.

Routine screening of patients with Gaucher disease includes evaluation of hepatosplenomegaly, skeletal involvement, hematological parameters, and careful neurological evaluation. In addition, clinicians evaluating adult patients should routinely screen for signs of parkinsonian manifestations including tremor, rigidity and bradykinesia. Their evaluation should include a careful history querying for parkinsonism and/or dementia in family members, and questions regarding sleep disturbances, signs of depression or memory changes, altered handwriting, olfaction, balance/gait difficulties, changes in voice tonality or facial expression, and bowel/urinary changes. Comprehensive neurological examinations, blood pressure measurements to detect orthostatic hypotension and screens for dementia should be performed on adult patients at regular intervals.

Studying genetics sometimes provides us with special opportunities. Our ability to use Gaucher disease as a window into understanding these common complex disorders is one of these circumstances. Advances in the field of Parkinson disease genetics provide the unique opportunity to focus our efforts on research that can be clinically applicable to at-risk individuals. This association is already providing new insights into the importance of the lysosome in Parkinson disease pathogenesis. Furthermore, the majority of patients with Gaucher disease as well as *GBA1* mutation carriers that do not go on to develop parkinsonism may also have great clinical relevance. These individuals too may provide unique insights into the identification of factors that could be protective for Parkinson disease, again providing new avenues for research and drug development.

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