Review Article
Gaucher Disease and the Synucleinopathies

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Several recent observations suggest a connection between Gaucher disease, the inherited deficiency of glucocerebrosidase, and the synucleinopathies. Rare patients have been observed who develop both Gaucher disease and parkinsonism. Autopsy studies on these subjects reveal synuclein-positive Lewy bodies and inclusions. An increased incidence of synucleinopathies also has been noted in relatives of Gaucher probands. In complementary studies, screening of patients with parkinsonism has identified a greater than expected frequency of glucocerebrosidase mutations. These glucocerebrosidase mutation carriers have a wide spectrum of associated parkinsonian phenotypes, ranging from classic L-dopa-responsive Parkinson disease to a phenotype more characteristic of Lewy body dementia. Despite this association, the vast majority of Gaucher carriers and patients with Gaucher disease never develop parkinsonism. However, mutations in this gene are likely to be a contributing risk factor in subjects otherwise prone to developing synucleinopathies.

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INTRODUCTION

The synucleinopathies, including Parkinson disease (PD), diffuse Lewy body dementia (DLBD), Lewy body variant of Alzheimer disease (LBVAD), and multiple system atrophy (MSA), are devastating adult-onset neurodegenerative diseases that affect millions of people worldwide. New insights into the genetics and pathophysiology of certain synucleinopathies have arisen from an unexpected source: a rare Mendelian disorder. Gaucher disease (GD) (MIM 230800, 230900, and 231000), the most common of the lipidoses, is the recessively inherited deficiency of the lysosomal enzyme glucocerebrosidase (EC.3.2.1.45). Affected individuals store the lipid glucocerebroside within lysosomes of macrophages, resulting in characteristic-appearing Gaucher cells. Associated clinical manifestations include hepatosplenomegaly, anemia, thrombocytopenia, easy bleeding, and bruisability, bony involvement and, in some cases, pulmonary involvement. Gaucher disease is classified into three major clinical types depending upon the degree of nervous system involvement. Patients with type 3, or chronic neuronopathic GD, have a varying degree of systemic involvement with at least one neurological manifestation; patients with type 2, or acute neuronopathic disease, have severe neurological involvement leading to death perinatally or in the first years of life. Type 1, the most common form, has no associated neurological symptoms by definition. In recent years, a small subgroup of patients has been identified that develop parkinsonian manifestations in adulthood. Several different and complimentary strategies have been used to investigate this association (Figure 1).

CLINICAL DESCRIPTIONS OF SUBJECTS WITH GAUCHER DISEASE AND PARKINSONISM

The first indications of a relationship between Gaucher disease and parkinsonism appeared in the literature as scattered case reports describing patients with Gaucher disease who developed early-onset, treatment-refractory parkinsonism [1–3]. Then, in 2003, a cohort of 17 such individuals was assembled, that included Ashkenazi Jewish probands as well as patients with diverse ethnicities [4]. The patients in this series had relatively mild Gaucher manifestations with a mean age at diagnosis of 35 years. In contrast, their parkinsonian symptoms had a rather early onset, with a mean age at diagnosis of 48 years. These individuals exhibited classic features, including asymmetric tremor, rigidity, akinesia and, at times, dementia. Four subjects in this series were treated with enzyme replacement therapy (ERT) with recombinant human glucocerebrosidase without any improvement or slowing of parkinsonian symptoms. It was also noted that some of these probands had a positive family history of parkinsonism in heterozygous relatives.
Several other papers have described Gaucher probands with differing degrees of parkinsonian manifestations [5, 6]. These ranged from mildly affected subjects diagnosed in their 70’s and 80’s, to early onset subjects who developed dementia in their 40’s. The spectrum appears to include both L-dopa-responsive and -resistant patients. Initial presentations have included the more classic unilateral tremor and others with progressive rigidity. The rate of progression also has been quite variable.

**PATHOLOGICAL FINDINGS**

The most consistent pathology observed in the brains from patients with neuronopathic type 2 and type 3 GD has been the periventricular accumulation of Gaucher cells [7]. Significant neuronal loss with atrophic neurons has been described in the basal ganglia, nuclei of the midbrain, pons and medulla, cerebellum, dentate nucleus, and hypothalamus [8, 9]. A recent neuropathological survey identified unique patterns of disease in neuronopathic patients, consisting of neuronal loss and gliosis specific to the hippocampal layers CA2-4 and layer 4b of the calcarine cortex [10]. Even in subjects with type 1 GD, which, by conventional definition, spares the CNS, astrogliosis of CA2 was noted.

In four individuals with Gaucher disease and parkinsonism, Lewy bodies were observed (Figure 2), as well as the involvement of hippocampal layers CA2-4 [10, 11]. Two of the patients had numerous intraneuronal, synuclein-positive inclusions in CA2-4, reminiscent of the brainstem-type Lewy bodies seen in the substantia nigra (SN) of idiopathic Parkinson disease. The other two patients lacked these hippocampal inclusions, but exhibited a Lewy body distribution consistent with diffuse Lewy body dementia. All four subjects exhibited hippocampal CA2-4 gliosis, depletion of SN neurons, SN gliosis, and brainstem-type Lewy bodies in the SN.

**GLUCOCEREBROSIDASE MUTATIONS IDENTIFIED IN SUBJECTS WITH PARKINSON DISEASE**

A molecular study was initiated to screen DNA extracted from brain tissue of individuals with pathologically confirmed, idiopathic Parkinson disease for alterations in the glucocerebrosidase gene (GBA). Remarkably, glucocerebrosidase mutations were detected in such subjects more often than expected, given the carrier frequency of Gaucher disease [11]. Direct sequencing of the entire glucocerebrosidase gene in 57 DNA samples collected from five different American brain banks revealed mutant alleles in eight (14%), including two homozygotes and six heterozygotes. Five of these had one or more alleles with the common N370S mutation, which is specifically associated with nonneuronopathic Gaucher disease. Four additional subjects carried E326K and T369M, which are considered polymorphic alterations in GBA. Brain samples from 44 age-matched controls without pathological evidence of PD were also sequenced and two were found to have the E326K allele, but no mutations were identified. In this series, the individuals with glucocerebrosidase mutations tended to be among the younger subjects screened, and most had documented Lewy bodies. Subsequently, DNA from 26 additional brain samples collected in Britain were sequenced and two (8%) carried glucocerebrosidase mutations [12]. These findings suggested that mutations in GBA, even in heterozygous individuals, might be an inherited risk factor for the development of parkinsonism.

These findings have since been substantiated by studies in other patient populations around the world. In many of the subsequent studies, however, the results were obtained by screening cohorts of patients diagnosed with Parkinson disease for one or more specific GBA mutations. Aharon-Peretz et al [13], in a clinic-based series of 99 Ashkenazi patients from Northern Israel with classic PD, screened blood samples for six common mutations in glucocerebrosidase. They identified 31 patients (31.3%) carrying glucocerebrosidase mutations N370S or c.84insG, including three N370S homozygotes. This frequency was over five-fold higher than the frequency of GBA mutations detected in their two control groups, which were composed of 74 patients with Alzheimer disease and 1543 Ashkenazi controls, respectively.

![Figure 1: Several different strategies are employed to elucidate the relationship between Gaucher disease and parkinsonism. From Sidransky [38].](image1)

![Figure 2: Lewy bodies seen in a patient with Gaucher disease and parkinsonism. (a) CA2 hippocampal region demonstrating pyramidal cell neurons with a brainstem-type Lewy body. H&E stain, ×400 magnification. (b) Synuclein-immunoreactive Lewy bodies in hippocampal CA4 neurons, indicated by arrowheads. Synuclein antibody, Ventana, ×200 magnification. From Tayebi et al [4].](image2)
Both control groups were far from ideal, as significant clinical overlap exists between subjects carrying the diagnoses of PD and AD, and individuals included in the Ashkenazi control group were of mixed ages and had not been screened clinically to determine their neurological status. While the number of PD probands with glucocerebrosidase mutations was quite remarkable, it would be premature to attempt to estimate the relative risk of developing parkinsonism in an Ashkenazi individual with one or two glucocerebrosidase mutations.

A second report [14] focused on 160 Ashkenazi Jewish probands with Parkinson disease and 92 clinically evaluated, age-matched controls of Jewish ancestry from a New York City clinic. Each subject was screened for the N370S mutation. Seventeen probands (10.7%) with N370S were identified, including two homozygotes, as compared to 4.3% of controls, but these results did not reach statistical significance. While this study was limited, in that only one glucocerebrosidase mutation was considered, the frequency of mutations was considerably lower than that described in the Israeli cohort. Clearly, larger-scale studies with appropriate controls are warranted in the Ashkenazi population.

Investigators from Toronto [15] screened for seven glucocerebrosidase mutations, including two very rare alleles, among 88 unrelated Caucasian subjects of Canadian origin with clinically diagnosed parkinsonism. This cohort was selected for an early age of onset or a positive family history, and was compared to 122 clinically screened controls. Mutations were identified in 5.6% of the cohort with Parkinson’s disease, as compared to 0.8% of the controls.

In a fourth study conducted in probands with early-onset Parkinson disease from Venezuela, the entire glucocerebrosidase gene was sequenced in 33 subjects and in 29 screened controls [16]. Four unrelated probands (12%) carried three different glucocerebrosidase mutations. Each of the four were L-dopa-responsive, and the ages at onset ranged from 29 to 47 years of age.

Thus, independent studies, despite differences in design and ascertainment, have detected mutations in glucocerebrosidase in subjects with parkinsonism at a frequency higher than expected in some populations. The approximate carrier frequency for GBA mutations is estimated at 0.0343 in the high-risk Ashkenazi Jewish population, and at 0.006 in the general population [7].

PHENOTYPIC FEATURES OF GAUCHER HETEROZYGOTES WITH PARKINSONISM

The phenotypic features encountered among subjects with parkinsonism carrying GBA mutations are quite varied. The group from Israel [17] compared the clinical characteristics of 40 subjects with PD and at least one mutant GBA allele with those of 108 subjects with PD without an identified GBA mutation. They concluded that the overall clinical manifestations, including initial presentation and the extent of rigidity, tremor, bradykinesia, hallucinations, and dementia, were not significantly different in the two groups. All of the reported subjects had a favorable response to L-dopa. These authors also did not find a significant difference in age at onset, sex, or family history of PD. In contrast, subjects with GBA mutations identified by the brain bank screenings tended to have an earlier age at onset [11]. The series from Venezuela identified GBA carriers with very early-onset parkinsonism [16]. Moreover, recent analyses have suggested a high incidence of GBA mutations in subjects who died with the diagnosis of diffuse Lewy body dementia [18]. Thus, at present, the phenotype appears to include a wide spectrum of parkinsonian features ranging from classic L-dopa-responsive PD to those with early-onset symptoms or prominent dementia.

PARKINSONIAN MANIFESTATIONS AMONG RELATIVES OF PATIENTS WITH GAUCHER DISEASE

Another indication that heterozygotes for Gaucher mutations may be at risk for the development of parkinsonism has arisen from family studies. In a small pilot project, all patients with Gaucher disease seen in the Gaucher clinics at the National Institutes of Health over an 18-month period were questioned specifically regarding a possible family history of Parkinson disease or dementia. These interviews resulted in the identification of ten families in which obligate or confirmed carriers of GBA mutations developed parkinsonian manifestations [19]. Often, these individuals were the parent or the grandparent of the Gaucher proband.

One illustrative example was the extended family of a 7-year-old proband with type 3 Gaucher disease, where, in the paternal lineage, multiple family members spanning several generations developed parkinsonism. Both affected and unaffected relatives were examined and DNA samples were collected. It was found that in this family, heterozygosity for mutation L444P correlated with Parkinson disease. In the nine other smaller pedigrees, an obligate or confirmed carrier was shown to have parkinsonism. This study, therefore, lends additional support to the conclusion that mutations in the glucocerebrosidase gene, even in carriers, may contribute to the development of parkinsonism.

POSSIBLE MECHANISMS FOR THE ASSOCIATION OF GAUCHER DISEASE AND THE SYNUCLEINOPATHIES

Alpha-synuclein pathology in the brain is a feature of several prevalent neurodegenerative disorders, including Parkinson disease, dementia with Lewy bodies, the Lewy body variant of Alzheimer disease, and rare conditions such as multiple system atrophy and neurodegeneration with brain iron accumulation (NBAL-1) [20]. These disorders all demonstrate abnormal fibrillation and accumulation of proteinaceous, insoluble alpha-synuclein inclusions in neurons and glia, indicating a shared cellular pathology in the handling and clearance of alpha-synuclein. Alpha-synuclein is one of several proteins with a high propensity to aggregate. While this protein has little or no detectable secondary structure in solution and is considered to be natively unfolded, binding of alpha-synuclein to a number of ligands and proteins alters this native state and leads to partially folded conformations [21]. The end products of alpha-synuclein aggregation
are insoluble polymers or fibrils, considered necessary for the formation of Lewy bodies. Lewy bodies, however, contain other proteins, including cytoskeletal-associated proteins such as tau. A common pathological finding in the synucleinopathies is abnormal accumulation of hyperphosphorylated alpha-synuclein, either with or without tau [22], suggesting that tau may contribute to the aggregation process. One hypothesis is that mutated glucocerebrosidase also could contribute to aberrant fibrillization of proteins responsible for neurodegeneration.

It has been demonstrated that mutations in alpha-synuclein result in aberrant aggregation [23]. In addition, increased expression of wild-type alpha-synuclein through gene triplication can cause rare genetic forms of parkinsonism through a toxic gain-of-function that leads to neuronal death [24]. The pathology associated with synuclein mutations is much more widespread and may resemble DLBD. Similarly, the pathology observed in both Gaucher homozygotes and heterozygotes encompasses the spectrum of synucleinopathies, including DLBD, which might provide further support for the hypothesis that glucocerebrosidase contributes to aggregation of alpha-synuclein through a gain-of-function mechanism.

All synuclein mutations promote formation of oligomers, referred to as protofibrils. Protofibrils are still soluble, but can form annular structures which are toxic and might cause membrane damage [25, 26]. Soluble forms of alpha-synuclein, such as the native wild-type form and, possibly, protofibrils, are degraded via a lysosomal degradation pathway, called chaperone-mediated autophagy (CMA) [27]. Cuervo and colleagues noted that wild-type alpha-synuclein has a pentapeptide motif shared by other proteins that use this pathway for degradation. Experiments in PC12 cells demonstrated that alpha-synuclein binds to the chaperone molecule hsc70 in the cytosol, and is then internalized via a receptor, Lamp2a, on the lysosomal membrane. Lysosomal inhibitors such as ammonium chloride blocked this process. In contrast, mutant alpha-synuclein could still form complexes with the chaperone, but failed to internalize and remained bound to the receptor. This occupation of Lamp2a subsequently could inhibit the degradation of other CMA substrate proteins, resulting in a cellular logjam. Mutations in glucocerebrosidase, therefore, might cause lysosomal dysfunction or interfere with receptor binding of alpha-synuclein at the lysosomal membrane, resulting in cell toxicity.

Other evidence indicates that the ubiquitin-proteasome system (UPS) may be compromised in PD [28, 29]. The accumulation and aggregation of potentially cytotoxic proteins in Lewy bodies suggest generalized protein mishandling and subsequent proteolytic stress. Thus, another mechanistic possibility is that GBA mutations that result in misfolded protein might overwhelm the UPS ability to degrade other abnormally accumulated proteins, including alpha-synuclein.

Another proposed mechanism for the association of GD and the synucleinopathies involves the potential role of lipids. Alpha-synuclein adopts a helical conformation when bound to lipid membranes, which would inhibit the conversion into fibrillar forms [30]. Other studies, however, indicate that lipids can also promote alpha-synuclein aggregation and toxicity through formation of protofibrils [31]. Alpha-synuclein has been shown to bind brain-derived glycosphingolipids that contain glucocerebroside as their core structure [32]. Therefore, potential changes in membrane lipid structure due to accumulation of the substrates glucocerebroside and/or the more toxic glucosylsphingosine might enhance both aggregation and cytotoxicity of synuclein, leading to the pathology associated with glucocerebrosidase mutations. As Gaucher carriers generally have no demonstrable lipid accumulation, however, this mechanism appears to be less likely.

**THERAPIES**

At present, available treatment options for the synucleinopathies provide no more than a temporary slowing of neurodegeneration and the concurrent functional deficits. The ability to prevent or delay onset is the best medical strategy, but progress in the early diagnosis and treatment of these disorders has been limited by an incomplete understanding of etiology and pathogenesis.

While enzyme replacement therapy is available for patients with Gaucher disease, there is no evidence that this treatment has any benefit for subjects with parkinsonism carrying GBA mutations. First, the recombinant enzyme does not cross the blood-brain barrier and has limited utility in the treatment of the neurological symptoms encountered in type 2 and 3 patients. Furthermore, several subjects with Gaucher and parkinsonism have received ERT with no improvement or slowing of their neurological manifestations [4, 5]. As heterozygotes have sufficient glucocerebrosidase activity to prevent glucocerebroside storage, additional enzyme would not be expected to have significant impact. Likewise, therapies designed to reduce substrate accumulation are not likely to be of benefit. If misfolding or impaired trafficking of mutant glucocerebrosidase, however, contributes to the protein aggregation encountered in the synucleinopathies, it is possible that specific chemical chaperone therapy could be of use in these patients.

**IMPLICATIONS FOR GENETIC COUNSELING**

The broader implications of these preliminary findings have the potential to generate considerable alarm. Clearly, caution is recommended in translating these findings to the patient community. From the general experience of treating thousands of patients with Gaucher disease, it is evident that the vast majority never develop Parkinson disease [33]. Furthermore, it is evident that the majority of Gaucher carriers do not have parkinsonism. Even in families where Gaucher disease and parkinsonism is found, not all carriers develop a neurodegenerative disorder [19]. Currently, especially in light of the different frequencies reported in these studies, [11, 13–16] it would be prudent to counsel families that mutations in this gene are just one of a multitude of potential risk factors that contribute to the development...
of parkinsonism. There also are no current therapies for Gaucher disease that would likely to be of benefit to at-risk individuals.

For clinicians, however, awareness of this association may enable a better ascertainment of its frequency. Questions regarding a family history of tremor or dementia should be included in the evaluation of all patients with Parkinson disease. In addition, patients evaluated in Parkinson disease clinics should be asked whether any relatives have Gaucher disease.

The concept of heterozygous individuals being at risk for other disorders is not unique to Gaucher disease. There is growing evidence that heterozygosity for a Mendelian disorder may be a risk factor for the development of other common complex diseases [34–37]. These preliminary data suggest that heterozygosity for Gaucher mutations could be an additional inherited risk factor in an individual otherwise prone to parkinsonism. Explorations into the molecular and pathophysiological mechanisms underlying this association are being pursued aggressively, and will lead to a better understanding of both disorders.

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