Comparison of Parkinson Risk in Ashkenazi Jewish Patients With Gaucher Disease and GBA Heterozygotes

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IMPORTANCE Information on age-specific risk for Parkinson disease (PD) in patients with Gaucher disease (GD) and glucocerebrosidase (GBA) heterozygotes is important for understanding the pathophysiology of the genetic association and for counseling these populations.

OBJECTIVE To estimate the age-specific risk for PD in Ashkenazi Jewish patients with type 1 GD and in GBA heterozygotes.

DESIGN, SETTING, AND PARTICIPANTS The study included patients with GD from 2 tertiary centers, Shaare Zedek Medical Center, Jerusalem, Israel (n = 332) and Mount Sinai School of Medicine, New York, New York (n = 95). GBA noncarrier non-PD spouse control participants were recruited at the Center for Parkinson’s Disease at Columbia University, New York (n = 77). All participants were Ashkenazi Jewish and most patients (98.1%) with GD carried at least 1 N370S mutation.

MAIN OUTCOMES AND MEASURES The main outcome measure was a diagnosis of PD. Diagnosis was established in patients with GD on examination. We used a validated family history interview that identifies PD with a sensitivity of 95.5% and specificity of 96.2% to identify PD in family members. Kaplan-Meier survival curves were used to estimate age-specific PD risk among patients with GD (n = 427), among their parents who are obligate GBA mutation carriers (heterozygotes, n = 694), and among noncarriers (parents of non-PD, non-GD control participants, n = 154). The age-specific risk was compared among groups using the log-rank test.

RESULTS Among those who developed PD, patients with GD had a younger age at onset than GBA heterozygotes (mean, 54.2 vs 65.2 years, respectively; P = .003). Estimated age-specific risk for PD at 60 and 80 years of age was 4.7% and 9.1% among patients with GD, 1.5% and 7.7% among heterozygotes, and 0.7% and 2.1% among noncarriers, respectively. The risk for PD was higher in patients with GD than noncarriers (P = .008, log-rank test) and in heterozygotes than noncarriers (P = .03, log-rank test), but it did not reach statistical significance between patients with GD and GBA heterozygotes (P = .07, log-rank test).

CONCLUSIONS AND RELEVANCE Patients with GD and GBA heterozygotes have an increased age-specific risk for PD compared with control individuals, with a similar magnitude of PD risk by 80 years of age; however, the number of mutant alleles may play an important role in age at PD onset.
utations in the glucocerebrosidase (GBA) gene have emerged as a common risk factor for the development of Parkinson disease (PD). This association was originally reported in case reports and case series involving patients with Gaucher disease (GD), an autosomal recessive lysosomal storage disease resulting from mutations in both alleles of GBA. Gaucher disease is the most common genetic disorder in the Ashkenazi Jewish (AJ) population. Among AJ individuals, most patients with GD carry at least 1 N370S allele, a missense mutation associated with type 1 GD, the milder nonneuronopathic form. Glucocerebrosidase heterozygosity is also associated with PD based on case-control studies comparing mutation frequency in patients with PD and control participants in different ethnic groups. Among patients with PD, at least 15% of AJ individuals and 3% of non-AJ individuals carry 1 of the 2 most common GBA mutations (N370S and L444P). A multicenter analysis estimated the odds ratio for carrying a GBA mutation in patients with PD vs control participants at 5.43 (95% CI, 3.89-7.57). However, data on the reverse association—the risk for PD in GBA heterozygotes—have been limited and widely variable, with penetrance estimations between 10.9% and 29.7% by 80 years of age. Furthermore, it is unclear whether the risk for PD is different among those carrying 2 mutant GBA alleles (ie, patients with GD) and those with 1 mutant allele (heterozygote carriers).

In this study, we aimed to estimate the age-specific risk for PD associated with either 1 or 2 mutant GBA alleles among AJ participants by obtaining PD history and family history data from 2 of the world’s largest AJ GD centers, Shaare Zedek Medical Center (SZMC) in Jerusalem, Israel, and Mount Sinai School of Medicine (MSSM) Comprehensive Gaucher Disease Treatment Center in New York, New York. A major advantage of this approach was the ability to easily access a large number of GBA heterozygotes including the parents of patients with GD, who are obligate carriers of a GBA mutation. We compared the estimated risk for PD between patients with type 1 GD who have 2 GBA mutations, carriers of a single mutation (parents of patients with GD), and presumed non-carriers (parents of non-PD, non-GBA carrier AJ participants). We hypothesized that the age-specific risk for PD would increase with the number of mutated alleles (lowest in control participants, higher in heterozygotes, and highest in patients with GD).

Methods

Participants with GD were recruited from 2 outpatient centers, SZMC and MSSM; diagnosis of GD was established at both sites in a similar fashion. Initial workup included glucocerebrosidase enzymatic activity and a panel of the common AJ mutations (6-8 mutations). Full sequencing was offered in cases where enzymatic activity was consistent with GD but the panel revealed only heterozygous or no mutations. Control participants were recruited from the Center for Parkinson’s Disease at Columbia University Medical Center (CUMC), New York, and were spouses of patients with PD. To compare participants with a similar genetic background (given that control individuals were available only in New York), participants were included only if they reported all 4 grandparents were Jewish. All study procedures were approved by the local ethics committees of the participating centers, and all participants provided written informed consent.

Participants

Shaare Zedek Medical Center

Adult patients (≥18 years of age) with confirmed GD evaluated at SZMC from October 1, 2011, to March 31, 2013, were approached irrespective of family history of PD, GD severity, or frequency of visits (patients who were asymptomatic or mildly symptomatic were also included). Information was collected on 332 adult patients with GD. One patient was not included in the study because of a personal history of dementia and inability to provide informed consent, and 1 patient was not included because of an inability to speak either Hebrew or English. Three patients (0.9%) declined to participate. Seven interviews of participants with GD who lived remotely and who were not treated with enzyme replacement were conducted by telephone.

Mount Sinai Medical Center

Participants from the Comprehensive Gaucher Disease Treatment Center have been previously described. For the current analysis, only data from adult (≥18 years of age) participants with AJ ancestry (n = 95) were included, including 3 participants not previously described.

Columbia University Medical Center

Control participants without GD or PD were recruited among spouses of patients with PD from the Center for Parkinson’s Disease at CUMC between 2010 and 2013. Control participants were screened for the 8 most common GBA mutations in the AJ population; when combined, these mutations account for more than 96% of GBA mutations in AJ patients. Only participants (n = 77) whose test results were negative for GBA mutations and who reported AJ ancestry were included.

Clinical Evaluation

Demographic characteristics and GBA genotype were obtained from the medical records of all participants with GD. Participants with GD previously diagnosed with PD were examined by a movement disorders specialist (R.N.A) to confirm PD diagnosis. Control participants reported not having PD and were clinically examined by R.N.A to rule out the presence of PD. A validated family history interview (FHI) was used to elicit family history of PD from patients with GD and control participants in each of their first-degree relatives. Although relatives were not genotyped or examined, the survey identifies PD with a sensitivity of 95.5% and specificity of 96.2% using an algorithmic conservative diagnosis of PD. The same FHI was previously used for Parkin and LRRK2 penetrate estimations. Participants reported their first-degree relatives’ current age or age at death, as well as the age at onset of PD symptoms/signs, if applicable.
Comparisons of the demographic characteristics and genotype of participants from MSSM participated in the study (Three-hundredthirty-two AJGD probands from SZMC and 95 individuals from MSSM). Results:

Descriptive statistics (means, standard deviations, t test, and analysis of variance for continuous variables; proportions, frequencies, χ² test, and Fisher exact test for categorical variables) were used to compare the demographics of participants with GD with their parents and noncarrier parents of control participants, as well as to compare demographic characteristics of participants from SZMC and MSSM. When participants with GD were related to one another (multiplex families), only 1 FHI per family was included. Primary analyses were restricted to parents of patients with GD and non-GD, non-PD control participants, whom we estimated to be independent observations (none of the participants reported consanguinity), and in the case of parents with GD, they were each obligate carriers of GBA mutations. In all survival analyses, time to event was defined as age at onset of PD. Participants were censored at either their current age or at death if they did not reach a PD event. We used Kaplan-Meier survival curves to estimate survival free of PD (penetrance) in patients with GD who, by definition, carry 2 GBA mutations (GD probands from MSSM and SZMC), carriers of a single GBA mutation (parents of participants with GD from MSSM and SZMC), and noncarrier individuals (parents of control participants from CUMC). We used the log-rank test to compare survival free of PD among patients with GD, GBA heterozygotes, and noncarrier control participants. We then analyzed whether the following 2 characteristics of the GD probands are associated with increased risk for PD. First, we used Cox proportional hazards models, adjusted for recruitment site, parent’s sex, and proband’s sex to compare the risk for PD between parents of patients with GD with and without a diagnosis of PD. Second, we compared the risk for PD in parents of GD N370S homozygotes (whose parents are obligate N370S carriers) and parents of compound heterozygote patients with GD (where at least 1 of the parents carries a non-N370S mutation) using similarly adjusted Cox models. Analyses were performed using SPSS Statistics version 19.0 software (IBM).

**Table 1. Demographic Characteristics of Participants With GD, Their Parents (Obligate Carriers), and Control Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With GD (n = 427)</th>
<th>Obligate GBA Carriers (Parents) (n = 694)</th>
<th>Control Participants’ Parents (Presumed Noncarriers) (n = 154)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>47.1 (16.2)</td>
<td>69.1 (12.8)</td>
<td>76.0 (13.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>201 (47.1)</td>
<td>347 (50.0)</td>
<td>77 (50.0)</td>
<td>.64</td>
</tr>
<tr>
<td>Diagnosed as having PD, No. (%)</td>
<td>11 (2.6)</td>
<td>34 (4.9)</td>
<td>3 (1.9)</td>
<td>.06</td>
</tr>
</tbody>
</table>

**PD cases**

<table>
<thead>
<tr>
<th></th>
<th>Age at PD onset, mean (SD), y</th>
<th>Male, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54.2 (8.6)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>PD</td>
<td>65.2 (10.7)</td>
<td>18 (52.9)</td>
</tr>
<tr>
<td></td>
<td>72.0 (19.3)</td>
<td>1 (33.3)</td>
</tr>
</tbody>
</table>

Abbreviations: GD, Gaucher disease; PD, Parkinson disease.

**Statistical Analysis**

Descriptive statistics (means, standard deviations, t test, and analysis of variance for continuous variables; proportions, frequencies, χ² test, and Fisher exact test for categorical variables) were used to compare the demographics of participants with GD with their parents and noncarrier parents of control participants, as well as to compare demographic characteristics of participants from SZMC and MSSM. When participants with GD were related to one another (multiplex families), only 1 FHI per family was included. Primary analyses were restricted to parents of patients with GD and non-GD, non-PD control participants, whom we estimated to be independent observations (none of the participants reported consanguinity), and in the case of parents with GD, they were each obligate carriers of GBA mutations. In all survival analyses, time to event was defined as age at onset of PD. Participants were censored at either their current age or at death if they did not reach a PD event. We used Kaplan-Meier survival curves to estimate survival free of PD (penetrance) in patients with GD who, by definition, carry 2 GBA mutations (GD probands from MSSM and SZMC), carriers of a single GBA mutation (parents of participants with GD from MSSM and SZMC), and noncarrier individuals (parents of control participants from CUMC). We used the log-rank test to compare survival free of PD among patients with GD, GBA heterozygotes, and noncarrier control participants. We then analyzed whether the following 2 characteristics of the GD probands are associated with increased risk for PD. First, we used Cox proportional hazards models, adjusted for recruitment site, parent’s sex, and proband’s sex to compare the risk for PD between parents of patients with GD with and without a diagnosis of PD. Second, we compared the risk for PD in parents of GD N370S homozygotes (whose parents are obligate N370S carriers) and parents of compound heterozygote patients with GD (where at least 1 of the parents carries a non-N370S mutation) using similarly adjusted Cox models. Analyses were performed using SPSS Statistics version 19.0 software (IBM).

**Results**

**Participants With GD**

Three-hundred thirty-two AJ GD probands recruited at SZMC and MSSM, family history of PD was analyzed in 347 unrelated families with GD, including 257 families from SZMC and 90 families from MSSM. Family of 80 patients with GD and PD were not included because they belonged to multiplex families in which more than 1 sibling or a parent and child were enrolled. The data included information on 1766 first-degree relatives. None of the 460 children of patients with GD (obligate GBA carriers) and 1.3% of siblings (8 of 612) were diagnosed as having PD. Subsequent analyses, discussed in the next section, were restricted to the 694 parents. As a control group, we studied parents of noncarrier, non-PD AJ control individuals (n = 154); this group was older than the parents of patients with GD (Table 1).

**PD Risk in Patients With GD, GBA Heterozygotes, and Noncarriers**

Eleven of the 427 patients with GD (2.6%), 34 of the 694 heterozygote parents (4.9%), and 3 of the 154 noncarriers (1.9%) were diagnosed as having PD (Table 1). Among those diagnosed as having PD, patients with GD had an earlier age at onset of PD compared with both GBA heterozygotes (P = .003) and noncarrier control participants (P = .03), suggesting that carrying 2 mutant GBA alleles leads to the onset of PD at a younger age.

The probability of having PD by a specific age (using Kaplan-Meier plots) among patients with GD, GBA heterozygotes, and noncarriers is presented in Table 2 and the Figure. Log-rank tests confirm higher age-specific risk for PD in patients with GD compared with control participants (P = .008).
Table 2. Age-Specific Risk (Penetrance) for Parkinson Disease Among Ashkenazi Jewish Individuals
With and Without GBA Mutations Using Kaplan-Meier Plots

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th>Age-Specific Risk, % (95% CI)</th>
<th>60 y</th>
<th>70 y</th>
<th>80 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarriers (n = 154)</td>
<td>0.7 (1.37)</td>
<td>0.7 (1.37)</td>
<td>2.1 (2.94)</td>
<td></td>
</tr>
<tr>
<td>Obligate GBA carriers (n = 694)</td>
<td>1.5 (0.98)</td>
<td>5.2 (1.96)</td>
<td>7.7 (2.74)</td>
<td></td>
</tr>
<tr>
<td>Obligate N370S carriers (n = 464)</td>
<td>1.2 (0.98)</td>
<td>3.5 (1.96)</td>
<td>5.9 (3.14)</td>
<td></td>
</tr>
<tr>
<td>Patients with GD (N370S homozygotes or compound heterozygotes) (n = 427)</td>
<td>4.7 (3.33)</td>
<td>9.1 (6.07)</td>
<td>9.1 (6.07)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: GD, Gaucher disease.

Discussion
This study estimated the age-specific penetrance of PD among patients with GD and GBA heterozygotes based on the largest number of obligate carriers published to date. Our age-specific estimation of PD risk among patients with GD (9.1% by age 80 years) is similar to estimations derived from the International Collaborative Gaucher Group Registry data (9%-12% by age 80 years). The fact that only 11 of 427 patients with GD were diagnosed as having PD is reassuring when compared with prior odds ratio estimations of an almost 20-fold increased lifetime risk for developing PD in this population.

However, our estimations of GBA heterozygotes’ risk for PD (7.7% by age 80 years) are lower than those obtained in the United Kingdom (15% by age 80 years) and France (29.7% by age 80 years). The large difference between our penetrance estimations and those reported by Anheim et al from France may be explained by differences in methods—how GBA heterozygotes were ascertained—and differences in the type of GBA mutations observed. In this study, we collected data on heterozygotes regardless of family history of PD, while heterozygotes in the article by Anheim et al were all ascertained through a familial PD cohort, i.e., by family history of PD. Therefore, it is possible that these GBA heterozygotes, by virtue of belonging to families with familial PD, have other risk factors for PD in addition to the GBA mutations.

Further, it is possible that the higher prevalence of the non-N370S mutations in French and British populations, who are mostly non-AJ individuals, conveys a higher risk for PD than those observed in the AJ population. Two studies reported that milder GBA mutations, including the N370S mutation, are associated with lower risk for PD than more severe mutations (e.g., L444P or 84GG). In this study, we examined this issue by comparing the risk for PD in the parents of N370S homozygotes with parents of N370S compound heterozygotes. While we did not find a statistically significant difference between parents of N370S homozygotes and parents of compound heterozygotes (HR = 1.8, P = .08), our study may have been underpowered to detect such a difference.

The availability of data on both patients with GD and GBA heterozygotes provides a unique opportunity to assess the effect of 1 vs 2 GBA mutations on PD risk. Patients with GD who carry 2 GBA mutations developed PD at an earlier age compared with heterozygote carriers, i.e., those with a single mutant GBA allele (54.2 vs 65.2 years, respectively; P = .003). However, by age 80 years, the difference in the age-specific risk for PD between the 2 groups had diminished (9.1% in patients with
GD and 7.7% in heterozygotes). Together, these data suggest that the incremental risk for carrying a second GBA mutant allele lies in developing PD at an earlier age rather than having a substantially greater overall risk for developing PD. The mechanisms underlying the link between GBA mutations and PD are unknown. The most common hypotheses linking GBA mutations to PD suggest either a loss of function of glucocerebrosidase enzymatic activity or a toxic gain of function.23 It is possible that glucocerebrosidase activity modifies age at PD onset because patients with GD had an earlier PD onset than heterozygotes, and heterozygotes’ age at onset is earlier than that of noncarriers.7 Reduced glucocerebrosidase activity has been implicated in the pathogenesis of neuronal loss and alpha synuclein deposits in a mouse model of GBA homozygotes26,27; however, to our knowledge, an animal model of heterozygote animals with neuronal damage resembling PD does not exist. In addition, the similar magnitude of PD risk among patients with GD and heterozygotes by age 80 years suggests additional, more complex biological mechanisms are involved, perhaps including a toxic gain of function (eg, disrupted clearance of α-synuclein by a mutated glucocerebroside enzyme).25,28

Our findings may help clinicians and genetic counselors provide penetrance estimations for GBA heterozygotes in the AJ population. Many AJ individuals undergo preconception and prenatal GBA testing in both Israel and the United States, as recommended by the American College of Medical Genetics, and are therefore aware of their genotype.29 Accurate penetrance estimates are important in enabling clinicians to inform heterozygotes of their risk for PD and address concerns about the association.

The strengths of this study include the large number of patients with GD and heterozygotes included in the analysis. In this study, 694 obligate carriers were analyzed, a 3-fold increase from our previous report.31 Furthermore, we used the same validated FHI questionnaire36 in all 3 genetic groups from an exclusively AJ cohort.

The major limitation of our study was that the information on the parents (obligate heterozygotes and noncarriers) was obtained by proband report, and we neither examined nor directly genotyped the parents. It is possible that probands may not recall the accurate age at PD onset of their parents. We could not assess the parents for previously reported risk modifiers,30 including LRRK2 mutations,31 for nonpaternity or for carrying homozygous mutations themselves. However, given the practice of offering genetic counseling and testing to first-degree relatives of patients with GD (we had to exclude family data from 80 probands with GD who came from multiplex families), it is likely most parents with GD had been identified. In addition, we have not genotyped the parents of the noncarrier control participants, and it is possible that members of this cohort carry a GBA mutation on the allele not inherited by their genotyped offspring. However, this limitation would bias our results toward the null hypothesis.

Conclusions

Despite the fact that GBA mutations are among the most common genetic risk factors for PD, our results (as well as others) indicate that most patients with GD and GBA heterozygotes will never develop PD.23 To refine the estimation of the age-specific risk for PD in these populations and to identify genetic and environmental risk modifiers, long-term follow-up of patients with PD and GBA heterozygotes is required. Detailed longitudinal evaluation of GD/PD and GBA heterozygotes/patients with PD will allow us to compare disease severity, disease progression, cognition, and other PD characteristics, in addition to age at onset between these groups.
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REFERENCES