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Greater risk of parkinsonism associated with non-N370S *GBA1* mutations

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Abstract

Mutations in β-glucosidase (*GBA1*) are the most common genetic risk factor for Parkinson disease (PD). There is evidence to suggest that PD risk is greater (1) in *GBA1* heterozygotes with non-N370S *GBA1* mutations compared to N370S mutations and (2) in GD type 1 (GD1) patients compared to *GBA1* heterozygotes. This study aimed to determine the comparative risk of parkinsonism in individuals who are affected or carriers of Gaucher disease (GD) and to ascertain the influence of different *GBA1* mutations on risk/clinical expression. We conducted a secondary analysis of cross-sectional data assessing the prevalence of parkinsonism in a population of GD1 patients and their heterozygote and non-carrier family members. Two logistic regression models, both employing a family-specific random effect, were used to assess (1) the association between *GBA1* mutation (N370S or non-N370S) and parkinsonism among *GBA1* heterozygotes and (2) the association between *GBA1* genotype and parkinsonism. Parkinsonism was present in 8.6 % of GD1 (7/81), 8.7 % of *GBA1* heterozygotes (18/207), and 2.2 % of non-carriers (1/45). For those greater than 60 years old, parkinsonism was present in 38.5 % (5/13) of GD1 (5/13), 15.3 % of *GBA1* heterozygotes (13/85), and 7.1 % of non-carriers (1/14). Among *GBA1* heterozygotes, non-N370S mutations were associated with a significantly increased risk of parkinsonism compared to N370S (OR=22.5; p=0.035; 95%CI: 1.24, 411). In this population, each additional *GBA1* mutation was associated with a non-significant two-fold increased risk of parkinsonism. *GBA1* heterozygotes with non-N370S mutations associated with Gaucher disease have an increased risk of parkinsonism compared to those with N370S mutations.

Introduction

Mutations in β-glucosidase (*GBA1*) are the most common genetic risk factor for Parkinson disease (PD). The association was first suggested by reports of parkinsonism in Gaucher disease type 1 patients (GD1) (OMIM 230806)(Bembi et al 2003; Machaczka et al 1999; Neudorfer et al 1996). A later prospective study calculated the risk of PD in GD1 patients to be 21 times greater than the general population(Bultron et al 2010). Following reports of parkinsonism in GD1 patients and their heterozygote family members,(Goker-Alpan et al 2004) PD populations were screened for *GBA1* mutations. Full mutation screening revealed that 4–9 % of PD patients in Asian and Northern European populations were heterozygous for *GBA1* mutations (Mitsui et al 2009; Ziegler et al 2007; Bras et al 2009; Kalinderi et al 2009; Sidransky et al 2009). A large meta-analysis found that PD patients had a five-fold increased risk of carrying a *GBA1* mutation compared to non-PD controls (Sidransky et al 2009). Moreover, a meta-analysis of genome-wide association studies found that PD patients were 3.5 times more likely to carry the N370S allele compared to controls (Lill et al 2012).

One factor that has been reported to modify risk of PD in *GBA1* heterozygotes is mutation severity. PD patients have been shown to be more likely to carry severe GBA mutations,

defined as those that result in a neuronopathic phenotype (type 2 or type 3) when inherited with another severe or null mutation, compared to mild mutations (Gan-Or et al 2008). Severe *GBA1* mutations have also been associated with an earlier onset of PD symptoms (Gan-Or et al 2008; Gan-Or et al 2009). In both of these studies, N370S was the only mild mutation encountered in PD subjects. Another factor expected to influence risk of PD is the number of inherited *GBA1* mutations. This has not been previously assessed in a population of related GD1 and *GBA1* heterozygotes, i.e., affected versus carrier individuals. The objectives of this study were to determine whether the risk of parkinsonism is greater in *GBA1* heterozygotes with non-N370S mutations compared to those with the N370S mutation and to assess whether the risk of parkinsonism is greater in GD1 patients compared to *GBA1* heterozygotes.

Methods

Between June 2006 and July 2009, questionnaires assessing the presence of neurological symptoms and diseases (Supplementary Fig. 1) were completed by GD1 probands, first degree relatives, and second degree relatives from 87 families. The results of these questionnaires, specifically the prevalence of various neurological symptoms, was previously reported (Giraldo et al 2011). Among the neurological symptoms assessed were PD and dementia. If present, the age at symptom onset and diagnosis were obtained. Only diagnoses of PD confirmed by a neurologist using the guidelines published by the Spanish Neurological Society (SEN) (2009) were retained. Once completed, survey data were associated with previous demographic and disease data available in the Spanish Gaucher Disease Registry (SGDR). The original study was approved by the Ethics Committee of the “Instituto Aragones de Ciencias de la Salud” (CEICA). The secondary analysis was performed with deidentified data and was exempted from review by the Beth Israel Medical Center institutional review board.

For the purposes of this analysis, individuals were considered to have parkinsonism if they reported PD or dementia with parkinsonism (1 patient). Because the diagnosis of PD is very rare before the age of 30, (Van Den Eeden et al 2003) subjects were only included if they were older than 30 at the time of questionnaire completion. Seven *GBA1* heterozygotes with only action tremor and two GD1 subjects with only rest tremor were not included in the analysis. For analysis, *GBA1* heterozygotes were divided into two groups according to whether or not they carried an N370S mutation (N370S and non-N370S). *GBA1* mutations may also be subdivided into mild, severe, null, and frameshift mutations, a stratification scheme partly based on phenotype-genotype correlations (Beutler et al 2005). These designations have been used by other investigators and are included in Table 1.

Statistical analysis

Bivariate associations were tested with Mann-Whitney, chisquared, and Fisher’s exact tests as appropriate. Logistic regression with a family-specific random effect to account for familial genetic homogeneity was used to assess the association between *GBA1* genotype and parkinsonism under an additive model adjusting for gender and age at ascertainment (model 1). For this model non-mutation carriers were used as the baseline risk group. A

second logistic regression model with a family-specific random effect was used to assess the association between *GBA1* mutation (N370S versus non-N370S) and parkinsonism among *GBA1* heterozygotes adjusting for gender and age at ascertainment (model 2). The p values for both logistic regression models were generated with a Wald test. A logistic regression model to assess the association between GD severity and parkinsonism among GD1 subjects was not used because there were no cases of parkinsonism among subjects with mild genotypes.

Results

After excluding those less than 30 years old at enrollment, 81 GD1, 207 *GBA1* heterozygotes, and 45 non-carrier relatives were included in the analysis. Parkinsonism was reported by 8.6 % (7/81) of GD1, 8.7 % (18/207) of *GBA1* heterozygotes, and 2.2 % (1/45) of non-carriers (Table 2). For those enrolled after age 60, 38.5 % (5/13) of GD1, 15.3 % (13/85) of *GBA1* heterozygotes, and 7.1 % (1/14) of non-carriers reported parkinsonism.

Among GD1 subjects, 11 were N370S homozygotes, 68 were compound heterozygotes with one N370S allele, and two had the genotype G377S/D409H. The seven cases of parkinsonism were among the compound heterozygotes (7/ 68, 10.5 %). The distribution of *GBA1* mutations among heterozygotes is detailed in Table 1. The majority of the non-N370S mutations (89.8 %) could be characterized as severe, null, or frameshift mutations (Beutler et al 2005). The other mutations were either mild (1.8 %), mild/severe (2.8 %), or could not be defined (5.6 %).

Among the 18 *GBA1* heterozygotes with parkinsonism, there was no significant difference in the median age of symptom onset for the 3 with N370S compared to the 15 with non-N370S mutations (63 and 62, respectively; p= 0.68). There were five families with more than one individual with parkinsonism. Genotypes for these subjects by family were two N370S/ IVS4-2a>g +c.(−203)A>G; two E326K+N188S heterozygotes; one N370S/R257Q and one R257Q heterozygote; two N370S heterozygotes; and three L444P heterozygotes. Other characteristics of the sample are detailed in Table 3.

In a logistic regression model with a family specific random effect and adjustment for gender and age at ascertainment, *GBA1* heterozygotes with non-N370S mutations had an increased risk of parkinsonism compared to *GBA1* heterozygotes with N370S mutations (OR=22.5; p=0.035; 95%CI: 1.24, 411). In an additive logistic regression model including a family specific random effect and adjustment for gender and age at enrollment, a mutation in *GBA1* was associated with a non-significant increased risk of PD (OR=1.98, p=0.13, 95%CI: 0.82, 4.76). The results were similar if N370S heterozygotes and homozygotes were excluded from the analysis (OR=2.5, p=0.09, 95%CI: 0.85, 7.01). There was no interaction between age of enrollment and *GBA1* mutation severity nor between age of enrollment and *GBA1* genotype.

Discussion

Among *GBA1* heterozygotes, those with non-N370S mutations had a 22 times greater risk of parkinsonism compared to those with N370S. This is consistent with a previous analysis that

found the risk of PD patients carrying severe heterozygous *GBA1* mutations was greater than PD patients with the mild mutation N370S (Gan-Or et al 2008). Contrary to previous reports that found an early age of symptom onset in severe mutation carriers compared to those with N370S, (Gan-Or et al 2008; Gan-Or et al 2009) we did not find a discrepancy in the age of symptom onset between non-N370S mutation carriers and those with N370S. This may be a result of the small number of *GBA1* heterozygotes with parkinsonism in our population. This study is distinguished from prior reports because the risk of parkinsonism was assessed in a sample of *GBA1* hetero-zygotes, allowing the risk associated with non-N370S *GBA1* mutations to be compared directly to the risk associated with N370S. While the two previous studies that examined the association between specific *GBA1* mutations and parkin-sonism characterized mutations as either mild or severe mutations, N370S was the only mild mutation considered (Gan-Or et al 2008; Gan-Or et al 2009). Our study also included a greater number of non-N370S mutation carriers. Because the majority of non-N370S mutations are rare, calculating the risk of developing parkinsonism associated with each mutation will be difficult. Grouping non-N370S mutations together, especially those occurring in Gaucher disease patients, is a useful way to assess the risk of parkin-sonism associated with these mutations. In assessing whether *GBA1* mutations exert a gene-dosage effect on PD risk, we found that each additional *GBA1* mutation was associated with twice the risk of parkinsonism. This finding was not significant however and needs to be evaluated in a larger sample size.

How *GBA1* mutations contribute to the pathogenesis of PD is not currently understood. Although systemic manifestations of GD are mediated by reduced β-glucosidase activity, (EC 3.2.1.45) it is not clear that reduced enzyme activity is entirely responsible for CNS disease. In the same manner, severe mutations might be expected to result in greater reduction of enzyme activity, although this is not apparent when enzyme activity is measured in peripheral blood (Aerts et al 1990). Thus, it is not clear if *GBA1* mutations contribute to GD and PD via a shared mechanism, namely β-glucosidase deficiency, or via different mechanisms. The presence of different pathogenic mechanisms is supported by the idea that *GBA1* heterozygotes have sufficient β-glucosidase activity to prevent the accumulation of its substrate (glucocerebroside) (Horowitz et al 2011). Toxic-gain-of-function mechanisms have been proposed to explain how *GBA1* mutations contribute to PD. Proposed mechanisms include overwhelming the endoplasmic-reticulum associated degradation pathway with mutant β-glucosidase protein (Ron and Horowitz 2005) and aggregation of α-synuclein after interaction with mutant enzyme (Goker-Alpan et al 2010). These hypotheses and others, however, do not adequately explain the increased risk of PD among *GBA1* null mutation carriers, e.g., c.84insG, individuals without mutant protein(Gan-Or et al 2008). Unfortunately our sample did not include adequate numbers of null mutation carriers to assess the risk of PD in this group separately. Hypotheses congruent with the loss-of-function basis leading to systemic GD propose that accumulated glycolipids contribute to PD by either impairing autophagy and mitophagy or altering lipid raft and membrane composition (Westbroek et al 2011). A recent study provided evidence for a positive feedback loop between β-glucosidase activity and -synuclein: reduced enzyme activity was associated with α-synuclein accumulation and α-synuclein was shown to inhibit normal β-glucosidase activity (Mazzulli et al 2011). Studies evaluating in vivo β-glucosidase

activity in *GBA1* mutation carriers with and without parkinsonism, especially as it pertains to N370S and non-N370S carriers, may provide insight into the pathogenesis of *GBA1* mutations. Regardless of the mechanism by which mutant *GBA1* mutations contribute to PD, it is important to remember that only a minority of those with *GBA1* mutations develop PD, underscoring the importance of other genetic and environmental modifiers. The presence of genetic modifiers is supported by the clustering of parkinsonism in some of the families included in this study.

Because PD is an age-dependent disease, assessing the importance of risk factors in younger populations does not fully reflect disease risk over a lifetime. We were able to partially correct for this limitation by adjusting for age at ascertainment. The importance of age in modifying PD risk is underscored by a recent study reporting penetrance of 7.6 %, 13.7 %, 21.4 %, and 29.7 % among *GBA1* heterozygotes at 50, 60, 70, and 80 years, respectively (Anheim et al 2012). It is also important to remember that enzyme replacement therapy for GD1 has only been available for 20 years. Therefore, the current GD1 population now at greatest risk for PD may have on average milder GD1 phenotypes.

A strength of this study is that parkinsonism was assessed directly in every individual and we did not rely upon family history taking. A limitation is that the diagnosis of parkinsonism was not determined by a single neurologist or movement disorder specialist in all cases. However, diagnoses were confirmed using guidelines published by SEN. We recognize that even when clinical diagnostic criteria are used, PD is diagnosed incorrectly in about 25 % of patients (Tolosa et al 2006). While misclassification may have affected our prevalence estimates of parkinsonism in this population, we would not expect differential misclassifica-tion based on *GBA1* genotype. Nevertheless, our results should ideally be confirmed in a prospective cohort receiving regular neurological exams.

In conclusion, among *GBA1* heterozygotes, non-N370S mutations occurring in Gaucher disease are associated with an increased risk of PD compared to the mutation N370S. Any future understanding of the pathomechanism of *GBA1* mutations must incorporate this finding.

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Table 1

GBA1 mutations for heterozygote family members

***GBA1* mutation**	**Number**	**Number with parkinsonism**	**Mutation severity[a]**
N370S	99	3	Mild
L444P	49	7	Severe
E326K + N188S	6	2	Severe[b]
IVS4-2a>g +c.(−203)A>G	5		Null
G202R	5	1	Severe
G195W	5		Severe
G377S	3		Mild/severe
R463C	3		Severe
R257Q	3	1	Severe
T134P	2		Unknown
R120W	2		Severe
R257X	2		Null
S364R	2		Severe
V398I	2	1	Mild[c]
c.l249_1251delTGC	2	1	Unknown[d]
c.953delT	2	1	Null
deb55	2		Null
W(−4)X	1		Null
D409H	1		Severe
c.l098insA	1		Null
P182L	1		Severe
P391L	1		Unknown
R163X	1		Null
R47X	1		Null
Y313H	1		Unknown
c.l207insA	1		Frameshift
c.l439_1445del7	1	1	Frameshift
c.500insT	1		Null
c.708delC	1		Frameshift
c.84insG	1		Null
Total	207	18	

[a] All designations of mutation severity are according to Beutler et al 2005 unless otherwise indicated

[b] The two brothers in the SGDR with L444P/E326K + N188S have neuronopathic phenotypes (type 2 and type 3)

[c] Two V398I homozygotes were reported with a GD1 phenotype (Rozenberg et al 2006)

[d] The two GD1 subjects in the SGDR with N370S/c.1249_1251delTGC have mild type 1 phenotype and do not require treatment

Table 2

Population characteristics

	Parkinsonism *n*=26	**No parkinsonism *n*=307**	**p values**
Women, n (%)	17 (65.4)	150 (54.9)	0.11
Age of onset of parkinsonism, y	61 (42, 66)	-	
Age at ascertainment, y	66.5 (60, 72)	50(41,65)	0.0002
Ascertained at age >60, n (%)	19 (73.1)	93 (44.9)	<0.001
Ascertained family member with parkinsonism, n (%)	11 (42.3)	77(25.1)	0.056
GBA1 genotype, n (%)			0.40*
GDI	7/81 (8.6)	74/81 (91.4)	
GBA1 heterozygotes	18/207 (8.7)	189/207 (91.3)	
Wild type	1/45 (2.2)	44/45 (97.8)	

Years are reported as medians with interquartile ranges unless otherwise specified

* p value is for 3×2 Fisher's exact test

Table 3

Characteristic of Gaucher disease type 1 patients, *GBA1* heterozygotes, and non-carriers

	Parkinsonism	No parkinsonism	p values
Gaucher disease type 1	*n*=7	*n*=74	
Women, n (%)	6 (85.7)	42 (56.8)	0.23
Age of onset of parkinsonism, y	41 (40, 65)	-	
Age at ascertainment, y	63 (42, 72)	47 (42, 54)	0.03
Ascertained at age >60, n (%)	5 (71.4)	8 (10.8)	0.001
Ascertained family member with parkinsonism, n (%)	3 (42.9)	19 (25.7)	0.38
Age GD diagnosis, y	47 (31,60)	32 (21, 42)	0.02
GD treatment, n (%)	3 (42.9)	82 (78.4)	0.06
Age GD treatment, y	54 (33,65)	40 (34,47)	0.28
GBA1 heterozygotes	*n*=18	*n*=189	
Women, n (%)	10 (55.6)	87 (46.0)	0.44
Age of onset of parkinsonism, y	62.5 (55, 67)	-	
Age at ascertainment, y	67.5 (60, 72)	50 (41, 68)	0.006
Ascertained at age >60, n (%)	13 (72.2)	72 (38.1)	0.005
Ascertained family member with parkinsonism, n (%)	8 (44.4)	46 (24.3)	0.09
Genotype, n (%)			0.006*
N370S	3 (16.7)	96 (50.8)	
non-N370S	15 (83.3)	93 (49.2)	
Non-carriers	*n*=1	*n*=44	
Women	1	21 (47.7)	
Age of onset of parkinsonism, y	63	-	
Age at ascertainment, y	65	53 (40, 62)	
Ascertained at age >60, n (%)	1	13 (29.5)	
Ascertained family member with parkinsonism, n (%)	0	3 (6.8)	

Years are reported as medians with interquartile ranges unless otherwise specified

* p value is for the 2×2 chi-squared test