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The risk of Parkinson's disease in type 1 Gaucher disease

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Abstract

In Gaucher disease, defective lysosomal glucocerebrosidase due to mutations in the GBA1 gene results in lysosomal accumulation of glucocerebroside in mononuclear phagocytes and a multisystemic phenotype. Observations of occurrence of Parkinson's disease in some patients with non-neuronopathic type 1 Gaucher disease (GD1) and their first degree relatives has led to the identification of GBA1 heterozygous mutations as a genetic risk factor for idiopathic Parkinson's disease (PD). However, the magnitude of risk of PD in patients with known GD1 has not been determined, and it is not known whether GD1/PD represents a specific sub-phenotype of GD1 with distinctive genotype/phenotype characteristics. We estimated the risk of PD in a cohort of 444 consecutively evaluated patients with GD1 compared to that in the general population. Eleven patients developed parkinsonian syndrome during a 12-year follow-up period. The adjusted life-time

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risk ratio of PD in GD1 compared to that in the general population was 21.4 [95% confidence interval (95% CI) 10.7–38.3], with a higher risk in men compared to women. In our cohort, GD1/Parkinson's disease phenotype (GD1/PD) was characterized by higher GD1 severity score, due to higher incidence of avascular osteonecrosis. The clinical spectrum of PD varied from mild to potentially life-threatening disease. All but one patient with GD1/PD phenotype had at least one N370S GBA1 allele. In conclusion, compared to the general population, patients with GD1 have an almost 20-fold increased life-time risk of developing PD.

Introduction

While Gaucher disease (GD) is a rare Mendelian lysosomal storage disease that has served as a model for pathophysiologic and therapeutic delineation of orphan diseases, and lysosomal diseases in particular (Grabowski 2008), Parkinson's disease (PD) is a common complex disorder found throughout the world affecting up to 1% of the population aged >65 years (Lees et al. 2009). Recent insights into the phenotypic spectrum of GD that links it to PD promise to open up novel approaches to our understanding of PD and eventually its treatment (Hruska et al. 2006; Beutler 2006). GD occurs because of defective lysosomal glucocerebrosidase due to mutations in the GBA1 gene that results in the accumulation of glucocerebroside in the lysosomes of mononuclear phagocytes (Grabowski 2008). A minor substrate, glucosylsphingosine, also accumulates in the tissues. The resulting phenotype is complex and highly heterogeneous, involving variable combinations of hepatomegaly, splenomegaly, a complex bone phenotype and, rarely, lung involvement. Type 1 Gaucher disease (GD1) accounts for >90% of cases, and it is distinguished by the absence of neurologic involvement; however, the association of GD1 with PD has challenged this traditional classification. In type 2 and type 3 GD there is, in addition, fulminant or chronic neurologic involvement, respectively. Within the vast phenotypic spectrum of GD1, unusual but distinct phenotypes have been described, such as those associated with cancers (Taddei et al. 2009; Zimran et al. 2005; Rosenbloom et al. 2005), pulmonary hypertension (Elstein et al. 1998; Mistry et al. 2002), end-stage liver disease (Lachmann et al. 2000) and Parkinson's disease (Sidransky 2005). During the past decade, there have been sporadic case reports and small series of GD1 patients with PD associated with an early onset of PD (i.e., before the age of 50 years) and a variety of GBA1 mutations (De Marco et al. 2008; Bras et al. 2009; Socal et al. 2009; Nichols et al. 2009; Neumann et al. 2009; Kalinderi et al. 2009; Neudorfer et al. 1996; Tayebi et al. 2001, 2003; Varkonyi et al. 2002; Bembi et al. 2003). While these studies indicated a propensity for a minority of patients with GD1 to develop PD, the magnitude of its overall risk in GD1 is not known. Nevertheless, these early observations led to a seminal study that revealed that patients with idiopathic PD had a higher risk of harboring GBA1 mutations compared to the general population (Aharon-Peretz et al. 2004). Similar findings have been replicated in other populations throughout the world (Mitsui et al. 2009; Lwin et al. 2004; Clark et al. 2005; Sato et al. 2005; Toft et al. 2006; Sidransky 2006; Ziegler et al. 2007; Tan et al. 2007; Wu et al. 2007; Spitz et al. 2008). A more recent, larger study confirmed these findings and, in addition, showed that severe GBA1 alleles (i.e., 84 dupl G and IVS 2+1) conferred a higher risk of PD compared to the milder GBA1 alleles, i.e., N370S (Gan-Or et al. 2008). A worldwide meta-analysis of 5,691 patients with PD and 4,898 controls has provided definitive proof that the odds ratio for a known patient with idiopathic PD to harbor one GBA1 mutant allele is 5.4 compared to controls without PD; moreover patients with the GBA1 mutant allele and PD had an earlier onset of the PD, were more likely to have a positive family history of PD and to have atypical PD features (Sidransky et al. 2009). The pathophysiology as well as genetic and environmental modifiers of GD1 that result in the GD1/Parkinson's disease (GD1/PD) phenotype is not known; moreover, how such a mechanism might operate in otherwise healthy heterozygote carriers is not yet understood. It is important to understand the risk of PD in patients with GD1, and the determinants of this phenotype, in order to provide genetic

counseling and plan appropriate monitoring. Furthermore, an understanding of the basis of this association may eventually lead to therapeutic approaches that may be applicable to idiopathic PD. We studied a large cohort of patients with GD1 who were followed for up to 12 years to estimate the risk of PD in GD1, define the spectrum of parkinsonian manifestations and determine whether there were unique distinguishing characteristics of GD1 in these patients.

Methods

Patients

This was an observational study of consecutive patients in which all patients received the standard of care. The data collection was approved by the Institutional Review Boards of Yale University School of Medicine and New York University (NYU) School of Medicine. Between 1996 and 2009, consecutive patients with GD (confirmed by demonstration of low, i.e., <10% of normal, leukocyte acid β-glucosidase activity and/or GBA1 genotyping) underwent comprehensive phenotyping by staging of severity in individual disease domains, i.e., quantitative assessment of hepatosplenomegaly by volumetric magnetic resonance imaging (MRI), hematologic parameters, and severity of bone disease (Charrow et al. 1998), and, in those affected by PD, the severity of Parkinson's disease was expressed on the unified Parkinson's disease rating scale (UPDRS) (Lees et al. 2009). The diagnosis of Parkinson's disease was confirmed by a neurologist who also assigned the severity score. Age at diagnosis of GD, age at onset of Parkinson's disease, GBA1 genotype, severity of GD1 in each domain, overall GD1 severity score index, UPDRS score and age at initiation of macrophage-targeted recombinant enzyme replacement therapy (ERT) with imiglucerase were recorded. The database was maintained and developed by one of the authors (P.K.M.) and included patients in the GD clinics of P.K.M., M.B. and G.P. Severity score index and Hermann scores were calculated as described previously (Zimran et al. 1992; Hermann et al. 1997). A Hermann score >3 represents the presence of avascular osteonecrosis.

Genotyping

GBA gene analysis was performed as previously described by polymerase chain reaction (PCR) and DNA sequencing. The presence of a 55 base pair deletion spanning the N370S mutation was ascertained by PCR to avoid the misclassification of an N370S/55 base pair deletion as N370S/N370S.(Tayebi et al. 1996)

Statistics

Descriptive statistics were computed for gender, age at presentation, genotype, ethnicity, mode of presentation, spleen status, treatment status, and years of follow-up. Lifetime probability of Parkinson's disease was assessed. In this analysis we estimated the number of expected cases of PD in the patient population by calculating the cumulative lifetime probability of their having developed PD by the attained age. Attained age was defined in this analysis as the date of the last follow-up examination or the date of diagnosis of PD when known. The patient population was assigned to mutually exclusive 5-year age- and gender-specific subgroups. The probability of having developed PD was calculated using data from three published studies (Schrag et al. 2000; Mayeux et al. 1992; Guttman et al. 2003). The numbers of cases of PD expected in this cohort were summed over all age groups and compared with the numbers observed in our cohort of patients with GD1. We calculated the relative risk (RR) by dividing the observed number of PD cases by the expected number of PD cases, using exact methods for the Poisson distribution.

Results

During the 12-year observation period, 444 consecutive patients with GD1 were examined (Table 1). Ten patients developed PD during this observational period, but, for one (patient no. 7 in Table 2), the diagnosis of Parkinson's disease preceded that of Gaucher disease when we first examined the patient (Table 2). Mean age at diagnosis of PD was 55.0±8.8 years (range 40–65 years). When patients with GD1/PD were compared with patients with GD1 who had not developed PD, the age at onset of GD-related symptoms, age at diagnosis of GD1, gender distribution, splenectomy rates and GBA1 genotype distribution were similar in the two groups of patients (Table 1). All but one patient harbored at least one N370S GBA1 allele (5/11 N370S homozygous, 3/11 N370S/84GG, 2/11 N370S/L444P and 1/11patient was L444P/W312C). GBA allele distribution in the GD1/PD group was similar to that in the group with GD1 alone (Table 1). Overall severity score index and bone disease score (Hermann score) were significantly higher in patients who had developed Parkinson's disease than in those that had not developed this specific phenotype: severity score index 10.8±0.8 vs 6.9± 3.7, P=0.02; Hermann score 4.6±0.5 vs 2.5±1.5, P=0.002 by the chi square test). Mean age at diagnosis of GD1 among the 11 patients with Parkinson's was 30 years (range 3–69 years), and mean age at diagnosis of Parkinson's disease was 55.0±8.8 years (range 40–65 years). In one patient (patient no. 7) the diagnosis of Parkinson's disease had preceded the diagnosis of GD1. There was a wide clinical spectrum of Parkinson's disease, with UPDRS scores ranging from 14–76, i.e., mild to potentially life-threatening disease requiring full-time nursing home care. All patients with GD1/PD received ERT, starting at a mean age of 49.2±14.9 years (range 28–73 years). In contrast, among the patients with GD without PD, the mean age at initiation of ERT was 37.1±19.6 years (P=0.045 compared to patients with GD1/PD). Five patients experienced the onset of parkinsonian symptoms before commencing ERT, and the remaining six patients developed parkinsonian symptoms while receiving ERT. As described by others, there was no effect of ERT on parkinsonian symptoms in our cohort of patients.

We estimated the age- and gender-adjusted risk of Parkinson's disease using three reference populations from New York, USA, Ontario, Canada, and London, UK (Table 3). Age-adjusted relative risk of parkinsonian syndrome in our cohort was increased in both male and female patients. The range of risk of PD in GD1 relative to the three populations was increased 11.0-fold to 31.3-fold in male patients and 5.7-fold to 13.8-fold in female patients. In each analysis there was a trend for risk being higher in men than in women, but this did not achieve statistical significance. We estimated average risk by combining data from men and women using the New York (NY) reference population. The relative risk of developing Parkinson's disease in GD1 was thus estimated to be 21.4 [95% confidence interval (95% CI) 10.7–38.3].

Discussion

Reports from around the world have documented simultaneous occurrences of GD1 and Parkinson's disease (GD1/PD) in a subset of patients. In a series of 17 patients with GD1/PD, mild Gaucher manifestations were found, with patients having a mean age at GD1 diagnosis of 35 years but relatively early presentation of Parkinson's disease at a mean age of 48 years (Tayebi et al. 2003). The most common GBA1 allele in these patients was N370S, the presence of at least one copy of which is assumed to protect against neuronopathic disease (Grabowski 2008). Another series of seven patients with GD1 (and three additional GBA1 mutation heterozygote carriers) confirmed these findings and, in addition, defined the wide spectrum of parkinsonian manifestations reflected by UPDRS scores 13 to 38 (Goker-Alpan et al. 2008). In that study, six patients were diagnosed with PD, three patients had Lewy body dementia (LBD), and one was diagnosed with a “Parkinson plus” syndrome. However, the precise risk of patients with GD1 developing PD is not known, and whether there are unique distinguishing features of (GD1) in these patients remains a topic of investigation.

In our series of 444 consecutively examined patients with GD1, we found that, compared to the general population, the life-time relative risk of developing Parkinson's disease was 21.4 (95% CI 10.7–38.3). The magnitude of life-time relative risk of a heterozygote carrier of the GBA1 mutant allele for developing PD is not known. However, among idiopathic PD patient populations, the odds ratio for the presence of the GBA1 mutant allele has been estimated to be 5.4 in a worldwide meta-analysis of >5,000 patients with PD and controls (Sidransky et al. 2009). The answer to the question of whether the relative risk of PD in heterozygote carriers compared to affected GD1 patients harboring two mutants alleles of GBA1 is additive or multiplicative will have to await studies assessing the relative risk of PD in large populations of known GBA1 mutation carriers. An early indication that there may be a gene dosage effect in the association between GD1 and PD is derived from a study by Gan-Or et al. (2008). In this study of PD patients, the odds ratio of harboring severe heterozygote GBA1 mutations (i.e., 84GG and IVS 2+1) was 13.6 compared to an odds ratio of only 2.2 for the milder GBA1 mutations such as N370S. Moreover, the average age at onset of Parkinson's disease in carriers of severe and mild GBA1 mutations was 55.7 years and 60.7 years, respectively; for the six asymptomatic GD1 patients with two mutant alleles of GBA1 discovered in this study, the average age at onset of Parkinson's disease was 51.2 years. In our study, we also found a trend toward early onset Parkinson's disease among GD1 patients with more severe genotype (2/3 patients with onset of PD before the age of 50 years were of N370S/84GG GBA1 genotype, and overall mean age at onset of PD was slightly lower for those with severe mutations than for those with milder mutations).

It is important to delineate the pathophysiology of Parkinson's disease associated with GBA1 mutations, since these insights may eventually have therapeutic implications for this specific subset of GD1 patients as well as the more common idiopathic PD. Two contrasting theories have been proposed, i.e., gain of function mutations in lysosomal glucocerebrosidase that result in protein misfolding that could promote alpha synuclein aggresomes in dopaminergic neurons of the substantia nigra. In our study, as in a previous study, all patients with GD1/PD harbored at least one N370S GBA1 mutant allele, a known misfolding mutation (Grabowski 2008). However, other studies have also implicated GBA1 mutant alleles that do not encode glucocerebrosidase protein, i.e., the 84GG allele, in the association between GD1 and PD. These observations have led to consideration of the potential role of glycolipids in the association between GBA1 mutations and PD.

In our study we found the entire spectrum of PD symptoms associated with GD1, from tremor and rigidity to severe incapacity, requiring nursing home care, and potentially life-threatening disease. Within the GD1/PD patient population there was no association between severity of PD and GD1 disease severity, spleen status or GBA1 genotype. However, we found that patients with GD1/PD appeared to have, overall, more severe GD1 than those that did not exhibit PD. This was reflected by a higher severity score index and Hermann score >3 of patients with the GD1/PD phenotype compared with those with GD1 alone. It could be speculated that prolonged bouts of systemic inflammation, for instance during avascular osteonecrosis, might accentuate the formation of alpha synuclein aggresomes in predisposed individuals. Contrary to the trend towards a higher incidence of avascular osteonecrosis (AVN) in patients with GD/PD1, the mean age at initiation of ERT among the GD1/PD patients was greater than that of the GD1 patients who did not develop PD. This seemed counterintuitive, but it should be noted that the patients with N370S Gaucher disease, who comprised the majority of our patients, tended to present with mild visceral/hematologic disease but worse skeletal disease in adulthood (Taddei et al. 2009). This aspect of N370S GD might have contributed to the later commencement of ERT.

There are several limitations to our study. Firstly, during the ascertainment of Parkinson's disease, we might have missed early subtle presentation, leading to an underestimation of the

prevalence of parkinsonian symptoms in our GD population. Secondly, this was an observational study, and the comparison of the incidence of Parkinson's disease was made by reference to that published for a general population of mixed ethnicities. We made a reasonable assumption that, in these reference populations, the frequency of carriers of GBA1 mutations is extremely low, i.e., ~1 in 100 (Grabowski 1997). Thirdly, our cohort was predominantly of Ashkenazi Jewish ancestry, and the reference population was of mixed ethnicity. The fact that the patients with (GD1/PD) were older than the patients with GD1 alone might have been a confounder for our finding of apparently greater severity of (GD1) among those with PD than among those without PD. We are also aware that Parkinson's disease could be viewed as a primarily pathological diagnosis, rather than a clinical diagnosis.

In conclusion, we determined that the risk of a patient with GD1 developing PD was approximately 20-times that of the control population. These results have implications for genetic counseling and monitoring of patients with GD1. Delineation of the basis of the association of GBA1 mutations and PD may improve our understanding of idiopathic Parkinson's disease and its therapy.

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Table 1

Demographic characteristics and clinical presentations of the patients with type 1 Gaucher' disease in the study cohort, comparing patients with GD1 alone and those with the GD1/PD phenotype (SD, standard deviation)

Characteristic	Parkinson's (*n*=11)	Non-Parkinson's (*n*=433)	Combined (*n*=443)
Gender, number (%)			
Female	4 (40)	230 (53)	234 (52.7)
Male	7 (60)	204 (47)	210 (47.3)
Age at onset of GD symptoms (years)	*n*=11	*n*=270	*n*=280
Mean (SD)	29 (21.9)	24 (18.9)	24 (19.0)
Median (5th, 25th, 75th, 95th percentiles)	(3, 12, 28, 47, 69)	(3, 8, 21, 36, 61)	(3, 8, 21, 36, 61)
Age at diagnosis (years)	*n*=11	*n*=337	*n*=347
Mean (SD)	30 (22.1)	27 (19.0)	27 (19.0)
Median (5th, 25th, 75th, 95th percentiles)	(3, 12, 28, 47, 69)	(3, 11, 26, 39, 65)	(3, 11, 26, 40, 65)
Genotype, number (%)	*n*=11	*n*=433	*n*=443
N370S/N370S	5 (45)	228 (53)	233 (53)
N370S/84GG	3 (27)	73 (17)	76 (17)
N370S/IVS2+1	0	14 (3)	14 (32)
N370S/L444P	2 (18)	59 (14)	61 (14)
N370S/Other	1(9)	59 (14)	59 (13)
Ethnicity, number (%)	*n*=8	*n*=365	*n*=373
Ashkenazi	6 (75)	333 (91)	339 (91)
Non-Ashkenazi	2 (25)	32 (9)	34 (9)
Spleen status, number (%)			
Intact	7 (63)	315 (75)	321 (75)
Partial splenectomy	0	8 (2)	8 (2)
Total splenectomy	4 (37)	96 (23)	100 (23)
Years of follow-up	*n*=11	*n*=433	*n*=443
Mean (SD)	6.7 (6.0)	3.2 (3.4)	3.3 (3.5)

Table 2

Characteristics of Gaucher disease and Parkinson's disease in 11 patients exhibiting the GD1/PD phenotype (SSI, symptom severity score; UPDRS, unified Parkinson's disease rating scale; m, male; F, female; N, no; Y, yes)

Patient	Gender	Genotype	Age at GD diagnosis (years)	Age at PD diagnosis (years)	Age at start of ERT (years)	SSI	Hermann score	Splenectomy	UPDRS score[a]
1	M	N370S/N370S	39	55	41	11	4	N	42
2	M	N370S/84GG	3	44	35	7	1	N	25
3	F	N370S/L444P	28	58	50	6	3	N	176
4	M	N370S/84GG	7	64	52	5	4	Y	33
5	M	N370S/N370S	29	40	28	11	5	Y	56
6	M	N370S/N370S	15	64	47	11	4	Y	14
7	F	N370S/L444P	69	65	73	10	5	N	56
8	M	N370S/84GG	12	44	39	10	4	Y	85
9	F	L444P/W312C	15	53	55	11	4	Y	27
10	F	N370S/N370S	56	60	66	12	5	N	28
11	M	N370S/N370S	47	58	62	5	2	N	148

[a]The UPDRS is a rating tool to follow the longitudinal course of Parkinson's disease. It is made up of (1) the mentation, behavior, and mood section; (2) activity of daily living (ADL) and (3) the motor section. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points is possible: 199 represents the worst (total) disability), 0 represents no disability

Table 3

Risk ratio of Parkinson's disease in patients with GD1 compared to that in three reference populations, adjusted by age and gender

Reference population	Observed	Expected	RR (95% CI)	*P*
Men, NY, N.Y. (Mayeux et al. 1992)	7	0.224	31.3 (12.6, 64.4)	<0.0001
Women, NY, N.Y. (Mayeux et al. 1992)	4	0.290	13.8 (3.8, 35.3)	<0.0001
Men, Ontario (Guttman et al. 2003)	7	0.636	11.0 (4.4, 22.7)	<0.0001
Women, Ontario (Guttman et al. 2003)	4	0.703	5.7 (1.6, 14.6)	<0.0001
Men, London (Schrag et al. 2000)	7	0.399	17.5 (7.1, 36.1)	<0.0001
Women, London (Schrag et al. 2000)	4	0.351	11.4 (3.1, 29.2)	<0.0001