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GBA mutations in Parkinson disease: Earlier death but similar neuropathological features

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Abstract

Background—Mutations in the glucocerebrosidase (GBA) gene are known to be a risk factor for Parkinson's disease (PD). Data on clinicopathologic correlation is limited. The purpose of this study was to determine the clinicopathological findings that might distinguish PD cases with and without mutations in the GBA gene.

Methods—Data from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), was used to identify autopsied PD cases that did or did not have a GBA gene mutation. Clinical and neuropathological data was compared.

Results—Twelve PD cases had a GBA mutation and 102 did not. The GBA mutation cases died younger (76 vs. 81 years of age) but there was no difference in disease duration or clinical exam findings. No neuropathological differences were found in total or regional semi-quantitative scores for Lewy-type synucleinopathy, senile plaques, neurofibrillary tangles, white matter rarefaction, or cerebral amyloid angiopathy scores.

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Conclusions—In longitudinally assessed, autopsied Parkinson's disease cases, those with GBA mutations had a younger age at death but there was no evidence for clinical or neuropathological differences compared to cases without GBA mutations. Due to the small GBA group size, small differences cannot be excluded.

Keywords

Parkinson's disease; GBA; genetics; neuropathology; glucocerebrosidase

INTRODUCTION

Parkinson's disease (PD) has a number of genetic associations, with mutations of the glucocerebrosidase (GBA) gene being the most common risk factor for sporadic PD. The reported prevalence is approximately 4–7%.[1–3] Additionally, it has been reported that sporadic PD cases have decreased GBA enzymatic activity in the CSF as well as in several brain regions.[4–6] Homozygous GBA mutations are implicated in Gaucher's Disease, and both heterozygous and homozygous GBA mutations have also been implicated in PD.[7] Multiple mechanisms have been proposed to explain the process by which mutations in GBA can predispose to the development of PD, but no clear link has been established.[8] Clinically PD patients who carry the GBA mutation are indistinguishable from idiopathic PD patients as regards motor examination, although they may have an earlier age of onset and an increased prevalence of non-motor symptoms,[8] including dementia and autonomic dysfunction.[9–11] Glucocerebrosidase catabolizes the sphingolipid glucosylceramide to ceramide.[12] Patients with Gaucher's Disease, without clinical signs of parkinsonism, do not have synuclein pathology in the brain.[13, 14]

Here, we report a comparison of the clinical and neuropathological findings of PD cases with and without GBA mutations.

METHODS

Subjects

Subjects enrolled from 1997–2013 in an ongoing longitudinal clinical-neuropathological study, the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), with autopsies performed by the Banner Sun Health Research Institute Brain and Body Donation Program (www.brainandbodydonationprogram.org), were included.[22]

Standard Protocol Approvals, Registrations, and Patient Consents

All subjects, or a legal representative of the individual, signed written informed consent approved by the Banner Sun Health Institutional Review Board.

Clinical Assessments

Subjects received annual standardized movement disorder examinations as previously described.[22, 23] Examinations included a full Unified Parkinson's Disease Rating Scale (UPDRS)[24] (performed in the practically-defined off state whenever possible), medication history, and neuropsychological test battery, as has previously been described.[22, 23] These

data were included if obtained within three years of the date of death with the last evaluation before death being presented. The clinical diagnosis of PD was made, as previously published,[23] if subjects had 2 of 3 cardinal features (bradykinesia, rest tremor, rigidity), no symptomatic cause, improvement when treated with dopaminergic medications and continued response if still being treated, or if lack of current response, then an explanation for why treatment was no longer working.

Neuropathological Assessments

The postmortem diagnosis of PD was made based on previously reported neuropathological criteria (evidence of substantia nigra pigmented neuron loss and the presence of Lewy bodies) together with a clinical diagnosis of parkinsonism.[22, 23] Gross and microscopic neuropathologic assessments were made by a single observer (TB) initially blinded to clinical history and clinical diagnosis. Once the neuropathologic assessments were completed clinical information was reviewed to make an appropriate clinical-neuropathologic diagnosis.[22] Paraffin sections of nine standard brain regions were stained immunohistochemically using a polyclonal antibody raised against an α-synuclein peptide fragment phosphorylated at serine 129, after epitope exposure with proteinase K, to identify Lewy-type synucleinopathy (LTS).[22, 25, 26] Histologic evaluation of the substantia nigra was performed using 40–80μm sections stained with thioflavin S and hematoxylin & eosin.[27] Substantia nigra pigmented neuron density, Alzheimer's disease histopathology, white matter rarefaction, and cerebral amyloid angiopathy (CAA) were all evaluated as previously described.[22]

Genetic Analysis

DNA was extracted from ~30mg per sample of cerebellar tissue. The tissues were lysed overnight at 56°C in a solution of ATL buffer/proteinase K/RNase A and then DNA was extracted manually using a Qiagen DNeasy kit. DNA samples were normalized and an aliquot was sent for Sanger Sequencing by Beckman Coulter Genomics (BCG) (now part of GENEWIZ). The DNA samples underwent PCR amplification at BCG to generate products containing exons 1–9, respectively. The amplification primers were designed in the flanking intronic region and tagged with M13F and M13R sequences, allowing for M13F and M13R standard sequencing primers to be used. There is 96% sequence homology between *GBA* and *GBAP1*, a pseudogene. While exons 1–9 coding sequences were divergent enough to enable design of *GBA*-specific primers (two for each exon), the regions of exons 10 and 11 were too similar to design *GBA*-specific primers that would capture the entire exon sequence. An alternate approach was used to sequence exons 10 and 11, by generating a large amplicon (547bp) that yielded product free of pseudogene contamination, and subsequently submitted the PCR products to BCG for sequencing (forward amplification primer sequence, in intron 9: AGAGCCAGGGCAGAGCCTC; reverse amplification primer sequence, downstream of the stop codon: GCAGGGCCAGTGTGAGCTTA). The sequence data was reviewed using Sequencer Project Software v4.10.1.

Statistical Analysis

Continuous variables for the GBA mutation group were compared to those without mutations by using the two-sample *t* test. Ordinal variables were compared using the Mann-

Whitney U-test and proportions were compared by using the Pearson chi-square test. The Fisher exact test was used instead of the Pearson chi-square test when the minimum expected cell count was less than five. Adjusting for age did not substantially change the results so data is not shown.

RESULTS

Demographics

A total of 114 subjects, 12 GBA positive and 102 GBA negative, met clinical and neuropathological criteria for a diagnosis of PD following autopsy, as previously described. [23] Age, gender, and disease duration at the time of death are presented in Table 1. PD cases that were GBA positive died at a younger age (75.7 ± 5.5 yrs) than non-GBA cases (80.9 ± 6.6)(p=0.01). There was a trend towards a younger age of onset of PD in the GBA positive group (Table 1), while overall PD disease duration was the same in both groups (Table 1). Specific demographics and the types of GBA mutations found are presented in Table 2.

Clinical findings

There was no difference between groups in the motor exams using either UPDRS OFF state scores for those subjects seen in the practically defined OFF state, UPDRS motor scores inclusive of all subjects even if not in the practically-defined OFF state (data not shown), or for Hoehn and Yahr stage (Table 1). Prevalence of dementia did not differ in the two groups with 10/12 (83%) GBA positive and 78/102 (76%) GBA negative cases having PD with dementia at the time of death. Separating the GBA positive cases into three with the N370S mutation and nine with other mutations did not change these findings (data not shown).

Neuropathological findings (Table 2)

There was no significant difference in the mean Unified Lewy Body Stage[27] or the total LTS score between the GBA positive and negative groups (Table 2). When individual regions were analyzed, no differences were found between groups for the olfactory bulb, limbic, brainstem, or neocortical Lewy body scores (Table 3). Similarly, there were no differences found in the total (Table 3) or regional (data not shown) plaque, tangle, cerebral amyloid angiopathy, or white matter rarefaction scores. There were 7/12 (58%) GBA positive cases that met neuropathological criteria for Alzheimer’s disease and 34/102 (33%) GBA negative cases that met AD criteria (p=0.11)(Table 2). Separating the GBA positive cases into three with the N370S mutation and nine with other mutations did not change these findings (data not shown).

DISCUSSION

These data are in agreement with previous studies[3, 10, 14, 28] suggesting that the presence of a GBA mutation in patients with PD is associated with an earlier death but not a greater severity of PD-related or comorbid neuropathology. While mean age of disease onset was 4 years earlier in the GBA mutation group, this did not reach statistical significance, and disease duration was the same in both groups. Due to the small GBA group size, however,

small group differences in clinical or neuropathological characteristics cannot be excluded. Additionally, as some GBA mutations may have more or less propensity to cause PD and possibly influence severity, data for the three cases with the N370S mutation was separated from the other mutations and there was still no difference between the groups.

There have been limited reports of pathologic findings in GBA positive PD cases. One study compared clinical findings in 33 GBA positive cases and 757 GBA negative cases.[3] GBA positive cases had an earlier age of onset and a higher male ratio. Cognitive impairment was present in 48% of their cases but there was no comparison to the non-GBA mutation group.[3] A further comparison was made of pathologic findings in 17 GBA positive PD cases with 16 GBA negative cases matched for age of onset, disease duration, and sex.[3] There was no difference in Braak PD staging with all 17 GBA cases being Braak stage 5 or 6.[3] There was also no difference in the overall Lewy body scores for cortical regions. A second study found no significant association between cortical Lewy body density and GBA mutation status after adjusting for sex, age at death, duration of PD, and presence of dementia.[28] There was also no association with AD pathology.[28] Furthermore, although lysosomal dysfunction from decreased glucocerebrosidase activity is thought to promote synuclein propagation, it is not significantly represented as pathologically different from idiopathic PD.[7] In a study of 16 GBA carriers (9 with dementia) and 16 non-carriers (8 with dementia) there was no difference in cortical Lewy body density nor in total Aβ cortical load or plaque scores, and Braak AD stage was the same.[28]

Another study has shown that GBA positive patients don't exhibit a significant pathological difference in glucosylsphingosine, sphingomyelin, gangliosides (GM2, GM3) or total cholesterol when compared to sporadic PD brains.[12] However, an increased trend in levels of gangliosides (GM2 and GM3) was proposed, albeit not significant.[7, 12] The authors of this study proposed decreases in GBA activity contributes to neuropathology by altering the lysosomal membrane properties and autophagy rather than by glucocerebroside accumulation.[12] Glucocerebrosidase has been shown to be contained within Lewy bodies, mainly in patients with mutations- 32–90% with mutations, vs. 10% without mutations.[29] However, the analyses were performed on the putamen and cerebellum only, due to insufficient tissue samples.[29] Perhaps examination of other brain areas more affected by LTS, including the cerebral cortex, amygdala, and substantia nigra, would yield different results.

The present study adds to the growing literature that the pathologic findings in GBA mutation positive PD subjects is similar as regards LTS brain load and AD pathology to GBA mutation negative PD subjects. Glucocerebrosidase activity has been found to be reduced in the caudate and substantia nigra of patients with PD.[15] Our group has recently found a reduction in the activity, and potentially the levels, of glucocerebrosidase in the putamen, cerebral cortex, and amygdala of autopsied PD cases without, and more so with, GBA mutations.[16] Glucocerebrosidase dysfunction has been implicated in various pathological processes including increased synuclein levels,[17] amyloid levels, and amyloid precursor protein accumulation.[18] Glucocerebrosidase dysfunction has also been shown to increase oxidative stress, neuronal susceptibility to metal ions, and cause microglial and immune activation.[19–21] One mouse study suggests a role for glial activation with

abnormal α-synuclein aggregation and reduced striatal dopamine release.[20] Therefore, it appears the effects of the GBA mutation on PD are likely multifactorial.

One limitation to the present study was the small number of GBA positive cases, as well as the heterogeneity of mutations, but this is similar to the previous studies cited. A strength of this study was the lack of selection bias, as GBA mutation status was determined after the autopsy and neuropathological analysis had been performed.

While larger studies of GBA positive cases are needed, to date it appears that the motor signs and the neuropathology of Parkinson's disease is not largely different in GBA positive versus GBA negative individuals.

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Table 1

Demographics and Clinical Findings

	GBA	Non-GBA	P
N	12	102	
PD Onset Age (yrs); mean (SD); range	62 (10) 44–82	66 (11) 41–90	.19
PD Disease Duration (yrs); mean (SD); range	13.6 (8.0) 2.1–29.1	14.4 (7.6) 0.8–44.5	.73
Age at Death (yrs); mean (SD); range	75.7 (5.5) 65–84	80.9 (6.6) 63–100	.01
Female; n/N (%)	5 (42%)	34 (33%)	.54
Dementia; n/N (%)	10 (83%)	78 (76%)	.73
H&Y Stage; mean (SD), N	3.8 (1.1), 11	3.4 (1.0), 94	.28
UPDRS OFF Motor Score; mean (SD), N	49 (26), 8	43 (19), 68	.40

Table 2

GBA positive cases

Case number	Gender	Age at death	Disease duration	GBA mutation	ClinicoPathologic Diagnosis*
1	M	84	2	T369M	PDD+AD***
2	M	78	8	E326K	PD*
3	F	65	8	S196P	PDD+AD***
4	M	77	9	T369M	PDD+AD***
5	M	76	9	N370S	PDD+AD***
6	M	74	10	T369M, C342	PDD+AD***
7	F	79	11	N370S	PDD+AD***
8	M	70	12	E326K	PDD**
9	F	82	19	T369M	PDD+AD***
10	M	69	20	T369M/V447E	PDD**
11	F	77	25	E326K	PD*
12	F	73	29	N370S/N370S	PDD**

*PD = PD without dementia

**PDD is PD with dementia but not concurrent AD

***PDD+AD is PD with dementia and concurrent AD

Table 3

Neuropathologic Findings.

	Gene Status		
	GBA Positive (N=12)	**GBA Negative (n=102)**	***P***
Unified LB * Stage; mean (SD), n	3.58 (0.67), 12	3.28 (0.67), 101	.14
Plaques Total (0–15); mean (SD), n	7.3 (5.5), 12	5.8 (5.4), 100	.38
Tangles Total (0–15); mean (SD), n	5.2 (3.6), 12	5.0 (2.4), 100	.82
White Matter Total (0–12); mean (SD), n	2.4 (3.3), 12	3.0 (3.0), 98	.53
Cerebral Amyloid Angiopathy Total (0–12); mean (SD), n	1.3 (1.8), 12	1.7 (2.5), 101	.61
Cerebral Infarct Volume >0; n/N (%)	4/12 (33%)	42/102 (41%)	.71
LB Total (0–40); mean (SD), n	27.4 (9.0), 11	25.2 (7.2), 88	.36
LB Olfactory bulb and track; mean (SD), n	2.9 (1.4), 11	2.8 (1.2), 99	.81
LB Cranial nerves IX, X; mean (SD), n	3.25 (0.97), 12	3.26 (0.89), 98	.99
LB Locus Coeruleus; mean (SD), n	3.08 (1.00), 12	3.24 (0.87), 99	.56
LB Substantia Nigra; mean (SD), N	2.82 (1.17), 11	2.73 (0.99), 99	.78
LB Amygdala; mean (SD), N	3.50 (1.17), 12	3.48 (0.81), 101	.92
LB Transentorhinal; mean (SD), N	3.3 (1.2), 11	2.8 (1.0), 98	.16
LB Cingulate; mean (SD), N	2.9 (1.2), 12	2.5 (1.1), 102	.20
LB Temporal cortex; mean (SD), N	2.0 (1.1), 12	1.5 (1.0), 102	.15
LB Frontal cortex; mean (SD), N	1.50 (1.17), 12	1.24 (0.88), 102	.34
LB Parietal cortex; mean (SD), N	1.50 (1.17), 12	1.22 (0.89), 102	.31

* LB (Lewy body)