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Occurrence of Amyotrophic Lateral Sclerosis in Type 1 Gaucher Disease

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Abstract

Objective

To report the association between type 1 Gaucher disease (GD1) and amyotrophic lateral sclerosis (ALS) in 3 unrelated families and to explore whether *GBA* variants influence the risk of ALS.

Methods

We conducted retrospective chart reviews of patients with GD1 or their family members diagnosed with ALS. To further investigate whether there is an association between ALS and GD, we performed exploratory analyses for the presence of *GBA* variants in 3 ALS cohorts from Toronto (Canada), Montreal (Canada), and Project MinE (international), totaling 4,653 patients with ALS and 1,832 controls.

Results

We describe 2 patients with GD1 and 1 obligate *GBA* mutation carrier (mother of GD1 patient) with ALS. We identified 0 and 8 *GBA* carriers in the Toronto and Montreal cohorts, respectively. The frequencies of *GBA* variants in patients with ALS in the Montreal and Project MinE cohorts were similar to those of Project MinE controls or Genome Aggregation Database population controls.

Conclusions

The occurrence of ALS in biallelic or monoallelic *GBA* mutation carriers described here, in addition to common pathogenic pathways shared by GD1 and ALS, suggests that *GBA* variants could influence ALS risk. However, analyses of *GBA* variants in ALS cohorts did not reveal a meaningful association. Examination of larger cohorts and neuropathologic studies will be required to elucidate whether patients with GD1 are indeed at increased risk for ALS.

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Glossary

AF = allele frequency; **ALP** = autophagy-lysosomal pathway; **ALS** = amyotrophic lateral sclerosis; **DLB** = dementia with Lewy bodies; **GD** = Gaucher disease; **GD1** = type 1 GD; **gnomAD** = Genome Aggregation Database; **LSD** = lysosomal storage disorder; **MND** = motor neuron disease; **PD** = Parkinson disease; **WES** = whole-exome sequencing; **WGS** = whole-genome sequencing.

Gaucher disease (GD) is a lysosomal storage disorder (LSD) caused by biallelic mutations in the *GBA* gene. *GBA* variants are also important risk factors for synucleinopathies, specifically Parkinson disease (PD) and dementia with Lewy bodies (DLB).[1] Of interest, other LSD-related genes have been implicated in neurodegeneration. For instance, *SMPD1* variants were recently associated with risk of PD.[2] Although multiple pathways are involved in PD pathogenesis, the main mechanism thought to underlie the association between LSD and PD is dysfunction in the autophagy-lysosomal pathway (ALP).[3]

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease (MND) that also likely results from several pathogenic mechanisms, including ALP dysfunction.[4] Recent case reports of patients diagnosed with both ALS and a LSD, such as Fabry disease or type 3 GD,[5,6] raise the possibility that common lysosomal abnormalities may underlie the co-occurrence of these disorders. The aims of this study are (1) to report the association between type 1 GD (GD1) and ALS in 3 unrelated families and (2) to explore whether *GBA* variants increase the risk of developing ALS.

Methods

Patients

Fifty-six patients with GD1 from the Mark Freedman & Judy Jacobs Program for Gaucher Disease at Mount Sinai Hospital (Toronto, Canada) underwent routine assessment by a neurologist (L.V.K.) between 2017 and 2020. One patient was diagnosed with ALS (case 1), and 1 patient had a first-degree relative with ALS (case 3). One GD1 patient with probable ALS (case 2) was identified at a medical center in Israel.

Genetic Analyses

We examined for *GBA* variants in 3 ALS cohorts: (1) 125 patients with ALS from Sunnybrook Health Sciences Centre (Toronto, Canada) who underwent whole-genome sequencing (WGS) at Genome Quebec (Montreal, Canada); (2) 162 French-Canadian patients with ALS who underwent whole-exome sequencing (WES) at the Montreal Neurological Institute (Montreal, Canada); and (3) 4,366 patients with ALS and 1,832 age- and sex-matched controls from the international Project MinE WGS data set.[7,8] Only exons 1–9 were analyzed; exons 10 and 11 were not analyzed due to similarities to the pseudo-*GBA* gene and limitations regarding reliability of WGS or WES findings in these exons. Only nonsynonymous and loss-of-function *GBA* variants were analyzed. We used the legacy glucocerebrosidase protein sequence nomenclature to describe the variants. For details, see e-Methods (links.lww.com/NXG/A428).

Standard Protocol Approvals, Registrations, and Patient Consents

Informed consent was obtained from case 1 and next of kin of case 3. Relatives of case 2 were not contactable, and thus, the case description was anonymized. Retrospective review of clinical data was conducted in accordance with the Helsinki Declaration. Informed consent for participation in the genetic study was obtained from the Toronto participants in accordance with the University of Toronto research ethics board (protocol #34754) and from the French-Canadian Montreal participants in accordance with the Montreal Neurological Institute and Hospital research ethics board (approval #2017-2740), affiliated with the McGill University Health Centre research ethics board.

Data Availability

All data relevant from case 1, case 3, and Project MinE are included in the article or uploaded as supplementary information. Anonymized data from case 2 may be shared by request from any qualified investigator.

Results

Patients

Case 1 was diagnosed with clinically probable laboratory-supported ALS. Case 2 presented with probable ALS, but ultimately developed clinically definite ALS. Case 3 was an obligate *GBA* mutation carrier who was also diagnosed with ALS. She was the mother of a patient with GD1 with PD. Clinical data and genetic investigations are described in table 1, figure e-1 and e-Results (links.lww.com/NXG/A428).

ALS Cohorts

We did not identify any patients with ALS with a *GBA* variant by WGS in the Toronto cohort. Eight patients in the French-Canadian ALS cohort were found to have one of the following *GBA* variants: E326K, T369M, N370S, and S52L (table 2). In 2 cases, there was a variant of uncertain significance in an ALS-related gene: (1) *CCNF* H69Y variant in a *GBA* T369M carrier and (2) *DCTN1* G467A variant in a *GBA* E326K carrier. The frequency of *GBA* variants in the French-Canadian ALS cohort was similar to that of European population controls in the Genome Aggregation Database (gnomAD) database. Thirty-five *GBA* variants were identified in patients with ALS or controls from the Project MinE data set and were rare (table 3). The frequency of these *GBA* variants in ALS patients was similar to that of Project MinE or gnomAD population controls.

Table 1 *GBA* Patients With ALS

	Case 1	Case 2	Case 3
Age	52	Mid-50s	70
MND signs and symptoms	Falls and muscle cramps, muscle flickering, limb weakness, and slurred speech	Dysarthria	Exhaustion, respiratory symptoms, UE and proximal LE weakness, and muscle twitches
GD diagnosis	GD1 diagnosed at age 2	GD1 diagnosed during preschool years	Daughter diagnosed with GD1
GD-related features	Splenomegaly, thrombocytopenia, fatigue, and recurrent upper respiratory infections	Hepatosplenomegaly, thrombocytopenia, life-threatening postpartum bleeding, and anemia. Secondary Ortner syndrome.	None
***GBA* gene mutation**	Compound heterozygous N370S/W378G	Compound heterozygous N370S/c.84dupG	NA (presumed obligate *GBA* carrier of N370S or P236T)
GD therapy	Velaglucerase alfa	Imiglucerase	None
Relevant family history	GD1 (sister), AD (mother), PD (father, paternal grandmother, and first maternal cousin once removed), reported DLB (paternal aunt), reported FTD (maternal uncle), and dementia (maternal aunt, maternal uncle)	None	GD1 and PD (daughter, *GBA* compound heterozygous N370S/P236T) and probable bipolar disorder (son)
Motor examination	Diffuse wasting of limb muscles. Fasciculations in the thoracic paraspinals and limb muscles. Severe weakness on foot dorsiflexion and great toe extension. Absent DTRs in the UE, 3+ at the knees, 1+ at the ankles. Extensor plantar response on the left	Weak facial and tongue muscles, questionable tongue fasciculations, and positive jaw jerk reflex. No limb atrophy. Full muscle power except for 4/5 in the deltoids. Limb hyperreflexia. Bilateral extensor plantar response	Mixed UMN and LMN findings
Other neurologic findings	Mild cognitive impairment. Moderate facial masking. Fine action hand tremor. No parkinsonism. Reduced sensation in feet	Hoarseness, dysarthria, and slowed speech	No noted parkinsonism
Neuroimaging	Brain MRI: normal. Total spine MRI: mild degenerative changes of the vertebral column. Mild diffuse atrophy of the thoracic spinal cord and conus	Brain MRI: normal. Cervical CT scan: normal	Lumbar MRI: evident wasting of the posterior paraspinal muscles. Multilevel disc degeneration. Old vertebral fractures. Mild L3-L4 spinal stenosis
NCS/EMG	Acute and chronic neurogenic changes in proximal and distal muscles of 3 limbs and in thoracic paraspinal muscles. Mild length-dependent sensory polyneuropathy	Few distal fibrillations	Consistent with typical ALS (full report not available)
ALS genetic analysis	Heterozygous c.1129C>G *SQSTM1*	NA	NA
ALS therapy	Riluzole	NA	BiPAP

Abbreviations: ALS = amyotrophic lateral sclerosis; AD = Alzheimer disease; BiPAP = Bilevel Positive Airway Pressure; DLB = dementia with Lewy bodies; DTR = deep tendon reflexes; FTD = frontotemporal dementia; GD = Gaucher disease; GD1 = Gaucher disease type 1; LE = lower extremities; LMN = lower motor neuron; MND = motor neuron disorder; NA = not available; NCS = nerve conduction study; PD = Parkinson disease; PMH = past medical history; *SQSTM1* = sequestosome 1 gene; UE = upper extremities; UMN = upper motor neuron.

The allele frequency (AF) of N370S present in case 1, case 2, and the daughter of case 3 was 0.003 in the French-Canadian cohort (similar to the AF found in European gnomAD controls) and 0.002176 in ALS Project MinE patients (similar to the AF found in ALS Project MinE controls). W378G, c.84dupG, and P236T found in case 1, case 2, and the daughter of case 3, respectively, were not present in any of the ALS cohorts.

Discussion

Although the co-occurrence of GD1 with PD and the increased risk of PD among *GBA* mutation carriers are well established, the association of GD1 with ALS is rare.[1] Of interest, 2 of 3 ALS cases reported here (1 patient with GD1 and 1 obligate *GBA* mutation carrier) have a family history of PD. Neurodegeneration in PD and ALS results from several shared mechanisms, including lysosomal dysfunction.[3,4] Furthermore, a complex overlap between parkinsonian and motor neuron syndromes has long been appreciated with parkinsonism and ALS co-occurring within families or even within an individual patient. A genetic basis may underlie some cases of parkinsonism and ALS overlap, most notably nucleotide repeats in *C9orf72* or *ATXN2*.[9,10] Rare cases with both parkinsonism and ALS have been reported with mutations in *DJ-1*,[11] *TARDBP*,[12] or *ANG*.[13]

One of the patients with ALS reported here (case 1) had GD1 due to W378G and N370S *GBA* mutations. N370S is one of

Table 2 *GBA* Variants Identified in the Montreal French-Canadian ALS Cohort

Variant	dbSNP ID	No. of carriers	AF	AF in gnomAD[a,20]
S52L		1	0.003	9×10^{-6}
E326K	rs2230288	3	0.009	0.012
T369M	rs75548401	3	0.009	0.009
N370S	rs76763715	1	0.003	0.002

Abbreviations: AF = allele frequency; ALS = amyotrophic lateral sclerosis = dbSNP = single nucleotide polymorphism database identification number; gnomAD = Genome Aggregation Database.
[a] Compared with European population controls.

the most frequent *GBA* mutations reported to be associated with increased PD risk.[1] W378G is a French-Canadian founder *GBA* mutation more recently linked to GD1 and synucleinopathies when found in compound heterozygosity with N370S.[14] Although case 1 did not have PD, there was a family history of PD and reported DLB (figure e-1, links.lww.com/NXG/A428). He was found to have a variant of uncertain significance in *SQSTM1*, but it did not segregate with the various neurodegenerative diseases in his family and therefore was not considered pathogenic. The increased risk of synucleinopathies with W378G and N370S raises the possibility of a synucleinopathy mimicking ALS in case 1 and possibly case 3. Lewy pathology can accompany typical MND pathology in patients with co-occurrence of ALS and parkinsonism[15] and sometimes in patients with ALS without clinical parkinsonism.[16] However, we did not find any definitive reports in the literature of Lewy pathology occurring in isolation (i.e., in the absence of MND pathology in both the brain and spinal cord) in patients presenting clinically with only ALS, without parkinsonian features. Yet, we cannot fully eliminate this possibility because we have no autopsy data for our patients.

Limitations of our study include the lack of neuropathologic data and lack of genetic data for ALS-related genes in 2 cases. In addition, genetic analyses only included exons 1–9 of the *GBA* gene and thus potentially excluded some *GBA* variants. This likely had a minimal effect on our results because mutations in the excluded exons in Europeans are rare.[17] Identification of complex alleles was also limited with our genotyping methods.

Our analyses of *GBA* variants among 4,653 patients with ALS and 1,832 controls did not support heterozygosity for a *GBA* variant (i.e., 1 mutant *GBA* allele) as a risk factor for ALS. In contrast, a strong association between *GBA* variants and PD was previously demonstrated in a study of 5,691 patients with PD and 4,898 controls.[18] Co-occurrence of GD1 (i.e., 2 mutant *GBA* alleles) and ALS in our reported cases could be coincidental; however, a previous report of ALS in a patient with type 3 GD [6] and the existence of common pathogenic pathways shared by GD and ALS suggest that GD could influence ALS risk. The association between GD1 and PD began with a suggestion from case reports, but definitive proof was obtained from a study of over 400 patients with GD.[19] Considering that ALS is approximately one hundred times less prevalent than PD, we expect that examination of much larger numbers of GD patients will be required to elucidate whether indeed there is a link between ALS and GD.

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Disclosure

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Table 3 *GBA* Variants Identified in Patients With ALS or Controls From the Project MinE Data Set[7,8]

Variant	ID	AF cases	AF controls	AF in gnomAD (WGS)[20]	AF in gnomAD (WES)[20]
R463P	chr1:155204986:C:G	0.0001145	0	NA	NA
D453V	chr1:155205016:T:A; rs771744004	0.0001145	0.0002729	NA	2.03282e-05
D453H	chr1:155205017:C:G; rs779958429	0.0001145	0.0002729	NA	2.03283e-05
D443N	chr1:155205047:C:T; rs75671029	0	0.0002729	0.00219709	0.000512291
K425T	chr1:155205100:T:G	0.0001145	0	NA	NA
D409H	chr1:155205518:C:G; rs1064651	0.0001145	0	0.00025895	0.000126416
R395C	chr1:155205560:G:A	0.0001145	0	NA	4.06128e-06
E388K	chr1:155205581:C:T; rs149171124	0.0005726	0.0005459	3.23039e-05	0.000178674
N370S	chr1:155205634:T:C; rs76763715	0.002176	0.002186	0.0016507	0.00232286
R359P	chr1:155206067:C:G	0.0001145	0	NA	NA
Q350H	chr1:155206093:C:G; rs761681845	0.000229	0	3.2329e-05	2.03041e-05
R329C	chr1:155206158:G:A; rs374306700	0.0001145	0	NA	1.21818e-05
E326K	chr1:155206167:C:T; rs2230288	0.01649	0.01528	0.012828	0.0106732
A269T	chr1:155207209:C:T; rs368425393	0	0	NA	2.03287e-05
T267I	chr1:155207214:G:A; rs199628072	0.0001145	0	0.000129232	5.2852e-05
R262H	chr1:155207229:C:T; rs140955685	0.0001145	0.0008188	0.000290698	8.94382e-05
F259L	chr1:155207237:G:T	0.0001145	0	NA	NA
H255Q	chr1:155207249:A:C; rs367968666	0.0003436	0	6.45995e-05	0.000239828
S237F	chr1:155207304:G:A; rs755512507	0	0.0002734	NA	8.12942e-06
F216Y	chr1:155207367:A:T; rs74500255	0	0.0002731	3.2306e-05	1.22561e-05
Y212H	chr1:155207935:A:G; rs121908300	0.0001145	0	NA	4.06062e-06
D140H	chr1:155208361:C:G; rs147138516	0.001038	0.0008228	9.72321e-05	0.000138342
R131C	chr1:155208388:G:A; rs398123530	0.0001147	0	NA	4.0658e-06
c.307+1G>T	chr1:155209676:C:A	0.0001145	0	NA	NA
T63R	chr1:155209679:G:C	0.0001145	0	NA	NA
R44C	chr1:155209737:G:A; rs1141812	0	0.0002731	6.46078e-05	8.53187e-05
R39C	chr1:155209752:G:A; rs146774384	0.0001145	0	9.69681e-05	9.34336e-05
Y22F	chr1:155209802:T:A	0.0001145	0	NA	NA
C18*	chr1:155209813:G:T	0.0001145	0	NA	NA
V15M	chr1:155209824:C:T	0	0.0002729	NA	NA
Q(-8)R	chr1:155210441:T:C	0.000229	0.0002729	NA	NA
V(-22)E	chr1:155210483:A:T	0	0.0002729	NA	NA
L(-25)S	chr1:155210492:A:G; rs1141802	0.0001145	0	6.45911e-05	3.66202e-05
K(-27)R	chr1:155210498:T:C; rs150466109	0.0001145	0.0002729	0.0224392	0.00544965
C(-29)S	chr1:155210505:A:T	0.0001145	0	NA	NA

Abbreviations: AF = allele frequency; ALS = amyotrophic lateral sclerosis; ID = variant identification; gnomAD = Genome Aggregation Database; NA = not available; WES = whole-exome sequencing; WGS = whole-genome sequencing.

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