


# The Spectrum of Movement Disorders in Childhood-onset Lysosomal Storage Diseases

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**Abstract:** Background: Movement disorders are a significant clinical problem in lysosomal storage diseases (LSD) and account for substantial morbidity. The spectrum of movement disorders in childhood-onset LSD, however, remains poorly defined.

Objectives: To define the spectrum of movement disorders in a well-characterized cohort of children with LSD.

Methods: A retrospective chart review at a single tertiary care center (Boston Children's Hospital). Patients up to the age of 18 years with a clinical, genetic, and/or biochemical diagnosis of an LSD and at least one predefined movement disorder (parkinsonism, dystonia, ataxia, tremor, chorea, myoclonus, ballism, restless leg syndrome) were included.

Results: Ninety-six patients were identified and 76 patients had a sufficiently documented biochemical and/or genetic diagnosis. Of these, 18 patients met inclusion criteria (mean age:  $10.3 \pm 5.8$  [SD] years, range: 3–18 years; 72% male). The most common LSD associated with a movement disorder was Niemann-Pick disease type C (NPC), followed by several types of neuronal ceroid lipofuscinosis (NCL), and different mucopolysaccharidoses. The most common movement disorder was ataxia followed by rest tremor, dystonia, and myoclonus. The other predefined movement disorders were rare. The majority of patients presented with more than one movement disorder. The movement disorder was slowly progressive in all patients. Brain MRI changes included diffuse cerebral volume loss, white matter abnormalities with thinning of the corpus callosum, and cerebellar atrophy.

Conclusions: Movement disorders develop in a significant number of LSD patients. Ataxia, often in patients with NPC and NCL, is the most common phenotype but significant heterogeneity exists within and between different LSD.

Lysosomal storage diseases (LSD) are a heterogeneous group of inborn errors of metabolism with a combined prevalence of about 1 in 5000 births.<sup>1,2</sup> Around 60 different LSD have been described, each sharing a genetic defect that leads to progressive substrate accumulation in many tissues, including the central nervous system. Most LSD affecting the brain are characterized by progressive neurologic dysfunction, often with onset in

childhood. Movement disorders are a significant clinical problem in LSD, accounting for a substantial part of the morbidity,<sup>3</sup> yet they remain poorly characterized. For example, generalized dystonia in certain LSD can be extremely difficult to treat and may lead to significant disability. Several types of movement disorders have been described in single case reports and smaller case series of individual disorders, mostly in adult patients.<sup>4–7</sup>

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However, systematic approaches are lacking. Clinical, genetic, and radiological features that associate with movement disorders in LSD remain poorly understood, although many LSD are recognized as genetic causes of movement disorders<sup>8</sup> and some are treatable.<sup>9</sup> Here, we systematically investigate a large and well-characterized cohort of patients with childhood-onset LSD and provide a description of associated movement disorders.

## Methods

This study was approved by the Institutional Review Board at Boston Children's Hospital (#IRB-P00023935). Patients were identified through a retrospective chart review at a single tertiary care center (Boston Children's Hospital) covering the time period from 2010 to 2017. Patients with (1) a clinical, genetic, and/or biochemical diagnosis of an LSD and (2) at least one predefined movement disorder (parkinsonism, dystonia, ataxia, tremor, chorea, myoclonus, ballism, restless leg syndrome) were included. Ninety-six patients were initially identified and 76/96 patients were found to have a sufficiently documented genetic or biochemical diagnosis (Fig. 1). In total, 18/76 patients presented with at least one of the predefined movement disorders and thus met both inclusion criteria (Fig. 1).

## Results

A detailed review of our cohort of 76 children with a sufficiently documented clinical and biochemical or genetically-confirmed diagnosis of a LSD (Fig. 1A) revealed a majority of patients with a mucopolysaccharidosis ( $n = 43$ ) followed by the neuronal ceroid lipofuscinoses (NCL,  $n = 12$ ), various sphingolipidoses ( $n = 9$ ), Niemann-Pick disease type C (NPC,  $n = 5$ ), lysosomal acid lipase deficiency ( $n = 4$ ), and various forms of oligosaccharidoses and mucolipidoses ( $n = 3$ ). This likely reflects the distribution of LSD in our pediatric population but also the referral pattern to our tertiary care center.

In this cohort, we identified a total of 18 patients from 16 pedigrees with at least one movement disorder, and thus met both inclusion criteria. Demographic and clinical data are summarized in Table 1 and Table S1. Mean age at last follow up was  $10.3 \pm 5.8$  (SD) years (range: 3–18 years; 72% male) with a mean age at diagnosis of a LSD of  $5.4 \pm 5.4$  (SD) years and a mean age at onset for the predominant movement disorder of  $6.9 \pm 4.2$  (SD) years. Two patients were deceased at the time of study completion. Most patients were of North American/European descent (50%), followed by Hispanics (22%), Arabs (17%), and other ethnic backgrounds (Table S1). No patient reported Ashkenazi Jewish ancestry. Consanguinity was reported in 6/18 patients (Table S1) and a positive family history was documented in three related cases from a single pedigree (P6, P7, P8).

The most common LSD associated with a movement disorder was NPC, followed by several types of NCL and mucopolysaccharidoses (Fig. 1B). The most common predominant movement disorder was ataxia, which was found in 12/18 patients, followed by rest tremor (6/18), dystonia (6/18), and myoclonus (6/18; Fig. 1C). The majority of patients (15/18)

presented with more than one movement disorder, commonly a combination of ataxia and either dystonia, myoclonus, or tremor. The movement disorder phenotype was slowly progressive in all patients. Brain MRI data were available for 15/18 of patients. Magnetic resonance imaging most commonly revealed diffuse cerebral volume loss (8/15) and white matter abnormalities (9/15) with thinning of the corpus callosum (5/15) as well as cerebellar atrophy (6/15). A correlation between imaging abnormalities and movement disorder severity was not readily apparent. Treatment of movement disorders was symptomatic, but 11/18 patients received treatment targeted at their LSD, including substrate-reduction therapy, enzyme replacement, allogenic stem cell transplantation, and novel treatments as part of clinical trials (Table 1). Levodopa was not systematically trialed in patients with generalized dystonia, mainly due to the predominance of ataxia (P6) and rapid disease progression in individuals with multiple neurological and medical comorbidities (P2, P6, P18).

## Niemann-Pick Disease Type C

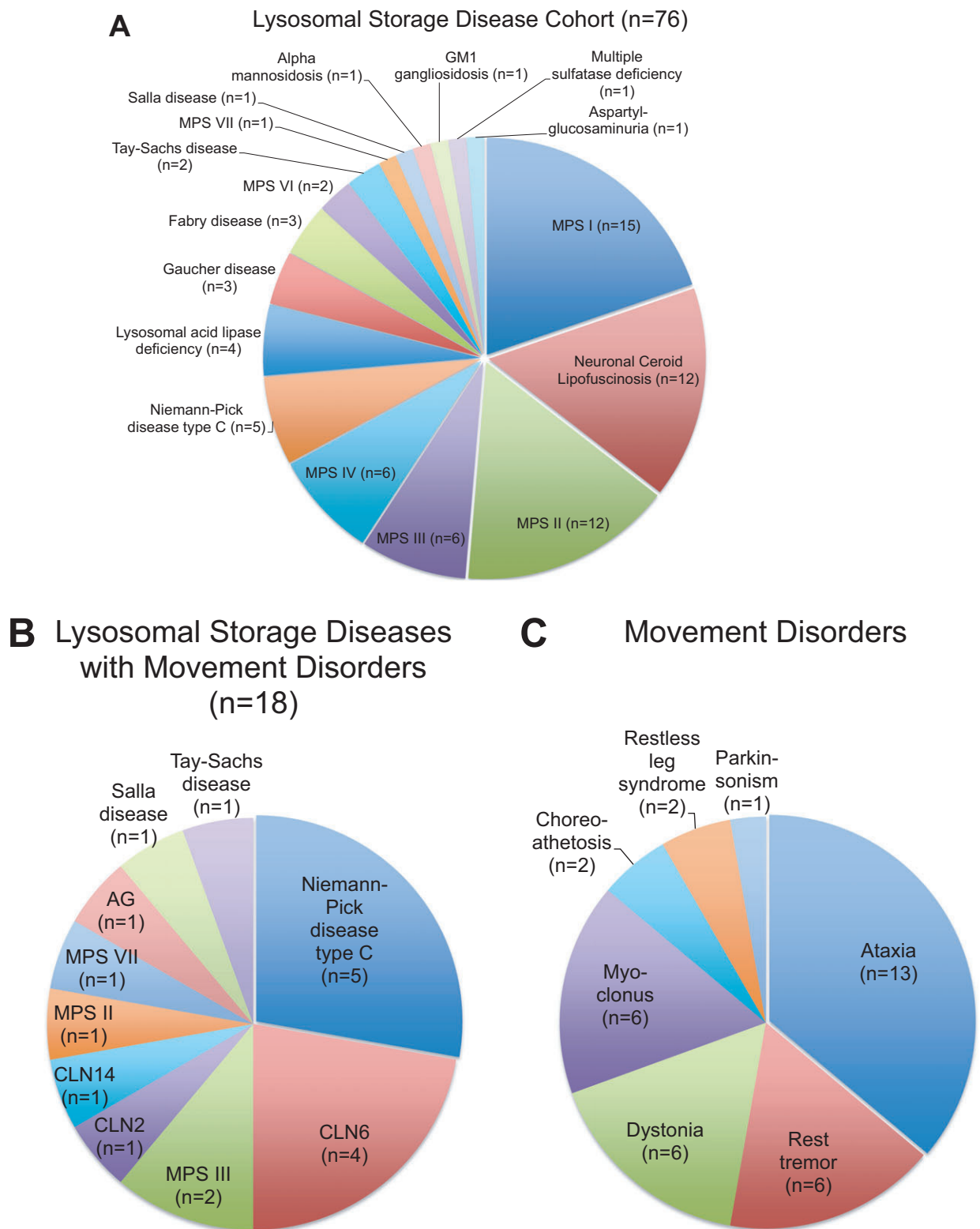
All five patients with NPC in our cohort presented with a prominent movement disorder. The predominant movement disorder was ataxia in four patients and dystonia in one (P3). Onset of the movement disorder was between 10 and 14 years of age and on a slowly progressive course. The ataxia involved the trunk and limbs, while dystonic movements were generalized and often severe. Facial and orolingual dystonia was described in one individual (P3). Gelastic cataplexy was present in two individuals (P2 and P5).

## Neuronal Ceroid Lipofuscinoses (CLN6, CLN2, CLN14)

Four patients with a molecularly confirmed diagnosis of CLN6, and a single patient with CLN2 and CLN14, with a prominent movement disorder, were identified. This included three CLN6 patients from a single consanguineous Arab pedigree (P6, P7, P8). All individuals with CLN6 presented with generalized ataxia. Rest tremor and myoclonus were found in two patients (P7 and P8). The CLN2 patient had a milder movement disorder with a prominent bilateral rest and intention tremor, while the patient with CLN14 presented with early-onset gait ataxia and myoclonus around the age of 2 years.

## Mucopolysaccharidoses (MPS-III, MPS-II, MPS-VII)

The spectrum of mucopolysaccharidoses (MPS) manifesting with movement disorders in our cohort included two individuals with MPS-III (Sanfilippo syndrome), one individual with MPS-II (Hunter syndrome), and one individual with MPS-VII (Sly syndrome). The spectrum of movement disorders was heterogeneous. Interestingly, the two individuals with MPS-III (P11 and P12) both displayed prominent choreoathetoid movements, which were otherwise rare in our study population.



**FIG. 1.** A: Distribution of different lysosomal storage diseases (LSD) in this cohort of 76 patients with a clinical, genetic and/or biochemical diagnosis of a LSD. B: Summary of 18 LSD patients who presented with at least one of the predefined movement disorders (parkinsonism, dystonia, ataxia, tremor, chorea, myoclonus, ballism, restless leg syndrome). C: Distribution of 36 movement disorders in these 18 patients. Abbreviations: AG, aspartylglycosaminuria; CLN, ceroid lipofuscinosis; MPS, mucopolysaccharidosis.

TABLE 1 Demographic, Clinical, and Genetic Characteristics

Pt./Sex	LSD	Genetic/biochemical Dx	Annotation	F/U, AoO, ADX (yr)	Treatment LSD	Main MDx (AoO)	MDx description	Brain MRI findings
P1/M	NPC	NPC1 [c.743G>T/c.3410_3411 insA]/filipin staining +	Chr18:21152107; Chr18:21115480-21115481	18/14/15	Cyclodextrin, miglustat	Ataxia (14 yr)	Dystonia (mainly b/l arms and legs), truncal and limb ataxia	Normal
P2/M <sup>a</sup>	NPC	NPC1 [c.2008_2011delTGCT/c.3565_3566insG]/filipin staining +	Patho/patho Chr18:21124246-21224249; Chr18:21114434-21114435	7/1/1	Cyclodextrin, miglustat	Ataxia (n.a.)	Dystonia (mainly b/l arms and legs), truncal and limb ataxia, gelastic cataplexy	Age 3 yr: delayed myelination, frontal lobe atrophy, thin CC, small optic nerves
P3/F	NPC	NPC1 [c.743G>T/c.3182T>C]/filipin staining +/-	Patho/patho Chr18:21140377; Chr18:21116700	18/8/16	Cyclodextrin, vorinostat	Dystonia (11 yr)	Facial/orolingual and b/l foot dystonia, akathisia, possible RLS	Age 18 yr: normal
P4/M	NPC	NPC1 [c.3182T>C/c.1319T>C]/Filipin staining +	Patho/patho Chr18:21116700; Chr18:21136250	18/10/10	Symptomatic	Ataxia (10 yr)	Dystonia (mainly b/l arms and legs), truncal and limb ataxia	n.a.
P5/M	NPC	Filipin staining +	n.a.	6/1/1	Miglustat	Ataxia (n.a)	Generalized ataxia, gelastic cataplexy	Age 6 yr: diffuse WM abnormalities
P6/M <sup>b</sup>	CLN6	CLN6 [c.793-795deITCC/c.793-795deITCC]	Likely patho Chr15:68500617-68500619	7/4/4.5	Symptomatic	Ataxia (4.5 yr)	Generalized ataxia, generalized dystonia (b/l arms and legs, trunk, neck), myoclonus	Age 5 yr: diffuse cerebral, brainstem and cerebellar atrophy, WM abnormalities
P7/F <sup>b</sup>	CLN6	CLN6 [c.793-795deITCC/c.793-795deITCC]	Likely patho Chr15:68500617-68500619	6/4/5	Symptomatic	Ataxia (5 yr)	Generalized ataxia, rest tremor, myoclonus	Age 6 yr: diffuse cerebral and cerebellar atrophy, WM abnormalities
P8/F <sup>b</sup>	CLN6	CLN6 [c.793-795deITCC/c.793-795deITCC]	Likely patho Chr15:68500617-68500619	6/4.5/4.5	Symptomatic	Ataxia (4.5 yr)	Generalized ataxia, rest tremor, myoclonus	Age 6 yr: diffuse cerebral and cerebellar atrophy, WM abnormalities
P9/M	CLN6	CLN6 [c.794_796deICCT/c.794_796deICCT]	Patho Chr15:68500618-68500620	7/2/5	Symptomatic	Ataxia (5 yr)	Generalized ataxia	Age 6 yr: diffuse cerebral and cerebellar atrophy, WM abnormalities
P10/M	CLN2	TPP1 [c.1093C>T/c.1600C>T]	Patho/patho Chr11:6637288; Chr11:6635849	6/3/3	ERT (clinical trial)	Tremor (3 yr)	B/l rest and intention tremor	Age 3 yr: normal
P11/F	MPS IIIB	MAGLU [c.192delC/alpha-N-acetylglucosaminidase activity not detectable]	Chr17:40688482	18/1/1	Symptomatic	Myoclonus (n.a.)	Generalized myoclonus, dystonia (b/l arms and legs), choreoathetosis	n.a.
P12/F	MPS III <sup>a</sup>	SGSH [c.877C>T/c.949G>C] skin biopsy +	Patho/likely patho Chr17:78185942; Chr17:78185999	13/1.5/1.5	Allogenic SCT	Tremor (n.a.)	Rest and intention tremor, choreoathetosis	Age 13 yr: diffuse WM loss, thin CC

TABLE 1 (Continued)

Pt./Sex	LSD	Genetic/biochemical DX	Annotation	F/U, AoO, ADx (yr)	Treatment LSD	Main MDX (AoO)	MDX description	Brain MRI findings
P13/M	AG	AGA [c.677G>A/c.677G>A] Low aspartylglucosaminidase activity	Patho Chr4:178357451	18/0.75/17	Symptomatic	Ataxia (n.a.)	Gait ataxia, bilateral extension tremors	n.a.
P14/M	SD	SLC17A5 [c.406>G/ c.406>G]	Patho/Likely patho Chr6:74351533	6/0.25/5	Symptomatic	Ataxia (n.a.)	Mild ataxia, b/1 intention tremor	Age 3 yr: hypomyelination, thin CC
P15/M	MPS II	IDS [c.410_411delTT/ c.410_411delTT]	Likely patho ChrX: 14854848- 14854849	8/1/1	Symptomatic	Ataxia (5.5 yr)	Progressive generalized ataxia	Age 8 yr: VM, vermis hypoplasia, basal encephaloceles
P16/M	MPS VII	Elevated GAG in urine GUSB [c.526C>T/ c.1169A>G]	Patho/VUS Chr7:65444769; Chr7:65439588	17/0.3/3	Symptomatic	Tremor (14 yr)	Rest tremor in all extremities, restless leg syndrome	Age 12 yr: diffuse WM abnormalities, thin CC
P17/M	CLN14	KCTD7 [c.334C>T/ c.334C>T]	Chr7:66103259	3/0.8/2	Symptomatic	Ataxia (2 yr)	Gait ataxia, myoclonus	Normal
P18/M	TSD	HEXA [c.533G>A/ c.1073+1G>A]	Patho/patho Chr15:72645446; Chr15:72640388	4/1.5/3	Miglustat	Parkinsonism (2.5 yr)	Parkinsonism with bradykinesia, hypomimia, hypophonia, tremor, postural instability, retropulsion. Gait ataxia, stimulus- induced myoclonus	Age 2.5 yr: mild diffuse WM loss, thin CC, PVL, diffusely abnormal cerebellar cortex

Variant classification according to ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar>; Single nucleotide variants of P1, P11, and P17 are not classified) or reporting laboratory (P12). Genomic location is shown according to on Assembly GRCh37. The movement disorder in all patients was described as slowly progressive with the exception of P18 who showed non-progressive parkinsonism but slowly progressive ataxia and myoclonus.

<sup>a</sup>Deceased.

<sup>b</sup>First-degree cousins.

Abbreviations: ADx, age at diagnosis; AoO, age at onset; AG, aspartylglucosaminuria; CC, corpus callosum; Dx, diagnosis; ERT, enzyme replacement therapy; F, female; F/U, follow up; GAG, glycosaminoglycans; LSD, lysosomal storage disease; M, male; MDX, movement disorder; MPS, mucopolysaccharidosis; NCL, neuronal ceroid lipofuscinosis; NPC, Niemann-Pick Type C disease; patho, pathogenic; PVL, periventricular leukomalacia; SCT, stem cell transplantation; SD, Salla disease; TSD, Tay-Sachs disease; VM, ventriculomegaly; VUS, variant of unknown significance; WM, white matter; yr, years.

## Other Lysosomal Storage Diseases

Other LSD that presented with movement disorders included an 18-year-old boy with aspartylglucosaminuria who presented with ataxia and intention tremors around 17 years of age (P13), a 6-year-old boy with Salla disease who developed mild ataxia with bilateral intention tremors (P14), and a 4-year-old boy with Tay-Sachs disease (P18) who presented with gait ataxia, myoclonus, and parkinsonism manifesting with bradykinesia, hypomimia, hypophonia, rest tremors, and postural instability with prominent retropulsion (Video S1).

## Discussion

With exciting new genetic and clinical links between LSD and adult-onset neurodegenerative diseases such as sporadic Parkinson's disease,<sup>10,11</sup> it is imperative to systematically define the spectrum of movement disorders in childhood-onset LSD. Here we systematically investigated the presence of movement disorders in a large cohort of children with genetically or biochemically confirmed LSD. Limitations of our study include its retrospective nature and the design as a single center study with a potential referral bias. We identified a total of 18 patients covering a wide spectrum of LSD, including NPC, several forms of NCL, and mucopolysaccharidoses as well as individual cases of aspartylglucosaminuria, Salla disease, and Tay-Sachs disease. Although the phenotypic spectrum for these disorders has been characterized, the spectrum of movement disorders has not been clearly defined in most. NPC is a very heterogeneous disorder both with regards to age of onset and clinical manifestations. Ataxia is a recognized manifestation, particularly in adult cases,<sup>6,12,13</sup> and was also common in our cohort. Dystonia was found in 4/5 of our pediatric and adolescent patients and was thus more frequent compared to previously published cohorts of older adolescent and adult patients.<sup>6,13</sup> Myoclonus has been reported as a variable manifestation in juvenile and adult cases, but was not prevalent in our pediatric cases. It is important to recognize that movement disorders, although not a presenting symptom in our patients, are among the most frequent initial symptoms, particularly in adolescents and adults, where a combination of two or more movement disorders, or a combination of psychiatric symptoms and movement disorders, should raise suspicion for NPC or other less common LSD, such as Tay-Sachs disease.<sup>14</sup> CLN6, a "variant" late infantile-onset form of NCL, is characterized by developmental delay and regression, vision loss, seizures, myoclonus, as well as cerebellar dysfunction with ataxia and dysarthria.<sup>15</sup> This was replicated in our four patients who developed a generalized ataxia around the age of 3 to 4 years. Myoclonus and tremor were also present in the majority of patients, consistent with published case reports.<sup>15</sup> CLN2, the classic late-infantile onset form, is characterized by rapid neurological decline with seizures, vision loss, and motor decline.<sup>16</sup> Prominent truncal and peripheral ataxia can be

initial symptoms. In our patient, movement disorders were more subtle and consisted of rest and cerebellar tremors. The mucopolysaccharidoses cause a wide spectrum of neurological dysfunction, but movement disorders have not been clearly defined. Our cohort revealed two patients with MPS-III, including an 18-year-old young woman with MPS-IIIb, who manifested with generalized myoclonus, dystonia, and choreoathetosis and a 13-year-old girl with rest and intention tremors and choreoathetoid movements. To our knowledge, our accounts of movement disorders in patients with MPS-II, MPS-VII, aspartylglucosaminuria, and Salla disease are the first in literature. Parkinsonism has been described in adult-onset cases of GM2 gangliosidosis<sup>17,18</sup> and dystonia has been documented in juvenile-onset cases.<sup>7,19</sup> However, in our cohort, we identified a 4-year-old boy with genetically confirmed Tay-Sachs disease who presented with a peculiar picture of parkinsonism with prominent postural instability and retropulsion (Video S1). This is, to our knowledge, the first description of parkinsonism in a child with Tay-Sachs disease.

In summary, our study reveals the presence of movement disorders in a significant portion of LSD patients. Ataxia is the most common phenotype, signifying a common cerebellar involvement in LSD, followed by tremors, dystonia, and myoclonus. Significant heterogeneity exists within and between different LSD. Additional longitudinal studies with larger sample sizes are needed to further delineate the genetic and imaging characteristics associated with movement disorders in LSD. With emerging treatments for LSD and an expanding array of therapies available to treat movement disorders, understanding the spectrum and clinical challenges of movement disorders in LSD will help guide clinical management and benefit patients.

## Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

D.E.-F.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

C.H.: 1B, 1C, 2B, 2C, 3B

P.E.D.: 1C, 2C, 3B

L.H.R.: 1C, 2C, 3B

I.A.: 1C, 2C, 3B

O.B.: 1A, 1B, 1C, 2A, 2B, 2C, 3B

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## Supporting Information

A video accompanying this article is available in the supporting information here.

**Table S1.** Detailed demographic, clinical and genetic characteristics of 18 patients with a lysosomal storage disease and movement disorder

**Video S1.** Patient #18 with Tay-Sachs disease. Examined at age 31 months. The patient is showing features of parkinsonism with bradykinesia, hypomimia, hypophonia, tremor, postural instability, and prominent retropulsion. Gait ataxia and stimulus-induced myoclonus developed later and are not shown here.