Adults with lysosomal storage diseases in the undiagnosed diseases network

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Abstract
Objectives: To review the referral and clinical characteristics of adult patients diagnosed with lysosomal storage diseases (LSD) through the Undiagnosed Diseases Network (UDN).

Methods: Retrospective review of both application and evaluation records for adults admitted to the UDN with a final diagnosis of a lysosomal storage disease.

Results: Ten patients were identified. Final diagnoses included late onset Tay Sachs, attenuated MPS I, MPS IIIA, MPS IIIB, and MPS IIIC. Most patients presented with neurocognitive changes. Prior to referral, all patients had been evaluated by neurology, four patients underwent phenotype specific panel testing that did not include the causative gene, and four patients had non-diagnostic clinical exome sequencing.

Conclusions: LSDs figure highly in the differential diagnosis of neurometabolic disorders in pediatric onset progressive diseases. In adults, their subtle initial presentations overlap with symptoms of more common disorders and less practitioner awareness may lead to prolonged diagnostic challenges.

KEYWORDS
adult metabolic medicine, Late Onset Tay Sachs, lysosomal storage disorders, MPS I, MPS III

1 | INTRODUCTION

Lysosomal storage diseases (LSD) represent a group of heterogeneous disorders defined by abnormal intracellular accumulation of substrate in various tissues due to the deficiency of specific lysosomal enzymes. Over 50 LSDs have been described, most as pediatric-onset, progressive multisystemic diseases with phenotypes dependent on the nature and location of the accumulated substrate and amount of residual enzyme activity. Most LSDs are associated with neurological manifestations including developmental delay, neurodegeneration, epilepsy, motor-neuronopathy, neuropathy, cerebrovascular events, or movement disorders; though findings such as visceromegaly, ophthalmologic, or skeletal pathology are also common (Pastores & Maegawa, 2013). While individually rare, the incidence of LSDs in the general population is about 1:5000 (Platt et al., 2018). Late-onset forms of some LSDs such as Gaucher disease (MIM 230800), Fabry disease (MIM 301500), Tay-Sachs (MIM 272800), and many of the mucopolysaccharidoses (MPS) are well described and increasingly recognized (Platt et al., 2018). Adults with these conditions often...
have milder organ involvement with slower progression, such as the case with the mucopolysaccharidosis, or can present in a way that mimics other adult-onset conditions, such as the case with late-onset Tay-Sachs. The true incidence and profile of LSDs in adults is not known, though patients affected are often underdiagnosed or misdiagnosed with a mean delay of almost 15 years from symptom onset to diagnosis (Pérez-López et al., 2017). Potential reasons for the diagnostic delay in this group include poor characterization of possible disease phenotypes, milder manifestations of symptoms that may mimic common conditions or delay patients seeking medical attention, and poor awareness of LSDs among adult providers.

The Undiagnosed Disease Program, later expanded to the Undiagnosed Diseases Network (UDN) was created in 2008 to take an integrated clinical and genomic approach in evaluating patients with unexplained diseases (Gahl et al., 2012). Applications are reviewed by experts with the goal of identifying patients with no diagnosis despite comprehensive workup, objective findings, novel presentations, or are likely to generate new knowledge about disease pathogenesis. To date, over 1400 patients have been evaluated of which around half were adults and one-third received a diagnosis. Since patient referrals occur after comprehensive evaluations at tertiary care facilities, we hypothesized that the characterization of adults diagnosed with LSDs through the UDN could illustrate limitations and pitfalls explaining the delay in LSD diagnosis.

2 | METHODS

We retrospectively queried UDN sites for applicants over 18 years of age at the time of application who received a final diagnosis of an LSD. Medical history, referral indication, prior medical evaluations and testing were reviewed. All subjects were enrolled on protocol 76-HG-0238 or 15-HG-1030, both approved by the designated and previously published IRB (Splinter et al., 2018). Molecular diagnoses were achieved by genomic analysis or re-analysis of prior clinical testing and independent confirmation by enzyme activity levels. Details for the UDN genomic analysis pipeline were previously published (MacNamara et al., 2019).

The medical records of accepted patients were reviewed by a multi-disciplinary group of experts. If a specific diagnosis is suspected, targeted genetic, biochemical, and clinical evaluations were performed. If a diagnosis is not reached or no specific genetic diagnosis is suspected, patients received an agnostic evaluation that included genomic testing.

Variant annotations were in reference to NM_000520.5 (HEXA), NM_000203 (IDUA), NM_152419 (HGSNAT), NM_000263.4 (NAGLU), and NM_000199.5 (SGSH).

3 | RESULTS

Ten adults were diagnosed with an LSD by the UDN through May 2020 (Table 1). The age at symptom onset ranged from 6 to 36 years while the age at diagnosis ranged from 25 to 41 years with a mean gap of 23 years between symptom onset and diagnosis. Five individuals were referred by neurology, four by medical genetics, and one by pediatric neurology at age 39. The most common reason for referral was cognitive decline (Table 1). By the time of referral, records contained an average of seven medical specialist evaluations representing 20 subspecialties. All participants were evaluated by adult neurologists prior to referral (Table 2) to the UDN and nine had primarily neurological symptoms. All patients had at least one genetic test performed prior to referral, including 6 karyotypes, 7 gene panels, 4 exomes, and 3 microarrays. Neuroimaging, enzyme analysis, and molecular data on all individual participants appear in Table 1.

4 | CASES

Patient 1 presented with progressive ataxia and weakness as a teenager. She saw multiple neurologists for muscle atrophy, fasciculations, and hyporeflexia consistent with lower motor neuron disease, eventually receiving a clinical diagnosis of Spinal muscular atrophy (SMA) after negative SMN testing. Her brain MRI demonstrated cerebellar atrophy. She was referred to the UDN as a case of unusual SMA, however upon reviewing her imaging late onset Tay-Sachs was suspected due to the combination of cerebellar atrophy and lower motor neuronopathy. β-hexosaminidase A enzyme activity was low and HEXA (MIM 606869) sequencing confirmed the diagnosis.

Patient 2 had progressive arthralgias in her teens and was diagnosed with sero-negative rheumatoid arthritis. She developed bilateral carpal tunnel syndrome and progressive aortic valve stenosis in her 20s, at which time exome sequencing (ES) was non-diagnostic. Brain MRI demonstrated prominent perivascular spaces interpreted as normal variation (Figure 1). Upon evaluation by the UDN, subclinical cataracts were discovered which, together with dilated perivascular spaces, suggested a MPS. After decreased alpha-L-iduronidase enzyme activity was found, reanalysis of her ES data uncovered one IDUA (MIM 252800) pathogenic variant which was previously not reported since only one variant was found for a recessive disease that was thought to be a poor fit for the patient’s phenotype. However, the second allele was poorly covered and a second pathogenic variant was identified after sequencing of the entire IDUA gene. After diagnosis, this patient was placed on enzyme-replace therapy with
| Case # | Race | Gender | Age at symptom onset | Age at diagnosis | Referring specialist | Referring reason | Pre-referral diagnoses | Final diagnosis | Molecular results | Molecular test | Enzyme testing | Neuro imaging | Pre-referral genetic testing workup |
|--------|------|--------|----------------------|-----------------|---------------------|------------------|---------------------|-----------------|-----------------|----------------|--------------|-------------|-------------------|
| 1      | White| Female | "Teens"              | 33              | Neurology           | SMA with cerebellar atrophy | Depression, anxiety, SMA | Late-onset Tay Sachs | HEXA c.805G > A, p.G269S and c.1274_1277dupTAAC, p.V427E*5 | HEXA Sequencing | Urine oligosaccharide and glycan screen - MALDI-TOF/TOF, GM2 m/z 1083. Lysosomal enzyme panel HexA 7.9 nmol/mg protein/hr (normal 37.4-242.7) | Cerebellar atrophy | SMA panel |
| 2      | Black| Female | 8                    | 41              | Medical Genetics    | Connective tissue abnormality | Connective tissue disease, seronegative rheumatoid arthritis, aortic stenosis, carpel tunnel syndrome | MPS I           | IDUA c.1499A > G, p.Q500R and c.876delC, p.D292Efs*25 | Exome reanalysis after Phenotyping | Urine Quantitative Macropolyasaccharide: 31.2 mg/mmol Cr (< 6.5), Leukocyte a-Ioduronidase 0.5 nmol/mg protein/hr (3.57-21.4) | Prominent Virchow-Robin paces | Exome, connective tissue panel |
| 3      | White| Female | 7                    | 36              | Medical Genetics    | ID, RP                | Dementia, RP, ADHD, neuronal ceroid lipofuscinosis, depression | MPS IIIC        | HGSNAT c.1300C > T, p.R444C and Intron 4 c.493+809T>C | Targeted testing after sibling's result | Fibroblast acetylCoA Glucosamine N acetylly Transferase (type C) testing low 1.78nmol/17hr/mg (normal 6.5-170.1) | Diffuse volume loss | Exome, SNP array, comprehensive eye disease panel |
| 4      | White| Male   | 7                    | 29              | Medical Genetics    | ID                   | Central auditory processing disorder, depression, ADHD | MPS IIIC        | HGSNAT c.1300C > T, p.R444C and Intron 4 c.493+809T>C | Exome reanalysis after RNA Sequencing | Fibroblast acetylCoA Glucosamine N acetylly Transferase (type C) testing low 1.43nmol/17hr/mg (normal 6.5-170.1) | Diffuse volume loss, increased brain iron accumulation | Exome, karyotype, subtelomeric FISH |
| 5      | White| Female | 7                    | 25              | Neurology           | Young onset dementia | ADHD, Soto syndrome, oppositional defiant disorder, pervasive developmental disorder, ID | MPS IIIB        | NAGLU c.1946G > T, p.W649H and c.1949G > A, p.G650E | Exome, brain iron accumulation panel | a-N-acetylgalactosaminidase 0.1 mm/mg/H (control 1.10) | Cerebral atrophy, periventricular white matter changes, increased brain iron accumulation | Karyotype |
| 6      | White| Female | 6                    | 29              | Neurology           | Young onset dementia | ASD, bipolar disorder, ADHD | MPS IIIB        | NAGLU c.1946G > T, p.W649H and c.1949G > A, p.G650E | Targeted testing after sibling's result | a-N-acetylgalactosaminidase 0.2 mm/mg/H (control 1.10) | Diffuse volume loss, periventricular white matter changes, increased brain iron accumulation | Karyotype and Fragile X |
| 7      | White| Male   | 25                   | 30              | Medical Genetics    | ASD, RP, Young onset dementia | ASD, ID, RP, epilepsy, mood disorder, ADHD, anxiety disorder, intermittent explosive disorder | MPS IIIB        | NAGLU c.19135G > T, p.E639K and c.1834A > G, p.S612G | Exome | Plasma for N-acetyl alpha glucosaminidase (type B) showed low level in affected range (1.3), urine MPS analysis showed elevated GAGs (1.30) with elevated heparan sulfate (1.13) | Diffuse volume loss | Karyotype, SNP array, Fragile X, retinitis pigmentosa panel, mtDNA sequencing |
| 8      | White| Female | "Childhood"          | 41              | Neurology           | Young onset dementia | Intellectual disability, epilepsy, young onset dementia, apraxia | MPS IIIA        | SGSH c.892T>C, p.S298P homozygous | Exome reanalysis after chart review | NA | Diffuse volume loss | Neurodegeneration panel, exome |

(Continues)
the goal of slowing progression of valvular and corneal involvement.

Patients 3 and 4 (brother/sister pair) presented with developmental arrest in late childhood, during which they initially received psychiatric diagnosis including major depressive disorder, attention deficit and hyperactivity disorder (ADHD), and auditory processing disorder. Retinal changes were noted during their teenage years around which time they had developmental regression, leading to a clinical diagnosis of neuronal ceroid lipofuscinosis. A genetic retinopathy panel and ES were non-diagnostic.

After referral for familial progressive intellectual disability and retinopathy, research RNA sequencing for early-onset dementia genes revealed under-expression of HGSNAT (MIM 610452). On our reanalysis of the exome data, bi-allelic pathogenic variants were found confirming MPS IIIC (MIM 252930).

Patients 5 and 6 (sister pair) presented with behavioral issues in childhood. Both received a sequence of psychiatric diagnoses including ADHD, autism spectrum disorder, bipolar disorder, pervasive developmental disorder, and oppositional defiant disorder until cognitive decline was noted in their late teens; this led to their referral from psychiatry to behavioral neurology. They were referred to the UDN for early onset dementia after they were unable to obtain genetic testing aside from a karyotype and Fragile X testing. During our evaluation, patient 6 was noted to have hepatomegaly and subsequent screening of LSD enzymatic activity showed deficient α-N-acetylglucosaminidase activity. Compound heterozygous variants in NAGLU (MIM 609701) confirmed the diagnosis of MPS IIIB (MIM 252920) and the same variants were identified in patient 5.

Patient 7 was diagnosed with mild autism spectrum disorder in childhood that was thought to be stable. Genetic testing in childhood included a normal karyotype, SNP array, and Fragile X testing. At age 25 he developed behavioral changes which led to the diagnosis of ADHD, anxiety, and intermittent explosive disorder. Further evaluation at this time noted pigmented retinopathy and genetic testing including mtDNA evaluation and a retinitis pigmentosa panel were non-diagnostic. He was referred for a syndrome of autism with retinopathy and possible cognitive decline. ES identified compound heterozygous pathogenic variants in NAGLU. Follow-up testing, including decreased α-N-acetylglucosaminidase activity and elevated urine heparan sulfate confirmed a diagnosis of MPS IIIB.

Patient 8 had mild intellectual disability noted in childhood but genetic evaluation for an underlying cause was not pursued until behavioral changes, seizures, and cognitive decline in her late 20s prompted her family to seek neurological evaluation. A commercial
### TABLE 2  Pre-referral specialist evaluations

| Specialista | Total | Case 1 (late onset Tay-Sachs) | Case 2 (MPSI) | Case 3 (MPSIIIC) | Case 4 (MPSIIIC) | Case 5 (MPSIIIB) | Case 6 (MPSIIIB) | Case 7 (MPSIIIB) | Case 8 (MPSIHA) | Case 9 (MPSIIIC) | Case 10 (MPSIIIA) |
|-------------|-------|--------------------------------|----------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Neurology   | 18    | 2                              | 2              | 1                | 1                | 1                | 1                | 1                | 3                | 3                | 1                |
| Medical Genetics | 11    | 2                              | 1              | 1                | 1                | 1                | 1                | 2                | 3                | 3                | 1                |
| Ophthalmology | 7     | 1                              | 1              | 1                | 1                | 1                | 1                | 4                | 1                | 1                | 1                |
| Orthopedics | 4     | 1                              | 2              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Child Neurology | 4    | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Child Psychiatry | 4    | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Psychiatry  | 3     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Developmental Pediatrics | 3    | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| ENT         | 3     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Cardiology  | 2     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Neurosurgery | 2    | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| GI          | 2     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Pulmonology | 1     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Dermatology | 1     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Endocrine   | 1     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Rheumatology | 1    | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Sleep       | 1     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Urology     | 1     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Pain        | 1     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |
| Physiatry   | 1     | 1                              | 1              | 1                | 1                | 1                | 1                | 1                | 1                | 1                | 1                |

*a Based on specialists notes in UDN application records.*
neurodegeneration panel followed by ES was non-diagnostic, prompting referral to the UDN. Reanalysis by our research genomics pipeline identified homozygous pathogenic variants in \textit{SGSH} (MIM 605270) consistent with MPS IIIA (MIM 252900).

Patient 9 had developmental delay noted at age 2 and had learning issues throughout grade school. He was diagnosed in childhood with depression, anxiety, and ADHD and did not receive genetic evaluation at that time. Progressive cognitive decline at age 24 triggered neurological evaluation notable for cerebral atrophy, orofacial dyskinesia, shuffling gait, apraxia, and aphasia. This prompted further workup including Fragile X testing and biochemical screening that were negative. Referral to the UDN was made for young onset neurodegeneration. ES done as part of UDNI intake showed bi-allelic pathogenic variants in \textit{HGSNAT} consistent with MPS IIIC.

Patient 10 was noted to have developmental delay at age 2 along with dysmorphic features (prominent supraorbital ridges, wide nasal bridge, prominent forehead, fleshy earlobes, thick lips and eyebrows, and a high-arched palate) reminiscent of Aarskog syndrome. At that time genetic evaluation including microarray, karyotype, \textit{PTEN}, and \textit{FGD1} sequencing were non-diagnostic. He developed mild hepatomegaly at age 4 at which time evaluation for a glycogen storage disorder was also negative. Evaluation was re-initiated at age 24 after loss of language skills and new urinary incontinence, at which time he was referred for nonspecific dysmorphic features and cognitive decline. UDN evaluation was notable for joint contractures, coarse facial features, hearing loss, and diffuse skeletal dysplasia. Genome sequencing identified bi-allelic pathogenic variants in \textit{SGSH} and follow-up leukocyte enzyme testing showing deficient heparan-N-sulfatase activity confirmed the diagnosis of MPS IIIA.

**FIGURE 1** Brain MRIs in select patients. Arrows used to indicate notable pathological findings. (a) Sagittal (top) and Coronal (middle) T1 weighted images for patient 1 with late-onset Tay Sachs demonstrating prominent cerebellar atrophy and mild cerebral atrophy. Sagittal T1 image with normal cerebellum anatomy (bottom) added for comparison. (b) Axial T2 weighted images for patient 2 with MPSI show perivascular spaces throughout the basal ganglia (top left, top right), thalamus (top right), midbrain (middle left), pons and cerebellum (middle right). Axial T2 images with normal basal ganglia and cerebellum anatomy (bottom left and right) added for comparison. (c) Gradient Echo images for patient 5 with MPS IIIB show symmetrical iron deposition in the globus pallidus and putamen (top) along with thalamus, substantia nigra, and red nucleus (middle). Representative of findings in cases 4, 5, and 6. Normal gradient echo image (bottom) for comparison. (d) Sagittal (top) and Coronal (middle) T1 weighted images for patient 3 with MPS IIIC demonstrating mild cerebellar atrophy and severe cerebral atrophy. Representative of findings in cases 3, 7, and 10. T1 coronal image with normal brain volume (bottom) for comparison.
Ten adult participants received a diagnosis of an LSD through the UDN. Nine endorsed symptom onset in childhood but they either did not seek medical attention due to their initial mild nature or sought medical attention but presented in a nonspecific fashion that mimicked common diagnoses. While some LSDs are known to be more prevalent in specific ethnic groups, we have no evidence this was a factor in our cohort and the predominance of white patients likely reflect referral biases.

Prior to UDN referral patients were evaluated by providers representing 17 subspecialties. Nine of ten patients had a neurological phenotype and all patients were evaluated by a neurologist or child neurologist during the course of their diagnostic odyssey (Table 1). Of the 8 patients who received a diagnosis of MPS III, seven received at least one psychiatric diagnosis and most were primarily followed by psychiatry early in their disease course. These findings suggest MPS III patients may be underrecognized and diagnosed with common psychiatric illnesses such as ADHD early in their disease course. Also, neurologists in particular should consider MPS III in patients with early-onset dementia and prior psychiatric diagnosis.

Prior to referral, 7/10 patients had molecular genetic testing via phenotype-specific gene panel or ES. Seven gene panels targeting various aspects of the clinical presentation such as neurodegeneration, retinitis pigmentosa, hepatomegaly, or motor neuron disease for 4 patients were performed but failed to provide a diagnosis because the disease-causing gene was not part of the panel. This is consistent with prior studies suggesting some phenotype specific panels have low diagnostic yield for patients with multisystemic disease in the absence of a clinically recognizable syndrome (Jiman et al., 2020). These findings underscore the limited negative predictive value of genetic and genomic tests.

Four patients, including one sibship, had ES interpreted as non-diagnostic prior to referral. In three of these four cases, biallelic causative variants were identified on reanalysis after other data pointed to a specific genetic diagnosis. For the sibling-pair cases 3 and 4, reanalysis was driven by RNA-seq data that was confirmed by enzyme analysis. In case 8 chart review refined the phenotype as young-onset dementia which led to a previously unreported output. For case 2, after the patient's phenotypic description was changed from connective tissue disease to MPS based on clinical and biochemical data, one pathogenic variant was identified on reanalysis while the second was inadequately covered, leading to the discovery of a second variant on targeted sequencing. These findings underscore the importance of clinical and biochemical context in the filtering and interpretation of genomic tests and the need for reanalysis when new data or phenotypic findings emerge. Since MPSs can be readily screened for via urine glycosaminoglycan testing and LSD enzyme panels are commercially available, these tests should be considered for patients with unexplained early onset dementia, progressive neuropsychiatric symptoms, or multisystemic disease.

Cranial MRI findings were consistent with previous studies. MRIs in the patient with MPS I revealed extensive and prominent perivascular spaces which often represent normal variation but are a feature of MPS. The majority of patients with MPS III had white matter changes or diffuse atrophy consistent with prior literature (Reichert et al., 2016). Patients 5 and 6, with MPS IIIB had brain iron accumulation as previously published (Brady et al., 2013).

In conclusion, we report 10 individuals diagnosed with LSDs in adulthood following long diagnostic odysseys. Since our cohort is not a representative section of the general population, we are unable to draw inferences about the prevalence of these conditions. However, the presence of these rare diseases, especially MPS III, in our study suggest affected patients are likely being underdiagnosed. Increased awareness and broader testing, especially in neurobehavior clinics can likely lead to earlier LSD diagnosis. In addition to reducing hardship and costs to patients and families an early diagnosis facilitates better care and proper genetic counseling. While disease-targeted therapy was only available for one patient with MPS I in our cohort, therapies for late-onset Tay Sachs and MPS III are active areas of investigation. Considering the progressive nature of LSDs early recognition will likely become imperative to achieving optimal outcomes in the future.

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CONFLICT OF INTEREST

Changrui Xiao declares that he has no conflicts of interest. Heidi Cope declares that she has no conflicts of interest.
Rebecca Spillman declares that she has no conflicts of interest. Khoon Tan declares that she has no conflicts of interest. Fuki M. Hisama declares that she has no conflicts of interest. Cynthia J. Tifft declares that she has no conflicts of interest. Camilo Toro declares that he has no conflicts of interest.

ETHICS STATEMENT
All subjects were enrolled on protocol 76-HG-0238 or 15-HG-1030, both approved by the designated and previously published IRB (Splinter et al., 2018). Written informed consent was obtained from all participants or their guardians.

DATA AVAILABILITY STATEMENT
Data available by request due to privacy/ethical considerations.

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