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Complex care of individuals with Multiple Sulfatase Deficiency: clinical cases and consensus statement

Rebecca Ahrens-Nicklas[1,*], **Lars Schlotawa**[2,*], **Andrea Ballabio**[3], **Nicola Brunetti-Pierri**[3,4], **Mauricio De Castro**[5], **Thomas Dierks**[6], **Florian Eichler**[7], **Can Ficicioglu**[1], **Alan Finglas**[8], **Jutta Gaertner**[9], **Brian Kirmse**[10], **Joerg Klepper**[11], **Marcus Lee**[12], **Amber Olsen**[13], **Giancarlo Parenti**[3,4], **Arastoo Vossough**[14], **Adeline Vanderver**[15], **Laura A. Adang**[15]

[1]Division of Human Genetics and Metabolism, Children's Hospital of Philadelphia, Philadelphia, PA, USA [2]Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK [3]Telethon Institute of Genetics and Medicine, Pozzuoli, Italy [4]Department of Translational Medicine, Federico II University of Naples, Italy [5]United States Air Force Medical Genetics Center, 81st Medical Group, Keesler AFB, MS, USA [6]Faculty of Chemistry, Biochemistry I, Bielefeld University, Bielefeld, Germany [7]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA [8]MSD Action Foundation, Dublin, Ireland [9]Department of Pediatrics and Adolescent Medicine, University Medical Center Göttingen, Germany [10]Department of Pediatrics, Genetic and Metabolism, University of Mississippi Medical Center, USA [11]Department of Pediatrics and Neuropediatrics, Children's Hospital, Klinikum Aschaffenburg-Alzenau, Germany [12]Division of Pediatric Neurology, Children's of Mississippi, University of Mississippi Medical Center, Biloxi, Mississippi, USA [13]United MSD Foundation [14]Division of Neuroradiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA [15]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Abstract

Multiple sulfatase deficiency (MSD) is an ultra-rare neurodegenerative disorder that results in defective sulfatase post-translational modification. Sulfatases in the body are activated by a unique protein, formylglycine-generating enzyme (FGE) that is encoded by *SUMF1*. When FGE is absent or insufficient, all 17 known human sulfatases are affected, including the enzymes associated with metachromatic leukodystrophy (MLD), several mucopolysaccharidoses (MPS II, IIIA, IIID, IVA,

Corresponding Authors: Name: Rebecca Ahrens-Nicklas, ahrensnicklasr@email.chop.edu, Address: Children's Hospital of Philadelphia, Abramson Research Center, 3401 Civic Center Boulevard; Philadelphia, PA 19104, Name: Lars Schlotawa, ls682@cam.ac.uk, Current Address: Cambridge Institute for Medical Research, University of Cambridge, Hills Road, Cambridge, CB2 0XY, UK, From 01/12/2017: lars.schlotawa@med.uni-goettingen.de, Address: Department of Pediatrics and Adolescent Medicine, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Goettingen, Germany, Name: Laura Adang, adangl@email.chop.edu, Address: Children's Hospital of Philadelphia; Colket Translational Research Building; 35th Street and Civic Center Boulevard; Philadelphia, PA 19104.

*These authors contributed equally to this work

Conflicts of Interest

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VI), chondrodysplasia punctata, and X-linked ichthyosis. As such, individuals demonstrate a complex and severe clinical phenotype that has not been fully characterized to date. In this report, we describe two individuals with distinct clinical presentations of MSD. Also, we detail a comprehensive systems-based approach to the management of individuals with MSD, from the initial diagnostic evaluation to unique multisystem issues and potential management options. As there have been no natural history studies to date, the recommendations within this report are based on published studies and consensus opinion and underscore the need for future research on evidence-based outcomes to improve management of children with MSD.

Keywords

Multiple Sulfatase Deficiency; Leukodystrophy; Mucopolysaccharidoses; Consensus; Therapy; Care; Outcomes; Prevention

1.0 Introduction

Multiple Sulfatase Deficiency (MSD, MIM# 272200) is an ultra-rare neurometabolic disorder inherited in an autosomal recessive manner. Approximately 100 cases of MSD have been described in the literature to date, with 50 living individuals identified through patient-advocacy group registries, although these numbers are likely an underestimation given under-recognition and under-reporting. MSD results from mutations in the *SUMF1* gene that encodes the sulfatase-activating protein formylglycine-generating enzyme (FGE) (1, 2). FGE post-translationally activates newly synthesized sulfatases in the endoplasmic reticulum (3). Because all known 17 cellular sulfatases are affected by defective FGE, the clinical presentation and course of MSD results from the combination of symptoms of each sulfatase deficiency (4). Patients have overlapping features with eight clinically characterized single sulfatase deficiencies, including six different types of lysosomal storage diseases (LSDs), (i.e. metachromatic leukodystrophy (MLD) and five mucopolysaccharidoses (MPS) subtypes), X-linked ichthyosis and X-linked chondrodysplasia punctata (Table 1). The additional contribution from the nine sulfatases without known clinical phenotypes has not yet been characterized (5).

Like many inborn errors of metabolism, MSD represents a spectrum of disease. Based on the onset and severity of the disease, MSD has been traditionally divided into several forms: neonatal, severe late infantile, mild infantile, and juvenile (6–8). The severity of the disorder is thought to be dependent on the stability and degree of residual enzymatic activity of dysfunctional FGE resulting in variable levels of residual sulfatase activities. Nevertheless, the correlation between specific *SUMF1* mutations, residual activities of individual sulfatases, and clinical symptoms remains poorly understood (8).

Individuals with MSD and their families encounter a complex range of health problems and challenges that are unique even among LSDs. The primary issues arise from a combination of neurologic disease, including developmental delay and regression, and extraneurologic manifestations such as cardiopulmonary complications and skeletal anomalies. Unfortunately, as is true for most lysosomal storage disorders, there are currently no curative

options for individuals with MSD. To date, no comprehensive care plan that focuses on preventative care and quality of life has been established (9–11).

In this report, we will discuss two individuals affected by MSD to illustrate the clinical spectrum of disease and present a clinical standard of care consensus statement that arose from the first International Conference on MSD (Dublin, July 2017). The aim of this work is to provide suggested diagnostic and screening tools and outline management options to subspecialty providers and families caring for MSD patients. In conclusion, this report underscores the importance of future natural history studies and investigations to understand the specific needs of individuals with MSD.

2.0 Case Reports

2.1 Clinical History

Individual 1 is a now 4-year-old Caucasian girl who was noted since birth to have poor growth and delayed development. She has had a relatively stable clinical course and was able to attain walking and babbling (Figure 1 and supplementary data). Individual 2 was a Caucasian boy, who had severe medical complications from birth (Figure 1 and supplementary data), including respiratory distress, recurrent ear and respiratory infections, dysostosis multiplex, gall bladder sludging, and severe hydrocephalus requiring ventriculoperitoneal (VP) placement. During Individual 2's life, he required extensive medical care, totally more than 150 days of inpatient or outpatient clinical treatment.

2.2 Neuroimaging

Individual 1 demonstrated progressive central demyelination with corpus callosal involvement (Figure 2B). Her brain magnetic resonance imaging (MRI) demonstrates symmetric confluent T2 hyperintensities in the periventricular and deep white matter with U fiber sparing. Imaging also reveals mild diffuse volume loss, including of the cerebellar vermis, with mild occipital ventriculomegaly. Additional findings include slightly prominent perivascular spaces, which is more characteristic of the imaging found in individuals with MPS. Additional imaging from an individual with MSD reveals (Figure 2A) reveals the findings typical of MLD (Figure 2D), with symmetric T2 hyperintense signal in the bilateral periventricular white matter with corpus callosum involvement (16).

Individual 2's imaging revealed globally delayed myelination and severe hydrocephalus (Figure 2C) that has been observed in individuals with MPS (Figure 2C–E). Individual 2's first brain MRI was performed at the age of 7 months and showed communicating hydrocephalus, mega cisterna magna, delayed myelination, and a thin corpus callosum. His serial imaging showed a slight progression of his myelination and the development of abnormal periventricular and deep white matter T2 and T1 signals without restricted diffusion. His imaging was notable for progressive global atrophy, which vermian volume loss and thin middle and superior cerebellar peduncles. The imaging findings of MPS are classically characterized by enlarged perivascular spaces, demyelination, hydrocephalus, and cortical atrophy (17).

2.3 Diagnostics

Biochemical diagnosis of MSD requires reduced activities of at least two sulfatases in leukocytes or fibroblasts (Table 1), typically arylsulfatase A and iduronate-2-sulfatase. Individuals may also demonstrate elevated excretion of urinary sulfatides and glycosaminoglycans (GAGs) with a pattern indicative for MSD on urine electrophoresis. Negative excretion of GAGs and sulfatides does not exclude MSD, nor does the presence of high activity levels of a single sulfatase (18). All individuals with a clinical suspicion for MSD and decreased sulfatase activity should have confirmatory genetic testing of *SUMF1*. If sequencing does not reveal bi-allelic mutations, deletion/duplication analysis should be considered as pathogenic deletions have been reported (as seen in Individual 1) (6).

For Individual 1, a SNP microarray was performed, which revealed a 28kb deletion on 3p26.1 (arr [hg19] 3p26.1(4,400,903–4,429,402)x1) that includes exons 8–9 of the *SUMF1* gene. *SUMF1* sequencing revealed a second, known pathogenic variant, c.836C>T (p.A279V). Individual 2's sequencing of the SUMF1 gene detected the homozygous mutation c.739G>C (p.G247R). Biochemical enzyme assays for both individuals confirmed reduced activity of multiple sulfatases, consistent with the diagnosis of MSD (supplemental table 1).

3.0 Comprehensive care for children with MSD

As these two clinical cases illustrate, MSD has a broad spectrum of clinical manifestations partly overlapping with the mucopolysaccharidoses and MLD. This underlies the importance of a comprehensive approach to this rare and devastating disease. Although there have not been prospective studies related to the clinical care of individuals with MSD, we can extrapolate from our collective experience with MSD and related disorders to create general recommendations, which should be personalized for each individual (Table 2). Given the great variation amongst individuals with MSD, not all affected people will experience symptoms in all organ systems (Figure 1 and supplemental table 1). Further studies are needed to better anticipate how *SUMF1* mutations and activity predict organ-specific manifestations and clinical phenotype.

3.1 Muscular Issues

Abnormalities of the musculoskeletal systems are among the most pervasive and problematic in children with MSD and have been noted in most published clinical reports (6, 7, 18–22). It is important to support quality of life and mobility with physical therapy, adaptive equipment, and tone management. Changes in muscle tone may include spasticity (as demonstrated in Individual 2), hypotonicity (as demonstrated in Individual 1), and hypertonicity. Spasticity is a velocity-dependent increased tone with hyperreflexia often accompanied by muscle weakness (23).

The examination of children with multiple sulfatase deficiency often reveals mixed tone, which may evolve over time (8). A sudden change in tone from baseline, however, should prompt a full medical assessment, as this may be triggered by infection and pain. Tone issues can result in secondary problems, including mobility issues, respiratory insufficiency,

swallowing dysfunction, and bony dislocation. A result of injury to the primary motor pathways, spasticity is a common issue in children with MSD. The Gross Motor Functional Classification System (GMFCS) is a standardized assessment of motor function, although it needs to be validated in the MSD population (24, 25).

In addition to tone changes, individuals with MSD are at risk of contractures due to deposition of storage material, including GAGs, in joints. Several affected joints have been reported including fingers, elbows, and hips (26, 27). Contractures may be progressive and very similar to those seen in individuals with other MPS disorders, as demonstrated by Individual 2. Because of the risk of peripheral neuropathy from ARSA deficiency as is found in individuals with MLD, individuals with MSD may also exhibit profound weakness from neurodegeneration and demyelinating peripheral neuropathy. Individual 2 demonstrated a progressive peripheral demyelination as demonstrated by serial nerve conduction studies, similar to previous reports (20).

The primary medical assessment can be augmented by evaluations by physical therapy and physiatry. Although none have been validated in MSD or other leukodystrophies, there are standardized scales for measuring and tracking issues with tone. The Hypertonia Assessment Tool (HAT) can differentiate between types of tone abnormalties, including dystonia, spasticity, and rigidity (28). The Modified Ashworth Scale (MAS) is a tool to measure passive resistance at the joint (29). Dystonia, a hyperkinetic movement disorder that results in involuntary muscle contraction, is common among children with leukodystrophies and can be measured using the Global Dystonia Rating Scale (GDS) (23, 28, 30). A more generalizable measure of function, the Vineland Scales of Adaptive Behavior, can be used to screen young children or those with significant impairments (31). The formal study of muscular-skeletal dysfunction in MSD is of critical need and the use of these scales should be validated in this unique population prior to their application in clinical therapeutic trials.

Hypertonicity and spasticity can be managed through stretching, physical therapy, and pharmacologic options, including baclofen and diazepam, although the use of these medications is non-Federal Drug Administration approved (29, 32–34). Trihexyphenidyl (Artane) can be used to help with more generalized dystonias (3, 17–22), as can dopaminergic drugs (e.g. L-dopa) and the dopamine-depleting drug tetrabenazine (29, 35–37).

3.2 Skeletal and Growth issues

Unique skeletal concerns found in the MSD population include dysostosis multiplex, as is associated with MPS, and the skeletal abnormalities of X-linked chondrodysplasia punctata (6, 8, 18, 26). The MPS-associated skeletal features in individuals with MSD include short stature, thickened, short metacarpal bones, irregular clavicles and ribs, irregular carpal and tarsal bones, vertebral and cranial abnormalities (8, 26). Dysplastic femoral heads can result in secondary hip dysplasia, compounding the baseline risk associated with most leukodystrophies. Individual 2 demonstrated dysostosis multiplex, and Individual 1 had short stature.

Spinal cord compression due to cervical spine instability and stenosis in both the cervical and thoracolumbar regions is common in several MPS subtypes (38, 39). In a recent study of individuals with MPS VI, 101/134 (75%) who underwent cervical spine imaging had documented cord compression (40). While cord compression has not been systematically evaluated in individuals with MSD, regular neurologic examination and serial spine imaging could be considered to monitor for spinal stenosis and instability. Neck hyperextension, often used to maintain airway patency during anesthesia, should be avoided if possible in children identified to be at risk for spinal cord compression.

Individuals with MSD may also demonstrate the skeletal features seen in X-linked chondrodysplasia punctata 1 (CDPX), a result of arylsulfatase E deficiency (41, 42). Although not fully characterized in MSD, children with CDPX can demonstrate maxillary hypoplasia and retrognathia, requiring reconstructive surgery. These children are also at risk for cervical spine instability (41). Again, children with a CDPX phenotype may be at increased risk with neck hyperextension, thus should have particular care with any elective intubations, sedation, or general anesthesia. We recommend visualization of the spine and airway prior to any procedures by neck CT or plain C-spine radiographs, and consideration for evaluation by otolaryngologists (43).

Common skeletal issues in individuals with neurodegenerative disorders include scoliosis, hip dislocation, and osteopenia, which may also affect children with MSD, as demonstrated in individual 2 and in the literature (18, 44). The scoliosis and hip dislocation can be secondary to increased tone and skeletal anomalies. Children are also at increased risk for bony fractures due to decreased mobility, decreased sun exposure (and thus low Vitamin D levels), and nutritional insufficiency (45). As such, bone health, mobility, and vitamin D (25-OH-D) status should be regularly monitored. Special attention should be paid to individuals who are non-ambulatory or who are on medications those compromise bone health, including proton-pump inhibitors, steroids and select anti-epileptic medications (46–48).

In addition to laboratory testing, basal bone density scans, such as dual-energy X-ray absorptiometry (DEXA or DXA, L–spine and Whole Body Less Head), can be used to screen for bone demineralization in at-risk individuals (46, 47, 49). Bone specialists, endocrinologists, and orthopedic surgeons can be helpful in the management of bone issues in complicated individuals with MSD. Physical therapists can help to select and fit adaptive equipment to help maximize mobility. As is common to the clinical considerations relevant to MSD, the incidence, impact, and management of skeletal abnormalities warrants future study.

3.3 Skin Issues

Children with MSD have unique skin challenges due to decreased activation of steroid sulfatase (arylsulfatase C), which is associated with X-linked ichthyosis, as demonstrated by Individual 2. The deficient enzyme, steroid sulfatase, helps to release keratinocytes from the substratum corneum, leading to overcornification (50). The ichthyosis of MSD typically manifests initially as dry skin and later on as thickened, dark leaf-like scales (6, 7, 18, 19, 22). Medications to soften the skin, including keratolytics or topical vitamin D, may be helpful (50). Children with MSD may also be hirsute, as found in Individual 2 and in prior

clinical reports (8, 18, 19, 22). Common challenges to skin integrity in the leukodystrophy population arise from a variety of issues, including peripheral neuropathies, limited mobility, adaptive equipment, and abnormalities in tone. Individuals should be monitored carefully for skin breakdown, especially in dependent areas and regions that are in contact with equipment.

3.4 Gastrointestinal and urinary issues

Children with MSD may encounter a range of gastrointestinal complications, including hepatosplenomegaly and gall bladder issues in addition to the typical concerns for the leukodystrophies (6, 18, 19, 22, 26, 51–56). Among the leukodystrophies, sialorrhea or excessive drooling, swallowing difficulty, poor intestinal motility, and reflux are common complaints (10, 57, 58). There are several important components to the comprehensive evaluation of upper gastrointestinal issues, including speech and physical therapy, gastroenterology, and pulmonology.

Although rarely a cause of medical morbidity, sialorrhea can be managed with positioning and medical interventions, including hyoscine (oral or transdermal Scopolamine), trihexyphenidyl (Artane) (37), and glycopyrrolate (59). More permanent interventions include serial botulinum toxin A (Botox) injections and salivary gland ligation surgery (58, 60, 61).

In children with MSD, safety with feeding and dietary sufficiency should be carefully followed as these issues can lead to secondary respiratory complications like aspiration pneumonia and malnutrition, as demonstrated by both of the individuals discussed above. Malnutrition compromises overall health and is influenced by intake, dysphagia, and metabolic demands (62–64). Preliminary screening questions regarding coughing with feeds or ease and duration of feeding can guide the needs for further evaluation by dieticians, occupational therapists, and speech pathologists (40, 42, 43, 54, 55). Possible studies could include a videofluoroscopic swallow study (VFSS) or modified barium swallow study (MBS). Following an evaluation and a discussion regarding goals of care, gastrostomy (G-tube) or jejunostomy (J-tube) tube placement may be considered. The diagnosis of gastroesophageal reflux (GER) can be made clinically. Initial management of GER should consist of positioning during meals and optimization of food consistencies (65, 66). Additional considerations include pharmacologic options (acid buffering, antisecretory, and prokinetic agents), and surgical options such as Nissen fundoplication with or without gastrostomy tube placement (10, 65, 67).

Constipation and slowed GI motility are common problems in children with neurologic disorders (10, 68). The first step in the evaluation of constipation is to ensure the child is receiving adequate hydration, followed by medication options, including fiber supplementation, stool softeners and stimulants, and enemas (69) (68).

As can be found in other MPS subtypes, children with MSD often have hepatosplenomegaly (Individual 2) due to accumulation of GAGs (7, 18–20, 22, 55, 56). While the clinical significance of this organomegaly has not been studied in MSD, in MPSII this organ enlargement is not typically associated with hepatic or splenic dysfunction (38).

Although its incidence has not been characterized in the MSD population, children with metachromatic leukodystrophy (MLD) are at increased risk for gallbladder complications. It is recommended that children with MLD have regular screening abdominal ultrasounds or abdominal computed tomography (CT) (51, 52). Typically, individuals with MLD have gall bladder wall thickening or polyps, although more serious complications such as cancer and obstruction have been reported (53). Individual 2 demonstrated gall bladder sludging. Because of pathologic kidney depositions, MLD also predisposes to metabolic acidosis that can worsen when under physiological stress (70). One of the concerning secondary effects of severe constipation is the risk for urinary retention and infection. Other potential urinary concerns include dysautonomia and neurogenic bladder. The true incidence of gall bladder and renal pathology in individuals with MSD should be characterized so that more formal recommendations can be made.

3.5 Respiratory and airway complications

Potential pulmonary clinical concerns in individuals with MSD include upper and lower airway obstruction, restrictive lung disease, and central and peripheral apnea, although the true incidence is unknown (26, 71). Studies have demonstrated obstructive sleep apnea (OSA) rates of 70– 85% in individuals with a variety of MPS disorders (72, 73). This is likely polyfactorial, from both central degeneration and peripheral airway obstruction. OSA has been noted in individuals affected by MSD as well, as seen in Individual 1 (18). Our individual 2 was noted to have choanal stenosis at birth, which has been reported for one additional individual (18).

For a variety of reasons, children with MSD are at high risk for recurrent pneumonia as well, as affected both of our individuals. As guided by a pulmonologist, evaluation of respiratory function could include spirometry, pulmonary function tests, and end tidal CO_2. Fiber-optic bronchoscopy to assess for airway obstruction and/or tracheomalacia may be helpful as well.

Due to issues with brainstem involvement, muscle tone, scoliosis, and strength, many children with leukodystrophies develop a progressive respiratory insufficiency. Children with neurologic disease are also at risk for complications such as pneumonia and aspiration (74). Like in MLD, the peripheral neuropathy can directly result in a primary respiratory failure as well. Potential screening questions for respiratory complications would include interrogations about coughing, stridor, or noisy breathing. Both individuals in this case study demonstrated noisy daytime breathing, and stridor has been a previously noted finding (7, 56).

After careful evaluation by specialists (pulmonology and/or otolaryngologists) and possible sleep studies, it may be determined that the child would benefit from supportive interventions such as mechanical ventilation or continuous positive airway pressure (CPAP). Less invasive options include home suction, physical therapy, and supplemental oxygen.

Common issues including obstructive sleep apnea and dysautonomia causing sleep and temperature regulation problems can compromise quality of life and daytime performance (75, 76). After optimizing sleep hygiene and evaluating for obstruction, medications to

facilitate sleep can be considered, such as off-label use of melatonin, antidepressants, clonidine, and benzodiazepines (75, 76).

3.6 Neurologic Issues

In children with MSD, the neurologic delay and regression are believed to be universal, although the onset and rate of progression appear to be highly variable (6, 7, 18–22, 55, 56, 77). It is important to provide adaptive communication devices to maximize the ability to communicate. Speech-language pathologists can help with this evaluation. Additional neurologic issues in children with MSD include peripheral neuropathy, pain, and seizures (6, 18, 20, 26). If a child is identified as being in pain, it is important to identify if the discomfort is secondary to medical cause, such as constipation, fractures or hip dysplasia, or a urinary tract infection as these triggers should be treated appropriately (78). Because MLD is associated with neuropathic discomfort from peripheral neuropathy, this is a potentially important consideration in children with MSD as well (20, 79). This can be extrapolated from the loss of reflexes in the later stages of disease in MSD. Although not FDA-approved, gabapentin (Neurontin) may be helpful with neuropathic pain (10, 78).

Although children with neurodegeneration, particularly in the later stages, are at risk for seizures, there are many prevalent mimics for seizures, including reflux, breath holding spells, movement disorders, and stereotypies (80). As guided by a neurologist, an electroencephalogram (EEG) may be helpful, although clinical history alone may be sufficient for the diagnosis of seizures or epilepsy (78). If determined necessary by the neurologist, children with recurrent seizures may benefit from a preventative medication (81). With a first-time seizure in particular, children should have an evaluation for any provoking factors, including infections or electrolyte abnormalities (11).

MPSIII and the adult-onset forms of several leukodystrophies, including MLD, can present with prominent neuropsychiatric symptoms as well, which may benefit from directed pharmacologic and behavioral management strategies. Individuals affected by prominent behavior issues have been described previously (18). Additionally, our individual 1 was noted to have a fine tremulousness of low amplitude and velocity that has been previously noted in two prior affected individuals, although the etiology of these involuntary movements remains to be characterized (18).

While some affected individuals are microcephalic (18, 21), MSD may be also associated with macrocephaly and acquired hydrocephalus (individual 2) (18, 55, 56), thus with any concerns for impaired mental status or an acute change in neurologic status, urgent brain imaging should be considered (82). Acute changes in neurologic examination should be considered an emergency given the possibility of hydrocephalus or acute cord compression as discussed above. As such, head circumference should be measured with every clinical encounter. The youngest reported case of hydrocephalus in a child with MSD was 2 months old (56). Hydrocephalus has been previously reported for MPS I, MPS II, and MPS III (82). The necessary frequency of screening has not been determined in the MSD population and should be evaluated in future formal research studies.

3.7 Cardiac Issues

Because of MPS-related symptomatology, children with MSD are at risk for cardiac problems, including cardiac hypertrophy, valvular depositions, arrhythmias, coronary artery disease and hypertension, in addition to the secondary cardiac problems associated with obstructive sleep apnea (6, 18, 83). Of note, the cardiac issues in MPS can worsen disproportionate to clinical progression (26). Individuals with MSD may also have valvular issues, including stenosis or insufficiency of mitral, tricuspid and aortic valves. The incidence in MSD is unknown, but valvular problems affect almost all individuals with MPS VI (84). With any clinical concerns, individuals may benefit from cardiology referral and regular electrocardiograms (ECG) and ECHOs, although the frequency of these tests has not been studied in this population.

3.8 Ophthalmologic Issues

Children with MSD have several unique ophthalmologic considerations as extrapolated from case reports on individual enzyme deficiencies (6, 18, 21). Eye manifestations of MPS disorders can include corneal clouding, retinal degeneration, optic atrophy, papilledema, and glaucoma (85). Children with MSD should be regularly monitored by formal ophthalmologic evaluation, visual fields testing, and intraophthalmic pressure (IOP) measurement (18, 26). In individuals with MPS VI, the incidence of glaucoma (50%) and corneal clouding (95%) are increased, although the frequency in MSD specifically is unknown (18, 26). Retinitis pigmentosa has been reported in MSD individuals as well (18). Individuals with X-linked ichthyosis (steroid sulfatase deficiency) have opacities of the corneal stroma, which are typically asymptomatic (86).

3.9 Auditory and oral-maxillary issues

MSD is associated with a variety of unique issues with the ears and throat that would benefit from specialist evaluation. Potential clinical concerns include airway obstruction, hearing disorders, and recurrent otitis media (6, 7, 18, 26, 56). A significant cause of morbidity, individuals may demonstrate progressive oral, pharyngeal, and upper airway obstruction with airway narrowing (26). Overall, over half of individuals with MPS have abnormal tracheal morphology (43). Dependent on clinical indication and guided by specialists, we often consider sleep studies to evaluate for obstruction and airway visualization by flexible endoscopy. We recommend audiology evaluation as clinically indicated as hearing loss is believed to be common in this population and can compound language and communication issues (6, 18, 56).

Dental symptoms are also common in MPS disorders and should be monitored regularly in MSD individuals by a pediatric dentistry specialist if possible. Several MPS subtypes are also associated with gingival hyperplasia and micro and/or retrognathia (7). Hunter syndrome may result in focal lesions in the jaw and abnormalities in tooth enamel, the latter of which can result in increased risk of tooth decay (87). As mucopolysaccharides accumulate, children can experience a progressive difficulty in their bite, teeth, and enamel (87). Sanfilippo syndrome results in tooth root injury (87). One clinical report described the impact of MSD on tooth enamel and dentin, affecting tooth thickness and mineralization (87).

4.0 Additional family supports

In addition to the primary medical team, all children and families affected by complicated neurodegenerative disorders often require additional multidisciplinary supports (54). Clinical social workers can help families navigate financial issues and provide social support resources. Early inclusion of pediatric palliative care specialists may be helpful to address issues of comfort, goals of care, and end of life issues.

5.0 Discussion

Multiple sulfatase deficiency is ultra-rare and represents a broad and diverse clinical spectrum. Given the pathophysiology, the phenotype can be incredibly complex and variably affect multiple organ systems. The two cases presented here illustrate that while disease progression is universal, the rate of deterioration, individual organ system involvement, and residual sulfatase activity can be highly variable between individuals (supplemental table 1). We can harness our knowledge of related disorders to help predict and anticipate MSD complications. For example, isolated loss of steroid sulfatase activity is associated with ichthyosis, while loss of arylsulfatase A activity leads to a MLD-like leukodystrophy. Adding to the complexity, the phenotype of MSD is more than a direct summation of individual sulfatase deficiencies. The combinatorial loss of several sulfatases simultaneously may result in novel pathophysiologic effects. Moreover, several of the sulfatases have uncharacterized clinical phenotypes, furthering the clinical uncertainty surrounding this rare disorder.

As is inherent to this disorder, individuals demonstrate a complicated and evolving phenotypes, as shown in Figure 1. We hypothesize that the clinical manifestations of individuals with MSD represent a spectrum from MLD-like to MPS-like, with each individual demonstrating an individual blend of findings. Individual 1 demonstrates the clinical course and radiographic findings most similar to MLD, but with features of MPS disorders (Figure 1 and 2, Table 1). Individual 2 demonstrated a clinical phenotype most similar to MPS, but with unique features of MLD (peripheral neuropathy and gall bladder sludging) (Table 1, Figure 1–2). Interestingly, the clinical symptoms found in each individual did not correlate with the measured residual enzyme activity of individual sulfatases (supplemental table 1). It is possible that the measured sulfatase activity, an indirect product of formylglycine-generating enzyme activity, varies between tissues and fluctuates over time. The clinical symptoms exhibited by an individual with MSD may be a result of other influences, such as epigenetic modifications and allelic variants. Clinical findings also may be the product of enzyme activity at key points in development. It should be noted that severe phenotypes have been described previously in individuals carrying the p.G247R mutation of individual 2 (8), while milder phenotypes have been reported in individuals harboring the p.A279V mutation, as found in individual 1 (88). Despite this consistency, the variability of enzyme activity and the correlation of the residual enzyme function to genotype and clinical phenotype remains an area of active interest for further investigation.

Because of the extreme rarity of this disorder and the complexity in phenotype, many individuals experience a delay in diagnosis. Once an individual is diagnosed, providers may have difficulty navigating the clinical needs of the family. To our knowledge, this is the first systematic overview of the organ systems involved in MSD. This structured collection of symptoms and their diagnostic measures can aid in the diagnosis of an individual with complex symptoms consistent with a possible MSD diagnosis. Also, it can help guide the initial evaluations needed for a comprehensive work-up and design of an individualized care plan for individuals with MSD.

As of yet, no curative therapy for MSD exists. A multidisciplinary, expert-driven approach to control and alleviate symptoms in combination with a tailored palliative treatment can help to restore, maintain and improve the quality of life for MSD individuals. Because of the rarity of the disease, information on every individual patient greatly expands our knowledge of MSD, and a comprehensive and collaborative approach is needed. Future systematic studies of larger numbers of individuals are required to better understand MSD, expand upon clinical guidelines, and ultimately assess response to potential therapeutics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACC	augmentative and alternative communication

AEP	auditory evoked potential
BiPAP	bilevel positive airway pressure
CPAP	continuous positive airway pressure
CRIES	*C*ry, *R*equires O_2, *I*ncreased Vital Signs, *E*xpression, *S*leeplessness scale
CT	computed tomography
DBS	deep brain stimulation
DEXA or DXA	dual-energy X-ray absorptiometry
EEG	electroencephalogram
EKG	Electrocardiogram
ECHO	Echocardiogram
FEES	fiberoptic endoscopic study
FGE	formylglycine generating enzyme
FLACC	*F*ace, *L*egs, *A*ctivity, *C*ry, *C*onsolability scale
G-tube	gastrostomy tube
GAG	glycosaminoglycan
GER	gastroesophageal reflux
GJ-tube	gastrojejunostomy tube
GMFCS	Gross Motor Functional Classification System
HSM	Hepatosplenomegaly
LSD	lysosomal storage disorder
MBS	modified barium swallow
MSD	multiple sulfatase deficiency
MLD	metachromatic leukodystrophy
MRI	magnetic resonance imaging
ND	not done
SEP	sensory evoked potentials
SUMF1	Sulfatase Modifying Factor 1
OAE	Otoacustic emissions

OSA	obstructive sleep apnea
PedsQL	Pediatric Quality of Life Inventory
PFO	persistent foramen ovale
QoL	quality of life
SLP	speech-language pathology
US	Ultrasound
UTI	urinary tract infections
VSD	ventricular septal defect

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Highlights

- Multiple sulfatase deficiency is an ultra-rare neurodegenerative disorder
- All 17 known human sulfatases are affected, including 6 lysosomal storage diseases
- Clinical phenotype complex and variable

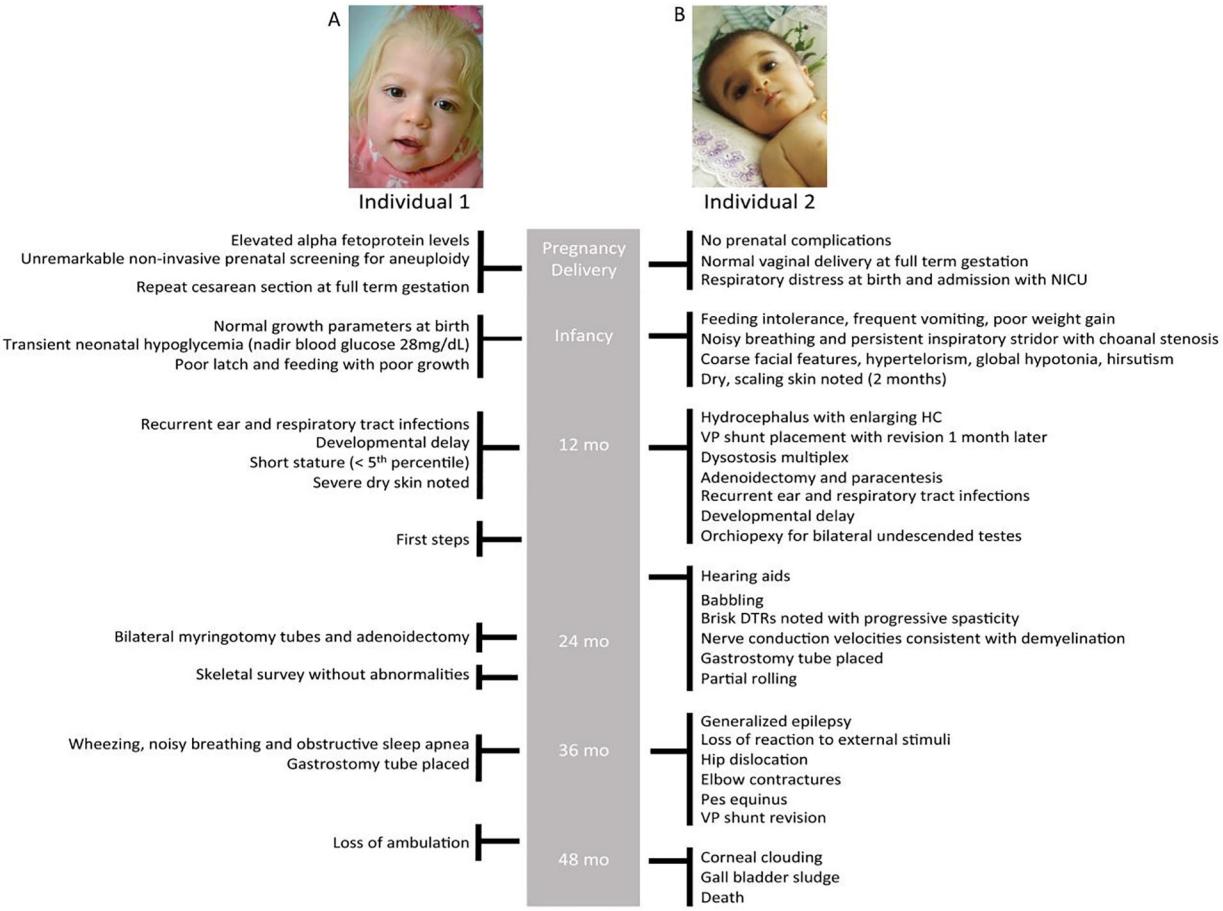

Figure 1: Timeline of two individuals affected by MSD demonstrating clinical variability.

Individual 1 shows a later onset and slower acquisition of symptoms, while Individual 2 presented earlier, with faster progression and multisystemic complications. (A) On physical examination of Individual 1, mildly dysmorphic features including midface hypoplasia, full cheeks, periorbital fullness, hypertelorism, and short, thick fingers were noted. Pertinent findings on neurologic exam included babbling, difficulties with motor planning, and tremulousness. (B) Individual 2 was noted to have coarse facial features, hypertelorism, choanal stenosis, global hypotonia, hirsutism, persistent inspiratory stridor, and ichthyosis. His psychomotor development slowly progressed over the following months with the highest achievement of babbling at the age of 16 months and partially rolling to one side at 22 months of age. He did not attain speech, sitting, or crawling. By 3.5 years of age, he developed severe spasticity and epilepsy with generalized tonic clonic seizures. Ultimately, he lost the ability to react to tactile or auditory stimuli and purposefully move.

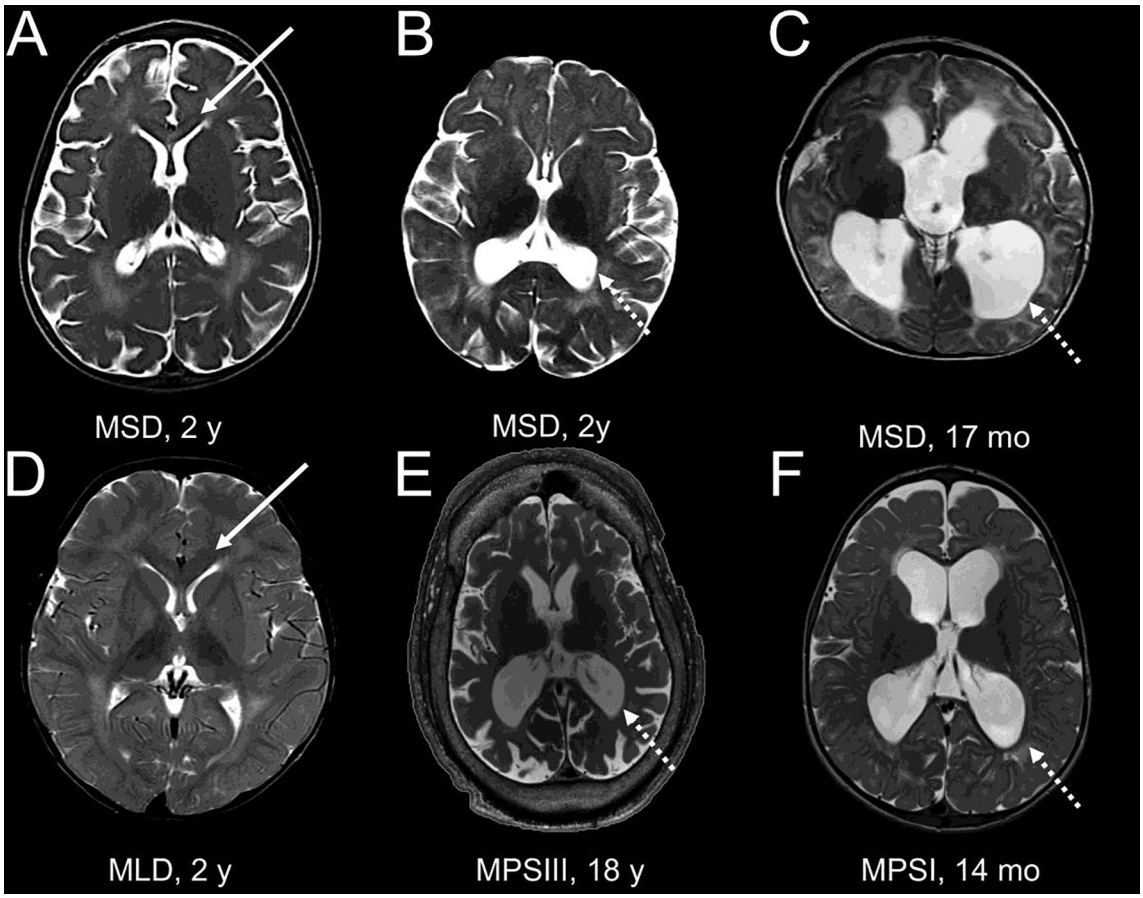

Figure 2: Comparative brain imaging findings of individuals with MSD, MLD, and MPS.

A-C represents the radiographic spectrum findings from children with MSD. This 2 year old individual with MSD (not presented in text) demonstrates periventricular and frontal white matter involvement (A) similar to the findings in individuals with MLD (D) (16). The solid arrows indicate corpus callosum involvement. Individual 1 (B) demonstrates periventricular white matter involvement with preservation of the U-fibers. Enlarged ventricles are indicated by dotted arrows. Individual 2 (C) imaging reveals diffuse hypomyelination and severe hydrocephalus. E and F demonstrate the typical imaging findings found in individuals with MPS disorders with diffuse hypomyelination, atrophy, and hydrocephalus. All images shown are T2 weighted MR images.

Table 1:

Multiple sulfatase deficiency affects 17 unique sulfatases, each with distinct subcellular localizations and pathogenic associations (4).

Subcellular localization	Sulfatase	Disease
Lysosome	Arylsulfatase A (Cerebroside-3-sulfatase)	Metachromatic Leukodystrophy (MIM 250100)
	Arylsulfatase B (N-Acetyl-Galactosamine-4-Sulfatase)	MPS VI Maroteaux-Lamy (MIM 253200)
	Iduronate-2-Sulfatase	MPS II Hunter (MIM 309900)
	Sulfamidase (N-Sulfoglucosamine-Sulfohydrolase)	MPS IIIA Sanfilippo (MIM 252900)
	N-Acetylglucosamine-6-Sulfatase	MPS IIID Sanfilippo IIID (MIM 252940)
	Galactosamine-6-Sulfatase	MPS IVA Morquio A (MIM 253000)
	Arylsulfatase G (N-Sulfoglucosamine-3-sulfatase)	MPS IIIE characterized in murine models (12–14)
	Arylsulfatase K (Glucuronate-2-sulfatase) (15)	unknown
Endoplasmic Reticulum	Arylsulfatase C (Steroid Sulfatase)	X-linked Ichthyosis (MIM 308100)
	Arylsulfatase D	unknown
	Arylsulfatase F	unknown
Cell surface	Sulfatase 1	unknown
	Sulfatase 2	unknown
Golgi	Arylsulfatase E	Chondrodysplasia punctata Type I (MIM 302950)
Unknown	Arylsulfatase H	unknown
	Arylsulfatase I	unknown
	Arylsulfatase J	unknown

Table 2:

Comprehensive systems-based approach to the clinical care of individuals with MSD.

System	Potential clinical concerns	Interventions to consider
Cardiac and vascular	• Cardiac hypertrophy • Cardiac valve issues • Arrhythmias • Hypertension	• Cardiology referral with serial evaluations by EKG and ECHO
Dermatologic	• Ichthyosis • Hyperpigmented plaques • Hirsutism	• Dermatology referral as clinically indicated, particularly for severe involvement or with any concerns for secondary infections
Metabolic	• Metabolic acidosis	• Serial blood and urinary acid–base balance monitoring, with particular attention to episodes of physiologic stress, including illnesses requiring medical attention
Musculoskeletal	• Dysostosis multiplex • Spine instability or stenosis leading to cord compression • Poor bone health • Abnormalities in tone (hypotonia and/or spasticity)	• Spine imaging (radiographs and/or MRI) with referral to neurosurgery as indicated • Referral to orthopedics as per clinical indication with consideration of radiographs or MRI (hip and/or spine) • Physical therapy and physiatry referrals to maximize mobility and optimize tone • Referral to bone health specialists with attention to vitamin D
Neurologic	• Peripheral neuropathy • Seizures • Progressive hydrocephalus and increased intracranial pressure	• Head circumference measurements with all clinical encounters • Urgent evaluation and head imaging with clinical concerns (including rapid clinical change such as a change in vision, new headaches, new vomiting) • EEG with clinical concerns for seizures • Neuropsychological testing as clinically indicated
Nutrition and gastroenterologic	• Poor GI motility (feeding intolerance, constipation) • Hepatosplenomegaly • Gallbladder issues • Gastroesophageal reflux	• Weight and height measurements with all clinical assessments • Referral to gastroenterologist as indicated, with special consideration for serial abdominal US with special attention to liver, gallbladder and spleen • Surgery or interventional radiology referral for consideration of gastrostomy tube placement if needed • Referral to nutritionist
Ophthalmic	• Glaucoma • Corneal clouding • Retinopathy, including retinitis pigmentosa • Strabismus • Optic nerve abnormalities • Cataracts	• Ophthalmology referral with special attention to intraophthalmic pressures
Oral	• Feeding difficulties with poor oral-motor coordination • Hyperplastic gums • Dental complications,	• Speech therapy referral for evaluation of oral feeding and guidance on further testing • Referral to a specialist in pediatric
	including abnormalities in tooth enamel	dentistry
Otolaryngologic	• Airway obstruction • Hearing disorders • Recurrent otitis media • Oral, pharyngeal, and upper airway obstruction with progressive airway narrowing	• Otolaryngology referral as indicated with consideration of direct airway visualization by flexible endoscopy • Sleep medicine referral with sleep studies • C-spine imaging, particularly prior to sedation or anesthesia as this may necessitate neck hyperextension • Audiology evaluation
Respiratory	• Obstructive lung disease • Restrictive lung disease • Central apnea • Peripheral apnea • Sleep issues • Recurrent pneumonia	• Pulmonology referral with consideration of spirometry and pulmonary function tests, end tidal CO_2, as well as fiber-optic bronchoscopy to assess for airway obstruction and/or tracheomalacia