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Multiple Sulfatase Deficiency

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Summary

Clinical characteristics

Initial symptoms of multiple sulfatase deficiency (MSD) can develop from infancy through early childhood, and presentation is widely variable. Some individuals display the multisystemic features characteristic of mucopolysaccharidosis disorders (e.g., developmental regression, organomegaly, skeletal deformities) while other individuals present primarily with neurologic regression (associated with leukodystrophy). Based on age of onset, rate of progression, and disease severity, several different clinical subtypes of MSD have been described:

- Neonatal MSD is the most severe with presentation in the prenatal period or at birth with rapid progression and death occurring within the first two years of life.
- Infantile MSD is the most common variant and may be characterized as attenuated (slower clinical course with cognitive disability and neurodegeneration identified in the 2nd year of life) or severe (loss of the majority of developmental milestones by age 5 years).
- Juvenile MSD is the rarest subtype with later onset of symptoms and subacute clinical presentation.

Many of the features found in MSD are progressive, including neurologic deterioration, heart disease, hearing loss, and airway compromise.

Diagnosis/testing

The diagnosis of multiple sulfatase deficiency is established in a proband with low activity levels in at least two sulfatase enzymes and/or biallelic pathogenic variants in *SUMF1* identified by molecular genetic testing.

Management

Treatment of manifestations: Progressive hydrocephalus, seizures, spasticity, spine instability or stenosis, eye anomalies, cardiovascular disease, hearing loss, poor growth, dental anomalies, developmental delays, and respiratory issues are managed in the standard fashion. Obstructive sleep apnea may be treated with

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adenoidectomy and/or tonsillectomy, although affected individuals have a higher surgical complication rate; ventilator support (CPAP, BiPAP) can also be considered. Precautions are needed during anesthesia to address airway maintenance, as progressive upper airway obstruction and cervical spine instability are common. Poor bone health may require supplementation with vitamin D and encouragement of weight-bearing exercises. Alternative routes for nutrition (tube feeding) are frequently necessary.

Surveillance: Monitoring of head circumference at each visit; serial brain/spine imaging, as needed based on symptoms; cervical spine imaging prior to any procedure that requires neck extension. At least annual vitamin D level, eye examination with intraocular pressure measurement, EKG, echocardiogram, and audiology evaluation. Abdominal ultrasound, sleep study and pulmonary function tests, neuropsychiatric testing, and assessment of blood and urine acid-base balance as clinically indicated.

Agents/circumstances to avoid: Neck hyperextension (including hyperextension used for intubation) because of the risk of spinal cord compression; foods that are a choking hazard.

Genetic Counseling

Multiple sulfatase deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% change of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible using molecular genetic techniques if the pathogenic variants in the family are known.

Diagnosis

Formal clinical diagnostic criteria for multiple sulfatase deficiency have not been established.

Suggestive Findings

Multiple sulfatase deficiency **should be suspected** in individuals with the following clinical, laboratory, and imaging findings.

Clinical findings

- Developmental delay with subsequent neurologic regression and psychomotor retardation
- Macrocephaly with or without hydrocephalus
- Epilepsy
- Poor growth with a progressive decrease in growth rate
- Coarse facial features
- Recurrent otitis media and/or upper respiratory tract infections
- Progressive hearing loss
- Hepatosplenomegaly
- Skeletal changes including kyphosis, gibbus deformity, hip dislocation, genu valgum
- Cardiac hypertrophy or thickening of cardiac valves
- Ichthyosis

Laboratory findings

- Decreased activity of at least two sulfatase enzymes on lysosomal enzyme testing analysis

  Note: Individual enzyme activities may be higher than those seen in individuals with single enzyme deficiencies and some may be within normal ranges.

- Elevated urinary glycosaminoglycan levels
- Elevated urinary sulfatides

Imaging findings

- Abnormal brain MRI showing progressive demyelination, prominence of the perivascular spaces, cerebral volume loss, and/or hydrocephalus
- Skeletal radiographs demonstrating features of dysostosis multiplex including anomalies of the vertebrae, hands, feet, long bones, and skull

Establishing the Diagnosis

The diagnosis of multiple sulfatase deficiency **is established** in a proband with low activity levels in at least two sulfatase enzymes and/or biallelic pathogenic variants in *SUMF1* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panels) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of multiple sulfatase deficiency is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of multiple sulfatase deficiency has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of multiple sulfatase deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SUMF1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *SUMF1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in unrelated genes. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene may vary by laboratory. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of multiple sulfatase deficiency is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which

gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Multiple Sulfatase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by This Method
SUMF1	Sequence analysis [3]	~98%-99% [5]
	Gene-targeted deletion/duplication analysis [4]	~1.5% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Review of all available cases in the literature revealed three large deletions and no duplications out of 201 alleles [Author observation, in preparation for publication].

Clinical Characteristics

Clinical Description

Multiple sulfatase deficiency (MSD) is a multisystem lysosomal storage disorder with variable age of onset and wide variability in clinical presentation and rate of progression. Initial symptoms can present from infancy through early childhood [Sabourdy et al 2015, Ahrens-Nicklas et al 2018]. Many individuals experience global regression between age two and six years, approximately 12-60 months after symptom onset. Earlier onset of regression correlates with increased disease severity [Sabourdy et al 2015]. Some individuals display the multisystemic features characteristic of mucopolysaccharidosis disorders, while others present primarily with neurologic regression (see Pathophysiology).

Natural History

Based on age of onset, rate of progression and disease severity, several different subtypes of MSD have been described [Eto et al 1987]. The severity of the condition may correlate with the stability of the enzyme and residual enzyme activity (see Genotype-Phenotype Correlations). The subtypes are as follows.

Neonatal MSD is the most severe form, in which affected Individuals typically have intrauterine growth restriction and respiratory distress at birth [Busche et al 2009, Garavelli et al 2014]. Dysmorphic features may include coarse facial features, thick eyebrows, hypoplastic nasal bone, bulbous nasal tip, posteriorly rotated ears, high arched palate, micrognathia, retrognathia, flared thorax, inverted nipples, and broad thumbs. Corneal clouding is frequently present. Disease progression is rapid and mortality is high, with death typically occurring within the first two years of life [Burch et al 1986, Busche et al 2009].

Infantile MSD, the most common clinical presentation, is characterized by progressive neurodegeneration with loss of sensory and motor skills, similar to arylsulfatase A deficiency (metachromatic leukodystrophy). Typically,

symptom onset is within the first three years of life. This phenotype may be further subdivided into attenuated (formally called "mild") and severe subtypes.

- **Attenuated infantile MSD** is characterized by a slower clinical course in which affected individuals are noted to have growth deficiency (1.5-3 SD below the mean), feeding difficulties, and developmental delay [Ahrens-Nicklas et al 2018], with cognitive disability and neurodegeneration identified in the second year of life (range 3-36 months).
  - The ability to ambulate and communicate with a limited vocabulary may be preserved into late childhood (age 3-9 years), although by age nine most have significant impairments.
  - Among eight individuals with infantile MSD, all demonstrated psychomotor retardation, hypotonia, and neurodegeneration, while 75% had ichthyosis and 25% had dysmorphic features [Sabourdy et al 2015]. In a second series, nine individuals identified to have infantile MSD all demonstrated cognitive delay, neurodegeneration, and ichthyosis [Schlotawa et al 2011].
  - Dysmorphic features, if present, are subtle but may become more prominent with age.
  - Prenatal manifestations, hepatosplenomegaly, and corneal clouding are rare [Sabourdy et al 2015].
- **Severe infantile MSD** is characterized by a faster rate of disease progression and more extensive systemic involvement. Symptoms present within the first year of life and most individuals lose a majority of developmental milestones by age five years [Sabourdy et al 2015, Jaszczuk et al 2017].
  - Dysmorphic features, skeletal changes, and organomegaly are common [Schlotawa et al 2011].
  - Life span is significantly shortened, and many die within the first decade of life.

Juvenile MSD is a rare subtype, although this could be influenced by ascertainment bias. It has a later onset with an attenuated clinical presentation. The diagnosis can sometimes be difficult to make owing to borderline residual sulfatase activity [Church et al 2018]. Brain MRI findings are nonspecific and may include white matter signal abnormalities, corpus callosum thinning, and cerebellar atrophy.

- Age of onset is between three and seven years with an insidious clinical presentation and neurologic decline.
- Presenting symptoms can include generalized tremor, hypotonia, and mild-moderate developmental delays [Sabourdy et al 2015].
- Affected individuals can also develop ichthyosis, visual loss (although corneal clouding is rare), and behavioral abnormalities, and may have minor dysmorphic features (broad thumbs and index fingers) that frequently become more prominent with age [Blanco-Aguirre et al 2001].
- The oldest known person with the condition survived until the fourth decade of life [Author, personal communication].
- Individuals with juvenile MSD can retain the ability to walk into their teenage years.

Clinical Features Common To All Subtypes

Many of the features found in MSD can be progressive, including the neurologic deterioration, heart disease, hearing loss, and airway compromise. The progressive nature of the disease is at least in part due to the accumulation of glycosaminoglycans (GAGs) and other substrates, including sulfatides.

Neurologic features include:

- Developmental delay and progressive neurologic deterioration, including long track signs (spasticity)
- Ataxia
- Autistic features
- Epilepsy [Incecik & Herguner 2017]
- Microcephaly [Miskin et al 2016] or macrocephaly; hydrocephalus has been reported [Incecik & Herguner 2017].

Musculoskeletal features:

- Short stature
- Irregular ribs (typically paddle-shaped with widening anteriorly and tapering posteriorly) associated with dysostosis multiplex
- Scoliosis and/or kyphosis
- Vertebral abnormalities, including odontoid dysplasia, atlanto-axial instability, cervical spinal canal stenosis, and vertebral body abnormalities (wedge-shaped vertebral bodies, anterior beaking with posterior scalloping, and platyspondyly)
- Vertebral instability and risk of spinal cord compression, which can be dangerous with neck hyperextension (such as occurs during intubation)
- Short metacarpals
- Joint stiffness and contractures, which may pose a prominent issue that can impede mobility [Burk et al 1984]
- Broad thumbs and toes [Santos & Hoo 2006]

Growth restriction may be of prenatal onset, particularly in the neonatal form [Incecik et al 2013, Sabourdy et al 2015].

Ophthalmologic features:

- Glaucoma
- Strabismus
- Retinal degeneration
- Corneal clouding
- Cataracts
- Retinitis pigmentosa [Sabourdy et al 2015]
- Myopia

Cardiovascular manifestations may include atrial septal defects [Incecik et al 2013] and aortic insufficiency [Guerra et al 1990]. Individuals with MSD are at risk of developing cardiac manifestations similar to those seen in other lysosomal storage disorders: secondary valve disease, cardiac hypertrophy, coronary artery disease, arrhythmias, and hypertension [Braunlin et al 2011, Sabourdy et al 2015, Jaszczuk et al 2017].

Ear, nose, and throat. Progressive conductive and/or sensorineural hearing loss and recurrent otitis media are common [Sabourdy et al 2015].

Skin. Ichthyosis (dry, scaly skin) and hypertrichosis are common [Incecik et al 2013].

Dental abnormalities can be detected early in life and are progressive. They can include thin enamel of deciduous and permanent teeth, dark discoloration of dentin, malocclusion, and anterior open bite [Zilberman & Bibi 2016].

Gastrointestinal system. Many affected individuals develop hepatosplenomegaly, which is possibly secondary to GAG accumulation. Swallowing dysfunction may lead to sialorrhea and feeding difficulties. Many individuals require feeding tubes to safely and efficiently meet their caloric needs.

Respiratory. Individuals are at risk of progressive upper airway obstruction. Many individuals experience both central and peripheral sleep apnea. Individuals are also at risk for aspiration pneumonia.

Metabolic acidosis. Loss of arylsulfatase A (ARSA) activity has been associated with renal dysfunction and increased predisposition to metabolic acidosis [Lorioli et al 2015]. The true risk in MSD is not currently known, but given that most affected individuals have decreased ARSA activity, this should be considered.

Brain MRI features. The most common findings are white matter (periventricular) abnormalities with U fiber sparing, radiating stripes, and severe white matter atrophy [Prasad et al 2014]. Other abnormal imaging findings include [van der Knaap & Valk 2013, Sabourdy et al 2015, Ahrens-Nicklas et al 2018]:

- Cerebral atrophy and/or cerebellar atrophy
- Abnormalities of the corpus callosum
- Dilatation of the ventricular system
- Prominence of the sulci
- Enlarged perivascular spaces
- Cervical cord compression
- Delayed myelination

Pathophysiology

The wide clinical spectrum seen in MSD is largely a function of the unique pathophysiology of this condition, as multiple pathways are affected by a common enzymatic defect. All known 17 human sulfatases may be affected; thus, the clinical presentation is a composite of the effects of each individual sulfatase deficiency [Hopwood & Ballabio 2001]. Of these sulfatases, nine have each been implicated in distinct human diseases (albeit with overlapping features) [Dierks et al 2009, Khateb et al 2018]. The clinical presentation is a combination of these nine enzymatic defects, with affected individuals having signs and symptoms of arylsulfatase A deficiency (metachromatic leukodystrophy), Maroteaux-Lamy syndrome, X-linked ichthyosis, mucopolysaccharidosis type II (Hunter syndrome), mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), and mucopolysaccharidosis type IVA (Morquio syndrome). The contribution to clinical phenotype from the sulfatases without a clinically defined phenotype is unknown.

Genotype-Phenotype Correlations

Sulfatase-modifying-factor-1 (SUMF1) protein stability and residual formylglycine-generating enzyme (FGE) activity influence the clinical presentation in individuals with pathogenic changes in *SUMF1*. Individuals with unstable SUMF1 protein and low residual FGE activity display a severe late-infantile onset phenotype with rapid progression of MSD and neurologic deterioration. Individuals with higher levels of residual FGE enzyme activity often have attenuated forms of MSD with fewer symptoms, slower disease progression, and later onset of regression. Biallelic nonsense variants and deletions have been reported and are associated with a severe neonatal presentation [Schlotawa et al 2008, Schlotawa et al 2013, Sabourdy et al 2015].

For a small subset of pathogenic missense variants, experimental evidence for residual SUMF1 activity and FGE stability has been published and specific genotype-phenotype correlations exist.

- Homozygosity for the p.Gly263Val or p.Ala279Val *SUMF1* alleles is associated with attenuated late-infantile MSD.
- Homozygosity for the p.Ser155Pro, p.Gly247Arg, or p.Arg349Trp *SUMF1* alleles is associated with severe late-infantile MSD [Cosma et al 2004, Schlotawa et al 2008, Schlotawa et al 2011, Schlotawa et al 2013].

Non-experimental prediction methods attempting to correlate a particular *SUMF1* variant with FGE stability and clinical phenotype are not exact. There is no reliable genotype-phenotype correlation possible for affected individuals with compound heterozygous pathogenic missense variants. Finally, laboratory parameters, especially single sulfatase activity, GAG, and sulfatide levels, do not correlate well with the clinical presentation and can be normal in some cases [Sabourdy et al 2015, Ahrens-Nicklas et al 2018].

Nomenclature

Other terms used to describe MSD are Austin disease (named after Dr James Austin, who first described the condition [Austin et al 1964]), juvenile sulfatidosis, and mucosulfatidosis.

Prevalence

The estimated prevalence of MSD is one in 1.4 million individuals. There have been approximately 75-100 cases reported to date [Hopwood & Ballabio 2001, Ahrens-Nicklas et al 2018], with approximately 50 living affected individuals identified through support and advocacy groups. MSD has been reported in individuals of all ethnicities throughout the world [Artigalás et al 2009, Incecik et al 2013, Meng et al 2013, Garavelli et al 2014]. It is likely that this condition is underrecognized and underdiagnosed, particularly in areas of the world where access to advanced molecular genetic testing is not readily available.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SUMF1*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Multiple Sulfatase Deficiency (MSD)

Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MSD	Distinguishing from MSD
Arylsulfatase A deficiency (metachromatic leukodystrophy; MLD)	*ARSA*	AR	All MLD features can be found in MSD, incl central & peripheral demyelination & progressive neurologic deterioration	Absence of other systemic findings assoc w/MSD
Saposin B deficiency (OMIM 249900)	*PSAP*	AR	All saposin B deficiency features can be found in MSD, incl central & peripheral demyelination & progressive neurologic deterioration	Absence of other systemic findings assoc w/MSD
Mucolipidosis II (I-cell disease)	*GNPTAB*	AR	Severe infantile onset, progressive neurologic deterioration, skeletal deformities (incl dysostosis multiplex), postnatal growth restriction, cardiac involvement, skin thickening, recurrent ear infections	Severe contractures (although joint mobility issues may be seen in MSD)
Krabbe disease	*GALC*	AR	Central & peripheral demyelination, progressive neurologic deterioration	Absence of: cardiac & ophthalmologic complications, skeletal involvement (incl dysostosis multiplex), ichthyosis, hydrocephalus, hepatosplenomegaly, oral & dental issues, hearing loss, recurrent ear infections, upper airway obstruction
Alexander disease	*GFAP*	AD	Central demyelination & hydrocephalus, progressive neurologic deterioration	Absence of: cardiac & ophthalmologic complications, skeletal involvement (incl dysostosis multiplex), ichthyosis, hepatosplenomegaly, oral & dental issues, hearing loss, recurrent ear infections, upper airway obstruction

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MSD	Distinguishing from MSD
Canavan disease	*ASPA*	AR	Central demyelination, progressive neurologic deterioration, macrocephaly	Absence of: cardiac & ophthalmologic complications, skeletal involvement (incl dysotosis multiplex), ichthyosis, hepatosplenomegaly, oral & dental issues, hearing loss, recurrent ear infections, upper airway obstruction
Fucosidosis (OMIM 230000)	*FUCA1*	AR	Progressive neurologic deterioration, dysostosis multiplex, coarse facial features	Absence of: cardiac & ophthalmologic complications, ichthyosis, hepatosplenomegaly, oral & dental issues, hearing loss, recurrent ear infections, upper airway obstruction
MPS I [1]	*IDUA*	AR	DD, skeletal involvement, growth restriction, corneal clouding, cardiac involvement, hepatosplenomegaly, dysmorphic features	Facial dysmorphic features & cardiac involvement are more prominent in MPS I.
MPS II (Hunter syndrome)	*IDS*	XL	DD, short stature, skeletal involvement, hepatosplenomegaly, dysmorphic features	Females rarely affected; corneal clouding not a typical feature
MPS III (Sanfilippo syndrome) (OMIM 252900, 252920, 252930, 252940)	*GNS* *HGSNAT* *NAGLU* *SGSH*	AR	Neurodegeneration, DD, hepatosplenomegaly (<50% of persons w/Sanfilippo syndrome)	May have slower, more insidious course presenting mainly w/cognitive & neurologic signs & symptoms
MPS IV (Morquio syndrome) (See MPS IVA, *GLB1*-Related Disorders.)	*GALNS* *GLB1*	AR	Skeletal involvement, hearing loss, facial dysmorphic features	More severe skeletal involvement; MPS IVA does not present w/ID.
MPS VI (Maroteaux-Lamy syndrome) (OMIM 253200)	*ARSB*	AR	Dysmorphic features, hepatosplenomegaly, short stature, corneal clouding, skeletal involvement	More severe skeletal involvement; absence of ID
X-linked ichthyosis (OMIM 308100)	*STS*	XL	Corneal opacities, ichthyosis	Females rarely affected; absence of DD & neurodegeneration
Chondrodysplasia punctata 1, X-linked	*ARSL* (*ARSE*)	XLR	DD in 15%-20% of affected persons, short stature, epiphyseal stippling, cataracts, hearing loss	Females rarely affected; characteristic facial appearance; absence of neurodegeneration
Hexosaminidase A deficiency (Tay-Sachs disease)	*HEXA*	AR	Progressive neurodegeneration, DD, spasticity, blindness, death in infancy	Cherry red spot of the fovea [2]; absence of skeletal abnormalities & hepatomegaly
Hexosaminidase A/B deficiency (Sandhoff disease)	*HEXB*	AR	Progressive neurodegeneration, DD, spasticity, blindness, death in infancy	Cherry red spot & ↑ startle response [3]; hepatomegaly & skeletal abnormalities are less common than in MSD

AD = autosomal dominant, AR = autosomal recessive, MOI = mode of inheritance: XL = X-linked; DD = developmental delay; ID = intellectual disability; MPS = mucopolysaccharidosis

1. Severe or attenuated MPS I; Note: while individuals with MPS I have traditionally been classified as having one of three MPS I syndromes (Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome), no easily measurable biochemical differences have been identified and the clinical findings overlap; thus, affected individuals are best described as having either severe or attenuated MPS I.

2. Cherry red spot of the fovea is not a typical finding in MSD.

3. Cherry red spot and increased startle response are not typical findings in MSD.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with multiple sulfatase deficiency, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Multiple Sulfatase Deficiency

System/Concern	Evaluation	Comment
Neurologic	Consultation w/neurologist	Due to risk for central & peripheral demyelination, seizures, & hydrocephalus
	Consideration of brain imaging	• To assess for hydrocephalus w/↑ intracranial pressure • Consider urgent head imaging for any rapid neurologic changes.
	EEG	If seizures are suspected
Musculoskeletal	Consideration of spine imaging (radiographs &/or MRI), incl C-spine images	• To assess for spine instability or stenosis leading to cord compression • Consultation w/neurosurgeon as indicated
	Assessment of overall bone health w/ consideration of 25(OH) vitamin D levels	If clinical concerns, addl testing (e.g., DXA scan) can be obtained.
Ophthalmologic	Consultation w/ophthalmologist for eval of eye complications & measurement of intraophthalmic pressure	To assess for glaucoma, corneal clouding, retinopathy, strabismus, optic nerve abnormalities, & cataracts
Cardiovascular	Consultation w/cardiologist for baseline EKG & echocardiogram	To assess for presence of cardiac hypertrophy, cardiac valve issues, arrhythmias, & hypertension
Otolaryngologic	Audiologic evaluation, w/consideration of brain stem auditory-evoked response testing	To assess for hearing loss
	Consultation w/otolaryngologists if neck manipulation &/or anesthesia is needed	Consideration of direct airway visualization & C-spine imaging due to progressive airway obstruction (particularly w/neck hyperextension)
Skin	Consider consultation w/dermatologist.	For those w/severe skin involvement or concerns for secondary infections
Dental	Consider consultation w/pediatric dentist.	To assess for tooth enamel abnormalities &/or hyperplastic gums
Gastrointestinal	Assessment of growth parameters & feeding ability	Many persons w/MSD are unable to safely & efficiently meet caloric needs by mouth; consider alternate routes (e.g., gastrostomy tubes).
	Consideration of baseline swallowing study	To assess for swallowing dysfunction
	Abdominal ultrasound & serum liver enzyme testing [1]	To assess for hepatosplenomegaly & liver dysfunction
Respiratory	Consideration of baseline sleep study	To assess for obstructive sleep apnea
	Consideration of pulmonary function assessment, end tidal CO_2, &/or bronchoscopy	To assess for obstructive &/or restrictive airway disease, central &peripheral apneas, recurrent pneumonia, & tracheomalacia
Renal/metabolic	As the renal dysfunction is under-characterized at this time, labs should be obtained as clinically indicated.	Consider consultation w/nephrologist for those w/metabolic acidosis.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Developmental	Developmental assessment	To incl assessment of age-appropriate motor, speech/language, cognitive skills
Miscellaneous/ Other	Baseline measurement of sulfatase activity, urinary extretion of sulfatide, & GAGs	Measurement of levels not needed for clinical monitoring
	Consultation w/clinical geneticist &/or genetic counselor	

DXA = dual-energy x-ray absorptiometry; GAGs = glycosaminoglycans
1. Measurement of serum AST, ALT, and GGT

Treatment of Manifestations

A detailed clinical management guide was recently published delineating a symptomatic management strategy [Ahrens-Nicklas et al 2018] (full text).

While there are no targeted therapeutic options to date, many complications are amenable to symptomatic management [Adang et al 2017]. An individualized care plan can be designed by the primary and specialist providers. In addition to the primary care provider, the care team will often include neurologists, metabolic geneticists with genetic counselors, gastroenterologists, ophthalmologists, cardiologists, and physiatrists. Additional care providers may include speech therapists, occupational therapists, physical therapists, nutritionists, and dentists. Special efforts should be made to maintain mobility and social communication skills until such skills are lost.

Table 4. Treatment of Manifestations in Individuals with Multiple Sulfatase Deficiency

Manifestation/Concern	Treatment	Considerations/Other
Progressive hydrocephalus	Standard management by neurosurgery	Urgent head imaging should be considered in anyone w/sudden changes in neurologic status (e.g., altered mental status, ↑ vomiting)
Seizures	Standard anti-seizure medication [1]	
Spasticity	Standard therapeutic options may incl baclofen &/or botulinum toxin type A.	Physical therapy & physiatry consultations for optimization of mobility & tone
Spine instability or stenosis	Referral to orthopedist &/or neurosurgeon	
Poor bone health	Supplementation w/vitamin D	Consider referral to endocrinology
	Encourage weight-bearing exercise as tolerated.	Physical therapy & physiatry consultations for optimization of mobility & tone
Glaucoma, strabismus, corneal clouding, &/or cataracts	Standard treatment per ophthalmologist	
Cardiac hypertrophy, cardiac valve issues, arrhythmias, & hypertension	Standard therapy per cardiologist	
Hearing loss	Treatment of SNHL & conductive hearing loss per ENT/audiologist [2]	
Anesthesia precautions	Safe airway maintenance particularly during procedures that may require neck hyperextension	Due to progressive upper-airway obstruction & risk for cervical spine instability
		Assessment of airway constriction so that if required, appropriate-size devices (e.g., endotracheal tubes) are used

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Poor growth	Standard treatment per nutrition specialists	
Feeding difficulties	Consideration of alternative routes for nutrition (e.g., NG or G-tube)	Speech therapy consultation if concerns re efficiency or safety of oral feeding; GI or surgery consultation as clinically indicated
Tooth & gum anomalies	Standard treatment per pediatric dentist	
Obstructive sleep apnea	Many children w/MPS receive an adenoidectomy &/or tonsillectomy, although a higher complication rate should be noted.	Consider referral to sleep medicine specialist &/or pulmonologist.
	Some children may benefit from ventilatory support (CPAP, BiPAP).	Advanced testing such as PFTs & sleep studies can be considered.
Respiratory issues	Standard treatment per pulmonologist	

G = gastrostomy; NG = nasogastric; PFTs = pulmonary function tests
1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. See Hereditary Hearing Loss and Deafness Overview for details about treatment options.

Surveillance

No definitive surveillance guidelines have been established, although particular attention to and monitoring of the cardiac, respiratory, ophthalmologic, neurologic, skeletal, and gastroenterologic systems is indicated [Ahrens-Nicklas et al 2018].

Table 5. Surveillance to Consider for Individuals with Multiple Sulfatase Deficiency

System/Concern	Evaluation	Frequency
Neurologic	Head circumference measurement	At each visit
	Serial brain/spine imaging [1]	As needed based on symptoms
Musculoskeletal	Vitamin D level [2]	Annually or as needed
	C-spine imaging (radiographs &/or MRI)	Prior to any procedure (incl intubation) that requires neck extension
Ophthalmologic	Eye exam & intraocular pressure assessment	At least annually or as needed
Cardiovascular	Serial EKG & echocardiography [3]	At least annually
Otolaryngologic	Audiology eval	At least annually, or as needed
Gastrointestinal/ Nutrition	Weight & height measurements	W/all clinical assessments
	Serial abdominal ultrasound eval [4]	As clinically indicated
Respiratory	Consideration of sleep study& PFTs	Periodically
Renal/Metabolic	Monitoring of blood & urine acid-base balance	As clinically indicated & w/episodes of physiologic stress
Developmental	Assessment of developmental milestones & current developmental level	At each visit
	Neuropsychiatric testing	As clinically indicated

PFT = pulmonary function test
1. To screen for progressive hydrocephalus and/or cord compression
2. To monitor bone health
3. To monitor for cardiac hypertrophy, progressive valvular abnormalities, arrhythmia, and hypertension
4. With special attention to the liver, gallbladder, and spleen

Agents/Circumstances to Avoid

Individuals should avoid neck hyperextension, including hyperextension used for intubation, because of the risk of spinal cord compression. Foods that are choking hazards should also be avoided.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

A multi-institutional natural history study is underway through the Myelin Disorders Biorepository Project (Clinical Trials Identifier: NCT03047369).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Multiple sulfatase deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SUMF1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with multiple sulfatase deficiency are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SUMF1* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *SUMF1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SUMF1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MSD Action Foundation**
  Grattan Lodge
  Dublin
  Ireland
  Email: alanfinglas@gmail.com; info@msdactionfoundation.org
  www.MSDactionFoundation.org

- **United MSD Foundation**
  Phone: 228-295-7084
  www.curemsd.org

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org

- **MPS Society**
  United Kingdom
  Phone: 0345 389 9901
  Email: mps@mpssociety.org.uk
  www.mpssociety.org.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Multiple Sulfatase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SUMF1	3p26.1	Formylglycine-generating enzyme	SUMF1 database	SUMF1	SUMF1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Multiple Sulfatase Deficiency (View All in OMIM)

272200	MULTIPLE SULFATASE DEFICIENCY; MSD
607939	SULFATASE-MODIFYING FACTOR 1; SUMF1

Molecular Pathogenesis

Multiple sulfatase deficiency (MSD) is the result of a defect of the post-translational modification of cellular sulfatases. Sulfatases are a group of enzymes necessary for the breakdown of sulfate residues on macromolecules in cells (e.g., sulfatides, glycosaminoglycans, transcription factors). All newly synthesized sulfatases require activation by formylglycine-generating enzyme (FGE), encoded by *SUMF1*, for full catalytic activity. As the majority of cellular sulfatases are located in the lysosome, sulfatase dysfunction induces lysosomal storage of several substrates and cellular pathology (e.g., blockade of autophagy) leading to the symptoms that individuals with MSD experience [Dierks et al 2003, Cosma et al 2004, Dierks et al 2005, Sardiello et al 2005, Settembre et al 2008]).

Gene structure. *SUMF1* encodes a 2,152-bp transcript that contains nine exons. Eight alternatively spliced transcripts – encoding five protein isoforms with unknown clinical significance – have been predicted.

See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. More than 50 pathogenic *SUMF1* variants have been reported. Variant types include missense variants, insertions and deletions, and splicing and nonsense variants. Large copy number changes have also been reported. The most frequently observed MSD-causing variants are p.Gly247Arg, p.Ser155Pro, p.Arg349Trp, p.Ala279Val, p.Arg345Cys, and p.Gly263Val. Abundant hot spots for missense loss-of-function variants are p.Asn259 (variants p.Asn259Ile,Lys,Ser) and p.Arg349 (variants p.Arg349Gly,Glu,Trp). 31% of all variants are private [Authors, unpublished data].

Table 6. *SUMF1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.463T>C	p.Ser155Prp	NM_182760.3 NP_877437.2
c.739G>C	p.Gly247Arg	
c.788G>T	p.Gly263Val	
c.836C>T	p.Arg279Val	
c.1033C>T	p.Arg345Cys	
c.1045C>T	p.Arg349Trp	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *SUMF1* encodes the sulfatase-modifying-factor-1 protein, alternatively named formylglycine-generating enzyme (FGE), a 374-amino acid protein. FGE contains a single core domain with an

N-terminal extension (amino acids 34-72) and a low amount of secondary structure. It is stabilized by two cysteine interactions. Four additional cysteine residues are involved in the enzyme's catalytic function with p.Cys336 and p.Cys341 forming the active site of FGE.

FGE recognizes newly synthesized sulfatases via an amino acid motif (CXPSR) that is present in all sulfatases. FGE oxidizes the cysteine to an aldehyde, C-alpha-formylglycine,which is indispensable for sulfatase catalytic function [Dierks et al 2005, Sardiello et al 2005].

Abnormal gene product. MSD occurs though a loss-of-function mechanism as evidenced by missense variants reducing protein stability and enzymatic activity. The majority of disease-associated missense variants result in an unstable FGE protein with a reduced half-life and reduced enzymatic activity.

A minority of FGE protein pathogenic variants alter regulation by the ER quality-control process, protein-disulfide-isomerase (PDI). These variants result in an abnormal arrangement of intramolecular stabilizing disulfide bridges; PDI recognizes the misfolded FGE and induces early degradation [Dierks et al 2005, Schlotawa et al 2008, Schlotawa et al 2011, Schlotawa et al 2013, Meshach Paul et al 2018, Schlotawa et al 2018].

Both the *SUMF1* and sulfatase genes and protein structures are highly evolutionarily conserved. No alternative sulfatase activation mechanism exists in eukaryotes. FGE is predominantly localized to the endoplasmic reticulum but is also secreted. The function of secreted FGE is unknown. Known interacting partners are redox proteins in the ER (e.g., PDI and ERp44) and its nonfunctional homolog SUMF2 (pFGE) [Landgrebe et al 2003, Preusser-Kunze et al 2005, Fraldi et al 2008, Mariappan et al 2008a, Mariappan et al 2008b].

Chapter Notes

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