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Arylsulfatase A Deficiency

Synonyms: ARSA Deficiency, Metachromatic Leukodystrophy

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Summary

Clinical characteristics

Arylsulfatase A deficiency (also known as metachromatic leukodystrophy or MLD) is characterized by three clinical subtypes: late-infantile, juvenile, and adult MLD. The age of onset within a family is usually similar. The disease course may be from several years in the late-infantile-onset form to decades in the juvenile- and adult-onset forms.

Late-infantile MLD: Onset is before age 30 months. Typical presenting findings include weakness, hypotonia, clumsiness, frequent falls, toe walking, and dysarthria. Language, cognitive, and gross and fine motor skills regress as the disease progresses. Later signs include spasticity, pain, seizures, and compromised vision and hearing. In the final stages, children have tonic spasms, decerebrate posturing, and general unawareness of their surroundings.

Juvenile MLD: Onset is between age 30 months and 16 years. Initial manifestations include a decline in school performance and the emergence of behavioral problems, followed by gait disturbances. Progression is similar to but slower than in the late-infantile form.

Adult MLD: Onset occurs after the age of 16 years, sometimes not until the fourth or fifth decade. Initial signs can include problems in school or job performance, personality changes, emotional lability, or psychosis; in others, neurologic symptoms (weakness and loss of coordination progressing to spasticity and incontinence) or seizures predominate initially. Peripheral neuropathy is common. The disease course is variable, with periods of stability interspersed with periods of decline, and may extend over two to three decades. The final stage is similar to earlier-onset forms.

Diagnosis/testing

The diagnosis of MLD is established in a proband with the suggestive findings of progressive neurologic dysfunction, brain MRI evidence of leukodystrophy, or arylsulfatase A enzyme deficiency by identification of

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biallelic *ARSA* pathogenic variants on molecular genetic testing, elevated urinary excretion of sulfatides, or – less commonly – metachromatic lipid deposits in nervous system tissue.

Management

Targeted therapy: Allogeneic hematopoietic stem cell transplantation (HSCT) can treat primary central nervous system manifestations in those with pre- and very early symptomatic juvenile- or adult-onset MLD. Autologous HSCT using gene-modified hematopoietic stem cells (also known as ex vivo gene therapy) is approved in the European Union and United Kingdom for individuals who have either asymptomatic late-infantile or early juvenile disease. or early symptomatic early juvenile MLD with maintained ability to walk independently and before the onset of cognitive decline.

Supportive care: Developmental and educational support. Treatment per orthopedist, physical medicine and rehabilitation, and physical and occupational therapists to avoid contractures and falls and maintain neuromuscular function and mobility, muscle relaxants for contractures, and safety measures for gait or movement limitations. Feeding therapy, swallowing aids, suction equipment, and other standard treatments for drooling, swallowing difficulty, and gastroesophageal reflux. Gastrostomy tube as needed for feeding. Treatment of seizures using anti-seizure medications in standard protocols. Standard treatments for impaired vison and/or hearing and respiratory issues. Family support to enable parents and/or caregivers to anticipate decisions on walking aids, wheelchairs, feeding tubes, and other changing care needs.

Surveillance: Brain MRI examination to monitor the status of demyelination using MLD brain MRI severity scoring with frequency per neurologist. Assess motor function and support needs using gross motor function measurement (GMFM). Monitor for disease exacerbations following febrile infections. At each visit, assess physical mobility, self-help skills, development, neurobehavioral and psychiatric issues, growth, nutrition, safety of oral intake, need for feeding support, constipation, respiratory issues, and family needs. Vision and hearing assessment as needed.

Genetic counseling

MLD is inherited in an autosomal recessive manner. 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. Carrier testing of at-risk family members and prenatal testing for a pregnancy at increased risk are possible if both *ARSA* pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Arylsulfatase A deficiency (also known as metachromatic leukodystrophy or MLD) **should be suspected** in individuals with the following:

- **Progressive neurologic dysfunction.** Presenting signs may be behavioral or motor. Symptoms can occur at any age beyond one year and follow a period of normal development.
- **Evidence of a leukodystrophy on brain MRI.** Diffuse symmetric abnormalities of periventricular myelin with hyperintensities on T_2-weighted images. Initial parieto-occipital preponderance is observed in most individuals with late-infantile MLD, with subcortical U-fibers and cerebellar white matter spared. The abnormal white matter is often described as having a tigroid pattern or radial stripes. As the disease progresses, MRI abnormalities become more pronounced in a rostral-to-caudal progression, and cerebral atrophy develops [Groeschel et al 2011]. Anterior lesions may be more common initially in individuals

with later onset. Not all persons with MLD show white matter lesions initially. Isolated cranial nerve enhancement preceding intraparenchymal white matter involvement has been reported [Morana et al 2009, Singh et al 2009].

- **Arylsulfatase A enzyme deficiency.** Arylsulfatase A enzyme activity in leukocytes that is less than 10% of normal controls using the usual synthetic-substrate-based assay. Decreased arylsulfatase A enzyme activity is not sufficient for the diagnosis of MLD, as it may reflect arylsulfatase A enzyme pseudodeficiency.

  Note: (1) The use of low-temperature assays can minimize interference by other arylsulfatases and lower the baseline level [Rip & Gordon 1998]. (2) Cultured skin fibroblasts have often been used to confirm deficiency of arylsulfatase A enzyme activity and to evaluate the capacity of intact cells for sulfatide breakdown (sulfatide loading test). Such testing is usually not necessary for establishing the diagnosis but can be useful when the diagnosis is ambiguous (pseudodeficiency vs late-onset MLD) or made presymptomatically. (3) Enzyme activity and sulfatide loading can be performed in cultured amniocytes or chorionic villus sampling (CVS) cells for prenatal diagnoses (see Genetic Counseling, Prenatal Testing and Preimplantation Genetic Testing).

Arylsulfatase A enzyme pseudodeficiency. Pseudodeficiency is suggested by arylsulfatase A enzyme activity in leukocytes that is 5% to 20% of normal controls. Pseudodeficiency is difficult to distinguish from true arylsulfatase A enzyme deficiency by biochemical testing alone.

Note: For MLD, the term "pseudodeficiency" refers to very low levels of arylsulfatase A enzyme activity in an otherwise healthy individual. The term has been applied to other enzyme deficiency disorders, such as hexosaminidase A deficiency, where specific variants are associated with reduced enzymatic activity when measured using a synthetic substrate but have normal enzymatic activity when measured using a natural substrate.

Newborn screening for MLD. Newborn screening (NBS) for MLD is under consideration due to advancements in therapy. However, the enzyme activity-based approach faces challenges, primarily due to the frequent occurrence of arylsulfatase A enzyme pseudodeficiency and the difficulty distinguishing MLD from pseudodeficiency. To address this, a two-tier algorithm has been developed for screening MLD in dried blood spots (DBS) [Hong et al 2021]. This algorithm utilizes C16:0 sulfatide as the primary test and assesses arylsulfatase A enzyme activity when abnormal C16:0 sulfatide levels are detected. The feasibility of this algorithm was demonstrated through testing on 27,335 newborns [Hong et al 2021].

MLD is among the 14 disorders included in ScreenPlus, a pilot NBS study including 100,000 infants [Kelly et al 2024] designed to evaluate feasibility, efficacy, accuracy of screening assays, and the prevalence of the disease. The data acquired through this pilot program will be instrumental in the federal US Recommended Uniform Screening Panel (RUSP) nomination process, potentially paving the way for introducing MLD NBS in other regions and countries.

Establishing the Diagnosis

The diagnosis of MLD **is established** in a proband with suggestive findings (e.g., progressive neurologic dysfunction, brain MRI evidence of leukodystrophy, or arylsulfatase A enzyme deficiency) by ANY of the following:

- Identification of biallelic *ARSA* pathogenic variants on molecular genetic testing (See Table 1.)
- Identification of increased urinary excretion of sulfatides (See Other Testing.)
- Identification of metachromatic lipid deposits in nervous system tissue following a nerve or brain biopsy (See Other Testing.)

Molecular Genetic Testing

Three classes of *ARSA* alleles resulting in reduced arylsulfatase A enzyme activity need to be distinguished (see Genotype-Phenotype Correlations):

- *ARSA* pathogenic variants that cause MLD (*ARSA*-MLD alleles) in the homozygous or compound heterozygous state
- *ARSA* alleles with sequence variants resulting in pseudodeficiency (*ARSA*-PD)
- Alleles with two *ARSA* sequence variants on the same chromosome (*cis* configuration). For example, individuals can have *ARSA*-MLD and *ARSA*-PD alleles in *cis*.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype. Parental testing may be necessary to determine the phase of the identified variants in the proband.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with progressive neurologic dysfunction are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ARSA* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *ARSA* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (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 phenotype is indistinguishable from many other inherited disorders characterized by progressive neurologic dysfunction, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most used; **genome sequencing** is also possible.

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 Arylsulfatase A Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ARSA	Sequence analysis [3]	90%-95% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are undetected. For issues to consider in the interpretation of sequence analysis results, click here [Karczewski et al 2020].
4. This test method also detects the *ARSA* pseudodeficiency alleles (termed *ARSA*-PD), common variants that result in lower-than-average arylsulfatase A enzyme activity but **do not cause MLD** either when biallelic or compound heterozygous with an *ARSA*-MLD allele.
5. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Complete deletion of *ARSA* associated with MLD has been reported [Eng et al 2004, Bisgaard et al 2009].

Other Testing

Urinary Sulfatides

Individuals with all types of MLD excrete abnormally high sulfatides in urine. These can be quantified by high-performance liquid chromatography (HPLC), mass spectrometry, and thin-layer chromatography (TLC). TLC is a semiquantitative method. For HPLC and mass spectrometry, reference and pathologic values vary by laboratory. For sample preparation, it is important to note that wipes containing soaps and lotions should be avoided before collection, as these products may interfere with the accuracy of the test results. Lab specimen collection recommendations also vary. Some require a first morning, random urine specimen, while others may require a 24-hour collection. The samples are stable refrigerated or at ambient temperature for up to 45 days. Samples can also be frozen and remain stable for up to 19 months.

ARSA-PD/*ARSA*-MLD compound heterozygotes can excrete higher-than-normal amounts of sulfatides but urinary sulfatide excretion is not as elevated as in individuals with MLD (usually >10x normal).

Note: Elevated urine sulfatides and arylsulfatase A enzyme deficiency in the presence of dysmorphic features, dysostosis multiplex, or ichthyosis should prompt evaluation for multiple sulfatase deficiency (see Differential Diagnosis).

Metachromatic Lipid Deposits in a Nerve or Brain Biopsy

Sulfatides interact strongly with certain positively charged dyes used to stain tissues, resulting in a shift in the color of the stained tissue termed metachromasia. When frozen tissue sections are treated with acidified cresyl violet (Hirsch-Peiffer stain), sulfatide-rich storage deposits stain a golden brown. The finding of metachromatic lipid deposits in nervous system tissue is pathognomonic for MLD.

Note: (1) Fixing the tissue with alcohol before staining extracts the sulfatides such that the metachromasia is no longer observed. (2) Although still considered by some to be the diagnostic "gold standard" for MLD, this highly invasive approach is now used only in exceptional circumstances (e.g., confirmation of a prenatal diagnosis of MLD following pregnancy termination).

Clinical Characteristics

Clinical Description

The clinical presentation of arylsulfatase A deficiency (also known as metachromatic leukodystrophy or MLD) is heterogeneous with respect to the age of onset, the rate of progression, and the initial symptoms. Three clinical subtypes of MLD are primarily distinguished by age of onset:

- Late-infantile MLD, comprising 50%-60% of affected individuals
- Juvenile MLD, approximately 20%-40%
- Adult MLD, approximately 10%-20%

The age of onset within a family is usually similar, but exceptions occur [Arbour et al 2000]. Although the presenting symptoms and age of onset vary, all individuals eventually develop complete loss of motor, sensory, and cognitive functions. The disease course may be from several years in the late-infantile-onset form to decades in the juvenile- and adult-onset forms [Gieselmann & Ingeborg 2019]. Death most commonly results from pneumonia or other infection. Life span correlates roughly with the age of onset but can be quite variable, particularly in the later-onset forms. Furthermore, the presenting symptoms appear to correlate with the rate of disease progression. Motor symptoms predict a faster deterioration compared to cognitive symptoms [Kehrer et al 2021].

Late-infantile MLD. Age of onset is before age 30 months, following a period of apparently normal development. In the initial stage, weakness, hypotonia, and depressed deep tendon reflexes are observed. Other presenting signs are coordination difficulties (e.g., clumsiness, frequent falls, delayed or abnormal walking, strabismus, nystagmus, and dysarthria), clonus/tremor, and cognitive changes (e.g., cognitive delays, irritability, extreme fatigue, and nocturnal awakenings) [Eichler et al 2022]. Symptoms may first be noted following anesthesia or a febrile illness and may subside for weeks before continuing to progress. Less commonly, seizures are the first neurologic sign. Peripheral neuropathy with slow nerve conduction velocities (NCVs) is common. Brain auditory and visual evoked response testing demonstrate impairment in hearing and vision [Kehrer et al 2011a, Fumagalli et al 2021].

As the disease progresses, language, cognitive development, and gross and fine motor skills regress. Peripheral neuropathy can lead to pain in the arms and legs. In one study, individuals with the late-infantile form had lost the ability to sit without support and to move by age three years, and all had lost both trunk and head control by age three years, four months [Kehrer et al 2011a]. Eventually spasticity becomes prominent and bulbar involvement can result in airway obstruction and feeding difficulties, requiring gastrostomy tube placement. Notably, one study found that gastrostomy tube placement did not prolong survival in a cohort with late-infantile MLD [Fumagalli et al 2021]. Generalized or partial seizures can occur, and vision and hearing become progressively compromised. Eventually, the child becomes bedridden with tonic spasms, decerebrate posturing, and general unawareness. Most children die within five years after the onset of symptoms, although survival can extend into the second decade of life with current levels of care.

Juvenile MLD. Age of onset is between ages 30 months and 16 years, with a median age of six years, two months [Gieselmann & Ingeborg 2019]. Symptoms start insidiously and can include motor symptoms such as difficulty with coordination, tremors, abnormal movements, and a regression of fine motor skills. Cognitive symptoms may also manifest, such as learning difficulties, concentration issues, and behavioral disorders (e.g., personality changes, impulsive behavior, sleep problems, and loss of interest in activities) [Kehrer et al 2014, Eichler et al 2022].

Some medical professionals distinguish between early-onset and late-onset juvenile MLD, and recent studies support measurable differences between these two subgroups [Fumagalli et al 2021, Kehrer et al 2021]. The

early-onset juvenile form is typically diagnosed before the age of six years and shares many similarities with the late-infantile form. Some of the initial symptoms may include motor and gait disturbances. In contrast, the late-onset juvenile variant often presents initially with behavioral abnormalities, followed by a decline in school performance, language regression, and gait disturbances. For prognostic purposes, the age at onset and quality of symptoms should be considered, with presence of motor symptoms at onset being a negative prognostic factor [Kehrer et al 2021]. In general, the rate of motor deterioration is variable, but regardless of the age of onset, once motor deterioration begins, the regression tends to be rapid in all individuals with juvenile MLD [Kehrer et al 2011a]. Most individuals die before age 20 years, but survival is variable.

Adult MLD. Symptoms are first noted after sexual maturity (age ~16 years) but may not occur until the fourth or fifth decade. As with late-onset juvenile MLD, presenting symptoms vary. Initial signs are often related to cognitive dysfunction, such as emerging problems in school or job performance. Alcohol or drug use, poor money management, emotional lability, inappropriate affect, and frank psychosis often lead to psychiatric evaluation and an initial diagnosis of dementia, schizophrenia, or depression. In others, neurologic symptoms (weakness and loss of coordination progressing to spasticity and incontinence) predominate initially, leading to diagnoses of multiple sclerosis or other neurodegenerative diseases. Among published cases of adult MLD, 72% presented with dementia and behavioral difficulties, 16% with psychosis and schizophrenia, 28% with neuropathy, and 12% with seizures [Mahmood et al 2010]. Peripheral neuropathy is usually mild or not present.

The course is variable. Periods of relative stability may be interspersed with periods of decline. Inappropriate behaviors and poor decision making become problems for the family or other caregivers. Dressing and other self-help skills deteriorate. Eventually, bowel and bladder control are lost. As the disease advances, dystonic movements, spastic quadriparesis, or decorticate posturing occurs. Severe contractures and generalized seizures may occur. The duration of the disease ranges from several years to decades.

Other findings in MLD

- MRI of the brain is a powerful tool to investigate the involvement of the central nervous system in this disease. MLD primarily affects the white matter, and its changes during the disease can be seen on T_2-weighted MRI as hyperintense areas. Several scoring systems have been developed to evaluate disease severity and progression consistently [Eichler et al 2009, Sessa et al 2016]. The initial pathologic hallmarks of the disease include changes in the signal of periventricular white matter and involvement of the corpus callosum [Groeschel et al 2011, Fumagalli et al 2021, Schoenmakers et al 2022]. Longitudinal assessments show that the cerebellum is initially spared. Advanced MRI techniques and computational tools are being implemented to evaluate demyelination load and volume loss more accurately [Amedick et al 2023, Feldmann et al 2023].
- Several studies have addressed the electrophysiologic findings of peripheral neuropathy in MLD and their progression over time. Studies show that both motor and sensory NCVs show uniform slowing, as is expected for a demyelinating polyneuropathy [Raina et al 2019]. Measurement of NCVs is no longer necessary for diagnosis but can be used to monitor disease progression or responses in therapeutic trials.
- Brain stem auditory evoked responses (BAERs) are frequently found to be abnormal in individuals with late-infantile MLD. When studying the progression of late-infantile MLD, it has been observed that central waves in BAERs tend to disappear early, which is contrary to the expected pattern of progressive shortening of the I-V interpeak latency seen in healthy children during the first years of life, reflecting normal brain stem myelination. However, the use of BAERs is less straightforward in individuals with juvenile and adult MLD. Some individuals may exhibit recordings that are close to normal or maintain stable I-V interpeak latencies despite experiencing psychomotor deterioration [Fumagalli et al 2021].
- Sulfatide accumulation has been found outside the central nervous system in other organs. Accumulation n the gallbladder, hyperplastic polyps, hemobilia, and gallbladder carcinoma has been reported [van

Rappard et al 2016b]. Polypoid masses in the stomach and duodenum complicated by intestinal intussusception have also been reported [Yavuz & Yuksekkaya 2011].

Pathogenesis. MLD is a disorder of impaired breakdown of sulfatides (cerebroside sulfate or 3-O-sulfogalactosylceramide), sulfate-containing lipids that occur throughout the body and are found in greatest abundance in nervous tissue, kidneys, and testes. Sulfatides are critical constituents in the nervous system, where they comprise approximately 5% of the myelin lipids. Sulfatide accumulation in the nervous system eventually leads to myelin breakdown (leukodystrophy) and a progressive neurologic disorder [Gieselmann & Ingeborg 2019].

Genotype-Phenotype Correlations

There are three classes of *ARSA* alleles resulting in reduced arylsulfatase A enzyme activity:

- *ARSA* pathogenic variants that cause MLD (*ARSA*-MLD alleles) in the homozygous or compound heterozygous state
- *ARSA* alleles with sequence variants resulting in pseudodeficiency (*ARSA*-PD)
- Alleles with two *ARSA* sequence variants on the same chromosome (*cis* configuration). For example, individuals can have *ARSA*-MLD and *ARSA*-PD alleles in *cis* (*ARSA*-PD-MLD).

Arylsulfatase A enzyme activity

- The genotypes *ARSA*-MLD/*ARSA*-MLD, *ARSA*-PD-MLD/*ARSA*-MLD, and *ARSA*-PD-MLD/*ARSA*-PD-MLD result in arylsulfatase A enzyme activity that is 0%-10% of control values in synthetic-substrate-based assays.
- The genotype *ARSA*-PD/*ARSA*-MLD usually results in arylsulfatase A enzyme activity that is approximately 10% of control values.
- The genotype *ARSA*-PD/*ARSA*-PD results in arylsulfatase A enzyme activity that is approximately 10%-20% of control values.

Age of onset of MLD

- **Early-onset (late-infantile) MLD.** Affected individuals are usually homozygous or compound heterozygous for *ARSA*-MLD alleles that make no detectable functional arylsulfatase A enzyme (0-type or null alleles) [Cesani et al 2009]. The most common 0-type alleles are c.465+1G>A, c.1210+1G>A, and p.Asp257His.
- **Later-onset MLDs.** Affected individuals have one or two *ARSA*-MLD alleles that encode for an arylsulfatase A enzyme with some residual functional activity (≤1% when assayed with physiologic substrates) known as R-type alleles. The most common R-type *ARSA*-MLD alleles are p.Ile181Ser and p.Pro428Leu.
  - **Juvenile-onset MLD.** Often these individuals are compound heterozygous for an 0-type and an R-type allele.
  - **Adult-onset MLD.** Both alleles provide some residual enzyme activity (R-type *ARSA*-MLD alleles).

Adult MLD subtypes

- **Neurologic type.** Affected individuals are usually homozygous for the p.Pro428Leu R-type *ARSA*-MLD allele [Rauschka et al 2006].
- **Psychiatric type.** Affected individuals are usually compound heterozygous for the p.Ile181Ser allele and any other R-type *ARSA*-MLD allele [Rauschka et al 2006].

There are substantial limitations to using these genotype-phenotype correlations in predicting an affected individual's clinical presentation and natural history. The predictive value is best for individuals homozygous for

two 0-type alleles. Still, individuals with one or two R-type alleles show considerable phenotypic variability, implicating other genetic and/or environmental factors. Additional variants in the same allele can further affect enzyme function and disease severity [Regis et al 2002].

Arylsulfatase A pseudodeficiency

- ***ARSA*-MLD/*ARSA*-PD genotype.** Associated arylsulfatase A enzyme activity is 5% to 10% of normal controls.
  - The polyadenylation site variant c.*96A>G appears to contribute most strongly to the low arylsulfatase A enzyme activity characteristic of clinical pseudodeficiency [Harvey et al 1998].
  - The glycosylation site alteration p.Asn352Ser is associated with increased excretion of the newly synthesized enzyme from cells and a possible decrease in the arylsulfatase A enzyme within the lysosome [Harvey et al 1998].
  - The most common *ARSA*-PD allele in the European and North American populations has these two sequence variants in *cis* configuration, designated c.[1055A>G;*96A>G].
- ***ARSA*-PD/*ARSA*-PD genotype**
  - Homozygosity for the c.*96A>G variant (almost always in *cis* with p.Asn352Ser) is associated with arylsulfatase A enzyme activity that is approximately 10% of normal controls and could result in diagnostic uncertainty.
  - Homozygosity for the p.Asn352Ser variant alone results in 50% or more of the mean control arylsulfatase A enzyme activity in leukocytes.

Nomenclature

The term "metachromatic leukodystrophy" (*metachromatischen Leukodystrophien*) was first used by Peiffer [1959] to describe what had previously been known as "diffuse brain sclerosis."

The term "metachromatic leukoencephalopathy" has also been used.

MLD has also been referred to as "Greenfield's disease" after the first report of the late-infantile form of MLD.

Prevalence

Arylsulfatase A deficiency (MLD). The overall prevalence of MLD has been reported to be between 1:40,000 and 1:170,000 in different populations [Gieselmann & Ingeborg 2019]. Assuming the prevalence stated, the overall carrier frequency is predicted to be between 1:100 and 1:200. Based on data from the Genome Aggregation Database (gnomAD), it is estimated that the frequency of pathogenic and likely pathogenic variants (allele frequency) in *ARSA* is approximately 1 in 360. Using the Hardy-Weinberg formula, this frequency suggests an overall incidence of 1:130,000 [Karczewski et al 2020]. This is likely an underestimate, as variants currently classified as of unknown significance may be pathogenic [Trinidad et al 2023]. The disorder is pan ethnic; however, most data come from European and North American populations.

The following populations have an increased prevalence of MLD due to the presence of founder variants (figures are approximate; see Table 6):

- 1:75 in Habbanite Jewsish population in Israel
- 1:8,000 in Israeli Arabs
- 1:2,500 in individuals of Yup'ik ancestry from Alakanuk, Alaska
- 1: 6,400 in individuals of Navajo ancestry from the western portion of the Navajo Nation in the United States

***ARSA*-PD alleles.** The frequency of *ARSA*-PD variants is significantly higher as compared to *ARSA*-MLD variants. The p.Asn352Ser *ARSA*-PD variant is commonly found in all populations examined, including

African / African American (33.88%), Admixed American (27.81%), Middle Eastern (19.85%), Amish (18.09%), East Asian (16.40%), South Asian (14.73%), Ashkenazi Jewish (13.91%), European (non-Finnish) (12.68%), European (Finnish) (6.482%), and Other (14.85%) [Karczewski et al 2020] (see also gnomAD). Thus, individuals with biallelic *ARSA*-PD variants are more common than individuals with biallelic *ARSA*-MLD variants and individuals compound heterozygous for *ARSA*-PD/*ARSA*-MLD variants. *ARSA*-MLD variants can be found on a wild type allele or in *cis* on an *ARSA*-PD allele (*ARSA*-PD-MLD alleles).

Genetically Related (Allelic) Disorders

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

Individuals with 22q13.3 deletion syndrome (see Phelan-McDermid Syndrome) often have a deletion that involves *ARSA*. Presence of an *ARSA*-MLD or *ARSA*-PD allele on the homologous chromosome resulting in MLD or arylsulfatase A pseudodeficiency, respectively, has been reported in individuals with 22q13.3 deletion syndrome [Ahn et al 2020, Mingbunjerdsuk et al 2021].

Differential Diagnosis

Arylsulfatase A deficiency (metachromatic leukodystrophy or MLD). The two phenotypes that show notable overlap with MLD are multiple sulfatase deficiency and saposin B deficiency (see Table 2a).

Table 2a. Phenotypes That Show Notable Overlap with Arylsulfatase A Deficiency

Gene	Disorder	Age at Onset	Main Clinical Manifestations	Urinary Excretion	Enzyme Activity
SUMF1	Multiple sulfatase deficiency	1-4 yrs; probably variable	MLD-like clinical picture w/↑ CSF protein & slowed NCVs; MPS-like features; ichthyosis	↑ sulfatides ↑ glycosaminoglycans	Very low arylsulfatase A enzyme activity; deficiency of most sulfatases in leukocytes or cultured cells [1]
PSAP	Saposin B deficiency (OMIM 249900)	Variable	MLD-like clinical picture	↑ sulfatides ↑ ceramide trihexosides ↑ other glycolipids	Arylsulfatase A enzyme activity in normal range

CSF = cerebrospinal fluid; MLD = metachromatic leukodystrophy; MPS = mucopolysaccharidosis; NCV = nerve conduction velocity
1. Including arylsulfatase B, arylsulfatase C, galactose-6-sulfatase, glucuronate-2-sulfatase, iduronate sulfatase, heparan-N-sulfamidase, and N-acetylglucosamine-6-sulfatase

Note: Arylsulfatase A enzyme activity is also deficient in many tissues in defects of the phosphomannosyl lysosomal recognition pathway, such as mucolipidosis II (see *GNPTAB*-Related Disorders). The phenotype in mucolipidosis II is severe in infancy and is not likely to be confused with MLD.

Other leukodystrophies and lysosomal storage diseases. MLD is difficult to differentiate from other progressive degenerative disorders that manifest after a period of normal development. Delayed development in late infancy, coupled with loss of acquired abilities, should prompt brain MRI examination. If a generalized leukodystrophy is evident, other conditions to consider include those summarized in Table 2b.

Table 2b. Selected Progressive Degenerative Disorders That Manifest After a Period of Normal Development in the Differential Diagnosis of Arylsulfatase A Deficiency

Gene	Disorder	MOI	Clinical Characteristics
ABCD1	X-linked adrenoleukodystrophy (ALD)	XL	• *Childhood cerebral ALD*: Manifests most commonly in males between age 4-8 yrs. Initially resembles attention-deficit/hyperactivity disorder; progressive impairment of cognition, behavior, vision, hearing, & motor function follows the initial symptoms & often leads to total disability w/in 6 mos to 2 yrs. Most persons have impaired adrenocortical function at the time that neurologic disturbances are first noted. • *Adrenomyeloneuropathy*: Typical presentation is a male in his 20s or middle age who develops progressive stiffness & weakness in the legs, abnormalities of sphincter control, & sexual dysfunction.
ASPA	Canavan disease	AR	*Neonatal/infantile form:* Although such infants appear normal early in life, by age 3-5 mos hypotonia, head lag, macrocephaly, & DD become apparent. With age, children often become irritable & experience sleep disturbance, seizures, & feeding difficulties. Swallowing deteriorates, & some children require nasogastric feeding or permanent feeding gastrostomies. Joint stiffness increases, so that these children resemble persons w/cerebral palsy.
FUCA1	Fucosidosis (OMIM 230000)	AR	Fucosidosis is a condition that can be classified into two main types. • Type 1 is characterized by rapid psychomotor regression & severe neurologic deterioration, usually starting around age 6 mos. Assoc w/↑ sweat sodium chloride levels, & persons may not live beyond a decade. • Type 2 is characterized by milder DD & neurologic symptoms, development of angiokeratoma corporis diffusum, normal salt levels in sweat, & longer life expectancy.
GALC	Krabbe disease	AR	Spectrum ranging from infantile-onset disease (i.e., onset of extreme irritability, spasticity, & DD at age <12 mos) to later-onset disease (i.e., onset of manifestations at age >12 mos & as late as 7th decade). Infantile-onset disease is characterized by normal development in the first few mos followed by rapid severe neurologic deterioration. Later-onset Krabbe disease is much more variable in its presentation & disease course.
GFAP	Alexander disease	AR	Continuous clinical spectrum, most recognizable in infants & children, w/range of nonspecific neurologic manifestations in adults. • *Infantile form:* Variable developmental issues; initially some have delayed or plateauing of acquisition of new skills, followed in some by loss of gross & fine motor skills & language during 1st decade, or in others a slow disease course that spans decades. • *Juvenile form:* Manifestations in early childhood are milder than those in the infantile form (e.g., mild language delay may be the only developmental abnormality or, w/language acquisition, hypophonia or nasal speech may alter the voice, often prior to appearance of other neurologic features). Vomiting, poor growth, scoliosis, & autonomic dysfunction are common.
HEXA	Tay-Sachs disease & other gangliosidoses (See *HEXA* Disorders.)	AR	• *Classic clinical phenotype:* Progressive weakness, loss of motor skills beginning between age 3-6 mos, ↓ visual attentiveness, & ↑ or exaggerated startle response w/a cherry-red spot observable on retina followed by developmental plateau & loss of skills after 8-10 mos. • *Subacute juvenile:* Normal developmental milestones until age 2 yrs, when the emergence of abnormal gait or dysarthria is noted followed by loss of previously acquired skills & cognitive decline.

Table 2b. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
PLP1	Pelizaeus-Merzbacher disease (See *PLP1* Disorders.)	XL	Typically manifests in infancy or early childhood w/nystagmus, hypotonia, & cognitive impairment; findings progress to severe spasticity & ataxia.

AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance; XL = X-linked

Although some mucopolysaccharidoses can have a similar presentation to MLD, the characteristic physical features seen in most mucopolysaccharidoses (e.g., short stature, dysostosis multiplex, coarse facial appearance, corneal clouding, hepatosplenomegaly, pulmonary congestion, and heart problems) are not found in individuals with MLD. The evaluation of appropriate lysosomal enzymes can distinguish the disorders.

Arylsulfatase A pseudodeficiency. Because of the high prevalence of the *ARSA* pseudodeficiency (*ARSA*-PD) alleles, low arylsulfatase A enzyme activity caused by arylsulfatase A pseudodeficiency can be found in association with many disorders and can be erroneously implicated in individuals diagnosed with common psychiatric or neurologic disorders.

Management

Clinical practice guidelines for arylsulfatase A deficiency (also known as metachromatic leukodystrophy or MLD) have been published [Wang et al 2011] (full text).

Evaluations Following Initial Diagnosis

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

Table 3. Arylsulfatase A Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	• Neurologic eval • Measurement of arylsulfatase A enzyme activity • Measurement of urinary sulfatide excretion • Brain MRI to assess myelin integrity • EEG if concern for seizures • Peripheral nervous system eval, such as nerve conduction studies, can be used to monitor disease progression or responses in therapeutic trials. • BAERs can be used to assess progression in late-infantile MLD.	To assess disease progression & evaluate need for possible intervention
	Referral for HSCT eval, either allogeneic HSCT (US) or autologous gene-modified HSCT (EU & UK), preferably at institution w/expertise in allogenic HSCT in persons w/metabolic disorders	For those identified presymptomatically or predicted to have late-onset MLD (For more specific criteria see Targeted Therapy.)
Development	Developmental assessment	• To assess disease progression • To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl ADHD, school & work performance issues, & psychiatric manifestations

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Hearing	Audiologic eval	Assess for hearing loss.
Vision	Visual assessment	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of MLD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; BAERs = brain stem auditory evoked responses; EU = European Union; HSCT = hematopoietic stem cell transplantation; MLD = metachromatic leukodystrophy; MOI = mode of inheritance; UK = United Kingdom; US = United States

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Hematopoietic stem cell transplantation (HSCT) is an available therapy that attempts to treat the primary manifestations of MLD in the central nervous system. It can be performed using donor-derived stem cells (allogeneic HSCT) or gene-modified cells from the affected individual (autologous HSCT). Regardless of clinical type, HSCT should not be offered to individuals with significant neurologic involvement at the time of evaluation. Engraftment typically requires myeloablative conditioning, often with high doses of busulfan, which can cross the blood-brain barrier and cause neurologic decline [Boelens & van Hasselt 2016].

- **Allogeneic HSCT.** Despite significant improvement in allogeneic transplantation, this therapy remains controversial because:
  - Systematic outcome data are limited and difficult to generalize due to the use of different eligibility criteria and transplantation protocols;
  - Outcome data from older cohorts do not predict current outcomes given constantly improving transplant-related morbidity and mortality due to advances in donor-recipient human leukocyte antigen (HLA) typing and matching, conditioning, infectious disease detection and management, and the use of non-carrier donors; and
  - Different types of MLD have shown different responses.

  However, in the absence of alternative approaches, HSCT should be discussed with families, particularly with those with slower progressing, late-onset forms of MLD. At-risk relatives diagnosed by biochemical or molecular genetic testing before symptoms occur could benefit most from this intervention. Despite mounting evidence of utility, HSCT is not expected to fully abrogate the manifestations of the disease.

- **Juvenile and adult MLD.** Taken together, the data support that HSCT is a relatively safe procedure for individuals with pre- and early symptomatic juvenile or adult MLD [Krägeloh-Mann et al 2013, Martin et al 2013, Solders et al 2014, Boucher et al 2015, Chen et al 2016, Groeschel et al 2016, van Rappard et al 2016a, Beschle et al 2020, Videbæk et al 2021]. In these clinical types, HSCT can result in disease stabilization and high disease-burden-free survival. Compared with non-transplanted individuals, transplanted individuals are less likely to lose their gross motor or language function and demonstrate significantly lower brain MRI severity scores. Motor and cognitive function at the time of HSCT evaluation are good predictors of outcome: van Rappard et al [2016a] propose that individuals with affected motor (inability to walk without support) and cognitive (IQ <75) function receive no benefit from HSCT. Brain stem auditory evoked responses, visual evoked potentials, electroencephalogram, and/or peripheral nerve conduction velocities have been shown to stabilize or improve in individuals with juvenile MLD [Martin et al 2013]. Long-term neuroimaging after HSCT suggest that remyelination occurs [Ding et al 2012].
- **Late-infantile MLD.** Allogenic HSCT even at a presymptomatic stage has been shown to be ineffective and is not recommended [Bredius et al 2007, van Rappard et al 2016a]. Disease progression in late-infantile MLD is faster than the pace of engraftment and subsequent CNS migration of bone marrow-derived monocyte/macrophages, even in clinically asymptomatic individuals.

- **Autologous HSCT.** Atidarsagene autotemcel (Libmeldy®) is an autologous hematopoietic stem cell gene therapy product. It involves the ex vivo transduction of autologous $CD34^+$ stem cells using a lentiviral vector containing human *ARSA*. This treatment has shown sustained and clinically relevant benefits in children with early-onset MLD. It helps preserve cognitive and motor function while slowing the demyelination process and brain atrophy [Sessa et al 2016, Fumagalli et al 2022]. Atidarsagene autotemcel received marketing authorization for MLD treatment in December 2020 in the European Union and in January 2021 in the United Kingdom, and subsequent approval for the National Health Service (NHS, publicly funded healthcare system in the UK) by the National Institute for Health and Care Excellence (NICE) in February 2022 [Horgan et al 2023]. However, licensing criteria for this treatment are strict. It is approved only for individuals who have either asymptomatic late-infantile or early-juvenile MLD or early symptomatic early-juvenile MLD. These individuals must have early clinical signs of the disease but maintain the ability to walk independently and have not yet experienced cognitive decline.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in neurology, biochemical genetics, and pediatrics (see Table 4). Whether the intent is to prolong life or to let the disease run its natural course, an extended period of nursing care with changing needs can be anticipated. Supportive therapies to maximize the retention of physical and neuromuscular functions help avoid many end-stage care problems. The Evanosky Foundation has a very helpful document based on their family's experience, Suggestions for Caring for a Child with MLD (pdf). For further information on the specific nursing care requirements for those with MLD who undergo HCST or in late stages of the disease, see Barrell [2007].

Table 4. Arylsulfatase A Deficiency: Supportive Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	• See Developmental Delay / Intellectual Disability Management Issues. • Provision of enriched environment to support maintenance of intellectual abilities as long as possible	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Neuromuscular manifestations	• Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls & maintain neuromuscular function & mobility as long as possible • Aggressive PT is recommended. • Muscle relaxants for contractures • Safety measures for gait or movement limitations • See Motor Dysfunction.	Consider need for positioning & mobility devices, disability parking placard.
Feeding/Nutrition/ Gastrointestinal	• Feeding therapy, swallowing aids, suction equipment, & other standard treatments for drooling & swallowing difficulty • Gastrostomy tube placement may be required for persistent feeding issues. • Standard treatments for gastroesophageal reflux & constipation	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Eyes	No specific treatment	
Central visual impairment	No specific treatment	Early intervention program to stimulate visual development
Hearing	No specific treatment	Community hearing services through early intervention or school district
Anesthesia / Surgical complications	Anesthesia (if required) should be administered by experienced anesthesiologist.	Exacerbation of symptoms has been noted following anesthesia, as affected persons may have altered responses to sedatives & anesthetics. [2]
Bowel dysfunction	Treatments for constipation incl stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Respiratory	Standard treatments for respiratory failure & respiratory infections	
Family/Community	• Education re likely progression of disorder to facilitate decisions re future care needs • Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; MLD = metachromatic leukodystrophy; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Mattioli et al [2007], Birkholz et al [2009], Cappuccio et al [2013]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Arylsulfatase A Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	• Brain MRI to monitor status of CNS demyelination • MLD brain MRI severity scoring method to monitor progression & response to therapy [1]	Perform brain MRI based on clinical indication & rate of disease progression.
	Assess motor function & support needs using GMFM for MLD. [2]	Assessment of motor function & motor scoring should be performed at each visit.
	• Monitor those w/seizures as clinically indicated. • Monitor for disease exacerbations following febrile infections. • Assess for new manifestations such as seizures, contractures, changes in tone, & movement disorders.	At each visit
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Vision	Follow-up ophthalmology exam	As clinically indicated based on rate of disease progression
Hearing	Follow-up hearing exam	
Development	Monitor developmental progress & educational needs.	At each visit
Neurobehavioral/Psychiatric	Assessment for anxiety, ADHD, aggression, & self-injury	At each visit or as needed
Feeding/Nutrition	• Measurement of growth parameters • Eval of nutritional status, safety of oral intake, difficulties w/feeding or swallowing • Assessment of need for gastrostomy tube placement	At each visit
Gastrointestinal	Monitor for constipation.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Family/Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

CNS = central nervous system; GMFM = gross motor function measurement; MLD = metachromatic leukodystrophy; OT = occupational therapy; PT = physical therapy
1. Eichler et al [2009], Sessa et al [2016]
2. Kehrer et al [2011b]

Agents/Circumstances to Avoid

While environmental factors are thought to influence the onset and severity of MLD manifestations, no specific exacerbating agents are known. Initial symptoms are often noted following a febrile illness or other stress, but it is unclear if a high fever accelerates progression.

Excessive alcohol and drug use are often associated with later-onset MLD, but it is unclear if this is caused by the disease or is simply an attempt at self-medication in the face of increasing cognitive difficulties [Alvarez-Leal et al 2001].

Evaluation of Relatives at Risk

It is appropriate to consider evaluation of apparently asymptomatic sibs of a proband to identify those who could potentially benefit from HSCT and other treatment options. Although substantial risk is involved and long-term effects are unclear, the best clinical outcomes are obtained when HSCT occurs before clinical symptoms have appeared (see Targeted Therapy). Evaluations can include the following:

- Perform molecular genetic testing if the pathogenic variants in the family are known.
- If the pathogenic variants in the family are not known, workup should begin with measurement of urinary excretion of sulfatides.
- Measurement of arylsulfatase A enzyme activity in peripheral blood leukocytes or cultured fibroblasts can support the diagnosis but is not sufficient by itself. See Suggestive Findings, **Arylsulfatase A enzyme pseudodeficiency.**

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

Therapies Under Investigation

In vivo gene therapy. Allogeneic HSCT and autologous HSCT with gene-corrected cells is showing great benefit, primarily in presymptomatic individuals. These are promising therapies for individuals identified at

presymptomatic stages with a family history of MLD or perhaps individuals identified on future newborn screening. Unfortunately, most individuals diagnosed with MLD have no family history of MLD. Hence, most children with severe forms of MLD would not be diagnosed at the presymptomatic phase of the disease, making it unlikely for this therapeutic option to be offered or effective for many individuals with MLD. Accordingly, there is a need for therapies that can get to the brain quickly. One way to achieve this is with in vivo gene therapy via intrathecal or intracerebral delivery of viral vectors. A Phase I/II, open-labeled, monocentric study of direct intracranial administration of a replication-deficient adeno-associated virus gene transfer vector serotype rh.10 expressing the human *ARSA* cDNA to children with MLD is currently active (ClinicalTrials.gov). Other gene therapy vectors using different serotypes and mode of delivery are in earlier stages of development [Miyake et al 2021, Mullagulova et al 2023, St Martin et al 2023].

Enzyme replacement therapy (ERT). An alternative to in vivo gene therapy is ERT. For the most part, ERT has been considered impractical because of the difficulty of bypassing the blood-brain barrier. Clinical testing of intravenous recombinant human enzyme was discontinued in 2010 after a Phase I/II study failed to show substantial improvement [Í Dali et al 2021]. Intrathecal delivery of the enzyme is being tested in individuals with late-infantile form (ClinicalTrials.gov) and has thus far proven safe [Í Dali et al 2020].

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

Arylsulfatase A deficiency (also known as metachromatic leukodystrophy or MLD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ARSA* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ARSA* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ARSA* pathogenic variant, each sib of an affected individual has at conception 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. Unless an affected individual's reproductive partner also has MLD or is a carrier (see **Family planning**), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ARSA*.

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

Carrier Detection

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

Biochemical testing. Analysis of arylsulfatase A enzyme activity in leukocytes or cultured fibroblasts for carrier detection is reliable if the range of enzyme activity within a family is known; however, it is much less reliable for testing individuals with no family history of MLD because of the substantial variation in "normal" enzyme activity resulting from the high frequency of pseudodeficiency alleles.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk 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 affected, are carriers, or are at risk of being carriers.
- Carrier testing for reproductive partners of known carriers should be considered, particularly if consanguinity is likely and/or if both partners are of the same ethnic background. *ARSA* founder variants have been identified in the Yup'ik population of Alakanuk, Alaska, the Navajo population, and Habbanite and Yemenite Jewish populations (see Table 6).

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

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

Biochemical testing. Measurement of sulfatides in the amniotic fluid supernatant is feasible and can be useful in the prenatal diagnosis of MLD [Kubaski et al 2022]. Analysis of arylsulfatase A enzyme activity in cultured amniotic fluid cells or chorionic villus cells has also been used for the prenatal diagnosis of MLD.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **MLD Foundation**
  Phone: 503-656-4808; 800-617-8387
  Email: info@mldfoundation.org
  mldfoundation.org
- **MLD Newborn Screening**
  mldnewbornscreening.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Metachromatic Leukodystrophy
- **Canadian MPS Society for Mucopolysaccharidoses and Related Diseases**
  Canada
  Phone: 800-667-1846
  Email: info@mpssociety.ca
  www.mpssociety.ca
- **European Leukodystrophy Association (ELA)**
  Phone: 03 83 30 93 34
  www.ela-asso.com
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  www.ulf.org
- **MLD Initiative - International MLD Registry**
  www.mldinitiative.com
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  Myelin Disorders Bioregistry Project

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. Arylsulfatase A Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

ARSA	22q13.33	Arylsulfatase A	ARSA database	ARSA	ARSA

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 Arylsulfatase A Deficiency (View All in OMIM)

250100	METACHROMATIC LEUKODYSTROPHY; MLD
607574	ARYLSULFATASE A; ARSA

Molecular Pathogenesis

Arylsulfatase A synthesis and function. Arylsulfatase A has a precursor polypeptide of approximately 62 kD that is processed by N-linked glycosylation, phosphorylation, sulfation, and proteolytic cleavage to a complex mixture of isoforms that differs from tissue to tissue. During post-translational processing, the p.Cys71 must be converted to formylglycine before the sulfatase becomes active [Lukatela et al 1998, Dierks et al 2005].

In general, alleles with pathogenic splice site variants, insertions, or deletions do not produce any active enzyme (I-type *ARSA*-MLD variants). Approximately half of the variants involving an amino acid substitution also fall into this class but are more likely to express an immuno-cross-reactive material.

Between 20% and 25% of the single amino acid changes are associated with a low level (≤1%) of arylsulfatase A enzyme activity (A-type *ARSA*-MLD variants). In instances in which the properties of the mutated arylsulfatase A enzyme have been explored, processing and stability have been affected, leading to an altered enzyme or the altered ability of the protein to self-associate and an enhanced turnover of the mutated protein [von Bülow et al 2002, Poeppel et al 2005].

Pathophysiology. The molecular pathogenic processes involved in arylsulfatase A deficiency (also known as metachromatic leukodystrophy or MLD) need to be better understood. In MLD, the desulfation of 3-O-sulfogalactosyl-containing lipids is defective. Sulfatides are most abundant in the myelin of both the central and peripheral nervous systems and the kidneys. Additionally, they can be present in various other tissues, particularly those with specialized excretory cells, such as the respiratory epithelium, gastric mucosa, gallbladder, and uterine endometrium [Gieselmann & Ingeborg 2019]. Deficient arylsulfatase A activity results in progressive accumulation of sulfatides, mainly within lysosomes. The observed demyelination appears to be secondary to sulfatide-induced changes within the cells responsible for myelin maintenance, namely, the oligodendrocytes in the central nervous system and the Schwann cells in the peripheral nervous system. Psychosine sulfate (lyso-sulfatide) is also elevated in tissues from individuals with MLD, and a cytotoxic role parallel to that of psychosine in Krabbe disease has been suggested. Neuroinflammation has also been proposed based on experiments in murine models of MLD [Stein et al 2015].

Mechanism of disease causation. Loss of function

***ARSA*-specific laboratory technical considerations.** Molecular genetic testing also detects *ARSA* pseudodeficiency alleles (*ARSA*-PD), common variants that result in lower-than-average arylsulfatase A enzyme activity but **do not cause MLD** either in the homozygous state or in the compound heterozygous state with an *ARSA*-MLD allele. Disease-causing *ARSA*-MLD variants are as likely to be found in *cis* configuration with an *ARSA*-PD sequence variant as wild type alleles. One individual with intragenic recombination leading to somatic mosaicism has been reported [Regis et al 2006].

Table 6. *ARSA* Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_000487.6	c.*96A>G [2] (1524+96A>G)	--	*ARSA*-PD allele [2]
	c.465+1G>A (459+1G>A)	--	• Pathogenic variant (*ARSA*-MLD) typically assoc w/late-infantile onset (See Genotype-Phenotype Correlations.) • Common variant in persons of central & western European ancestry.
NM_000487.6 NP_000478.3	c.542T>G (536T>G)	p.Ile181Ser (Ile179Ser)	• Pathogenic variant (*ARSA*-MLD) typically assoc w/juvenile-or adult-onset (See Genotype-Phenotype Correlations.) • Common variant in persons of central & western European ancestry
	c.769G>C (763G>C)	p.Asp257His (Asp255His)	Pathogenic variant (*ARSA*-MLD) typically assoc w/late-infantile onset (See Genotype-Phenotype Correlations.)
NM_000487.6	c.854+1G>A	--	Pathogenic (*ARSA*-MLD) founder variant in Yup'ik population of Alakanuk, AK, & Navajo population [Pastor-Soler et al 1994, Pastor-Soler et al 1995]
NM_000487.6 NP_000478.3	c.1055A>G [2] (1049A>G)	p.Asn352Ser (Asn350Ser)	• *ARSA*-PD allele • Glycosylation site alteration • Common benign variant occurring in 15%-40% of persons. [2]
	c.1136C>T	p.Pro379Leu	Pathogenic (*ARSA*-MLD) founder variant in Habbanite & Yemenite Jewish populations [Zlotogora 2015]
NM_000487.6	c.1210+1G>A (1204+1G>A)	--	• Pathogenic variant (*ARSA*-MLD) typically assoc w/late-infantile onset (See Genotype-Phenotype Correlations.) • Common variant in persons of central & western European ancestry
NM_000487.6 NP_000478.3	c.1283C>T (1277C>T)	p.Pro428Leu (Pro426Leu)	• Pathogenic variant (*ARSA*-MLD) typically assoc w/juvenile-or adult-onset (See Genotype-Phenotype Correlations.) • Common variant in persons of central & western European ancestry

AK = Alaska; MLD = metachromatic leukodystrophy; PD = pseudodeficiency
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.
1. Variant designation that does not conform to current naming conventions
2. The most common *ARSA*-PD allele in the European and North American populations has two sequence variants in *cis* configuration, designated as c.[1055A>G;*96A>G].

Chapter Notes

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