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Consensus Guidelines for the Monitoring and Management of Metachromatic Leukodystrophy in the United States

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Abstract

Metachromatic leukodystrophy (MLD) is a fatal, progressive neurodegenerative disorder caused by biallelic pathogenic mutations in the *ARSA* (Arylsulfatase A) gene. With the advent of presymptomatic diagnosis and availability of therapies with a narrow window for intervention, it is critical to define a standardized approach to diagnosis, presymptomatic monitoring, and clinical care. To meet the needs of the MLD community, a panel of MLD experts was established to develop disease-specific guidelines based healthcare resources in the United States. This group developed a consensus opinion for best-practice recommendations, as follows: 1. Diagnosis should include both genetic and biochemical testing; 2. Early diagnosis and treatment for MLD is associated with improved clinical outcomes; 3. The panel supported the development of newborn screening to accelerate time to diagnosis and treatment; 4. Clinical management of MLD should include specialists familiar with the disease who are able to follow patients longitudinally; 5. In early onset MLD, including late infantile and early juvenile subtypes, ex vivo gene therapy should be considered for pre-symptomatic patients where available; 6. In late-onset MLD, including late juvenile and adult subtypes, hematopoietic cell transplant (HCT) should be considered for patients with no or minimal disease involvement. This document summarizes current guidance on the presymptomatic monitoring of children affected by MLD as well as the clinical management of

symptomatic patients. Future data-driven evidence and evolution of these recommendations will be important to stratify clinical treatment options and improve clinical care.

Keywords

newborn screening; transplant; gene therapy; leukodystrophy; metachromatic leukodystrophy

INTRODUCTION

In metachromatic leukodystrophy (MLD), insufficient arylsulfatase A (ARSA) activity results in progressive accumulation of sulfatides, leading to central and peripheral demyelination [1–5]. MLD is rare, with a birth prevalence from 0.16–1.85 per 100,000 live births [6]. MLD is stratified into subtypes based on the age at neurologic disease onset: late infantile (LI-MLD), early juvenile (EJ-MLD), late juvenile (LJ-MLD), and adult subtypes [7]. It is important in MLD to define the disease subtype as soon as possible, ideally presymptomatically, because there are age- and symptom-based limitations to treatment options [8–16].

Gene therapy [atidarsagene autotemcel (Lenmeldy)] for MLD has been demonstrated to be effective in presymptomatic LI-MLD and pre-/early symptomatic EJ-MLD, thus defining a narrow window for potential intervention in the youngest patients [11, 17]. This product is a hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy [15, 17]. It is approved for clinical use in the United States, European Union, UK, Iceland, Liechtenstein, and Norway. In late onset MLD (LJ- and adult MLD), there is potential benefit from early bone marrow transplant [18], although outcomes can be mixed [11, 13, 19–22]. In some cases, the transplantation process can accelerate disease progression especially when initiated after the onset of gait abnormalities [13]. This need for early diagnosis and subtype determination emphasizes the importance of newborn screening for MLD.

To define disease subtype prior to onset of neurologic symptoms, clinicians use a combination of genotype, residual enzyme activity, and sulfatide levels to predict disease subtype [1, 4, 23, 24]. This approach is effective in most cases [1, 4, 23, 24]. Family history can also be informative in predicting subtypes as age at onset strongly correlates between siblings [25]. Additionally, recent evidence suggests that in vitro modeling of the expression of ARSA enzyme in variants of uncertain significance (VUS) has the potential to assist in the classification of subtype-ambiguous cases [24]. Unfortunately, despite the overall strong genotype-phenotype correlation for MLD, disease onset cannot be predicted in all cases. With newborn screening pilots underway [26, 27], it is essential to establish preliminary clinical and monitoring guidelines [1, 3, 25, 28].

MLD subtypes

The most common disease subtype is the late infantile (LI-MLD) form, where rapid neurologic deterioration begins before 2.5 years of life [24, 28]. The first symptom of LI-MLD is often described as a plateau of gross motor skills or a failure to achieve

independent ambulation [3, 25, 28, 29]. The juvenile form of MLD (J-MLD) bridges both the rapid decline with prominent gross motor symptoms found in LI-MLD, and the slower progression with neuropsychiatric symptoms of the adult form [8, 14, 28, 30]. Because of this dichotomous progression, J-MLD is often divided into early (EJ-MLD) and late juvenile (LJ-MLD) subtypes. In early juvenile MLD (EJ-MLD), the neurologic decline occurs between 2.5 to 7 years of life. The rate of disease progression and symptoms in this form are similar to LI-MLD [3, 31]. Collectively LI-MLD and EJ-MLD are referred to as “early onset MLD”. When the neurologic presentation is between 7 and 16 years of age, this subtype is referred to as late juvenile (LJ-MLD). Adult MLD encompasses all individuals with onset after 16 years. Individuals with late onset MLD demonstrate a more chronic course, often with neuropsychiatric symptoms preceding motor involvement [3, 19, 32, 33].

Diagnosis of MLD

MLD is a lysosomal storage disease characterized by low enzyme activity (arylsulfatase A) leading to substrate elevation (sulfatides) (Figure 1) [1, 26, 34]. It is the result of biallelic pathogenic variants in the *ARSA* gene. *ARSA* variants can be broadly characterized based on predicted residual enzyme activity as ‘0’ (null or very low enzymatic activity) or ‘R’ (measurable residual enzymatic activity). In combination, 0/0 alleles are strongly associated with the LI-MLD subtype and early disease presentation [3, 35, 36]. Similarly, *ARSA* enzyme function can be categorized by level of residual activity [1, 24, 32, 35]. All individuals with MLD have reduced enzymatic activity. There are not standardized thresholds to stratify this reduction in activity, but generally enzyme activity below 1% of wildtype is strongly associated with early onset disease [1]. One proposed set of threshold parameters defines severe as 0 - < 2% of wild-type activity, moderate as 2 - < 4%, and mild as 4 – 13% [24]. Low *ARSA* activity results in an increase in sulfatide levels.

Current pilot newborn screening studies employ a sequential approach for MLD screening using dried blood spots (DBS). If DBS sulfatide levels are elevated, *ARSA* activity is then measured, with final confirmation by molecular testing [23, 26, 27, 37]. A combination of low *ARSA* activity, elevated sulfatide levels, and genotype definitively establishes the diagnosis of MLD. The presence of *ARSA* pseudodeficiency alleles also challenges the ability to interpret residual enzyme activity, underscoring the need for pairing sulfatide levels with enzyme activity [23, 38–41]. Without genotype, other rare phenotypically and biochemically similar disorders (prosaposin B deficiency and multiple sulfatase deficiency) cannot be excluded based on biochemical findings alone [42–44]. Multiple sulfatase deficiency is the result of disease-causing variants in formylglycine generating enzyme (FGE), which is required for the post-translational activation of all sulfatases, including *ARSA*. Prosaposin (PSAP) is a lysosomal protein important for *ARSA* activation.

The results of MLD diagnostic testing inform disease subtype stratification in most cases, which is further supported by family history when available [25, 45]. As such, it is important to test biological parents at the time of diagnosis as well. At risk family members, such as siblings, should be tested as clinically indicated. There are some variants that when present in the homozygous state can reliably predict age at disease onset. One example is genotype c. 465–1 G>A, that when present in homozygous state is strongly associated

with very low enzyme activity and early disease onset [24, 35]. Despite these strong risk stratification biomarkers, a gap remains in our ability to predict disease subtype for all cases, and exceptions to these diagnostic patterns have been described [24, 46]. There is a future potential to validate additional biomarkers, including neurofilament light chain (NfL) and sulfatide quantification in urine, to support disease stratification [2].

Presenting signs and symptoms

Until universal newborn screening is available, and all children are identified presymptomatically, it is important to identify how individuals with MLD may be presenting within the medical system, as this is an opportunity for potential earlier diagnosis. Common presenting signs and symptoms of MLD can be clustered by age (Figure 2). Because of the spectrum of early symptoms for MLD, individuals may present to a range of clinical providers, including general pediatricians, early interventionists, physical therapists, ophthalmologists, orthopedic surgeons, gastroenterologists, psychiatrists, or behavioral health providers (Table 1). The early recognition of symptoms related to MLD can facilitate more rapid triage and referral to the diagnosing specialist.

Especially in LI-MLD, the first provider may be a neuromuscular physician because of clinical examination consistent with a peripheral neuropathy. This subacute, demyelinating polyneuropathy often precedes the central demyelination. The initial MRI may be normal, demonstrate isolated cranial nerve involvement, or suggest delayed myelination [47]. Patients may be misdiagnosed with Guillain Barre Syndrome. The LI-MLD population may also present with ophthalmologic concerns, including strabismus and esotropia [48]. Of note, these eye movement abnormalities can be intermittent and may self-resolve. LI-MLD patients may also present with an unexpected decompensation following a typical viral infection. These non-specific or subtle presenting features makes presymptomatic testing through newborn screening for MLD essential (Table 5).

Individuals may also be diagnosed through presentation with gallbladder disease prior to onset of neurologic symptoms [49–53]. In the LJ-MLD population, the first symptoms may be cognitive/behavioral or be related to fine or gross motor difficulties. Adult MLD (onset after 16 years) is characterized by a predominance of early neuropsychiatric symptoms with a chronic progression. Due to increasing use of next generation sequencing in diagnostic evaluation of adults with peripheral and central nervous system demyelination, the presentation of adult MLD may prove to be more heterogeneous and common than previously reported.

APPROACH TO CONSENSUS

A panel of MLD experts was assembled across 18 US and 7 international major medical institutions. This workgroup group included adult and pediatric neurologists, metabolic specialists, pediatricians, transplant specialists, geneticists, and genetic counselors. Experts were identified based on existing collaborations, recent publications, and attendance of relevant scientific meetings. The consensus procedure began with a literature review of published cases, feedback from patient advocacy groups, review of the Externally Led Patient Facing Drug Development (EL-PFDD) transcript, and Voice of the Patient Report

to develop themes and clinical topics deemed relevant by patients and caregivers [54]. The EL-PFDD was organized by the MLD Foundation, Cure MLD, the United Leukodystrophy Foundation (ULF), and the Calliope Joy Foundation. The literature searches were conducted in PubMed using the keyword “metachromatic leukodystrophy” and included review of all publications in English from 2000 through 2023. Using this foundation, pilot statements were synthesized and provided to the workgroup for 4 rounds of iterative refinement, which included addition of statements, modification of concepts, and wording adjustments. Workgroup members also contributed their own supporting evidence and clinical experiences. Full consensus was reached for the final statements. Figures were generated with Biorender.

Standard Protocol Approvals, Registrations, and Patient Consents

This study is exempt from IRB approval as conclusions were reached with available data from the literature and expert opinion. No information on individual patients is included in this paper.

CONSENSUS RESULTS

Clinical Management and Monitoring

We would recommend all diagnosed children be referred to a specialty center to guide care and partner with local providers. The management of MLD, even in the presymptomatic phase, requires an informed multidisciplinary team. This begins at diagnosis and should include a genetic counselor knowledgeable in MLD. It is critical to identify at risk family members beyond the proband who may benefit from testing. Historically, most patients still eligible for intervention at the time of diagnosis have been diagnosed because of an older affected sibling [3, 15, 17]. This has simplified monitoring planning and intervention decision because siblings have a strong tendency to have the same subtype, with the strongest correlation seen with early-onset variants [25]. When children are identified without a family history of disease, it is important to develop and implement clinical guidelines that stratify the monitoring approach by risk of disease subtype.

Recommendations for cases of definitive pre-symptomatic LI-MLD

Children who are diagnosed presymptotically with definitive LI-MLD (based on genotype or family history) should have a comprehensive assessment as soon as feasible, ideally within the first 3 months of life, with urgent referral to a treatment center for consideration of interventions, such as a gene therapy. Baseline evaluations by MRI or nerve conduction studies (NCS) can occur in parallel but should not delay referral to a treatment center for evaluation. If presymptomatic children are identified outside of this newborn period, the evaluation should occur urgently, including developmental assessment, nerve conduction studies, and a brain MRI. In the known LI-MLD population, evaluation and potential intervention should be pursued as soon as possible as the window for intervention is narrow. Children at risk for early onset disease should be referred urgently to a specialized center with expertise in MLD.

Recommendations for cases of unknown subtype at risk for early onset MLD

When it is not possible to predict the phenotype because of a lack of family history [25], ambiguous genotype [35], or equivocal enzyme testing [26, 27], it is important to promptly begin longitudinal monitoring, including baseline MRI and NCS (Table 2–3). This monitoring should be continued until the appropriate therapeutic approach is identified either by evidence of subclinical disease on testing or by improved clarity within the medical literature.

Presymptomatic children who are at risk for early onset MLD [or when the disease subtype is unknown] should be followed closely by a neurologist with attention to developmental progress. Because of the early peripheral neuropathy in the LI- and J forms, reflexes are often diminished early in the course. In the later stages of disease, the reflexes may become pathologically increased and then ultimately lost. This is due to the changing predominance of peripheral and central demyelination. On gait examination, children may appear unsteady while walking or demonstrate foot drop. Children may have worsening skills with fatigue over the course of the day. Tone may be decreased initially in the lower extremities, while it typically increases over time. Spasticity and dystonia on examination are an indication of central demyelination.

Particularly, changes in peripheral nerve myelination may be one of the first signs of MLD and typically precedes radiographically detectable demyelination [55]. The radiographic evidence of cerebral involvement in early onset MLD can evolve quickly, with significant changes within weeks to months (Figure 3) [56–60]. The first radiographic images may appear to have normal or delayed myelination or demonstrate cranial nerve thickening and/or enhancement, which may result in misdiagnosis [47, 48, 61]. Similar to the Loes score in adrenoleukodystrophy [62], there is a quantitative scale to measure radiographic burden of disease in MLD [60]. MR diffusion parameters of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) and MR spectroscopy (MRS) also correlate with disease severity [59, 63]. The clinical utility of the MLD scale and imaging approaches will need to be validated longitudinally.

While central demyelination is a defining feature of MLD, the changes by brain MRI, especially in the early onset forms, often occur after onset of peripheral neuropathy [3, 55, 64]. This association between radiographically detectable central demyelination and onset of disease symptomatology is less clear in the later onset forms. Regarding peripheral demyelination, there is not a standardized approach determining which nerves should be assessed. Attention should be made to consistently measuring the same nerves using a standard protocol. Concomitant medications, including anesthetic exposure, may also affect the results [65]. The arsa-cel trial successfully used a composite index score with conduction measurements from four nerves [17]. One option is the deep peroneal nerve, which may be a sensitive indicator of demyelination in MLD [66]. Longitudinal monitoring of the peroneal nerve, however, may be challenging in a real-world setting as this nerve is vulnerable to neuropathy from compression and other injuries.

On history and by ophthalmologic examination, the early onset MLD population can demonstrate transient strabismus and esotropia [48]. This typically lasts for several weeks

to months and then often self resolves. These ophthalmologic abnormalities can return later in the disease course. Because the early signs and symptoms of MLD can be subtle, it is important to prioritize in person evaluations, as telemedicine approaches may not be sufficiently sensitive. A pathologic finding by neurologic examination or investigations should prompt urgent consideration of treatment eligibility.

Recommendations for cases with suspected late onset MLD

In cases where a later-onset subtype is suspected, longitudinal monitoring will be critical. This should include serial neuropsychological testing, nerve conduction studies, and brain MRIs. As part of all neurology encounters, a detailed examination should occur with attention to tone, eye movements, reflexes, and gait. Fine motor skills and behavioral dysfunction should also be a focus in this period.

If there were to be clinical concern for a change in neurologic performance, we would recommend an expedited evaluation. This could include more extensive nerve conduction studies, brain MRI, and neuropsychological testing. Early identification of mild symptomatic disease has the potential to inform treatment options and allow for more appropriate clinical support. As such, the required follow up for cases of MLD is lifelong and multidisciplinary. As new treatments are developed, it is critical to adapt these recommendations to identify patients within the therapeutic window.

Symptomatic management of MLD

Unfortunately, in the era before universal newborn screening, most children are diagnosed beyond the window for intervention. Even once symptoms have begun, it is critical to offer multidisciplinary care to improve quality of life. While a detailed review of the medical care of symptomatic MLD patients is discussed in other reviews [67–70], general considerations are summarized in Table 4. This can include management of feeding issues (including dysphagia and constipation), monitoring for gallbladder disease, and interventions to improve tone. These guidelines should be adapted to local differences in clinical practice and are based on practices in the United States.

A multidisciplinary team, including physiatry and physiotherapy, can recommend supportive equipment such as wheelchairs, standers, activity chairs, bath chairs, and augmentative communication devices. Additional issues affecting symptomatic patients may include pain, irritability, and dysregulation of sleep. These features may be attributable to a combination of increased tone, gastrointestinal dysmotility, central neuro-irritability, or peripheral neuropathy. A sudden change in comfort should prompt a medical evaluation [70]. Palliative care involvement can provide emotional and spiritual support, manage symptoms, and guide interventions to align with family's goals of care.

Feeding issues are also common, especially in early onset MLD and in the later stages of disease across the subtypes. This can include changes in swallowing efficiency, decreased feeding tolerance (increased vomiting), intestinal dysmotility, and constipation. As such, additional attention should be directed towards monitoring of swallowing function and growth trajectories. Once the neurologic decline has begun, placement of gastrostomy tubes can be considered to meet the nutritional needs. The combination of poor swallowing

function, peripheral neuropathy, and low muscle tone can result in increased risk for aspiration pneumonia [70, 71].

Gallbladder involvement is a unique feature of MLD. Serial abdominal ultrasounds can identify gallbladder disease prior to the development of complications, which can in rare cases include malignancy [72]. There have been case reports of early detection of MLD presenting with gallbladder disease [49, 51]. Overall, there is a gap in our understanding related to the frequency and rates of progression for gallbladder involvement [72, 73]. If gastrostomy tube placement is indicated, prophylactic removal of the gallbladder could be considered because of the potential risk for future cancer and contribution to GI discomfort [72]. The timing of gallbladder disease onset versus neurologic manifestations of MLD should be explored with longitudinal data collection. Additionally, MLD can be associated with metabolic acidosis, which should be considered during clinical admissions [74]. The incidence of this potential complication is unknown.

Seizures can also be associated with MLD; the reported incidence ranges from 14 to 39% [75, 76]. Seizures are more common in the later stages of MLD [76]. When seizures occur earlier in the disease course, subtle symptoms were often already present [75]. Focal seizures are the most common type, often associated with electroencephalogram findings of background slowing and focal or multifocal epileptiform discharges [77]. Various anti-seizures medications have been used with good general response to treatment [75].

Discussion

Metachromatic leukodystrophy is a severe neurodegenerative disorder that is the result of an inborn error of metabolism. Current therapies for MLD, including ex vivo gene therapy and hematopoietic stem cell transplant, require identification of presymptomatic patients, as such early diagnostic platforms, including as newborn screening, are important across the disease spectrum. When cases are identified, patients should be urgently referred to an expert for evaluation and consideration of treatment. This multidisciplinary leukodystrophy team should work in close collaboration with the local care team and family to provide longitudinal monitoring and care. The following recommendations should be considered as part of an evolving process and should be revised as more evidence becomes available. One challenge to the presymptomatic monitoring of patients affected by MLD is the lack of prospective natural history data from birth to inform evidence-based guidelines.

A key recommendation from the expert consensus workgroup is the need for newborn screening for MLD to identify presymptomatic individuals who can benefit from therapy. The consensus recommendation is that the diagnosis of MLD should include both genetic and biochemical testing (enzyme activity and sulfatide levels). Newborn screening would support the diagnosis of children during the critical presymptomatic phase. One critical advantage to newborn screening would be to reduce the diagnostic bias which affects non-white populations. This population is overall less likely to be diagnosed with a leukodystrophy or rare disease [78–80]. Of importance, there is a potential gap in our ability to appropriately classify disease-causing alleles across non-white populations, which has

been described for other rare diseases [81–83]. To this end, there is a need for validated biomarkers capable of presymptomatic disease stratification.

Another notable point is the difference in common clinical practices as well as access and availability to healthcare resources between countries. These differences can begin as early as birth with differences in newborn screening practices to variable access to gene therapy and transplant [18]. This impacts the ability to detect, monitor, and treat children with MLD. As such, these guidelines focus on the structure and common practices available within the United States. These consensus recommendations should be adapted to fit best local clinical practices.

While ongoing newborn screening studies have created an urgent need for standardized presymptomatic monitoring, one challenge is the lack of existing data to support the development of formal guidelines. Our knowledge of MLD is largely based on clinical experience and single institutional natural history studies. Because the diagnosis of MLD is typically reached later in the disease course (unless there is an affected sibling), our current understanding is biased to a deeper understanding of the later stages of disease. As the early, subtle signs and symptoms of disease may be underreported. Classically, the onset of MLD has been defined by the onset of central demyelination [15, 17], which may be preceded by peripheral neuropathy, ocular motor defects, developmental delay, or gallbladder involvement. The timing and incidence of these non-central nervous system manifestations is unknown. Prospective monitoring for these complications will help inform evidence-based guidelines and refine our definition of ‘disease onset’.

Despite these gaps in our understanding, with gene therapy approved in the United States and early diagnosis through newborn screening on the horizon, there is an urgent need to develop preliminary recommendations to support the monitoring of presymptomatic cases of MLD in the United States. These recommendations are based on the consensus of an MLD workgroup. It is essential to note that these recommendations will benefit from refinement as evidence emerges around the most appropriate monitoring and parameters to support presymptomatic disease subtype determination. Additionally, as novel therapies are developed across the lifespan, it will be important to adapt the clinical guidelines to ensure that patients can be identified within the therapeutic window.

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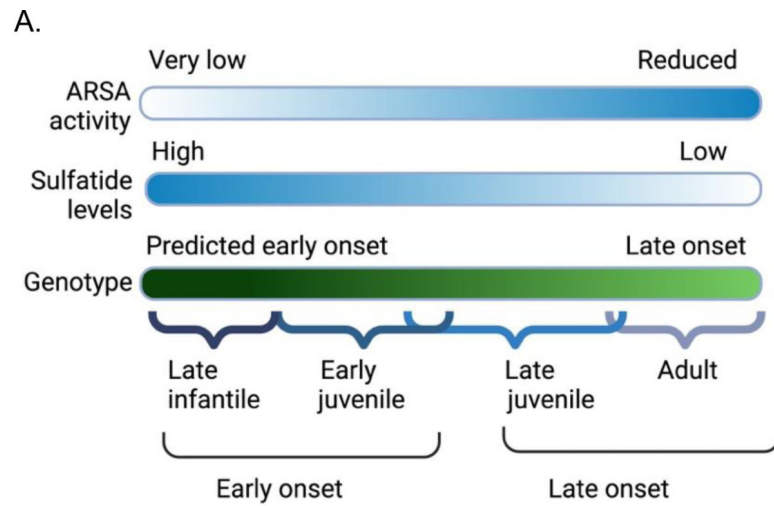
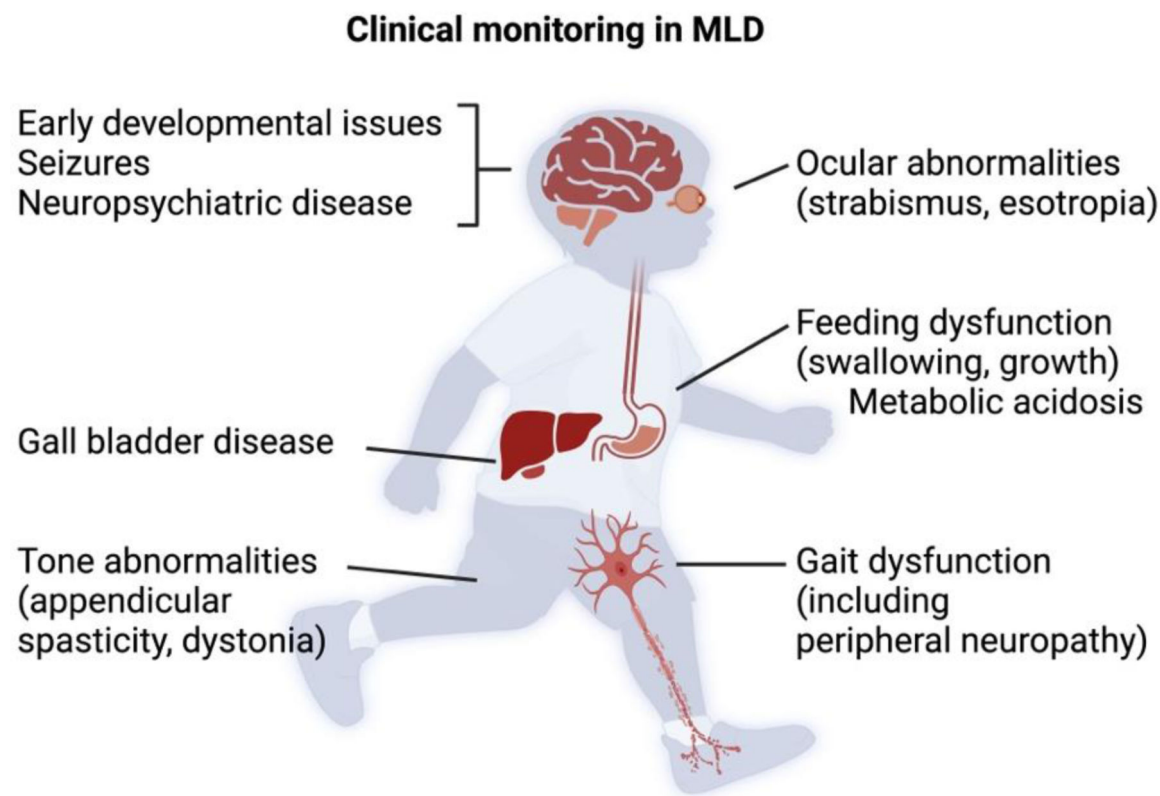


Figure 1. Disease stratification in MLD by diagnostic testing.

There are 2 main groupings of MLD subtype: early and late onset disease. The most common subtype, late infantile MLD, has the most defined genotype and biochemical thresholds.

A.



B.

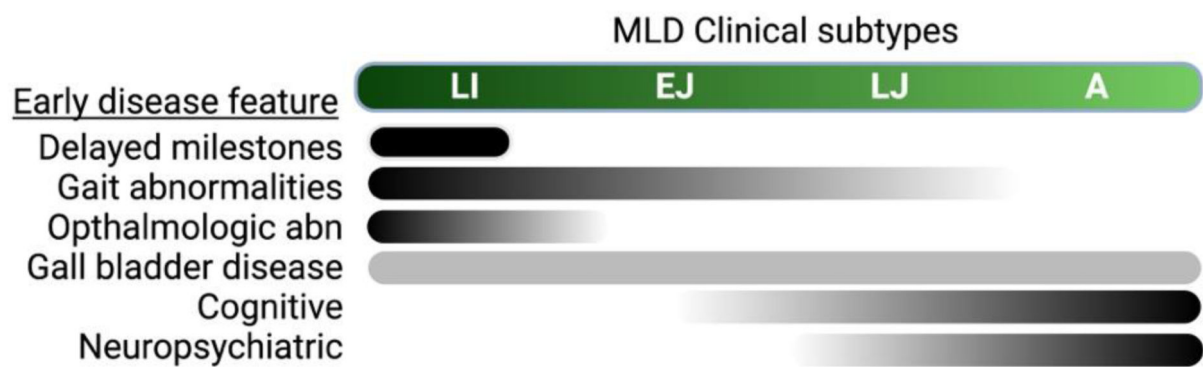


Figure 2. Clinical manifestations of MLD.
MLD is a disorder characterized by demyelination of the central and peripheral nervous systems accompanied by multisystemic complications. The breadth of complications is shown in (A), and the common presentations by disease subtype is shown in (B).

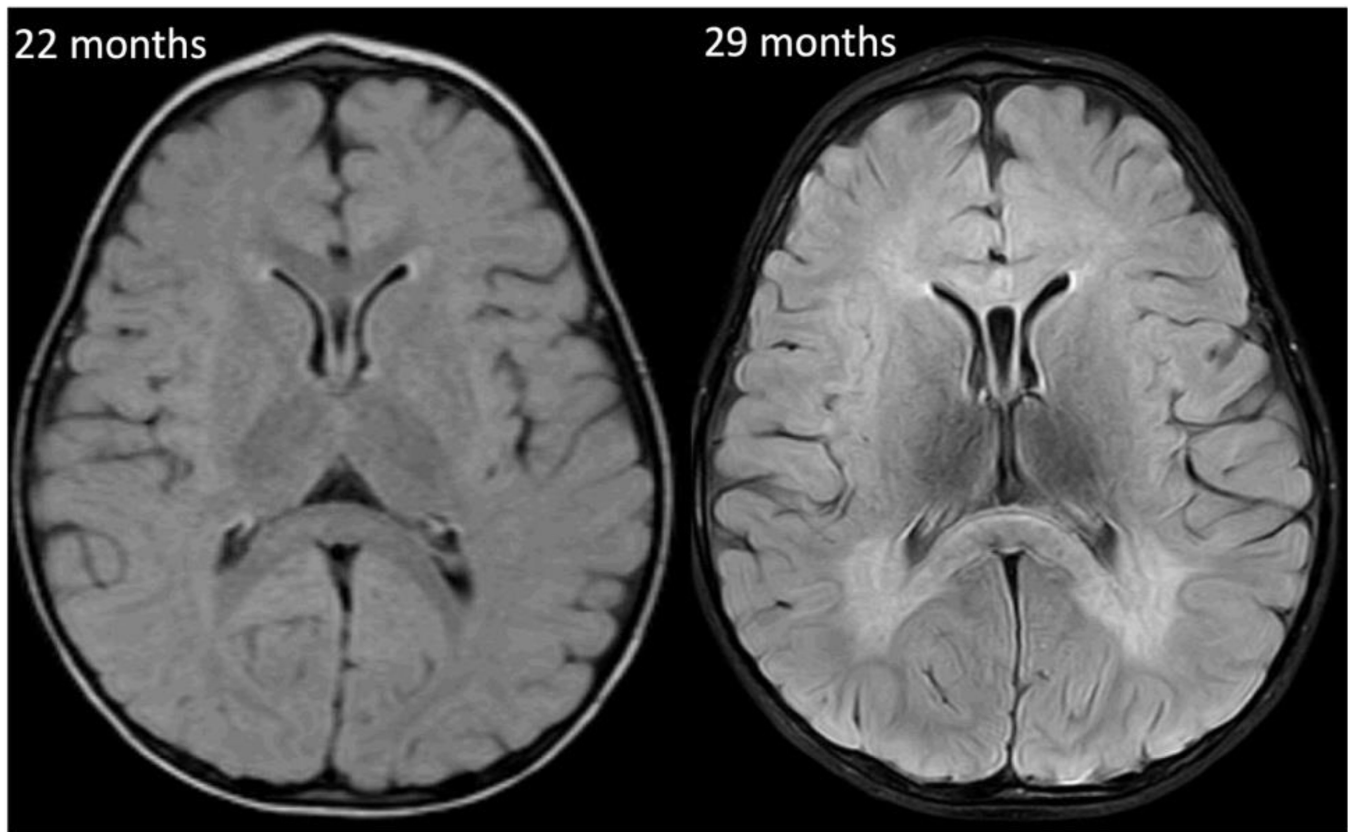


Figure 3. Initial neuroimaging studies may be nondiagnostic, even in cases of early onset MLD, but can change rapidly.

This pair of T2 FLAIR images were obtained from a child with late infantile MLD. At the time of the first MRI (age 22-months; left panel), he was unable to walk independently and had limited vocabulary, but no abnormalities noted on MRI. By his second MRI (age 29 months; right panel) he had lost the ability to crawl and his MRI demonstrated confluent, symmetric T2 prolongation throughout the cerebral white with sparing of periventricular white matter (tigroid pattern of T2 prolongation) and subcortical U-fibers.

Table 1.
Presentation of MLD in a clinical setting

Common clinical presenting symptoms of MLD	
	Delayed acquisition of developmental milestones (developmental stagnation)
	Gait abnormality (often foot drop, stumbling)
	Ophthalmologic abnormalities (esotropia, strabismus)
	Gallbladder disease (sludging, polyps, carcinoma)
	Cognitive decline (attention, school performance)
	Neuropsychiatric disease (depression, anxiety, personality change)
Common early referrals for patients affected by MLD	
	Early intervention (especially physical therapy)
	Orthopedic surgery
	Ophthalmology
	Neurology (especially neuromuscular)
	Gastroenterology
	Psychiatry/psychology

Table 2.
Suggested surveillance protocols for presymptomatic or early symptomatic cases of MLD are identified.

Note that when individuals are diagnosed outside of these windows, assessments should be initiated as soon as feasible.

MLD group	Early onset		Late onset		
MLD subtype	Late infantile	Early juvenile	Late juvenile	Adult	Unknown subtype
Monitoring					
MRI brain	Within 3 months of birth *	Within 9 months	Within 12 months	by adolescence	Within 3 months
Nerve conduction study	Within 3 months of birth *	Within 9 months	Within 12 months	by adolescence	Within 3 months
Therapy evaluation (as available and clinically indicated)	Before the age of 6 months	Before the age of 12 months	Before the age of 5 years	As clinically indicated	As clinically indicated (close follow up required)

* In cases of definitive presymptomatic late infantile MLD, the primary attention should be placed on therapy evaluation as the results of the nerve conduction studies and MRI are unlikely to change management.

Table 3.
Suggested longitudinal monitoring in presymptomatic MLD.

Disease feature	Target age range	Monitoring to be considered	Suggested interval
Developmental delay	Early childhood	Regular assessment of developmental milestone acquisition	For individuals at risk for early childhood onset, consider assessment every 3–4 months with special attention to acquisition of skills (e.g., standing and walking independently)
Peripheral neuropathy	All ages (especially early onset)	Nerve conduction studies (especially deep peroneal nerve)	Every 6 months in early childhood, then consider annually after 7 years old through adulthood
Central demyelination	All ages	Brain MRI with consideration of contrast in first 5 years of life to evaluate cranial nerve enhancement; MRI without contrast in late onset forms	Within early or unknown disease subtype, consider imaging every 6 months from 12 months until 7 years. After 7 years of age, consider annual imaging
Ocular abnormalities	Early childhood	Assessment of eye movements by parental interview and by examination with consideration of formal testing by ophthalmology with concerns	Consider when at risk for LI/EJ or unknown subtype; with all neurologic examination
Neuropsychiatric concerns	Childhood and adulthood	Assessment of mood, cognitive function with consideration of formal neuropsychiatric testing	Consider annually when at risk for non-LI MLD
Tone abnormalities	All ages	Assessment by physical examination	With all neurologic examinations
Gallbladder dysfunction	All ages	Gallbladder ultrasound	Annually
Feeding dysfunction	Early childhood	Assessment of swallowing function by history, biometric data (height, weight) with consideration of formal assessment by advanced testing such as video fluorometric swallowing study with concerns	With all neurologic examinations

Table 4.
Suggested care considerations for the common complications of symptomatic MLD.

See additional leukodystrophy care guidelines for more information [67–70].

MLD-related clinical complication	Evaluation/intervention to be considered
Developmental delay	Consideration of referral to physical therapy, occupational therapy, speech therapy [3]
Gait or mobility differences	Consideration of referral to physical therapy, physiatry. Consideration of evaluation for devices/equipment (e.g., orthotics, braces, gait trainers, walkers, lifts, bath chairs, and standers) [70].
Neuropsychiatric concerns	Referral for neuropsychiatric testing, psychiatry, and social work [70].
Tone abnormalities	Evaluation by physical therapy with consideration of referral to physiatry referral for medical management [69, 70].
Seizures	As per standard clinical management [76]
Pain	Consider treatment based on source of discomfort (spasticity, gastric motility issues, neuro-irritability) with management as clinically indicated [67, 70]
Feeding and gallbladder dysfunction	With concerns, assessment of swallowing function by speech therapy evaluation and by advanced testing [e.g., videofluoroscopic swallow study (VFSS), modified barium swallow study (MBS), or fiberoptic endoscopic study examination of swallow (FEES)] [68, 70]. Consideration of surgical referral for gastrostomy tube placement as clinically indicated [68, 70]. Consider additional gallbladder imaging with consideration of removal as clinically indicated [51, 72]
Low bone mass or density	With decreased mobility and nutritional insufficiency, risk for low bone mass and fractures. Consideration of screening imaging [e.g., dual-energy X-ray absorptiometry (DEXA)], Vitamin D testing, and referral to endocrinology [70].
Scoliosis and hip dislocation	With decreased mobility, consideration of regular screening X-rays of hips [70]. Consideration of spinal X-rays as clinically indicated to evaluate for scoliosis. Consider referral to physiatry and/or orthopedic surgery as clinically indicated.
Skin care	Because of decreased mobility, incontinence, and peripheral neuropathy, monitor for skin breakdown, especially with orthotic devices and diaper region [70]. Provide skin care as clinically indicated.
Urinary tract infections (UTI)	Consider referral to urology with increased risk for UTI (e.g., spastic lower extremities, neurogenic bladder) [70].
Respiratory compromise and sleep disruption	Consider referral to pulmonology with increased risk for pneumonia or respiratory compromise (e.g., poor swallowing function and central hypotonia) [70, 71]. Optimize sleep hygiene, reduce manageable causes of sleep disruption [e.g., temperature dysregulation (autonomic dysfunction), spasticity, and gastrointestinal discomfort] [67, 70]; referral pulmonology or sleep medicine with concerns for sleep apnea or obstruction.

Table 5.
Summary of MLD consensus recommendations

Diagnostic Recommendations	Newborn screening for MLD should be implemented
	Confirmation of diagnosis for MLD should include both genetic testing for <i>ARSA</i> variants and biochemical testing for residual arylsulfatase enzyme activity and sulfatide levels
	Testing for MLD should be considered at any age, including for symptoms of unexplained peripheral neuropathy, unexplained developmental delay or regression, gallbladder abnormalities, unexplained strabismus, or abnormal findings on MRI concerning for MLD
	Rapid access to testing should be offered because of opportunity for treatment
Interventional Recommendations	Ex vivo gene therapy should be considered for early onset MLD as clinically indicated and available
	Hematopoietic cell therapy (HCT) should be considered for late onset MLD who are pre- or minimally symptomatic
	All patients would benefit from comprehensive care, including those patients with symptomatic disease