The Latest Update on Metachromatic Leukodystrophy:

Screening, Diagnosis, and Emerging Treatments to Improve Quality of Life of Patients

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Please include the faculty member's name if the question is specifically for them.

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Learning Objectives:

1. Review the impact of diagnostic delay and misdiagnosis on patients with MLD
2. Implement early screening for patients with suspected MLD based on symptoms and clinical presentations
3. Indicate strategies for identifying patients with MLD at the pre-symptomatic phase of disease
4. Evaluate efficacy and safety data of emerging therapies for MLD

Audience Response

Which of the following delays in infantile development warrants suspicion for MLD?

A. Does not walk by 18 months
B. Does not hold head up by 6 months
C. Does not make vocal sounds by 6 months
D. Does not develop social smile by 5 months
E. I don't know

Late-Infantile MLD: Kai's Story

Kai is born a healthy baby boy to Indigenous/Native American parents.

Birth

Kai is developing typically. He can pick up objects, eat soft foods, say a few words, and crawl.

12 months

Kai loses his balance and falls when attempting to stand or walk. He is diagnosed with developmental delay and referred to orthopedics.

18 months

Kai is irritable, rarely speaks, and still cannot walk or stand. He is referred to neurology.

24 months

Kai struggles to eat and swallow and must be fitted for a G tube.

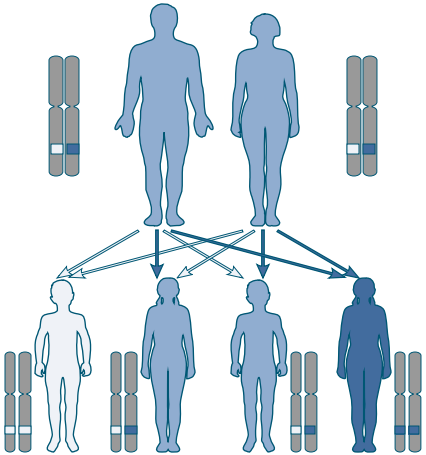
30 months

Kehrer C. *Dev Med Child Neurol*. 2011;53(9):850-855. Harrington M. *Orphanet J Rare Dis*. 2019;14(1):89

Metachromatic Leukodystrophy (MLD)

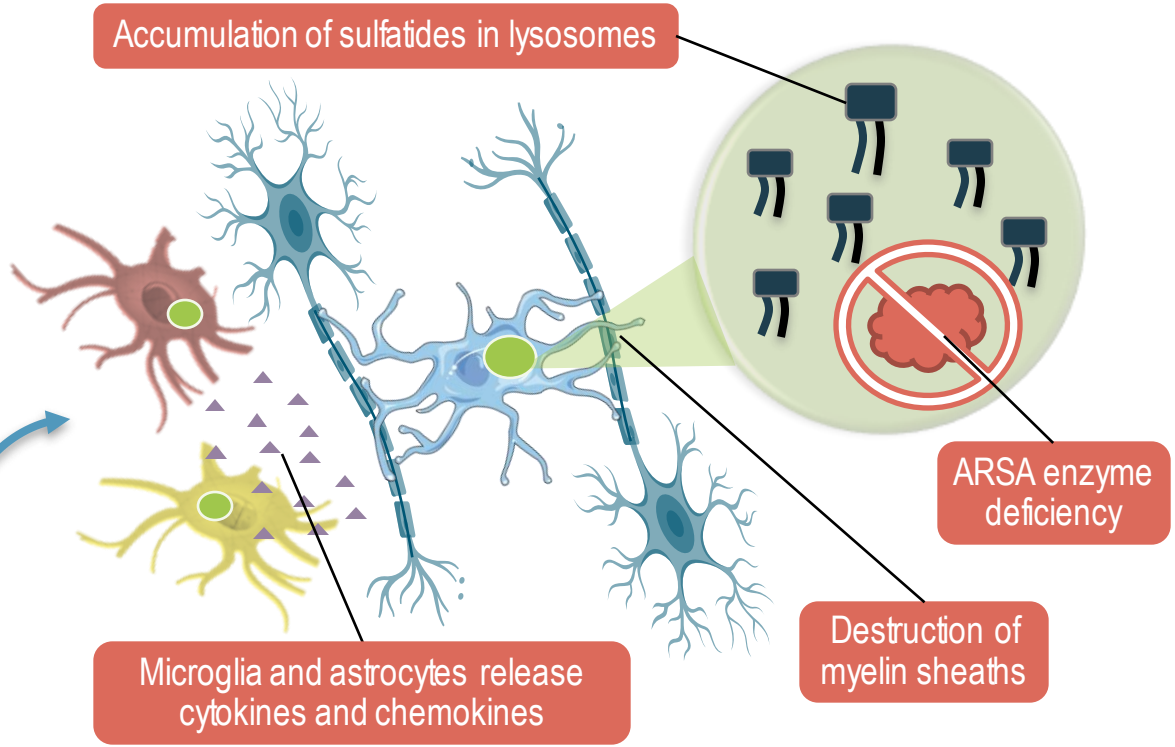
Etiology and Pathophysiology

Autosomal Recessive Lysosomal Storage Disorder



Variant Genes:

- Arylsulfatase A (*ARSA*)
- Prosaposin (*PSAP*) - *rare*



Lamichhane A. *StatPearls*. 2022. Platt FM. *Nature Reviews Disease Primers*. 2018;4(1):27.

MLD Phenotypic Presentations

	Onset	Symptoms	Prognosis
Late-Infantile ~50-60%	 6 to 30 months	**Motor regression**: ataxia, hypotonia, spasticity, hyporeflexia, Babinski sign, dysarthria, dysphagia, optic atrophy, respiratory distress, seizures	**Rapid progression:** 2 to 7 years life expectancy
Juvenile ~20-30%	 2.5 to 16 years	**Psychomotor regression:** intellectual decline, personality and behavioral changes, ataxia, motor neuron dysfunction, peripheral neuropathy, incontinence, seizures	**Heterogeneic progression:** 3 to 15 years life expectancy
Adult ~15-20%	 > 16 years	**Psychological regression:** cognitive impairment, loss of initiative, disinhibition, personality and behavior changes, social dysfunction, gait disturbances	**Insidious progression:** 5 to 35 years life expectancy

Schoenmakers DH. *Orphanet J Rare Dis*. 2022;17(1):48. Kehrer C. *Dev Med Child Neurol*. 2011;53(9):850-855. Harrington M. *Orphanet J Rare Dis*. 2019;14(1):89. Gieselmann V. *Neuropediatrics*. 2010;41(1):1-6.

Need for Early Recognition of MLD

U.S. Prevalence/Incidence:

- 1 in 40,000 prevalence (est.)
- 1 in 7,000 Indigenous/Native American live births; 1 in 2,500 on Navajo Nation
- Black, Hispanic disparately underdiagnosed

Median Diagnostic Delays:

- Late-infantile: 1.2 years
- Juvenile: 3.7 years
- Adult: 1.5 to 8 years

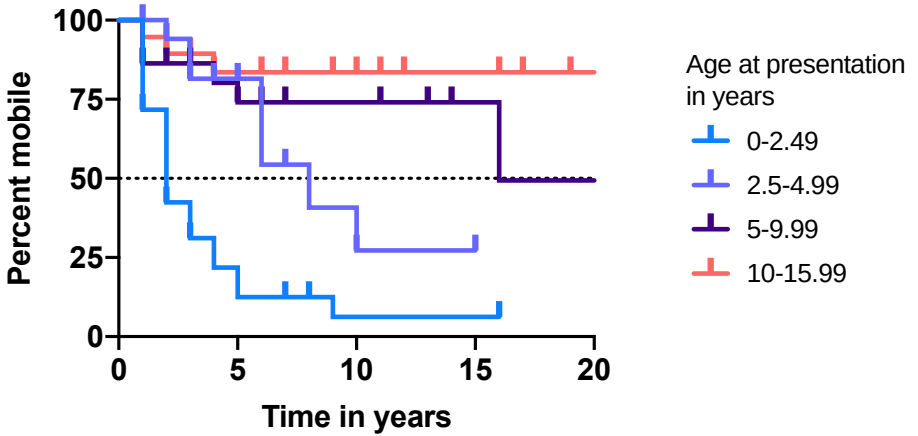
Common Misdiagnoses:

- Early-onset: developmental delay, CIDP, cranial neuropathy, ADHD, strabismus
- Late-onset: psychiatric disorders, substance use, brain tumor, dementia

MLD Caregiver Impact Questionnaire (CIQ):

Time from disease onset to loss of mobility

Unpublished data: retrospective natural history study (n=173)



Parikh S. *Mol Genet Metab*. 2015;114(4):501-515. Eichler FS. *J Child Neurol*. 2016;31(13):1457-1463. Sevin C. *Orphanet J Rare Dis*. 2022;17(1):329. Harrington M. *Orphanet J Rare Dis*. 2019;14(1):89. Bonkowsky JL. *JAMA Netw Open*. 2018;1(7):e185031. Holve S. *Am J Med Genet*. 2001;101(3):203-208. Harrington M. *J Patient Rep Outcomes*. 2019;3(1):44.

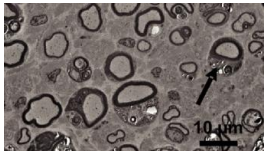
MLD Differential Diagnosis

Clinical Workup

- History and Physical
  - Symptom onset and progression
  - Family, perinatal, patient history
  - Neurological exam
- Ancillary Tests
  - Neuropsychological testing
  - Nerve conduction studies
  - CSF proteins
  - **CNS imaging**

Definitive Diagnostic Tests

- White Matter Biopsy (rarely done)



Metachromatic granules and hypomyelination

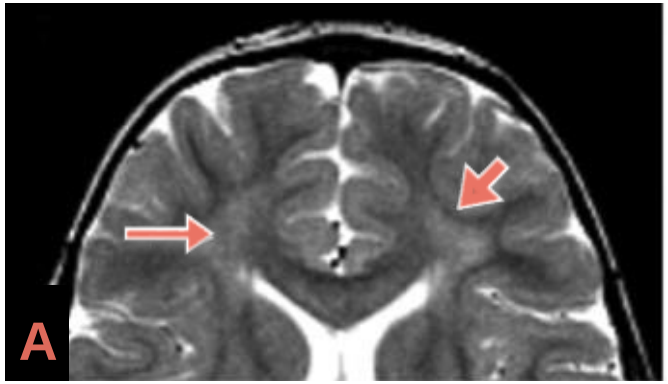
- Biochemical Labs

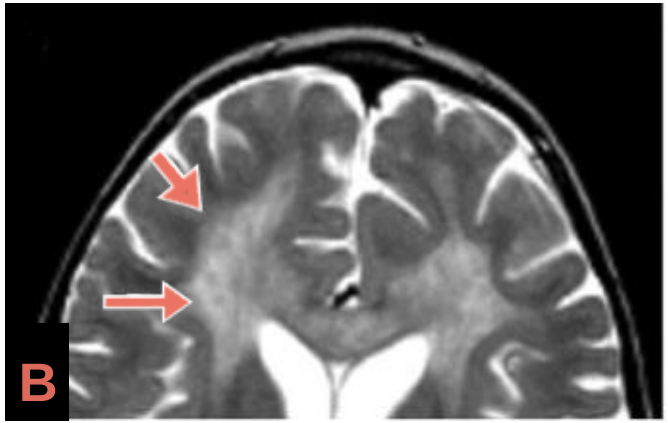
Low ARSA activity | **Urinary sulfatides** | ***ARSA* gene mutation(s)**

⚠ Pseudodeficiency
PSAP mutations
Multiple sulfatase deficiency

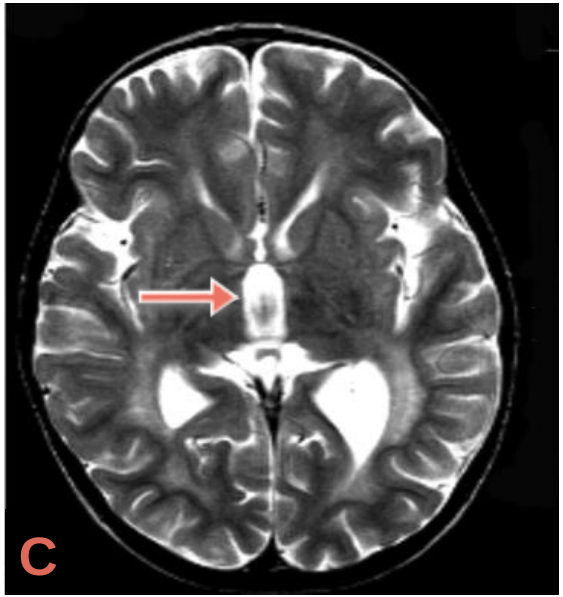
Shaimardanova AA. *Front Med (Lausanne)*. 2020;7:576221. Lamichhane A. *StatPearls*. 2022. Hong X. *Anal Chem*. 2020;92(9):6341-6348. Doherty K. *Genet Metab Rep*. 2019;19:100460. Laugwitz L. *JIMD Rep*. 2022;63(4):292-302. Dali C. *Ann Clin Transl Neurol*. 2015;2(5):518-533. Kohlschütter A. *Expert Rev Neurother*. 2011;11(10):1485-1496

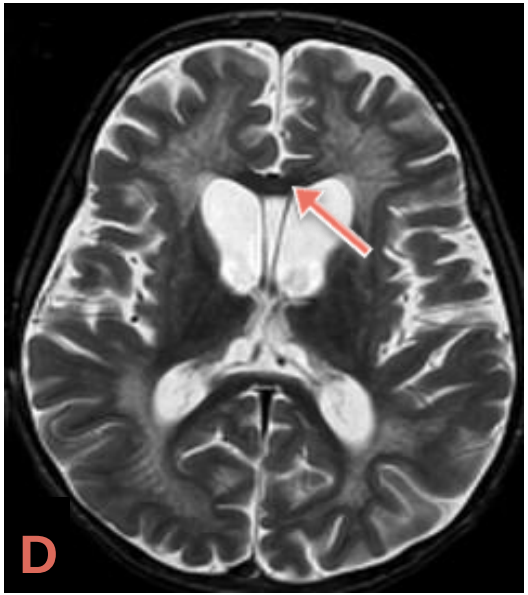
MLD Severity in Brain MRI





A) *Faint* periventricular and central involvement in frontal WM, preserved subcortical U-fibers. **B)** *Dense* periventricular and central involvement in frontal WM, subcortical U-fiber demyelination. **C)** Inner atrophy measured in third ventricle. **D)** Midline of the corpus callosum in advanced stages of MLD. T2 lesion hyperintensities in the midline are reduced compared with the adjacent supratentorial WM lesion signal intensity





Eichler F. *AJNR Am J Neuroradiol*. 2009;30(10):1893-1897.

CME

Brain MRI Scoring System for MLD

Eichler et al.

Brain Areas	Score			Max
Frontal WM				**6**
Periventricular	0	1	2	
Central	0	1	2	
U-fibers	0	1	2	
Parieto-occipital WM				**6**
Periventricular	0	1	2	
Central	0	1	2	
U-fibers	0	1	2	
Temporal WM				**6**
Periventricular	0	1	2	
Central	0	1	2	
U-fibers	0	1	2	
Corpus callosum				**4**
Genu	0	1	2	
Splenium	0	1	2	

Brain Areas	Score			Max
Projection fibers				**6**
IC posterior limb	0	1	2	
IC anterior limb	0	1	2	
Midline pons	0	1	2	
Cerebral atrophy	0	1	2	**2**
Thalamus	0	1		**1**
Basal ganglia	0	1		**1**
Cerebellum				**2**
WM	0	1		
Atrophy	0	1		
Total				**34**

Scoring: 0 = normal, 1 = faint hyperintensity, 2 = dense hyperintensity

Disease severity by total score: 1-6 = mild, 7-15 = moderate, 16-34 = severe

Eichler F. *AJNR Am J Neuroradiol*. 2009;30(10):1893-1897. Resende LL. *RadioGraphics*. 2019;39(1):153-168. Weerakkody Y. *Radiopaedia*. 2022. Doherty K. *Mol Genet Metab Rep*. 2019;19:100460

Case Study: Kai

30-month-old boy presents to neurology with 12-month history of progressive motor regression:

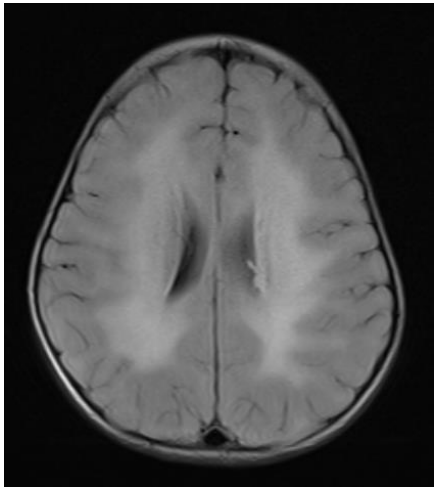
- ❑ Met all development milestones until ~18 months when he failed to develop independent walking and was diagnosed with developmental delay
- ❑ Orthopedist ruled out hip dysplasia at 20 months
- ❑ Recently had G-tube placed due to progressive dysphagia
- ❑ Strabismus and hyporeflexia noted by pediatrician in recent neurological exam

Audience Response

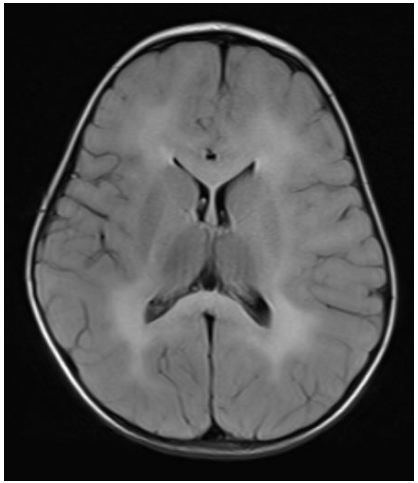
At 30 months, which ancillary study would be MOST useful in narrowing the differential for Kai?

A. EEG
B. Brain MRI
C. EMG/NCS
D. PET scan

Case Study: Kai



T2



Urinalysis:
+ Sulfatides

ARSA activity:
Not detected

Based on MRI findings, positive urinary sulfatides, and undetectable ARSA enzyme activity, you make the diagnosis of late-infantile MLD. **Kai's mother is currently pregnant in her third trimester.**

Audience Response

Which of the following evaluations should be immediately performed in asymptomatic siblings of patients diagnosed with MLD?

A. Close monitoring for s/s of MLD
B. Nerve conduction studies
C. Whole exome sequencing
D. *ARSA* gene sequencing
E. I don't know

Pre-symptomatic Screening for MLD

Family Screening

- Genetic counseling with patients and family
- Pre-symptomatic sibling(s) identification
- Prenatal diagnosis
- Carrier testing

Newborn Screening

Not currently in NBS panels, but research is ongoing

Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots
Xinying Hong, et al.

Wang RY. *Genet Med*. 2011;13(5):457-484. Gomez-Ospina N. *GeneReviews*. 2006; https://www.ncbi.nlm.nih.gov/sites/books/NBK1130/. Kubaski F. *JIMD Rep*. 2022;63(2):162-167. Hong X. *Genet Med*. 2021;23(3):555-561. Laugwitz L. *JIMD Rep*. 2022;63(4):292-302

MLD Disease Management

Standard therapies

Hematopoietic Stem Cell Transplant (HSCT)

- Variably effective for late-infantile; progression is too fast
- May slow progression in very early/pre-symptomatic late-onset phenotypes
- Major risks involved (GvHD); must weigh risk vs. benefit
- Variations: mesenchymal, cord blood, etc.

Supportive therapies

- Antispasmodics, antiepileptics, etc.
- Physical/occupational/speech/respiratory therapy
- Feeding tube
- Assistive medical devices (wheelchairs, etc.)

van Rappard DF. *Best Pract Res Clin Endocrinol Metab*. 2015;29(2):261-273.

Audience Response

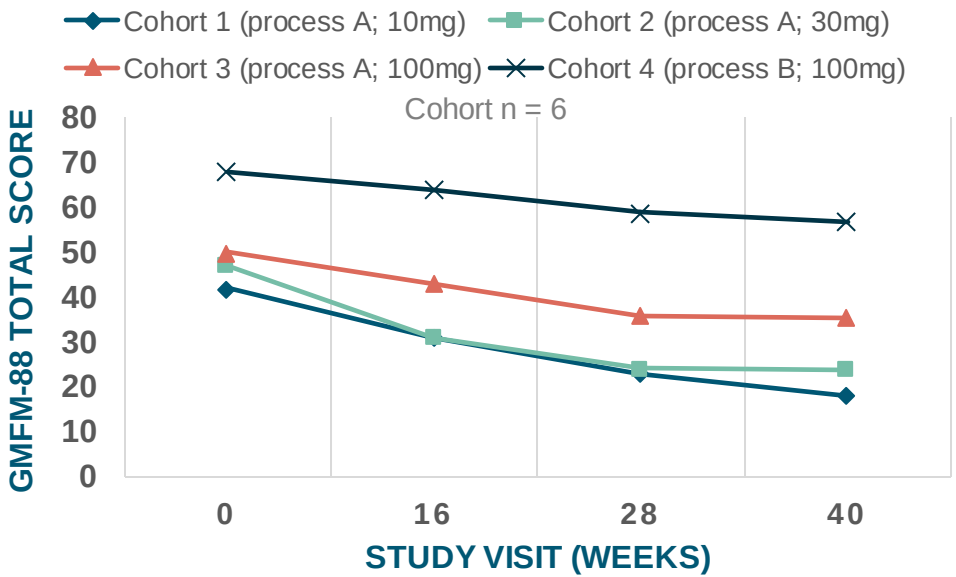
Which of the following has NOT been the subject of clinical trials for MLD?

A. Enzyme replacement therapy
B. Adeno-associated virus gene therapy
C. Antisense oligonucleotide therapy
D. Lentiviral hematopoietic stem-cell gene therapy
E. I don’t know

Emerging MLD Therapies

Enzyme Replacement Therapy (ERT)

Safety of intrathecal delivery of recombinant human ARSA in children with MLD: Results from a phase 1/2 clinical trial



ARSA ERT Clinical Trials

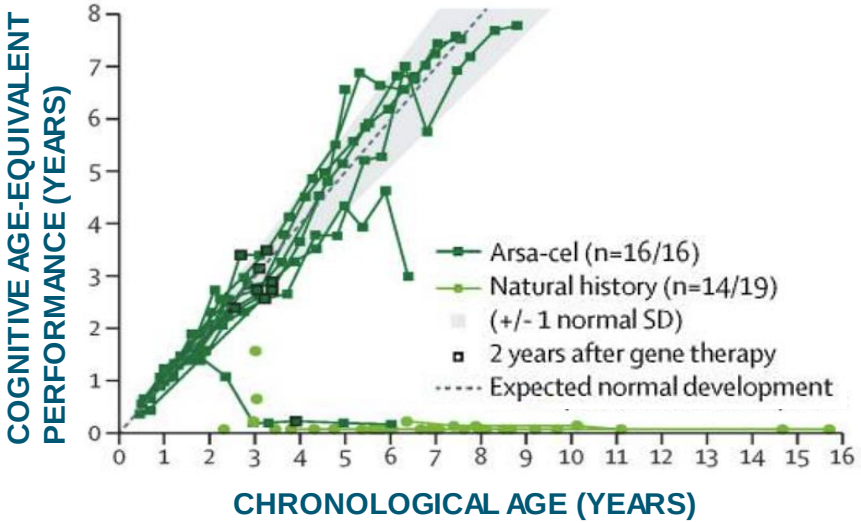
- Previous phase 1/2 IV rhARSA
  - Intravenous (IV) administration
  - Every other week infusions
  - Failed to prevent motor and cognitive deterioration
  - Relatively stabile peripheral nerve function
- Ongoing phase 2 IT rhARSA
  - Intrathecal (IT) administration
  - Weekly infusions
  - Results not released

I Dali C. *Mol Genet Metab*. 2020;131(1-2):235-244. Troy S. *Clin Pharmacol Ther*. 2020;107(6):1394-1404. I Dali C. *Ann Clin Transl Neurol*. 2021;8(1):66-80

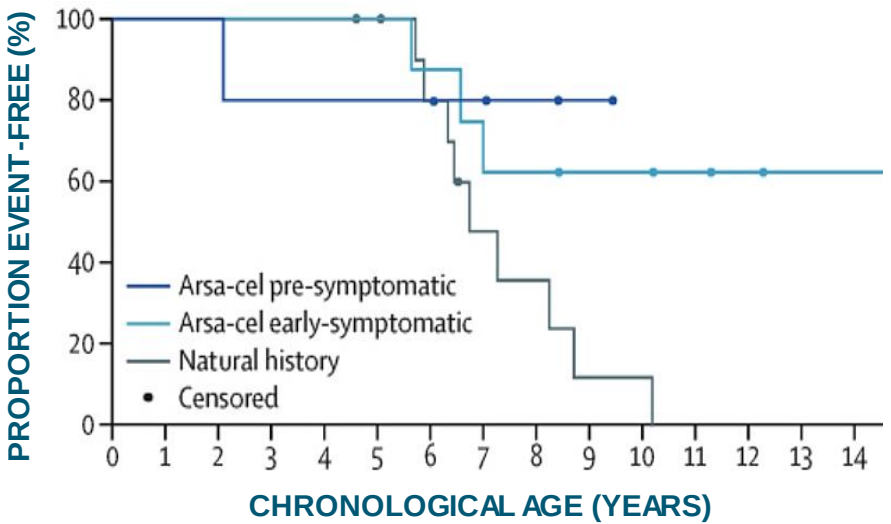
Emerging MLD Therapies

Arsa-cel Gene Therapy

Cognitive performance profiles



Age at severe motor impairment or death



Arsa-cel Gene Therapy

- Lentiviral vector encoding human ARSA cDNA introduced via autologous HSCT
- Approved in EU for very early/pre-symptomatic early-onset MLD

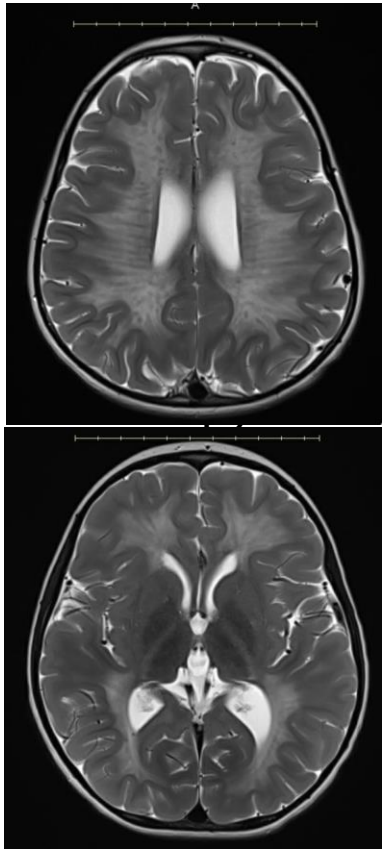
Fumagalli F. *Lancet*. 2022;399(10322):372-383. Sessa M. *Lancet*. 2016;388(10043):476-487

Case Study: Olivia

8 yo girl presents to neurology with 3-month history of clumsiness while walking.

- ❑ Diagnosed with ADHD 12 months ago with new onset learning issues at school related to processing and attention. Trials of atomoxetine and methylphenidate have not improved symptoms.
- ❑ Parents report she has been “acting strange” and “seems to be a different child” recently.

Based on MRI findings, positive urinary sulfatides and low ARSA enzyme activity, you make the diagnosis of **juvenile MLD**.



Audience Response

Which of the following is an early sign of juvenile MLD in school-aged children?

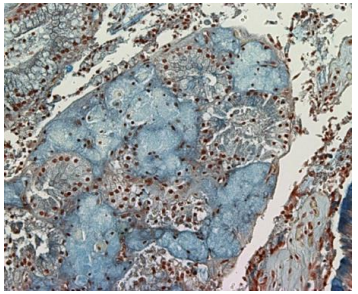
A. Adrenal insufficiency
B. Resting tremor
C. Macrocephaly
D. Behavioral/personality changes

Case Study: Marta

32 yo woman presents to GI from ED with severe vomiting, bloating, and upper right abdominal pain consistent with cholecystitis.

Medical history (as reported by husband):

- ❑ Bipolar II disorder dx ~10 years ago
- ❑ History of unpredictable and inappropriate behavior with increasingly frequent bursts of aggressiveness.
- ❑ Multiple trials of antidepressants and mood stabilizers have not improved symptoms.



Gallbladder pathology performed post-cholecystectomy revealed accumulation of macrophages with metachromatic material

Marta is referred to neurology for suspected MLD.
She and her spouse have two children, ages 5 and 7.

Audience Response

What chance do Marta's children have of inheriting her pathogenic *ARSA* genetic variants?

A. 25%
B. 50%
C. 75%
D. 100%
E. I don't know

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Audience Response

What would be the appropriate next step to clarify the risk to Marta's children for developing MLD?

A. *ARSA* gene sequencing in Marta's children
B. *ARSA* gene sequencing in Marta's spouse
C. Urinary sulfatide screening in Marta's children
D. Urinary sulfatide screening in Marta's spouse

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Recognize clinical signs and symptoms indicating suspicion for MLD early in disease-onset
- Perform differential investigations and confirmatory testing to achieve definitive diagnosis of MLD
- Screen family members of patients with MLD for pre-symptomatic disease and/or carrier status
- Implement supportive management for patients with MLD to optimize functioning and patient/caregiver QoL
- Explore emerging options in MLD diagnosis and disease management

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AFTER THE SHOW

Questions & Answers

To Receive Credit

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Go to the ***Evaluations*** tab and click on the link to complete the process.