MLD is a life-threatening disease now treatable

Think MLD
Test early – Refer urgently
Screen siblings

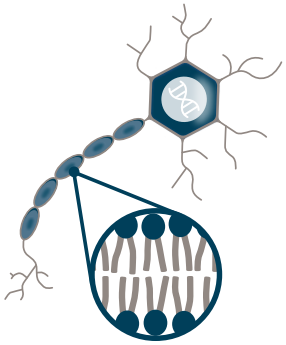
How to identify and diagnose MLD patients earlier and faster?

Metachromatic Leukodystrophy (MLD) is a rare, fatal and inherited neurometabolic disease causing progressive demyelination and neurodegeneration.

Orchard therapeutics™

MLD causes progressive demyelination and neurodegeneration

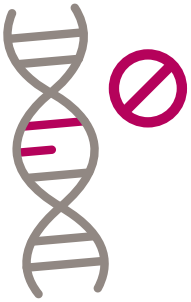
PHYSIOLOGICAL

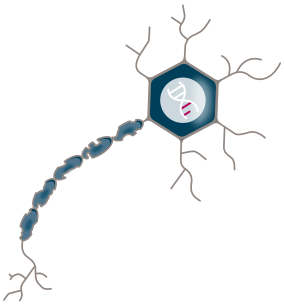


Sulfatides are a major component of the myelin membrane[1]

The **ARSA enzyme** usually breaks down sulfatides in the lysosome[2,3]

PATHOLOGICAL



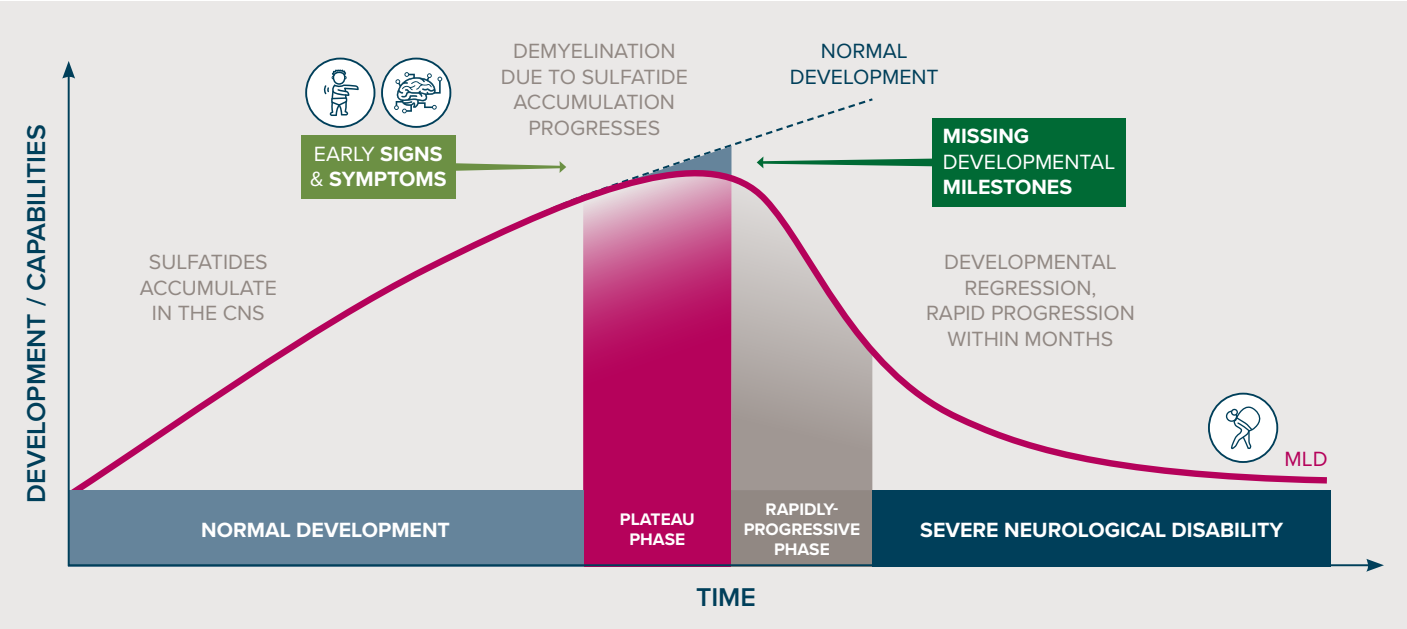


Mutations in the ***ARSA* gene** causes deficiency of the ARSA enzyme reducing sulfatide breakdown

Intra-lysosomal **sulfatides accumulation** leads to demyelination and neurodegeneration[1,2,4]

- Autosomal-recessive genetic disease caused by a deficiency of arylsulfatase A (ARSA) enzyme[1-3]

Clinical course of MLD



- Symptoms, age of onset and disease course vary, patients progress to severe neuromotor and cognitive disability and death[2,4-6]

Recognition of early symptoms of MLD

		LATE INFANTILE MLD	JUVENILE MLD
First Signs		<30 months	30 months – 16 years
EARLY SYMPTOMS (selected)			
Motor	**Hypotonia**	✓	
	Weakness	✓	
	Frequent falls	✓	
	Gait disturbances	✓	✓
	Abnormal movement patterns	✓	✓
Neuromotor and cognitive development	**Missing milestones**	✓	✓
	General regression	✓	✓
Cognitive	**Cognitive decline (school performance)**		✓
	Speech difficulties		✓
	Behavioural changes (education problems)		✓
Trigger		**MOTOR**	**MOTOR / COGNITIVE**
Time to diagnosis		12 months	24 months

- Early symptoms are difficult to recognise, missing developmental milestones and general neuromotor and cognitive regression should stimulate further investigations[7]

How to diagnose symptomatic MLD?

SUGGESTIVE
Clinical Symptoms

Early motor and/or **Behavioural/ cognitive**

Clinical signs and symptoms suggesting possible MLD diagnosis.

CONFIRMATORY
Laboratory

Biochemical testing
- ARSA enzyme activity
- 24 hour urinary sulfatides

and

Genetic testing
- Specific
- Multigene (panels)

Refer to QTC and consider sibling screening as soon as possible.

ONLY INDICATIVE
Magnetic Resonance Imaging

MRI

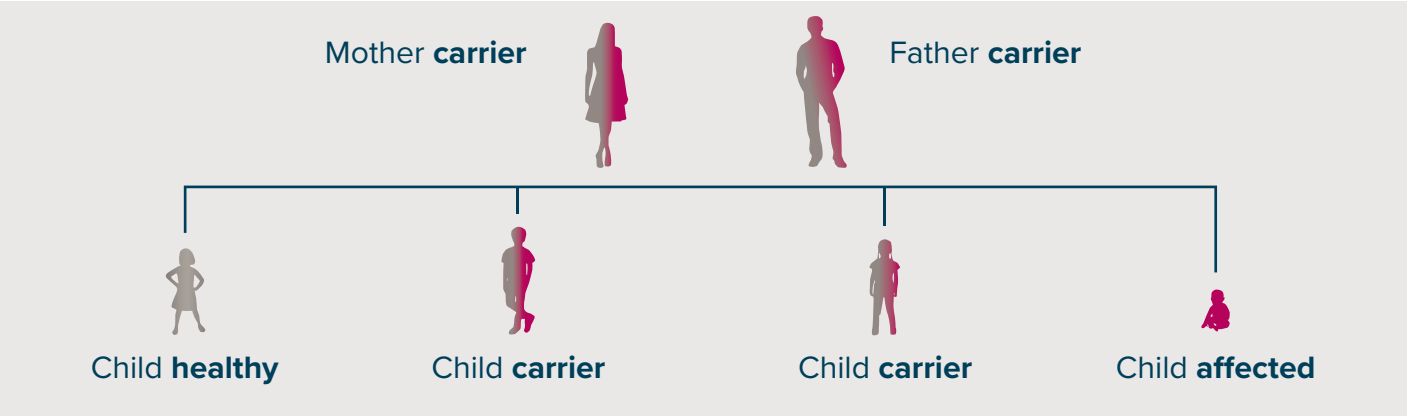
Patients may not have evidence on MRI early in the disease course. A normal MRI is not sufficient to rule out MLD.

- Blood ARSA levels should be used as screening tool once milestones are missed or general regression occurs[8]

Every day counts – identify MLD patients earlier

Expediting diagnosis – the 5 things to do

- Educate referral network to overcome “wait and see” mentality in the first line
- Symptomatic patients: expedited referral to a Neuropaediatrician is critical
- Confirming MLD diagnosis quickly can improve prognosis, especially in patients that can be treated
- **Pre-symptomatic patients: a family screening is urgently recommended to identify affected but still asymptomatic or early symptomatic unknown siblings**
- Counseling on family planning for affected families



Differential diagnosis: neurodevelopmental delay

Many other neurodegenerative diseases can mimic MLD[7]

- Elevated sulfatides or sulfatide accumulation
  - Multiple sulfatase deficiency (onset at 1 – 4 years, MLD-like clinical picture/MPS-like features, very low ARSA enzyme activity)
  - Saposin B deficiency (variable onset: MLD-like clinical picture, ARSA enzyme activity in normal range)
- Progressive degenerative disorders that manifest after a period of normal development
  - Krabbe disease, x-linked adrenoleukodystrophy, Pelizeus-Merzbacher disease, Alexander disease, Fucosidosis, Canavan disease, Gangliosidosis, Mucopolysaccharidoses
- Other genetic disorders for which neuromotor delays may be a presenting feature
  - Angelman syndrome, Becker muscular dystrophy, Fragile X syndrome, Mitocondrial myopathies, Noonan syndrome, Spinal muscular atrophy

References:

1. Kreysing J, *et al. Am J Hum Genet* 1993;**53**:339-346. **2.** Rosenberg JB, *et al. J Neurosci Res* 2016;**94**(11):1169-79. **3.** Kovacs E, *et al. Acta Med Marisiensis* 2015;**61**(3):233-235. **4.** Patil S, Maegawa GHB. *Drug Des Devel Ther* 2013;**7**:729-745. **5.** Ferreira CR, Gahl WA. *Transl Sci Rare Dis* 2017;**2**(1-2):1-71. **6.** Gieselmann V, Krägeloh-Mann I. *Neuropediatrics* 2010;**41**(1):1-6. **7.** von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy 2001. In: The metabolic and molecular bases of inherited disease, Vol. 3, 8th ed. New York, NY: McGraw-Hill; 2001:3695-3724. **8.** Parikh S, *et al. Mol Genet Metab* 2015;**114**:501-515. *The Global Leukodystrophy Initiative GLIA Consortium.