WHEN TO CONSIDER METACHROMATIC LEUKODYSTROPHY (MLD)

A disorder with progressive neurological involvement due to demyelination, affecting both the central (CNS) and peripheral nervous systems (PNS)

There are three forms depending on the age of onset and the rate of progression: late infantile (onset < 30 months), juvenile (2.5–16 years) and adult (> 16 years)

Clinical signs

Mainly neurological involvement

Initial manifestations (after a period of normal development):

- **LATE INFANTILE FORM (most common): stagnation of motor development, gait disturbances** with **ataxia,** muscle **weakness, reduced or absent deep tendon reflexes (DTRs):** prominent signs of **rapidly progressive peripheral neuropathy** often preceding symptoms of CNS involvement, **pyramidal syndrome**
- **JUVENILE FORM: decline in school performance,** impaired attention and reasoning, behavioural difficulties, impaired fine motor skills, followed by **gait disturbances** with **ataxia, reduced DTRs** and incipient **pyramidal involvement**
- **ADULT FORM:** typically, insidious onset with **neuropsychiatric symptoms** including **behavioural changes** (frontal syndrome, atypical psychotic features with hallucinations, emotional lability) **and/or cognitive difficulties** (memory impairment, apraxia etc), later followed by **motor deficits** (central and/or peripheral due to neuropathy) and epilepsy

Rare forms beginning with spastic paraparesis and ataxia with neuropathy +/- cognitive impairment Optic atrophy may also be observed

Progressive cognitive and motor decline leading to a bedridden state:

- Psychomotor regression (rapid in the late infantile form, variable in the juvenile form) with **deterioration of motor function** progressing to painful spastic tetraparesis, dystonia, cerebellar syndrome, **cognitive decline** followed by loss of speech, feeding difficulties (dysphagia, swallowing disorders), frequent epilepsy, visual and hearing impairment

Slower progression in the adult form, with death sometimes occurring decades after the onset of initial symptoms

Other manifestations

Gallbladder involvement
(main non-neurological manifestation, usually following neurological symptoms but may occur earlier):
gallbladder wall thickening,
gallstones, cholecystitis, small or enlarged gallbladder, gallbladder polyps

Intestinal polyps

Precocious puberty

Specialist assessment

Additional tests

Brain MRI: demyelinating changes, with bilateral and symmetrical T2 and FLAIR hypersignals starting in the corpus callosum (preferentially in the splenium in infantile form and the rostrum in adults), then spreading to the periventricular white matter (parieto-occipital in children, frontal in adults), sparing the U-fibres and with no contrast enhancement This is soon followed by marked diffuse cortical and subcortical atrophy.

Electromyogram: early reduction in nerve conduction velocities (often normal in adult neuropsychiatric forms).

Metachromatic leukodystrophy?

PROMPT specialist neuropaediatric or neurological opinion
SPECIFIC TREATMENT MAY BE POSSIBLE IN SOME CASES
DIAGNOSIS IS URGENT

Specialist assessment
in parallel with the investigation of other possible differential diagnoses[1]

Measurement of arylsulphatase A activity: reduced activity supports the diagnosis[2]

Measurement of urinary sulphatides: (elevated)

Confirmatory genetic testing (*ARSA* gene)

Seek urgent specialist opinion from an Expert Centre (Reference/Expert Centre for Rare Diseases):
https://www.filiere-g2m.fr/annuaire/

https://brain-team.fr/les-membres/les-centres-de-reference/leucodystrophies/

Initial assessment, specialised care and implementation of specific treatments (where indicated), coordinated by an expert centre for paediatric or adult forms of leukodystrophy:
https://brain-team.fr/les-membres/les-centres-de-reference/leucodystrophies/

For more information: Refer to the CETL (Lysosomal Disease Treatment Evaluation Committee) website: www.cetl.net

Genetic counselling, family screening in a specialist centre

Specialist medical opinion and reference laboratory

[1]Other causes of leukodystrophy or leukopathy (inflammatory, neoplastic or infectious), other causes of demyelinating polyneuropathy.
[2]Enzyme activity may be reduced but not absent in pseudodeficiency (not pathological).
Normal arylsulphatase A activity with elevated sulphatides may indicate activator deficiency (rare), diagnosed by *PSAP* gene sequencing.
Reduced activity of ARSA and other sulphatases in multiple sulphatase deficiency (rare; caused by mutations in the *SUMF1* gene).

BRAIN-TEAM Filière Nationale de Santé Maladies rares du système nerveux central

Maladies rares Héréditaires du Métabolisme Filière nationale de santé