ACMG American College of Medical Genetics and Genomics
Translating Genes Into Health®

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ACT Sheet

Newborn Screening ACT Sheet

[Elevated $C_{16:1}$-OH and/or $C_{16:0}$-sulfatide, reduced arylsulfatase A]

Metachromatic Leukodystrophy (MLD)

ACMG website: bit.ly/3ZgZTEg

Differential Diagnosis: Multiple Sulfatase Deficiency (MSD).

Condition Description: Metachromatic Leukodystrophy (MLD) is a lysosomal disorder that is due to a deficiency of arylsulfatase A (ARSA) enzyme, causing the accumulation of sulfatides, and resulting in the destruction of myelin. The subtypes of MLD are defined by the age at onset; all forms cause progressive motor and cognitive deficiencies. The most common form, the late-infantile form, has the earliest onset and the fastest progression. There are also juvenile and adult-onset forms. Multiple Sulfatase Deficiency (MSD) is caused by impaired posttranslational activation of sulfatases, including ARSA. Newborns with MLD and MSD are typically asymptomatic.

You Should Take the Following Actions:

- Inform family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Consult with an appropriate pediatric specialist experienced in managing MLD such as medical or biochemical geneticist or neurologist.
- Evaluate the newborn (newborns are expected to be asymptomatic).
- Initiate confirmatory/diagnostic testing, as recommended by the specialist.
- Provide the family with basic information about MLD and its management.

- Report final diagnostic outcome to the newborn screening program.

Diagnostic Evaluation: **Decreased leukocyte ARSA enzyme activity and elevated urine sulfatides:** is consistent with MLD or MSD. **Decreased leukocyte ARSA activity with elevated urine sulfatides and elevated urine glycosaminoglycans:** is consistent with MSD. **Molecular genetic testing:** can confirm the diagnosis of MLD or MSD.

Clinical Considerations:

The clinical presentation of MLD ranges from the rapidly progressive late-infantile form to the more slowly progressive juvenile-onset and adult-onset variants. All forms are characterized by neurologic decline affecting both motor and cognitive function. The late-infantile form is the most common and severe, with rapid loss of motor and language skills beginning before 30 months of age; survival beyond 10 years of age is uncommon without treatment. Autologous hematopoietic stem cell transplantation (HSCT) combined with gene therapy is most effective if initiated prior to the onset of symptoms. This therapy is indicated for pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile MLD which will be determined by further evaluation with a specialist. Allogeneic HSCT utilizing an unaffected donor may also be offered. Prompt referral for confirmatory testing is essential. If MLD is diagnosed, patients should be referred immediately to a specialized treatment center where individualized treatment options can be determined. Early evaluation and timely initiation of appropriate therapy are critical for achieving the best possible outcomes.

MSD is a neurodegenerative multisystem disorder of variable severity combining features of MLD and mucopolysaccharidoses with onset usually in infancy. MSD may present in the neonatal period with growth restriction, respiratory distress, corneal clouding, and dysmorphic features. Treatment for MSD is supportive.

Additional Information:

How to Communicate Newborn Screening Results
Gene Reviews
Medline Plus
United Leukodystrophy Foundation

Referral (local, state, regional, and national):

Find a Genetics Clinic Directory
Genetic Testing Registry