Newborn Screening ACT Sheet

[Elevated lysophosphatidylcholines] X-Linked Adrenoleukodystrophy (X-ALD)

Differential Diagnosis: X-linked adrenoleukodystrophy (X-ALD), other peroxisomal disorders, including Zellweger spectrum disorders.

Condition Description: X-ALD is an X-linked disorder caused by pathogenic variants in the *ABCD1* gene resulting in a defect in the adrenoleukodystrophy protein (ALDP). This results in an abnormal accumulation of very long chain fatty acids in the body affecting the nervous system white matter and the adrenal cortex. X-ALD has an estimated incidence of 1:17,000 live births. There are three variants of X-ALD: a childhood cerebral form that occurs primarily in males, Addison-only disease in males, and adrenomyeloneuropathy (AMN) occurring in both males and females. Zellweger spectrum disorders are rare and are also identified through this testing.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family to inform them of the newborn screening result. Ascertain clinical status. No clinical signs are expected in newborns with confirmed X-ALD. The presence of symptoms (poor feeding, bony abnormalities, abnormal liver function testing, hypotonia, renal cysts) in a newborn may be suggestive of another peroxisomal disorder.
- Elicit family history of sudden death in males and neurologic and neurodegenerative disorders.
- Consult with pediatric genetic or metabolic specialist.
- Report findings to state newborn screening program.

Diagnostic Evaluation: Confirmatory very long chain fatty acid analysis (VLCFA). Patients with elevated VLCFA indicative of X-ALD or another peroxisomal disorder should have follow-up molecular genetic testing. If Zellweger spectrum disorder is suspected based on early clinical signs and symptoms additional testing will be needed. Female *ABCD1* heterozygotes may also be identified.

Clinical Considerations: The childhood cerebral form of X-ALD manifests in approximately 1/3 of affected males most commonly at 4-10 years of age. Symptoms and signs may include attention deficit hyperactivity disorder, progressive cognitive and behavioral changes, adrenal impairment, and characteristic MRI abnormalities. From the time of diagnosis, the specialty center will arrange for regular MRI imaging and adrenal testing to determine when and if to initiate therapy. Adrenal steroid replacement is essential for treating adrenal insufficiency, however it does not prevent the development or the progression of neurological symptoms. Hematopoietic stem cell transplantation (HSCT) is the only proven successful treatment for the cerebral form of X-ALD but has to be performed in the earliest stages of the childhood cerebral form to be effective. Zellweger spectrum disorders have variable severity and clinical presentation and most lack specific therapy.

Diagnosis of adrenoleukodystrophy in newborns should raise concern about unrecognized disease in other family members.

Additional Information:
Gene Reviews
Genetics Home Reference
Leukodystrophy Care Network

Referral (local, state, regional, and national):
Testing
Find Genetic Services

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

LOCAL RESOURCES: Insert State newborn screening program web site links

State Resource site *(insert state newborn screening program website information)*

Name	
URL	
Comments	

Local Resource Site *(insert local and regional newborn screening website information)*

Name	
URL	
Comments	

APPENDIX: Resources with Full URL Addresses

Additional Information:

Gene Reviews
https://www.ncbi.nlm.nih.gov/books/NBK1315/

Genetics Home Reference
https://ghr.nlm.nih.gov/condition/x-linked-adrenoleukodystrophy

Leukodystrophy Care Network
https://www.huntershope.org/family-care/leukodystrophy-care-network/

Referral (local, state, regional and national):

Testing
https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=X+ALD

Find Genetic Services
https://clinics.acmg.net

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