Kansas Department of Health and Environment

Newborn Screening

ACT Sheet

KANSAS NEWBORN SCREENING PROGRAM

X-Linked Adrenoleukodystrophy (X-ALD)

Differential Diagnosis: X-Linked Adrenoleukodystrophy (X-ALD), disorders of peroxisomal biogenesis and beta-oxidation (including Zellweger syndrome), Aicardi-Goutières syndrome (AGS).

Condition Description: X-Linked Adrenoleukodystrophy (X-ALD) is an X-linked peroxisomal disorder caused by pathogenic variants in the *ABCD1* gene, resulting in a defect of the adrenoleukodystrophy protein. This causes an accumulation of very long chain fatty acids producing demyelination of the white matter and of the adrenal cortex. There are three main clinical presentations of X-ALD: a childhood cerebral form, an adrenal insufficiency form, and the adrenomyeloneuropathy (AMN) form, the latter of which occurs in both males and females. Zellweger syndrome is autosomal recessive and is characterized by the reduction or absence of peroxisomes, causing hypotonia, large fontanelles, and seizures. AGS is an autosomal recessive condition causing encephalopathy, microcephaly, and autoimmune dysfunction.

You Should Take the Following Actions:

- Inform family of newborn screening result; elicit family history of sudden death in males and of neurodegenerative disorders.
- Ascertain clinical status (newborns with X-ALD are expected to be asymptomatic; newborns with other peroxisomal disorders may exhibit hypotonia, poor feeding).
- Consult with pediatric geneticist, pediatric neurologist, pediatric endocrinologist, or metabolic specialist. • Evaluate the newborn (newborns with X-ALD are expected to be asymptomatic). Other peroxisomal disorders may present with hypotonia, abnormal LFTs, bony abnormalities in the neonatal period. If any of these signs are present or if the newborn is ill, transport to a hospital for further treatment in consultation with the metabolic specialist.
- Initiate confirmatory/diagnostic testing and management, as recommended by the specialist. • Provide the family with basic information about X-ALD/peroxisomal disorders.
- Report final diagnostic outcome to newborn screening program.

Diagnostic Evaluation: **Very-long-chain fatty acid analysis in plasma:** supports the differential diagnosis. **Molecular genetic testing:** confirms the specific diagnosis.

ACTION TO BE TAKEN IN 24 HOURS:

- ☐ **Consult with pediatric metabolic geneticist (see on next page)**
- ☐ **Contact family and inform them of results.**
- ☐ **Assess clinical status promptly. Adrenal insufficiency may be the first sign to appear. Other clinical signs and symptoms of X-ALD are not expected in well-appearing newborns, but presence of symptoms in ill newborns may indicate the presence of other peroxisomal disorder. Findings may include:**
  - *poor feeding*
  - *hypotonia*
  - *abnormal liver function*
  - *bony abnormalities*
  - *renal cyst*
- ☐ **Monitor infant for signs and symptoms of adrenal insufficiency:**
  - *poor feeding*
  - *vomiting*
  - *low blood sugar*
  - *pale or bluish skin*
  - *loose/floppy muscles*
  - *tremors, seizures, sweating*

Clinical Considerations: The childhood cerebral form of X-ALD generally presents by 3-10 years of age almost exclusively in males. Symptoms and signs can include attention deficit hyperactivity disorder, progressive cognitive and behavioral changes, vision problems, adrenal impairment, and characteristic MRI abnormalities. Regular MRI imaging and adrenal testing should be performed to determine the need for therapy. Hematopoietic stem cell transplantation and gene therapy are available treatments for the cerebral form of X-ALD. Corticosteroid replacement is essential for treating adrenal insufficiency. Diagnosis of adrenoleukodystrophy should prompt the assessment of other family members; different forms of X-ALD can present in the same family. Individuals with peroxisomal biogenesis disorders have variable severity and clinical presentation, are progressive, and most lack specific therapy with a high mortality rate. If a Kansas baby screens positive for C26:0 and the diagnosis is negative for X-ALD, the family should be referred for Zellweger Syndrome testing. Especially since the testing is offered to families at no charge. X-ALD has an extremely low false positive rate. We have Kansas listed as screening for Zellweger Syndrome in the NewSTEPS database since the X-ALD subcommittee recommended we refer babies for Zellweger testing if the X-ALD diagnosis was negative.

Reporting: Report diagnostic results to family and Kansas NBS program.

If MPS II is confirmed, Kansas Law 65-180 through 65-183 requires reporting findings back to KDHE by a physician. Financial assistance for MPS II clinic services and treatments may be available to the family upon application to the Special Health Care Needs (SHCN) program. A SHCN application will be sent to the baby's address. Parents or physicians can call SHCN at (785) 296-1313 for more information.

Specialists:

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