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An Update on Newborn Screening for Adrenoleukodystrophy in New York State: A Review of Management Protocol Changes and Confirmed Cases

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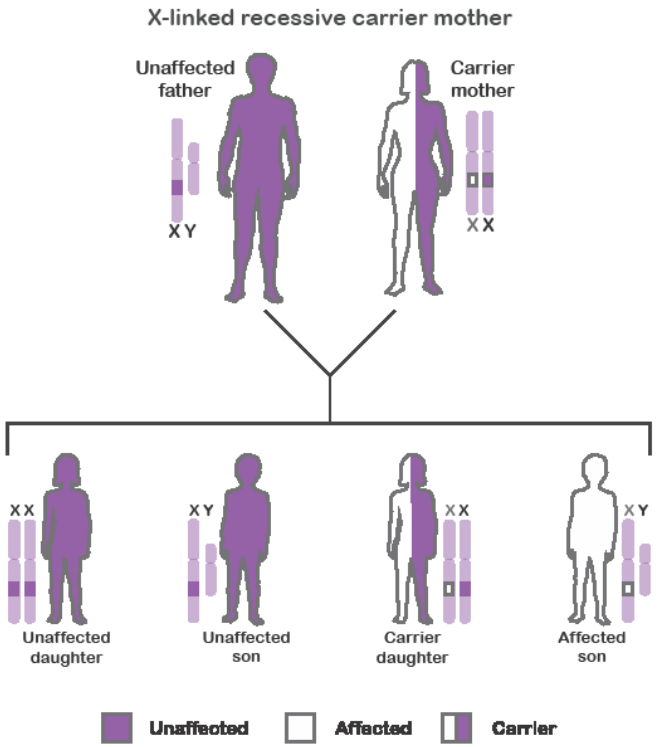
Outline

- ALD review
- NYS ALD data
- Management protocols
- Case review

ALD Review

- ALD is a peroxisomal disorder
- Caused by mutations in the *ABCD1* gene
- X-linked inheritance
- Two phenotypes
  - Childhood cerebral onset and adult onset (adrenomyeloneuropathy)

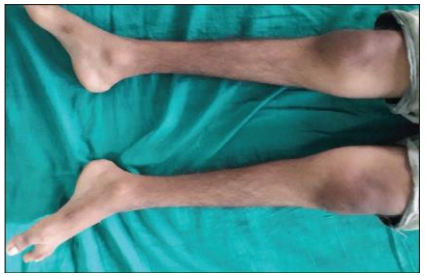


Symptoms
Childhood Cerebral Onset

- 35 to 50% of males
- Onset varies from three to ten years
- Symptoms: Addison disease, cognitive disturbances, hyperactivity, seizures, psychosis, vision and hearing loss
- Vegetative state and death within two to four years of the onset of neurological symptoms

Adrenomyeloneuropathy (AMN)

- Onset of symptoms from the second to fourth decade
- Progressive weakness of the legs, paresis, sphincter disturbance and sexual dysfunction
- About 70% also have Addison disease



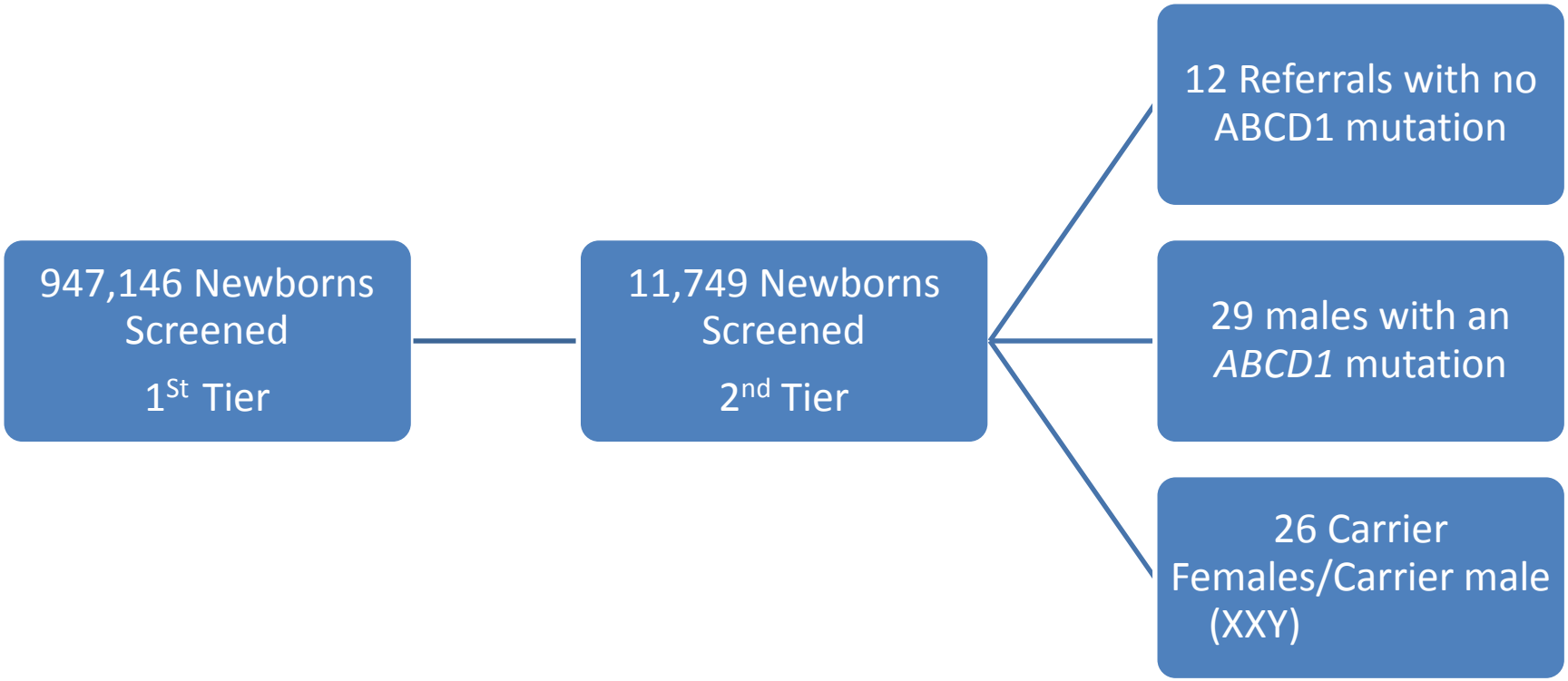
Carriers

- Approximately 10 to 50% of females with an *ABCD1* gene mutation have neurological symptoms
- Similar presentation to AMN
- Milder and more slowly progressive
- Onset of symptoms in the 30s

NYS Method of Screening for ALD

- 1st and 2nd tier: C26:0 lysophosphatidylcholine (C26:0 LPC)
  - 1st tier: MS/MS
  - 2nd tier: MS/MS with selective HPLC
- 3rd tier: sequencing of *ABCD1* gene

NYS ALD Screening Outcomes



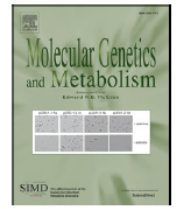
Management

- Management protocols used to follow boys with a confirmed diagnosis of X-linked adrenoleukodystrophy since December 30, 2013
  - Modified based on experience

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Newborn screening for X-linked adrenoleukodystrophy in New York State: Diagnostic protocol, surveillance protocol and treatment guidelines

B.H. Vogel [a,*], S.E. Bradley [a], D.J. Adams [b], K. D'Aco [c], R.W. Erbe [d], C. Fong [c], A. Iglesias [e], D. Kronn [f], P. Levy [g], M. Morrissey [a], J. Orsini [a], P. Parton [h], J. Pellegrino [i], C.A. Saavedra-Matiz [a], N. Shur [j], M. Wasserstein [k], G.V. Raymond [l], M. Caggana [a]

Asymptomatic Boys in Childhood

	Timing	Frequency
Endocrine		
Clinical evaluation	Age 12 months - 18 years	At least annually
ACTH	Age 6 months- 18 years	Every 6 months
Cortisol	Age 6 months- 18 years	Every 6 months
Neurology		
Clinical evaluation	Age 6 months - 18 years	Annually
Brain MRI without contrast	12 months and 24 months	Annually
Brain MRI without contrast	Age 36 months - 10 years	Every 6 months
Brain MRI without contrast	Age 10 years - 18 years	Annually
Genetics		
Clinical evaluation and counseling	Age 12 months - 18 years	At discretion of specialist

Changes to Neurology Surveillance Protocol

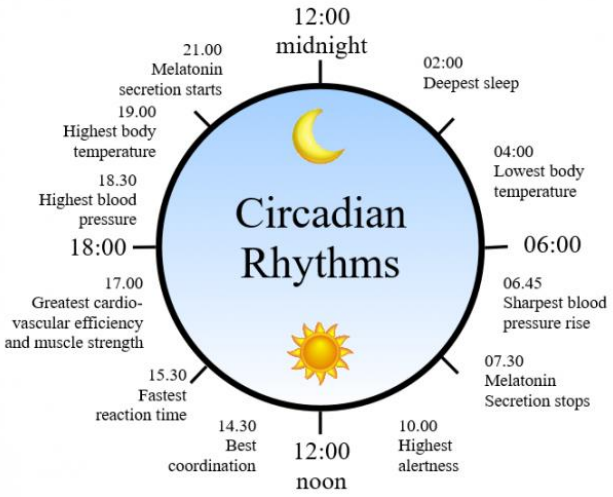
- First brain MRI delayed from 6 months to 12 months of age
  - The specialty centers across New York State report difficulty with interpretation and challenges with coordinating the brain MRI prior to six months of age.

Considerations for Referral to HCT

- HCT only recommended during early stages of cerebral disease due to risk for complications and mortality rate
- ALD MRI Score
  - ALD MR severity score is greater than one and less than nine
- performance IQ of greater than 80
- ALD MRI score of a boy with X-linked adrenoleukodystrophy should be independently confirmed by experts in ALD prior to recommendation for assessment for hematopoietic cell therapy

Endocrine Surveillance Protocol

- Difficulty interpreting ACTH and cortisol values in newborns prior to the regulation of the circadian rhythm
- Discussions are ongoing about the best approach
  - Discussion about utility of a cosyntropin stimulation test
- Discussions ongoing by Pediatric Endocrine Society



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ALD Case 1 (Baby Boy)

Newborn Screen Results:

C26:0 = 1.18 µM

HC26:0 = 0.84 µM

DNA Results: Hemizygous for c.1979G>T (Variant of uncertain significance; other variants at this location reported in ALD; maternally inherited)

Follow-up Results:

C26:0 = 3.76 nmol/ml (Normal < = 1.30)

C26:0/C22:0 = 0.132 (Normal < = 0.023)

C24:0/C22:0 = 2.24 (Normal < = 1.39)

Diagnosis: Definite ALD

ALD Case 2 (Baby Boy)

Newborn Screen Results:

1st Specimen

C26:0 = 0.40 µM; HC26:0 = 0.26 µM

2nd Specimen

C26:0 = 0.39 µM; HC26:0 = 0.26 µM

DNA Results: Hemizygous for R163H mutation (reported in a symptomatic carrier)

Follow-up Results:

Mild hypotonia

C26:0 = 2.20 nmol/ml (Normal < = 1.30)

C26:0/C22:0 = 0.039 (Normal < = 0.023)

C24:0/C22:0 = 1.45 (Normal < = 1.39)

Diagnosis: Definite ALD

ALD Case 3 (Baby Girl)

Newborn Screen Results:

C26:0 = 0.65 µM

HC26:0 = 0.50 µM

DNA Results: Heterozygous for Gln47Argfs*21 (Novel variant)

Follow-up Results:

Mutation not identified in either parent

Diagnosis: Carrier of ALD

ALD Case 4 (Baby Boy)

Newborn Screen Results:

C26:0 = 1.29 µM

HC26:0 = 1.33 µM

DNA Results: No *ABCD1* mutation detected

Follow-up Results:

Hypotonia, poor feeding, distinctive facies, seizures, hepatic dysfunction, renal cysts, respiratory distress, small muscular VSD, pneumothoraces, hemorrhage on brain ultrasound

C26:0 = 2.960 nmol/ml (Normal < = 1.30)

C26:0/C22:0 = 0.318 (Normal < = 0.023)

C24:0/C22:0 = 1.289 (Normal < = 1.39)

PEX DNA testing: Two mutations in PEX1

Diagnosis: Definite Zellweger spectrum disorder

ALD Case 5 (Baby Girl)

Newborn Screen Results:

C26:0 = 0.56 µM

HC26:0 = 0.36 µM

DNA Results: No *ABCD1* mutation detected; normal allelic variant c.*8G>C

Follow-up Results:

No abnormal clinical findings

C26:0 = 3.22 nmol/ml (Normal < = 1.30)

C26:0/C22:0 = 0.056 (Normal < = 0.023)

C24:0/C22:0 = 1.60 (Normal < = 1.39)

Normal plasmalogens

Normal ABCD1 MLPA studies

Normal VLCFA in father, mother and two brothers

Diagnosis: Possible peroxisomal disorder of unknown etiology, X-linked ALD ruled out

Thank you!
Questions?