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

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Beth Vogel, MS, CGC
Newborn Screening Program
Wadsworth Center
NYS Department of Health
Outline

• ALD review
• NYS ALD data
• Management protocols
• Case review
ALD Review

- ALD is a peroxisomal disorder
- Caused by mutations in the \textit{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

947,146 Newborns Screened
1\textsuperscript{st} Tier

11,749 Newborns Screened
2\textsuperscript{nd} Tier

12 Referrals with no \textit{ABCD1} mutation

29 males with an \textit{ABCD1} mutation

26 Carrier Females/Carrier male (XYX)
Management

• Management protocols used to follow boys with a confirmed diagnosis of X-linked adrenoleukodystrophy since December 30, 2013
  – Modified based on experience
# Asymptomatic Boys in Childhood

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<td>Clinical evaluation</td>
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<td>ACTH</td>
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<tr>
<td>Cortisol</td>
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| **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

Circadian Rhythms:
- 12:00 noon: Highest alertness
- 12:00 midnight: Melatonin secretion starts
- 02:00: Deepest sleep
- 04:00: Lowest body temperature
- 06:45: Sharpest blood pressure rise
- 07:30: Melatonin secretion stops
- 10:00: Highest alertness
- 12:30: Best coordination
- 14:30: Fastest reaction time
- 15:30: Greatest cardiovascular efficiency and muscle strength
- 18:00: Highest blood pressure
- 18:30: Highest body temperature
- 21:00: Melatonin secretion starts
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:
1\(^{st}\) Specimen
C26:0 = 0.40 µM; HC26:0 = 0.26 µM
2\(^{nd}\) 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?