Developing Short- and Long-term Follow-up for X-linked Adrenoleukodystrophy

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GENETIC COUNSELOR, NYS NEWBORN SCREENING PROGRAM
Outline

- Review of X-linked Adrenoleukodystrophy
- Newborn screening for ALD
- New York State (NYS) method
- Follow-up preparations
  - Diagnostic algorithm and case definitions
  - Medical management
  - Considerations for treatment
  - Genetic counseling considerations
  - Long-term follow-up
  - Educational materials
ALD Review

- ALD is a peroxisomal disorder
- Caused by mutations in the ABCD1 gene
- X-linked inheritance
- 1 in 21,000 males (~12 per year in NYS)
- Two phenotypes
  - Childhood cerebral onset and adult onset (adrenomyeloneuropathy)
Symptoms
Childhood 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

- 1\textsuperscript{st} and 2\textsuperscript{nd} tier: C26:0 lysophosphatidylcholine (C26:0 LPC)
  - 1\textsuperscript{st} tier: MS/MS
  - 2\textsuperscript{nd} tier: MS/MS with selective HPLC

- 3\textsuperscript{rd} tier: sequencing of ABCD1 gene

- More details from Joe Orsini, PhD
Differential Diagnoses

1. X-linked adrenoleukodystrophy (X-ALD)
2. Carrier of X-linked adrenoleukodystrophy
3. Adrenomyeloneuropathy (AMN)
4. Zellweger Spectrum Disorders (ZSD)
5. Single-enzyme deficiency (SED) of the peroxisomal β-oxidation enzymes
   1. D-bifunctional protein (D-BP)
   2. acyl-CoA oxidase (AOx)
6. CADDS
Follow-up Preparations

- Series of conference calls
  - metabolic geneticists
  - NBS Program Staff
  - Disorder expert – Dr. Gerald Raymond

- Separate calls with endocrinologists, neurologists and genetic counselors
Follow-up Preparations

1. Preliminary diagnostic algorithms and management recommendations were created prior to calls
2. These were reviewed and revised with the group on conference calls
Diagnostic Algorithm

- Goals of the algorithm:
  - To answer the question, does this baby have ALD
  - To recommend the minimum lab work and evaluations necessary in order to answer that question
Positive Newborn Screen (Tier 1 and Tier 2)

- Disease-causing mutation in ABCD1 identified by sequencing (NBS Tier 3)
- No mutation or VUS in ABCD1 on sequencing performed by NBS

**Initial Visit:** Order VLSCGA and plasmalogens in baby
Case Definitions

- Developed for
  - ALD
  - Zellweger spectrum disorders
  - Acyl CoA oxidase deficiency
  - D-bifunctional protein deficiency
  - Peroxisomal disorder of unknown etiology
<table>
<thead>
<tr>
<th>Category</th>
<th>VLCFA</th>
<th>Plasmalogen</th>
<th>Clinical symptoms</th>
<th>Mutation analysis</th>
<th>Fibroblast studies</th>
<th>Additional Comments</th>
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<tbody>
<tr>
<td>Definite</td>
<td>Elevated</td>
<td>Untested or unknown</td>
<td>Not present</td>
<td>Disease-causing mutation in ABCD1</td>
<td>Untested or unknown</td>
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<td>Definite</td>
<td>Elevated</td>
<td>Normal</td>
<td>Not present</td>
<td>Deletion/duplication on MLPA</td>
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<tr>
<td>Definite</td>
<td>Elevated</td>
<td>Normal</td>
<td>Not present</td>
<td>No mutation, deletion or duplication</td>
<td>ALDP Absent</td>
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<td>Probable</td>
<td>Elevated</td>
<td>Normal</td>
<td>Not present</td>
<td>No mutation on sequencing, deletion/duplication not done</td>
<td>Untested or unknown</td>
<td>Family history or family VLCFA studies suggestive of X-linked ALD</td>
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<td>Possible</td>
<td>Elevated</td>
<td>Normal</td>
<td>Not present</td>
<td>Variant of unknown significance inherited from the mother</td>
<td>Untested or unknown</td>
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<tr>
<td>Possible</td>
<td>Elevated</td>
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<td>Not present</td>
<td>No mutation on sequencing, deletion/duplication not done</td>
<td>Untested or unknown</td>
<td></td>
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<tr>
<td>No disease</td>
<td>Normal</td>
<td>Normal</td>
<td>Not present</td>
<td>No mutation on sequencing</td>
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Management Protocols

- At the time of diagnosis
- Asymptomatic boys in childhood
- Asymptomatic men after age 18
### At the Time of Diagnosis

<table>
<thead>
<tr>
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<th>Timing</th>
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<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
</tr>
<tr>
<td>Enter practice and Initial clinical evaluation</td>
<td>At Diagnosis</td>
</tr>
<tr>
<td>Serum ACTH</td>
<td>At Diagnosis</td>
</tr>
<tr>
<td>Cortisol</td>
<td>At Diagnosis</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td></td>
</tr>
<tr>
<td>Enter practice and Initial clinical evaluation</td>
<td>At Diagnosis</td>
</tr>
<tr>
<td>Genetic Counseling</td>
<td></td>
</tr>
<tr>
<td>Referral</td>
<td>At Diagnosis</td>
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## Asymptomatic Boys in Childhood

<table>
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<tr>
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<th>Timing</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical evaluation</td>
<td>Age 12 months - 18 years</td>
<td>At least annually</td>
</tr>
<tr>
<td>Serum ACTH</td>
<td>Age 6 months- 18 years</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Age 6 months- 18 years</td>
<td>Every 6 months</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical evaluation</td>
<td>Age 6 months - 18 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Brain MRI without contrast</td>
<td>Age 6 months</td>
<td>Initial</td>
</tr>
<tr>
<td>Brain MRI without contrast</td>
<td>Age 18 months - 30 months</td>
<td>Annually</td>
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<tr>
<td>Brain MRI without contrast</td>
<td>Age 36 months - 10 years</td>
<td>Every 6 months</td>
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<tr>
<td>Brain MRI without contrast</td>
<td>Age 10 years - 18 years</td>
<td>Annually</td>
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<tr>
<td><strong>Genetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical evaluation and counseling</td>
<td>Age 12 months - 18 years</td>
<td>At discretion of specialist</td>
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## Asymptomatic Men After Age 18

<table>
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<th>Timing</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Transition to adult Endocrinology and have clinical evaluation</td>
<td>Starting at 18 years</td>
<td>At least every other year</td>
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<tr>
<td>Serum ACTH</td>
<td>Starting at 18 years</td>
<td>Annually</td>
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<tr>
<td>Cortisol</td>
<td>Starting at 18 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enter adult practice and have clinical evaluation</td>
<td>Starting at 18 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Brain MRI without contrast</td>
<td>Starting at 18 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Genetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical evaluation and counseling</td>
<td>Starting at 18 years</td>
<td>At discretion of specialist</td>
</tr>
</tbody>
</table>
Considerations for Referral to HCT

- HCT only recommended during early stages of cerebral disease due to mortality rate

- ALD MRI Score
  - ALD MR severity score is greater than one and less than nine

- Performance IQ of greater than 80
Genetic Counseling Considerations

- Identification and counseling of potentially affected family members

- Identification of female carriers and males with AMN
  - Grief, anxiety, depression, despair
  - Life and long-term care insurance
  - Only give results to fathers with AMN in-person
Long-term Follow-up

- Data elements determined by the group
- 40 data elements
- Data includes general elements, endocrine, neurology, family history and prenatal history
Acknowledgements

- Dr. Gerald Raymond
- Dr. Melissa Wasserstein
- Dr. Alejandro Iglesias
- Dr. Patricia Parton
- Dr. David Kronn
- Dr. Darius Adams
- Dr. Natasha Shur
- Dr. Joan Pellegrino
- Dr. Chin-To Fong
- Dr. Kristin D’Aco
- Dr. Richard Erbe
Questions?

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