Outcome of patients diagnosed with short-chain acyl-CoA dehydrogenase deficiency in the Inborn Errors of Metabolism-Information System

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Introduction

Short-chain acyl-CoA dehydrogenase deficiency (SCADD) is an autosomal recessive disorder of mitochondrial beta-oxidation of short-chain fatty acids. It was first reported in 1987 in a patient who later died.

Clinical Significance of SCADD is Currently Unclear

1980’s & 90’s

• believed to cause a range of metabolic and neurological concerns
• believed to cause a range of metabolic and neurological concerns

Today

• most patients diagnosed by newborn screening (NBS) are asymptomatic
• might be a biochemical phenotype rather than a metabolic disorder
• might render an increased susceptibility to other metabolic or environmental stressors.

This disorder has become somewhat controversial, and a number of programs have removed it from their newborn screening panel. Understanding the clinical significance of SCADD is important to assure appropriate care is provided to individuals with this diagnosis and to avoid undue stress and unnecessary overmedicalization for families.
Methods

The Inborn Errors of Metabolism – Information System (IBEM-IS) is a federally-funded longitudinal database containing de-identified information on patients with inborn errors of metabolism as entered by their home metabolic center.

The 47 of 68 cases of SCADD submitted to the Inborn Errors of Metabolism-Information System (IBEM-IS) between 2007-2021 having DNA analysis were examined.

These 47 cases were divided into three groups based on genotype:

- **Group A** (18 cases): two pathogenic DNA variants (three of whom also had an additional common polymorphism)
- **Group B** (21 cases): one variant (19 of whom also had a common polymorphism)
- **Group C** (8 cases): no DNA variants but two common polymorphisms (7 homozygous for 625G>A and one homozygous for 511C>T)

The newborn screen C4, and the result interpretation of the follow-up studies including plasma acylcarnitine, urine ethylmalonic acid, urine organic acids, urine acylglycine, fatty acid oxidation probe, and occurrence of neonatal or later symptoms were compared between groups.

Jaundice and non-specific symptoms (e.g. prematurity) were not included in the analysis. Statistical analysis included t-test and Chi-square, as appropriate.

Results

Table 1 – Genotypes of patients reported to have two pathogenic or suspected pathogenic variants

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Protein</th>
<th>Frequency</th>
<th>Previously Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>529T&gt;C</td>
<td>W177R</td>
<td>15/36</td>
<td>Inactivating</td>
</tr>
<tr>
<td>319C&gt;T</td>
<td>R107C</td>
<td>5/36</td>
<td>Inactivating</td>
</tr>
<tr>
<td>826G&gt;A</td>
<td>A276T</td>
<td>3/36**</td>
<td></td>
</tr>
<tr>
<td>136C&gt;T</td>
<td>R46W</td>
<td>2/36</td>
<td>Inactivating</td>
</tr>
<tr>
<td>320G&gt;A</td>
<td>R107H</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>417G&gt;C</td>
<td>W139C</td>
<td>1/36</td>
<td>Inactivating</td>
</tr>
<tr>
<td>460G&gt;T</td>
<td>L154F</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>269G&gt;C</td>
<td>G90A</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>1174G&gt;A</td>
<td>E392K</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>815G&gt;A</td>
<td>R272H</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>682-683delGA</td>
<td>E228fs*16</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>988C&gt;T</td>
<td>R330C</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>332C&gt;G</td>
<td>S111F</td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>-56C&gt;G</td>
<td></td>
<td>1/36</td>
<td></td>
</tr>
<tr>
<td>820G&gt;A</td>
<td>G274S</td>
<td>1/36</td>
<td></td>
</tr>
</tbody>
</table>

** Twice allelic with 625G>A
Table 2 – NBS C4 and follow-up metabolites by group (not all values available for all subjects).

<table>
<thead>
<tr>
<th>Group</th>
<th>Source</th>
<th>NBS C4</th>
<th>Plasma AC</th>
<th>Urine EMA</th>
<th>Urine OA</th>
<th>Urine AG</th>
<th>FAOD Probe</th>
<th>Neonatal Symptoms</th>
<th>Later Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (2 variants)</td>
<td>16 NBS 1 Fam Hx 1 Sx</td>
<td>2.28</td>
<td>16 Abn</td>
<td>4 Abn</td>
<td>13 Abn</td>
<td>11 Abn</td>
<td>1 Diag</td>
<td>2 yes 15 no</td>
<td>2 yes 12 no 3 &quot;other&quot;*</td>
</tr>
<tr>
<td>Group B (1 variant)</td>
<td>20 NBS 1 Fam Hx</td>
<td>1.94</td>
<td>8 Abn</td>
<td>8 Abn</td>
<td>10 Abn</td>
<td>6 Abn</td>
<td>1 Diag</td>
<td>2 yes 17 no</td>
<td>4 yes 14 no</td>
</tr>
<tr>
<td>Group C (polymorph. only)</td>
<td>6 NBS 1 Abn labs/Sx 1 Unkn</td>
<td>1.74</td>
<td>3 Abn</td>
<td>3 Abl</td>
<td>4 Abn</td>
<td>1 Abn</td>
<td>3 Diag</td>
<td>2 yes 5 no</td>
<td>5 yes 3 no</td>
</tr>
</tbody>
</table>

Hx – history; Abn – abnormal; Sx – symptoms; Diag – diagnostic
* Not otherwise specified

General Observations

- Patients in all groups had diagnostic biochemical markers for SCADD deficiency.
- Fibroblast fatty acid oxidation probe was abnormal and frequently reported as “diagnostic” even in the absence of pathogenic variants.
- Overall, 15% of cases ascertained by NBS reported significant neurodevelopmental findings.
- Other symptoms included vomiting, muscle pain, failure to thrive, tube feeding, and others.
- Patients in Group C reported the highest incidence of neonatal (2/7) and later (5/8) symptoms.
Although the metabolic derangements appear statistically significant in cases with two pathogenic mutations, standard *biochemical testing alone is unable to clearly distinguish between individuals harboring two pathogenic variants, vs one pathogenic variant or only common polymorphisms.*
Discussion

Common biochemical testing alone is unable to distinguish the presence of two inactivating mutations in ACADS from one mutation or only polymorphisms.

In our series even the fibroblast fatty acid oxidation probe was unable to differentiate these cases without DNA analysis.

To date, there have been no convincing biochemical or genotype/phenotype correlations associated with neonatal or later symptoms.

Our findings confirm prior reports that most cases of SCADD diagnosed by newborn screening are generally asymptomatic. However, a troubling pattern of neurodevelopmental concerns persists in a small number of patients. In the Pederson et al (2008) series of 114 patients, there was no relationship between the clinical phenotype and the degree of ACADS dysfunction; in that series symptoms appeared to cluster into six groups: 1) failure to thrive, feeding difficulties and hypotonia; 2) seizures; 3) hypotonia without seizures; 4) failure to thrive, developmental delay and hypotonia; 5) dysmorphic features; 6) variable (myopathy, cardiomyopathy, hepatic steatosis and others).

The symptoms reported in our case series are closely related to these, with feeding difficulty/vomiting or gastrostomy reported four times, hypotonia four times, seizures four times, and developmental delay three times.

Further, other studies have also noted some of the most symptomatic patients to be the ones with only polymorphisms (Gallant 2012, van Maldegem 2006, Waisbren 2013). One hypothesis for the occurrence of more symptoms in patients having only polymorphisms compared to those having pathogenic variants is that protein misfolding in the common polymorphisms leads to more oxidative stress (Nochi 2017).

In summary, the significance of reduced levels of ACADS activity remains uncertain.

Biochemical testing alone cannot predict genotype.

Clearly, most infants ascertained by newborn screening appear healthy and normal, but a troubling pattern of neurodevelopmental concerns persists in a small percentage, and seems more pronounced in carriers of polymorphisms compared to those having inactivating variants.

To date there is no evidence that fasting prevention or other treatments are preventative for the small percentage who go on to manifest symptoms. The possibility that some cases might have adult onset (similar to that seen in CPTII deficiency or LCHADD) also remains a possibility, given one report of muscle weakness in three of five mothers identified as having SCADD through their child’s NBS. It remains possible that the ACADS variants may behave differently in vivo vs in vitro, or engender susceptibility to other metabolic or physical stressors.

References


