Long-term Cardiac Outcomes of Patients with Very Long Chain Acyl-CoA Dehydrogenase Deficiency after Clinical Identification through the Michigan Newborn Screening Program

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\textbf{Introduction}

- Long-chain fatty acid oxidation disorders, such as Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD) were thought to have been the underlying etiology for a portion of sudden infant deaths due to ventricular arrhythmias.
- The incidence of cardiomyopathy and/or arrhythmias in patients with VLCADD has been reported to be at least up to 52%.
- With the advent of newborn screening (NBS) in Michigan for VLCADD in 2005, there have been an increasing number of patients with a diagnosis of VLCADD who have been asymptomatic.
- It is possible that many of the patients diagnosed on NBS have a milder clinical course than patients diagnosed symptomatically prior to NBS.
- This may be secondary to the detection of mild cases in addition to early initiation of treatment.
- It is unclear to what extent these milder patients have a risk of developing cardiac complications such as arrhythmias and cardiomyopathy leading to sudden death.
- Marsden et al recently looked at clinical outcomes, including cardiomyopathy, in patients with medium or long chain fatty acid oxidation disorders. They found lower rates of cardiomyopathy after the initiation of newborn screening, including none in one cohort (see below).

![VLCAD deficiency](chart.png)

- NBS (n = 20)
- Clinical diagnosis (n = 10)
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**Results**

- We performed a review of the cardiac history in our cohort of patients diagnosed with VLCADD through the Michigan NBS.
- From April 2005 to May 2021, our center has diagnosed 28 patients with VLCADD since the onset of NBS.
- These patients range from 2 weeks of age to 16 years old.
- We classified these patients as mild, moderate, or severe based on GMDI guidelines (listed below) and found: 21 were mild, 7 were moderate, and 0 were severe.
- 10 patients carried the well known attenuated allele, V283A, whereas the rest mostly had private mutations

### GMDI Classification

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Newborn screen</th>
<th>Diagnosis</th>
<th>Clinical Symptoms (before treatment)</th>
<th>Biochemical monitoring</th>
</tr>
</thead>
</table>
| Mild      | Mild/moderately elevated long-chain acylcarnitines | ACP may be near normal | • Asymptomatic beyond infancy  
• Tolerates catabolic stressors without metabolic decompensation  
• May present with rhabdomyolysis, muscle pain and/or exercise intolerance during adolescence and adulthood | Often normal when healthy |
| Moderate  | Mild/moderately elevated long-chain acylcarnitines | Abnormal ACP | • Asymptomatic at diagnosis  
• Episodic hypoketotic hypoglycemia or rhabdomyolysis can occur  
• Cardiac presentation unlikely | Abnormal even when healthy |
| Severe    | Significantly elevated long-chain acylcarnitines | Abnormal ACP | • Symptomatic at diagnosis or within first months of life without treatment  
• May include hypertrophic or dilated cardiomyopathy, pericardial effusion and arrhythmias, as well as hypotonia, hepatomegaly, intermittent hypoglycemia and rhabdomyolysis | Abnormal even when healthy |
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Results continued

• EKG and echocardiograms are recommended at diagnosis and annually thereafter for all patients, as well as during significant hospitalizations.
• To date, only one patient has had cardiac complications detected initially through routine screening.
• This patient was classified as moderate, and died at age 6 following a severe hypoglycemic event.
• In our cohort, 29% of patients exhibited rhabdomyolysis under various circumstances. Of those patients, 87.5% remained stable from a cardiac standpoint.

![Michigan NBS Patient Cardiac Issues](chart1)

![Michigan NBS Patients with Rhabdomyolysis](chart2)

![Michigan NBS Patients with Rhabdomyolysis & Cardiac Issues](chart3)
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Patient Profile

- Severe hypoglycemic event at age 6 years 4 months following fast of 20+ hours
- PICU admission due to respiratory failure, hypoxia, and hypoglycemia (glucose 8)
- EEG showed diffuse slowing suggestive of underlying diffuse encephalopathy and neuronal dysfunction
- Brain MRI did not demonstrate any evidence of acute infarction initially but repeat 3 weeks later showed diffuse bilateral restricted diffusion associated with increased T2 signal in the cerebral cortical and deep gray matter likely related to the known incident of severe hypoglycemia.
- Peak CK was 1237 U/L
- Hospitalization lasted 3 months before patient was discharged to hospice care, where he died at age 7 years 1 month

<table>
<thead>
<tr>
<th>Initial NBS C14:1</th>
<th>2.67 umol/mL (reference &lt;0.78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmatory C14:1</td>
<td>4.95 umol/mL (reference &lt;0.16)</td>
</tr>
</tbody>
</table>

Genetic Variants


Cardiac History

<table>
<thead>
<tr>
<th>Age</th>
<th>Finding</th>
<th>Clinical Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 months</td>
<td>Non-obstructive hypertrophic cardiomyopathy; ST-T changes in inferolateral leads indicating myocardial process</td>
<td>Routine screening</td>
</tr>
<tr>
<td>17 months</td>
<td>Non-obstructive hypertrophic cardiomyopathy</td>
<td>Follow up to above study</td>
</tr>
<tr>
<td>2 years 8 months</td>
<td>Septal and postal wall hypertrophy, widespread T wave abnormalities</td>
<td>Scheduled follow up</td>
</tr>
<tr>
<td>3 years 4 months</td>
<td>Concentric left ventricular hypertrophy with septum and posterior wall 9 mm, T wave abnormalities</td>
<td>Scheduled follow up</td>
</tr>
<tr>
<td>4 years 0 months</td>
<td>Non-compaction cardiomyopathy, non-specific T wave abnormality in inferior and lateral leads</td>
<td>Scheduled follow up</td>
</tr>
<tr>
<td>4 years 8 months</td>
<td>Possible very mild right ventricular conduction delay, repolarization abnormality of left ventricle</td>
<td>Scheduled follow up</td>
</tr>
<tr>
<td>5 years 5 months</td>
<td>Noncompaction in apex</td>
<td>Scheduled follow up</td>
</tr>
<tr>
<td>6 years 4 months</td>
<td>Mild concentric left ventricular hypertrophy, sinus arrhythmia</td>
<td>severe hypoglycemic event with severe and sudden neurologic devastation (further details on next slide)</td>
</tr>
<tr>
<td>6 years 6 months</td>
<td>Mild concentric left ventricular hypertrophy, non-specific T wave abnormality</td>
<td>Follow up to above study</td>
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Conclusion

We found that patients with VLCADD detected via NBS who are otherwise asymptomatic may have a lower incidence of cardiac complications than previously suspected. This may lead to decreased need for routine cardiac screening particularly for those classified as mild via new GMDI guidelines.

References

