Malonyl Coenzyme A Decarboxylase Deficiency: Early Dietary Restriction and Time Course of Cardiomyopathy

abstract

Malonyl coenzyme A (CoA) decarboxylase (MCD) deficiency is a rare autosomal recessive organic acidemia characterized by varying degrees of organ involvement and severity. MCD regulates fatty acid biosynthesis and converts malonyl-CoA to acetyl-CoA. Cardiomyopathy is one of the leading causes of morbidity and mortality in this disorder. It is unknown if diet alone prevents cardiomyopathy development based on published literature. We report a 10-month-old infant girl identified by newborn screening and confirmed MCD deficiency with a novel homozygous ML YCD mutation. She had normal echocardiogram measurements before transition to high medium-chain triglycerides and low long-chain triglycerides diet. Left ventricular noncompaction development was not prevented by dietary interventions. Further restriction of long-chain triglycerides and medium-chain triglycerides supplementation in combination with angiotensin-converting enzyme inhibitors helped to improve echocardiogram findings. Patient remained asymptomatic, with normal development and growth. Our case emphasizes the need for ongoing cardiac disease screening in patients with MCD deficiency and the benefits and limitations of current dietary interventions. *Pediatrics* 2012;130:e456–e460

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KEY WORDS malonyl-CoA decarboxylase deficiency, left ventricular noncompaction, malonic acid, newborn screening, malonyl carnitine, medium-chain triglycerides, angiotensin-converting enzyme

ABBREVIATIONS ACE—angiotensin-converting enzyme
C3-DC—malonyl carnitine
CMAMMA—combined elevation of malonic acid and methylmalonic acid
CoA—coenzyme A
LCT—long-chain triglycerides
LVNC—left ventricular noncompaction
MA—malonic acid
MCD—malonyl-coenzyme A decarboxylase
MCT—medium-chain triglycerides
NBS—newborn screening

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Malonyl coenzyme A (CoA) decarboxylase (MCD) deficiency is a rare autosomal recessive disorder characterized by a variable phenotype of developmental delay, seizures, hypoglycemia, metabolic acidosis, and cardiomyopathy. Twenty-five cases have been reported in the literature, and only 2 were identified by newborn screening (NBS). MCD deficiency is routinely screened for in 50% of NBS state programs; malonyl carnitine (C3-DC) measurement is possible and will allow neonatal diagnosis of patients with MCD deficiency. Currently, there are no established dietary and therapeutic managements for this disorder, and there is limited information about the natural history and benefit of interventions before onset of symptoms.

Left ventricular noncompaction (LVNC) is a clinical heterogeneous disorder with variable phenotype. LVNC is a cardiomyopathy characterized anatomically by deep trabeculations in the ventricular wall and is associated with ventricular dysfunction, arrhythmias, and embolic events. Multiple genetic alterations have been identified in patients with LVNC. Patients with mutations in the taffazin gene may present with Barth syndrome, which includes myocardial dysfunction, abnormal urinary excretion of 3-methylglutaconic acid, skeletal myopathy, growth retardation, and cyclical neutropenia. Until this report, LVNC has not been reported in patients with primary organic acidemias. We describe dietary and treatment outcomes of a 10-month-old infant girl, who was treated before echocardiographic evidence of LVNC with dilated phenotype and confirmed MCD deficiency with a novel homozygous MLYCD mutation.

PATIENT PRESENTATION

This 10-month-old white girl was suspected of having MCD deficiency based upon an elevation of C3-DC on the newborn screen. She was asymptomatic at time of initial evaluation (1-month-old) at Cincinnati Children’s Hospital Medical Center. Acylcarnitine profile confirmed abnormal C3-DC levels of 4.05 μM (normal range, 0–0.06 μM). Urine organic acids showed marked elevation of malonic acid (MA: 340 μmol/mmol creatinine) and mild elevation of methylmalonic acid (17 μmol/mmol creatinine) without lactic acid elevation. She had normal weight gain and no history of hospitalizations, metabolic crisis, or hypoglycemia. She had no family history of cardiomyopathy, malonic acidemia, hypertension, and sudden or unexplained deaths.

The patient was started on levocarnitine 200 mg twice daily (100 mg/kg per day). Her dietary fat was transitioned at 1 month of age from 100% of long-chain triglycerides (LCTs) to 50%, and she was supplemented with 50% medium-chain triglycerides (MCTs) formula, Lipistart (Vitaflno, Liverpool, UK). MLYCD gene sequencing showed a novel homozygous deletion c.393_400del8. This mutation results in a frameshift starting with codon Leucine 133 and creates a premature stop codon that predicts loss of normal protein function confirming the diagnosis.

The results of echocardiogram and renal ultrasound at 2 months of age were normal. Repeat echocardiogram at 5 months revealed LVNC with dilated cardiomyopathy (Fig 1). No symptoms of heart failure were identified on examination, including increased sweating or feeding difficulties. LCT was further restricted from 50% to 30% of dietary fat. Enalapril (0.4 mg twice daily) was initiated based on imaging findings of LVNC with depressed systolic function and a calculated left ventricular ejection fraction of 43%. Table 1 summarizes the clinical, nutritional, and imaging findings of this patient.

At 10 months, her height was 75.6 cm (97th centile), weight 9.84 kg (90th centile), head circumference 46 cm (50th centile), blood pressure 77/42, and pulse 124. She was nondysmorphic. No chest wall deformities were observed. Her lungs were clear to auscultation, bilaterally. Her heart rate was regular, and no murmurs or other abnormal heart sounds were auscultated. Abdomen was soft, nontender, and nondistended, and no hepatosplenomegaly was palpated. Normal extremities and skin creases were observed. There was no abnormal muscle tone and no identifiable deficits in the neurologic examination.

The child is now 13 months old and in good health. Her development is on target for age, and she is able to walk, wave, hi and bye, and respond to her name. Her height and weight are tracking in the 90th centile. She is tolerating her angiotensin-converting enzyme (ACE) inhibition well with no further progression of her imaging findings and slight improvement in her left ventricular systolic function to 60%. She continues on a high-MCT diet (70%) with minimal LCT (30%), and levocarnitine supplementation.

DISCUSSION

We report the first patient with MCD deficiency and LVNC. Although early dietary intervention (50% LCT, 50% MCT) did not prevent development of cardiomyopathy, the patient exhibited improvement in cardiac function when restriction of LCT was increased (30% LCT, 70% MCT) and ACE inhibition was instituted. Indeed, serial echocardiography evaluations showed improvement of the left ventricular systolic function. It is unclear which of these interventions had greater effect.

All patients reported with MCD deficiency have the diagnostic finding of elevated urinary excretion of MA alone, or combined elevation of MA and methylmalonic acid (CMAMMA) with MA being higher than MMA. Recently, exomic sequencing performed by 2 independent groups has identified a new metabolic
disorder caused by mutations in the ACSF3 gene with CMAMMA elevation. The phenotype of this disease is milder than MCD deficiency, but symptoms are also variable and biochemically distinct, with MMA urinary excretion being higher than MA in patients with ACSF3 mutations.

MLYCD is the only gene associated with this disorder, and there is no clear genotype/phenotype correlation. Published clinical reports suggest that MCD deficiency overlaps with fatty acid oxidation disorders. MCD catalyzes the conversion of malonyl-CoA to acetyl-CoA and regulates intracellular concentration of malonyl-CoA. Because malonyl-CoA inhibits carnitine palmitoyltransferase 1, and MCD indirectly inhibits mitochondrial fatty acid oxidation, the relationship between the function of MCD and the pathogenesis of the disease phenotype remains unclear. Cardiomyopathy has been reported in up to 40% of patients with MCD deficiency.

FIGURE 1
A, Parasternal short-axis view showing left ventricular myocardium with characteristic trabeculations and intertrabecular recesses. B, Apical 4-chamber view showing characteristic left ventricular myocardium with color flow visible in intertrabecular recesses on color Doppler images.
similarly to fatty acid oxidation disorders.\textsuperscript{2,15} LVNC is not a common finding in patients with fatty acid oxidation disorders, but proper mitochondrial function is necessary for normal sarcomere function and embryological compaction of the left ventricular myocardium.\textsuperscript{16} Additional evidence indicates that MCD may have pleiotropic roles, because it has been detected in cytosolic, mitochondrial, and peroxysomal compartments.\textsuperscript{17,18} Currently, there are no established dietary recommendations for MCD deficiency or related disorders (CMAMMA).

Several children have been treated with low-fat, high-MCT, and high-carbohydrate diet with improvement in clinical condition when diet was modified before significant disease symptoms.\textsuperscript{4,5} These reports are also significant for the lack of a consistent biochemical response of MA excretion after dietary modifications. This lack of biochemical response makes clinical surveillance of known complications an important part of MCD deficiency management.

**CONCLUSIONS**

Cardiomyopathy development was not prevented by diet alone in this patient with MCD deficiency. LVNC with dilated phenotype is a potential complication and may cause rapid deterioration if treatment is not established before development of symptoms. This supports the need to add MCD deficiency to metabolic NBS programs. The pathogenesis remains unclear, but it may involve mitochondrial function impairment secondary to organic acid accumulation or disruption of normal fatty acid oxidation. This patient’s findings and previous reports\textsuperscript{4,5} support the use of high-MCT/low-LCT diet, carnitine supplementation, and ACE inhibition in patients with MCD deficiency and cardiomyopathy. As with many new disorders added to the NBS, early therapy does not completely prevent disease development. A larger study in patients with MCD deficiency is needed to determine limitations of early dietary interventions, prevalence of LVNC, and other cardiomyopathies to better delineate natural history and to develop new therapies for this disease. Finally, cardiac disease should be screened for at time of diagnosis and regular intervals for any patient with MCD deficiency.

**REFERENCES**


**TABLE 1** Clinical, Nutritional, and Imaging Findings by Age in the Patient With Malonyl-CoA Decarboxylase Deficiency and LVNC

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>MCT, %</th>
<th>LCT, %</th>
<th>Total Fat Diet, g</th>
<th>EFA</th>
<th>Weight/Height, centile</th>
<th>Cardiac Anomalies</th>
<th>Renal Anomalies</th>
<th>Seizures</th>
<th>Motor Development</th>
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<td>0</td>
<td>100</td>
<td>0</td>
<td>32.1</td>
<td>75th/90th</td>
<td>No</td>
<td>No</td>
<td>Normal renal ultrasound</td>
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<td>50</td>
<td>32.5</td>
<td>90th/90th</td>
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<td>50</td>
<td>No</td>
<td>No</td>
<td>Grasps objects</td>
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<tr>
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<td>56</td>
<td>44</td>
<td>32.7</td>
<td>90th/90th</td>
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<td>No</td>
<td>Rolling over</td>
<td>43</td>
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<td>65</td>
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<td>31.5</td>
<td>+</td>
<td>90th/90th</td>
<td>LVNC with dilated phenotype</td>
<td>43</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>30</td>
<td>35.5</td>
<td>+</td>
<td>90th/90th</td>
<td>LVNC with dilated phenotype</td>
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<td>No</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>30</td>
<td>35</td>
<td>+</td>
<td>90th/90th</td>
<td>LVNC with dilated phenotype</td>
<td>60</td>
<td></td>
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</table>

EFA, essential fatty acids; LVSF, left ventricular systolic function.
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