Favorable Outcome After Physiologic Dose of Sodium-D,L-3-Hydroxybutyrate in Severe MADD

abstract

Multiple acyl coenzyme A dehydrogenase deficiency (MADD) is a severe inborn error of metabolism. Experiences with sodium-D,L-3-hydroxybutyrate (3-HB) treatment are limited although positive; however, the general view on outcome of severely affected patients with MADD is relatively pessimistic. Here we present an infant with MADD in whom the previously reported dose of 3-HB did not prevent the acute, severe, metabolic decompensation or progressive cardiomyopathy in the subsequent months. Only after a physiologic dose of 2600 mg/kg of 3-HB per day were ketone bodies detected in blood associated with improvement of the clinical course, N-terminal prohormone of brain natriuretic peptide and echocardiographic parameters. Long-term studies are warranted on 3-HB treatment in patients with MADD. Pediatrics 2014;134:e1224–e1228

AUTHORS: Willemijn J. Van Rijt, BSc,a M. Rebecca Heiner-Fokkema, PhD,b Gideon J. du Marchie Sarvaas, MD,c Hans R. Waterham, PhD,d Robert G.T. Blokpoel, MD,e Francjan J. van Spronsen, MD, PhD,a and Terry G.J. Derks, MD, PhDa

aSection of Metabolic Diseases, bDepartment of Pediatric Cardiology, Center for Congenital Heart Diseases, and cDivision of Pediatric Intensive Care, Beatrix Children’s Hospital, University of Groningen, University Medical Center Groningen, Groningen, Netherlands; dLaboratory of Metabolic Diseases, Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; and eDepartment of Clinical Chemistry, Laboratory Genetic Metabolic Diseases, Academic Medical Center, University Hospital of Amsterdam, Amsterdam, Netherlands

KEY WORDS
multiple acyl coenzyme A dehydrogenase deficiency, mitochondrial fatty acid oxidation, cardiomyopathy, sodium-D,L-3-hydroxybutyrate

ABBREVIATIONS
ETF—electron transfer flavoprotein
IEM—inborn error of metabolism
MADD—multiple acyl coenzyme A dehydrogenase deficiency
mFAO—mitochondrial fatty acid oxidation
NT-proBNP—N-terminal prohormone of brain natriuretic peptide
3-HB—sodium-D,L-3-hydroxybutyrate

Ms Van Rijt collected and analyzed the metabolite and echocardiographic data, performed the statistical analysis, drafted the first version of the manuscript, and wrote the final manuscript; Dr Heiner-Fokkema was responsible for the metabolite diagnosis of multiple acyl coenzyme A dehydrogenase deficiency (MADD), performed and analyzed the metabolite studies, supervised the statistical analysis of the metabolite studies, and critically reviewed and revised the manuscript; Dr du Marchie Sarvaas was responsible for the cardiac follow-up, performed and analyzed the echocardiographic studies, supervised the statistical analysis of the echocardiographic studies, and reviewed the manuscript; Dr Waterham performed the molecular studies confirming the diagnosis at the DNA level and reviewed the manuscript; Dr Blokpoel was responsible for the treatment at the Division of Pediatric Intensive Care and reviewed the manuscript; Dr van Spronsen performed the overall clinical treatment and monitoring and critically reviewed and revised the manuscript; Dr Derks was responsible for the clinical diagnosis of MADD, performed the overall clinical treatment and monitoring, collected and analyzed the metabolite and echocardiographic data, initiated and drafted the first version of the manuscript, critically reviewed and revised the manuscript, and wrote the final manuscript; and all authors approved the final manuscript as submitted.

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Multiple acyl coenzyme A dehydrogenase deficiency (MADD; or glutaric aciduria type II; Online Mendelian Inheritance in Man (OMIM) no. 231680) is a rare inborn error of metabolism (IEM) caused by a defect in the electron transfer flavoprotein (ETF) or its electron acceptor, called ETF dehydrogenase. These enzymes form an important common metabolic pathway of at least 12 dehydrogenases from both mitochondrial fatty acid oxidation (mFAO) and amino acid metabolism toward the mitochondrial respiratory chain.

Patients with MADD are phenotypically classified into 3 groups: (1) neonatal onset with congenital anomalies, (2) neonatal onset without congenital anomalies, and (3) relatively milder, later onset. Treatment consists of dietary fat and protein restriction, along with supplementation of riboflavin, glycine, and l-carnitine. There is no effective treatment of patients with MADD who present in early infancy. However, successful experimental treatment with sodium-3-hydroxybutyrate (3-HB; a ketone body) has been described in 4 patients with MADD. Cardiac and neurologic improvement was observed with a dose up to 900 mg/kg per day, placing management of MADD in a new perspective.

Since then, no additional reports have been published. Theoretically, this may be caused by (a combination of) the low prevalence of the disease, the difficulty to establish the diagnosis, the hesitance to deviate from the original dose, and the high costs of 3-HB supplementation. Meanwhile, MADD has been implemented in several population neonatal bloodspot screening programs worldwide. Patients are additionally identified after false-positive neonatal screening test results for other IEMs. Because the use of ketone body supplementation requires further investigation, we report on an infant with MADD in whom the clinical course significantly improved after increasing the 3-HB dose >900 mg/kg per day.

**PATIENT PRESENTATION**

An infant girl presented on the first day of life with hypoglycemia and severe ventricular tachyarrhythmias. This combination suggested a defect of long-chain mFAO, which later proved to be MADD (homozygosity for a novel c.1-40G>A mutation in the ETF-α gene, pathogenicity confirmed by absence of protein expression by immunoblot studies in cultured skin fibroblasts). Dietary treatment included frequent feedings, restriction of fat, and supplementation of riboflavin and coenzyme Q10.

After 5 months, mild developmental delay was noted and the cerebral MRI displayed a global increase of atrophy and bilateral cytotoxic edema posteromedially in the lentiform nucleus and in the left frontal periventricular white matter. There were no cardiac symptoms or signs. First, continuous nocturnal gastric drip-feeding was initiated, but in contrast to previous observations, metabolic profiles did not improve in our patient. Second, 3-HB supplementation was started, initially at a dose of 450 mg/kg per day and increased after a week to 900 mg/kg per day according to the literature, without, however, significant amounts of ketone bodies in blood or urine. Table 1 presents the metabolic parameters in blood and urine during the different phases of 3-HB treatment.

The patient developed a gastroenteritis and severe metabolic decompensation with hypoglycemia and metabolic acidosis, requiring resuscitation. The subsequent intensive care period was complicated by diaphragmatic paralysis, malnutrition, and progressive cardiomyopathy. We hypothesized that the 3-HB dose could not entirely correct for the presumed severe metabolic block in our patient. On the basis of the results of quantitative stable isotope studies, we empirically increased the 3-HB dose from 900 toward 2600 mg/kg per day.

**DISCUSSION**

The relatively pessimistic view on management of severely affected patients with MADD is emphasized by at least 2 recent articles summarizing small cohorts of patients with MADD. Al-Essa et al reported 3 patients with MADD who received treatment since the first weeks of life after early detection by population neonatal screening in the city of Chicago. Two of the 3 patients died unexpectedly, and the remaining patient suffered an acute life-threatening event. Interpretation of previous case reports and cohort studies is complicated by incomplete and/or different approaches to characterize patients with MADD. Biochemically, diagnosis of MADD relies on the identification of increased excretions of urinary organic acids (mainly ethylmalonic, glutaric, 2-hydroxyglutaric, isovaleric, and dicarboxylic acids) and abnormal plasma amino acids (eg, sarcosine). Plasma or urine acylcarnitines may be increased to variable degrees. In vitro probe acylcarnitine assay using cultured fibroblasts facilitates the identification of the severity of the disorder.

In our patient, biochemical markers were frequently analyzed, and a large intraindividual variation for each marker was observed. One of the reasons could be the lack of standardization (time of the day and nutritional status). The significant relations between 3-HB dose and some biochemical markers (ie, glutaric acid, 2-OH-glutaric acid, isovalerylglucose, hexanoylglycine, and suberic acid)
TABLE 1 Metabolic Parameters in Blood and Urine During the Different Phases of 3-HB Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A = No</th>
<th>B = 450 mg/kg per day</th>
<th>C = 900 mg/kg per day</th>
<th>D = 1400 mg/kg per day</th>
<th>E = 2600 mg/kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFAs, mmol/L</td>
<td>555 (407–737)</td>
<td>345 (63–467)</td>
<td>194 (68–389)</td>
<td>181 (176–189)</td>
<td>236 (156–755)</td>
</tr>
<tr>
<td>AcA, mmol/L</td>
<td>0.05 (0.03–0.07)</td>
<td>0.03 (0.01–0.04)</td>
<td>0.02 (0.01–0.03)</td>
<td>0.02 (0.00–0.11)</td>
<td>0.10 (0.02–0.29)</td>
</tr>
<tr>
<td>BOHB, mmol/L</td>
<td>0.06 (0.05–0.10)</td>
<td>0.02 (0.01–0.03)</td>
<td>0.02 (0.00–0.03)</td>
<td>0.02 (0.01–0.16)</td>
<td>0.15 (0.02–0.49)</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>1217 (689–1744)</td>
<td>65263 (33 685–90 427)</td>
<td>11954 (54 686–47 039)</td>
<td>7790 (2515–13 941)</td>
<td>527 (241–2370)</td>
</tr>
</tbody>
</table>

Plasma acetylcarnitines, μmol/L

- Total carnitine
  - 38 (23–137)
  - 41 (23–58)
  - 45 (25–99)
  - 51 (27–113)
  - 101 (74–124)

- Free carnitine
  - 19 (12–102)
  - 14 (8–17)
  - 28 (18–70)
  - 27 (15–68)
  - 68 (42–87)

- CS
  - 28 (7–150)

- C6–C18
  - 5.3 (3.45–15.47)

Urinary organic acids

- Ethylmalonic acid
  - 0.27 (0.19–0.77)

- Glutaric acid
  - 2.11 (0.74–3.32)

- Adipic acid
  - 0.03 (0.01–0.21)

- 2-OH-glutaric acid
  - 0.86 (0.31–0.91)

- Isovalerylglycine
  - 0.06 (0.03–0.18)

- Hexanoylglycine
  - 0.02 (0.00–0.10)

- 3-HB
  - 0.00 (0.00–0.00)

- Suberic acid
  - 0.01 (0.00–0.03)

Data are presented as medians (ranges). Acute metabolic decompensation at the age of 7 months occurred during 3-HB supplementation at a dose of 450 mg/kg per day. Differences between groups were analyzed by Kruskal-Wallis test and subsequently by Mann-Whitney U test and were considered significant at P < .05. Aca, acetoacetate; BOHB, β-hydroxybutyrate; CS, isovalerylglycine; C6–C18, the sum of acylcarnitines of C6–C18; FFA, free fatty acid.

warrant further investigation. To date, MADD-like metabolic profiles have been associated with mutations in at least 6 different human genes.13 A relation between a severe clinical phenotype and the genotype has been reported, with severe neonatally ascertained patients having null mutations in ETF dehydrogenase or ETF—more likely having null mutations in ETF—more likely having null mutations in ETF. Interestingly, in our patient we found homozygosity for a novel mutation in the ETF-α gene.

The natural course of cardiac involvement in MADD is incompletely described. Singla et al15 have found that most of our knowledge on cardiomyopathy and MADD is derived from autopsies. To the best of our knowledge, this is the first report of a patient with well-characterized severe MADD in whom cardiac parameters were followed prospectively since birth. Interestingly, her echocardiographic function was normal 1 day after the metabolic decompensation at the age of 7 months. Because she developed severe functional and structural cardiomyopathy only after, but not immediately

TABLE 2 Echocardiographic Parameters and NT-proBNP During the Different Phases of 3-HB Treatment Measured in Parasternal Long Axis (M-Mode) and Two-Dimensional

<table>
<thead>
<tr>
<th>Date</th>
<th>Age, mo</th>
<th>3-HB, mg/kg per day</th>
<th>IVS mm</th>
<th>z Score</th>
<th>LVEDD mm</th>
<th>z Score</th>
<th>PW mm</th>
<th>SF, %</th>
<th>EF, %</th>
<th>NT-proBNP, ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 31, 2012</td>
<td>0.8</td>
<td>No</td>
<td>3</td>
<td>−0.92</td>
<td>18.8</td>
<td>+0.4</td>
<td>3.4</td>
<td>−0.18</td>
<td>29.4</td>
<td>59.6</td>
</tr>
<tr>
<td>February 26, 2013</td>
<td>6.8</td>
<td>No</td>
<td>5.7</td>
<td>+2.6</td>
<td>25</td>
<td>+0.8</td>
<td>6.7</td>
<td>+4.0</td>
<td>28</td>
<td>56.3</td>
</tr>
<tr>
<td>March 10, 2013</td>
<td>7.2</td>
<td>450</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 12, 2013</td>
<td>7.2</td>
<td>450</td>
<td>31</td>
<td>+4.1</td>
<td>5.9</td>
<td>+2.8</td>
<td>21.9</td>
<td>45.6</td>
<td>66</td>
<td>782</td>
</tr>
<tr>
<td>April 10, 2013</td>
<td>8.2</td>
<td>900</td>
<td>31</td>
<td>+4.1</td>
<td>5.9</td>
<td>+2.8</td>
<td>21.9</td>
<td>45.6</td>
<td>66</td>
<td>782</td>
</tr>
<tr>
<td>May 21, 2013</td>
<td>9.6</td>
<td>900</td>
<td>10.5</td>
<td>+3.0</td>
<td>32</td>
<td>+3.0</td>
<td>8.0</td>
<td>+6.0</td>
<td>16</td>
<td>35.0</td>
</tr>
<tr>
<td>June 7, 2013</td>
<td>10.1</td>
<td>900</td>
<td>5.7</td>
<td>+4.8</td>
<td>6.4</td>
<td>+3.4</td>
<td>7.7</td>
<td>+5.4</td>
<td>14.6</td>
<td>32.0</td>
</tr>
<tr>
<td>June 21, 2013</td>
<td>10.6</td>
<td>1400</td>
<td>7.5</td>
<td>+4.5</td>
<td>33.9</td>
<td>+3.2</td>
<td>9.1</td>
<td>+7.5</td>
<td>15.3</td>
<td>33.3</td>
</tr>
<tr>
<td>July 4, 2013</td>
<td>11.0</td>
<td>1400</td>
<td>8.7</td>
<td>+5.6</td>
<td>31</td>
<td>+1.6</td>
<td>7.8</td>
<td>+4.3</td>
<td>18.5</td>
<td>39.5</td>
</tr>
<tr>
<td>July 26, 2013</td>
<td>11.6</td>
<td>2600</td>
<td>6.8</td>
<td>+3.3</td>
<td>29</td>
<td>+0.4</td>
<td>7.4</td>
<td>+3.7</td>
<td>29</td>
<td>57.7</td>
</tr>
<tr>
<td>August 26, 2013</td>
<td>12.6</td>
<td>2600</td>
<td>8.7</td>
<td>+5.6</td>
<td>25.5</td>
<td>−0.6</td>
<td>8.3</td>
<td>+4.9</td>
<td>31.7</td>
<td>62.0</td>
</tr>
<tr>
<td>September 27, 2013</td>
<td>13.9</td>
<td>2600</td>
<td>7.9</td>
<td>+4.5</td>
<td>25.5</td>
<td>−1.3</td>
<td>8.1</td>
<td>+4.7</td>
<td>29.8</td>
<td>59.0</td>
</tr>
<tr>
<td>October 16, 2013</td>
<td>14.5</td>
<td>2600</td>
<td>8.2</td>
<td>+4.9</td>
<td>25.6</td>
<td>−1.2</td>
<td>7.8</td>
<td>+4.5</td>
<td>32.0</td>
<td>62.2</td>
</tr>
</tbody>
</table>

Acute metabolic decompensation at the age of 7 months occurred during 3-HB supplementation at a dose of 450 mg/kg per day. z Scores were obtained by using http://parameterz.blogspot.nl. EF, ejection fraction; IVS, interventricular septum; LVEDD, left-ventricular end-diastolic diameter; ND, not determined; No, no dose of 3-HB, PW, posterior wall; SF, shortening fraction.

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after, the second decompensation, we speculate that a chronic mechanism is involved. Despite the short-term reversal by high-dose 3-HB, it is important to realize that long-chain mFAO is a major source of energy for the heart after birth.\textsuperscript{16,17} Hence, it is not known whether 3-HB supplementation can prevent progression of long-term cardiac involvement.

The rationale for the use of 3-HB in MADD has been described in 2 case reports of supplementation up to 900 mg/kg per day with subsequent “measurable concentrations of physiologic ketone bodies at all times.”\textsuperscript{9} In our patient, this treatment could not help in weaning from mechanical ventilation, and biochemical (NT-proBNP) and echocardiographic parameters worsened. Ketone bodies were not detectable in blood or urine at this dose. In healthy children, the ketone body concentration is a function of age and duration of fasting.\textsuperscript{18} Endogenous ketone body production has been quantified by stable isotope infusion studies.\textsuperscript{7,8} Rates have been reported of 12.8 to 21.9 and 17.9 to 26.0 $\mu$mol/kg per minute in newborns fasted for $<$8 hours and in older infants fasted for $<$10 hours, respectively. This is within the range found in adults only after several days of total fasting.\textsuperscript{7} These data have been the rationale behind the increase toward 2600 mg/kg per day, corresponding to 17.8 $\mu$mol/kg of 3-HB per minute. In our patient, cardiac function improved only after this physiologic dose of 3-HB.

Theoretically, supplementation of 3-HB may increase the risk of ketoacidosis as is seen in diabetes, IEMs of ketolysis, and patients treated with a ketogenic diet. However, we estimate that in our patient the supplementation of 3-HB only partially replaces the severely deficient endogenous synthesis of ketone bodies, which is substantiated by the fact that even during her second metabolic decompensation, no ketone bodies were detected. Still, this dose of 3-HB needs to be considered with caution, because it is associated with a sodium supplementation of 20 mmol/kg per day. These high doses inevitably impair fluid and sodium homeostasis with potential secondary cardiovascular and cerebral effects.

CONCLUSIONS

The previously recommended dose of 900 mg/kg of 3-HB per day did not prevent the progressive cardiomyopathy. Blood ketone bodies were only detectable in our patient after increasing 3-HB dose up to 2600 mg/kg per day, which adequately compensated for the deficient endogenous synthesis of ketone bodies. Together with the clinical course, NT-proBNP, some biochemical markers, and echocardiographic parameters subsequently improved. Our observations emphasize the need for further long-term studies to personalize the dose of 3-HB in patients with MADD.

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REFERENCES


(Continued from first page)
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