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

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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.[1] 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.[1] 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.[1] However, successful experimental treatment with sodium-D, L-3-hydroxybutyrate (3-HB; a ketone body) has been described in 4 patients with MADD.[2,3] 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.[4,5] Patients are additionally identified after false-positive neonatal screening test results for other IEMs.[5] 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[6], 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[3], 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.[7,8]

Our patient subsequently improved clinically; Table 2 shows the course of echocardiographic parameters and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (Fig 1), an important biomarker for heart failure diagnosis and prognosis.[9]

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[10] described 7 patients with MADD of whom 5 presented neonatally. Four of these 5 patients died despite intensive supportive therapy. Angle and Burton[11] 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.[12] 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, isovalerylglycine, hexanoylglycine, and suberic acid)

TABLE 1 Metabolic Parameters in Blood and Urine During the Different Phases of 3-HB Treatment

Parameter	A = No	B = 450 mg/kg per day	C = 900 mg/kg per day	D = 1400 mg/kg per day	E = 2600 mg/kg per day
FFAs, mmol/L	535 (407–737)	345 (63–467)	194 (68–389)	181 (176–189)	236 (156–755)
AcA, mmol/L	0.05 (0.03–0.07)	0.03 (0.01–0.04)	0.02 (0.01–0.03)	0.02 (0.00–0.11)[e]	0.10 (0.02–0.29)[d]
BOHB, mmol/L	0.06 (0.05–0.10)	0.02 (0.01–0.03)	0.02 (0.00–0.03)	0.02 (0.01–0.16)[e]	0.15 (0.02–0.46)[d]
NT-proBNP, ng/L	1217 (689–1744)	65263 (33 685–90 427)[c,d,e]	11954 (5466–47 039)[b,d,e]	7790 (2515–13 941)[b,c,e]	527 (241–2370)[b,c,d]
Plasma acylcarnitines, μmol/L					
Total carnitine	38 (23–137)[e]	41 (23–58)[e]	45 (25–99)[e]	51 (27–113)[e]	101 (74–124)[a,b,c,d]
Free carnitine	19 (12–102)[b,e]	14 (8–17)[a,c,d,e]	28 (16–70)[b,e]	27 (15–69)[b,e]	68 (42–87)[a,b,c,d]
C5	2.71 (1.20–4.94)[c,d,e]	2.34 (1.03–6.29)	1.67 (0.59–2.38)[a]	1.46 (0.85–2.74)[a]	1.86 (1.28–2.41)[a]
C6–C18	5.32 (3.45–15.47)[e]	9.89 (5.41–17.40)	5.78 (3.56–12.91)	6.32 (4.25–14.65)	8.85 (7.10–14.60)[a]
Urinary organic acids					
Ethylmalonic acid	0.27 (0.10–0.77)	0.15	0.39 (0.27–0.64)	0.28 (0.09–0.38)	0.33 (0.02–0.41)
Glutaric acid	2.11 (0.74–3.32)[c,d,e]	5.64	0.58 (0.24–0.99)[a]	0.77 (0.25–1.12)[a]	0.45 (0.05–0.66)[a]
Adipic acid	0.03 (0.01–0.21)	5.55	0.07 (0.03–0.54)	0.12 (0.03–0.23)	0.13 (0.01–0.29)
2-OH-glutaric acid	0.86 (0.31–0.91)	0.29	0.70 (0.52–0.97)	0.63 (0.39–1.38)	0.55 (0.07–0.72)
Isovalerylglycine	0.06 (0.03–0.18)[e]	0.16	0.09 (0.03–0.12)[e]	0.05 (0.02–0.06)	0.02 (0.00–0.08)[a,c]
Hexanoylglycine	0.02 (0.00–0.10)	0.00	0.06 (0.02–0.17)[e]	0.06 (0.04–0.08)[e]	0.01 (0.00–0.05)[c,d]
3-HB	0.00 (0.00–0.00)[d,e]	0.00	0.00 (0.00–2.37)[e]	2.68 (0.18–5.32)[a]	16.70 (1.46–27.03)[a,c]
Suberic acid	0.01 (0.00–0.03)	0.25	0.02 (0.01–0.07)	0.02 (0.01–0.06)	0.01 (0.00–0.03)

Data are presented as medians (ranges). Acute metabolic decompensation at the age of 7 mo 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; C5, isovaleryl-/2-methylbutyrylcarnitine; C6–C18, the sum of acylcarnitines of C6–C18; FFA, free fatty acid.

[a] Significantly different from A.
[b] Significantly different from B.
[c] Significantly different from C.
[d] Significantly different from D.
[e] Significantly different from E.

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 more likely having null mutations in ETF dehydrogenase or ETF-β.[14] 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 al[15] have found that most of our knowledge on cardiomyopathy and MADD is derived from autopsy studies. 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 echocardiac 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

Date	Age, mo	3-HB, mg/kg per day	IVS mm	IVS z Score	LVEDD mm	LVEDD z Score	PW mm	PW z Score	SF,%	EF, %	NT-proBNP, ng/L
August 31, 2012	0.8	No	3	−0.92	18.8	+0.4	3.4	−0.18	29.4	59.6	ND
February 26, 2013	6.8	No	5.7	+2.6	25	+0.8	6.7	+4.0	28	56.3	ND
March 10, 2013	7.2	450			24	+0.2			30.7	60.0	75 714
March 12, 2013	7.2	450			31	+4.1	5.9	+2.8	21.9	45.6	66 762
April 10, 2013	8.2	900	6	+3.0	29	+3.0	8.0	+6.0	16	35.0	32 566
May 21 2013	9.6	900	7.7	+4.8	34.4	+3.4	7.7	+5.4	14.6	32.0	7147
June 7, 2013	10.1	900	7.5	+4.5	33.9	+3.2	9.1	+7.5	15.3	33.3	18 812
June 21, 2013	10.6	1400	6.2	+2.8	34.6	+3.4	8.1	+6.0	23	48.0	8380
July 4, 2013	11.0	1400	8.7	+5.6	31	+1.6	7.8	+4.3	18.5	39.5	2515
July 26, 2013	11.8	2600	6.8	+3.3	28	+0.4	7.4	+3.7	29	57.7	748
August 26, 2013	12.8	2600	8.7	+5.6	25.5	−0.6	8.3	+4.9	31.7	62.0	417
September 27, 2013	13.9	2600	7.9	+4.5	25.5	−1.3	8.1	+4.7	29.8	59.0	281
October 16, 2013	14.5	2600	8.2	+4.9	25.6	−1.2	7.8	+4.3	32.0	62.2	372

Acute metabolic decompensation at the age of 7 mo 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.
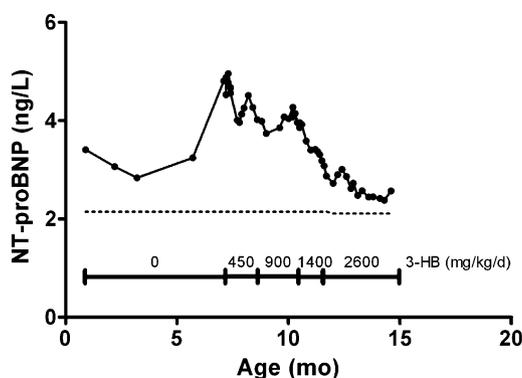
FIGURE 1
Logarithmic NT-proBNP concentrations in blood during the different phases of 3-HB treatment. The dotted line represents reference values for NT-proBNP, derived from Nir et al.[9]

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.[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."[3] 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.[18] Endogenous ketone body production has been quantified by stable isotope infusion studies.[7,8] Rates have been reported of 12.8 to 21.9 and 17.9 to 26.0 μmol/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.[7] These data have been the rationale behind the increase toward 2600 mg/kg per day, corresponding to 17.8 μmol/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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