Research letters

D,L-3-hydroxybutyrate treatment of multiple acyl-CoA dehydrogenase deficiency (MADD)

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Cardiomyopathy and leukodystrophy are life-threatening complications of multiple acyl-CoA dehydrogenase deficiency (MADD). A 2-year-old boy with this disorder developed rapidly progressive leukodystrophy resulting in complete paralysis within 4 months. Within a week of starting sodium-D,L-3-hydroxybutyrate he had improved. After 2 years, neurological function returned, including walking independently, with progressive improvement of brain MRI. Two additional infants with MADD developed life-threatening cardiomyopathy unresponsive to conventional treatment. On sodium-D,L-3-hydroxybutyrate treatment their cardiac contractility showed progressive and sustained improvement. D,L-3-hydroxybutyrate is a therapeutic option for cerebral and cardiac complications in severe fatty acid oxidation defects.

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Multiple acyl-CoA dehydrogenase deficiency (MADD) is a genetic defect of the electron transfer flavoprotein (ETF) chain causing dysfunction of dehydrogenases linked to flavin adenine dinucleotide (FAD), including those of fatty acid β oxidation.[1] The clinical presentation varies widely. Neonates sometimes die in infancy with malformations and severe metabolic decompensation. Infants and children present with metabolic decompensation, hepatic dysfunction, myopathy, and cardiomyopathy. Patients who are severely affected are treated with a low-fat diet, avoidance of fasting, and conjugation of toxic metabolites with L-carnitine and glycine, but the response is often poor.[1] We describe three patients with severe disease given D,L-3-hydroxybutyrate, a treatment previously reported in another patient.[2]

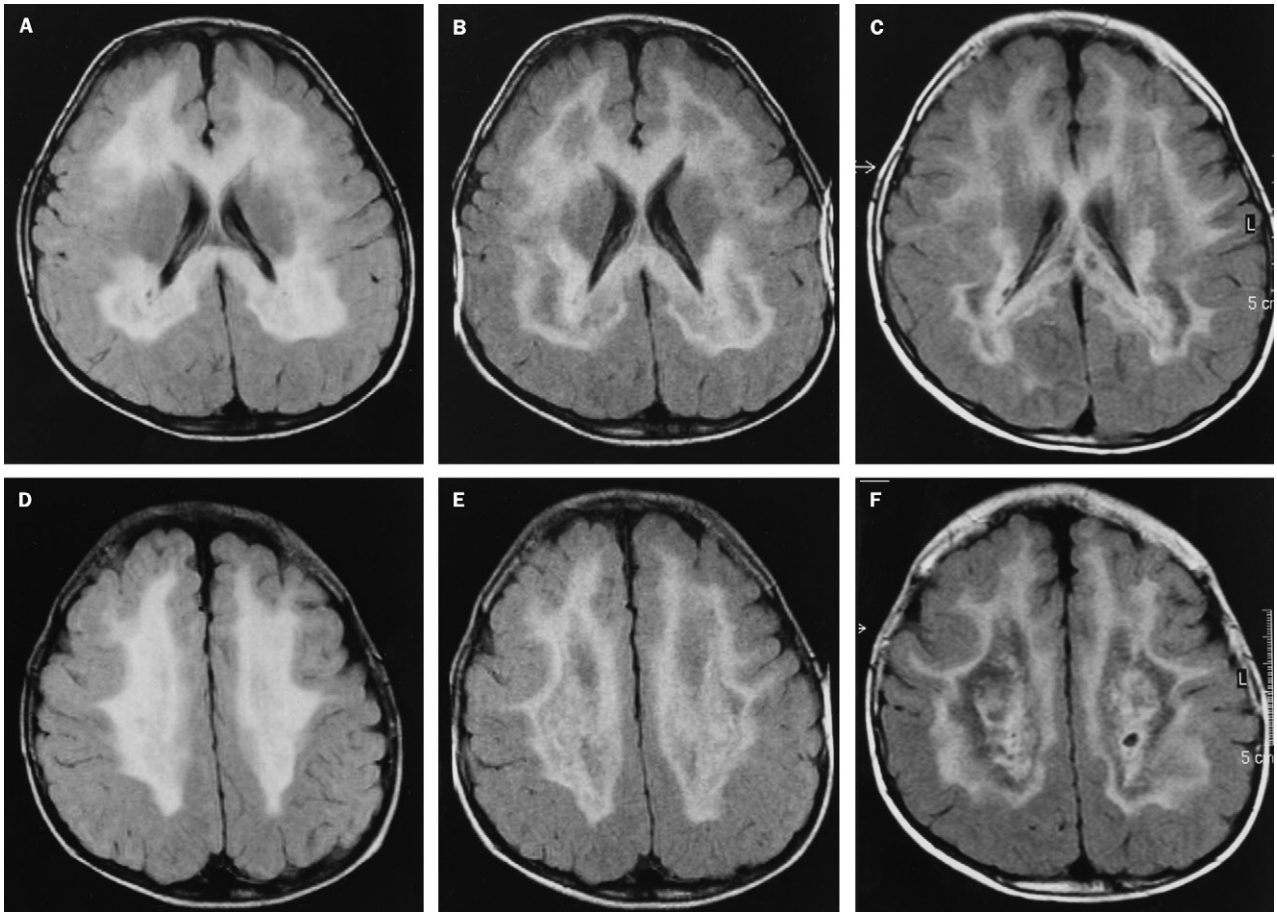
The first patient was a boy, the fifth child of first cousins, who presented at age 4 months with hypotonia, hepatomegaly, stridor, swallowing dysfunction, hyperammonaemia, and high transaminases and creatine kinase enzyme activity. Normal brain MRI excluded malformations. He had characteristic metabolites of MADD and enzymatic and molecular studies showed a deficiency of ETF-dehydrogenase (homozygous G381R). The boy responded to gastrostomy feedings of a fat-restricted diet every 4 h, L-carnitine, and glycine with nearly age-appropriate development. At 2 years, he started to have difficulty walking with spasticity of his right leg and arm. 2 weeks later, he could not stand and had persistent clonus. He deteriorated rapidly and was soon bedridden, could no longer talk, and had spastic quadriplegia with complete loss of the use of all four limbs. The MRI scan showed a leukodystrophy (figure), as described in MADD.[3,4] With informed consent, he was started on sodium-D,L-3-hydroxybutyrate every 4 h, increasing over 1 month from 80 to 900 mg/kg per day to obtain measurable concentrations of physiological ketone bodies at all times. There was a gradual clinical recovery. After 9 days, he could move his arms, and after 1 month lift both arms. After 4 months, he had head control and used his arms to drink from a cup. After 6 months, he could sit with support and spoke ten words. After 16 months, he talked in short sentences, was crawling, and rode a tricycle. He still had hyperreflexia, mild clonus, and extensor right plantar response. After 19 months, he walked independently. MRI showed progressive improvement but with regions of cavitation, that were probably results of the reparative processes (figure). Liver size and function tests returned to normal.

The second patient was a girl, the seventh child of consanguineous parents, whose three previous siblings had died in infancy of MADD, confirmed by analysis of metabolites and enzyme studies. This girl presented at age 5 months with heart failure. Cardiac ultrasound showed severe dilated cardiomyopathy with left-ventricular hypertrophy. She improved slightly on conventional treatment but remained very sick. Her trunk and limbs had very low tone and she had no head control. Organic acids and acylcarnitine studies were diagnostic of MADD. She rapidly deteriorated, and despite full intensive care including inotropic support she remained critically ill with a fractional shortening of 6% (table). She was started on sodium-D,L-3-hydroxybutyrate increasing over 2 weeks to 430 mg/kg per day and improved, becoming more stable, more alert and active. 4 weeks later, her fractional shortening had increased to 20%, and her muscle tone improved. At age 12 months she was walking while holding onto the furniture and could speak two words. At 19 months her cardiac dimensions and function were normal.

The third patient was a boy, the fifth child of first cousins, and distantly related to the second patient. He had one sibling who had died of cardiomyopathy in infancy. He presented at age 6 days with lethargy, poor feeding, and hypoglycaemia. At age 2 months he developed cardiac failure, hepatomegaly, and severe hypotonia. His cardiac ultrasound showed dilated hypertrophic cardiomyopathy with a shortening fraction of 16% (table). Studies of organic acids, acylcarnitines, and enzyme activity were diagnostic of MADD. He was admitted critically ill and unresponsive to intense conventional treatment. 1 month after starting sodium-D,L-3-hydroxybutyrate his shortening

fraction was 28%, he was more alert, and his tone improved. After 11 months' treatment, he walked with support, and had a normal fractional shortening of 35%, but biventricular hypertrophy persisted. Although he had frequent childhood infections, they did not result in metabolic decompensation. At age 2 years some left ventricular thickening remains, but with normal function.

In all three patients, pretreatment plasma concentrations of the physiological ketone bodies (sum of D-3-hydroxybutyrate and acetoacetate) were below the detection limit (<0·02 mmol/L). After a 150 mg/kg dose of D,L-3-hydroxybutyrate, plasma physiological ketone body concentrations peaked between 0·19 mmol/L and 0·36 mmol/L after 30 min to 1 h, and remained above pretreatment concentrations for 4 h. Free fatty acids decreased by up to 75% 1 h after administration, returning to pretreatment concentrations after 3 h. Medium-chain acylcarnitines, particularly decanoylcar-



Brain MRI of patient 1: evolution with treatment

Fluid-attenuated inversion recovery (TR/TE/TI=6500/105/2200 msec) MRI taken at the level of the lateral ventricles (A, B, and C), and one section above the level of the lateral ventricles (D, E, and F). Brain MRI scans were obtained before (A and D), after 2 months (B and E), and after 9 months of treatment (C and F). There is diffuse involvement of the supratentorial white matter both centrally and peripherally and in the corpus callosum (A, D). On the post-treatment scans there is a progressive change in the central white matter with a decrease in signal intensity. Cavitation can occasionally be seen (F).

Age	LV post wall	Septum (mm)	Shortening fraction	LVEDD	3-hydroxybutyrate (mg/kg per day)	Additional drugs
Patient 2						
5 months 3 weeks	6	8	17%	37	0	Riboflavin, carnitine, captopril, furosemide, digoxin
6 months	8	8	6%	36	Start 100	Add dobutamine, amiloride
6 months 1 week	8	8	13%	31	430	Dobutamine and amiloride stopped, spironolactone
8 months	7	7	20%		420	Stopped digoxin
12 months 2 weeks	5	5	16%	33	420	..
19 months	6	6	34%	25	670	Reduced furosemide
Patient 3						
2 months	8	8	16%	27	Start 233	Riboflavin, carnitine, captopril, furosemide
2 months 2 weeks	11	10	21%	20	700	Captopril stopped
3 months	7	6	28%	25	600	..
8 months	9	10	31%	20	600	Furosemide stopped
13 months	9	9	39%	24	480	..
24 months	10	9·6	Excellent		565	..

LV=left ventricular. LVEDD=left-ventricular end-diastolic diameter.

Cardiac measurements in patients 2 and 3 before and after treatment

nitine, also decreased for 2 h after a dose. Concentrations of physiological ketone bodies in the cerebrospinal fluid were 23% of those in plasma (patient 1).

These three patients had a severe infantile form of riboflavin-unresponsive MADD. Four siblings of patients 2 and 3 had died in infancy and all our patients had received intensive conventional treatment, despite which all were very sick when sodium-D,L-3-hydroxybutyrate was started.

We gave the racaemic mixture of D-3-hydroxybutyrate and L-3-hydroxybutyrate. Although fatty acids do not cross the blood brain barrier, ketone bodies do enter the brain, and this process is even better in childhood. They are used by heart, kidney, and fat tissue, and, to a lesser extent, by muscle. All brain cells use ketone bodies for energy. Rat brain also uses both D-3-hydroxybutyrate and L-3-hydroxbutyrate for synthesis of lipids; the increase of this in infancy is even more pronounced for L-3-hydroxybutyrate than for D-3-hydroxybutyrate, making it particularly suited for restoration of myelination.[5]

Use of fatty acids is reduced in the myocardium of patients with defects in oxidation of fatty acids, and cardiomyopathy is a frequent cause of death in MADD[1] warranting experimental treatment. D,L-3-hydroxybutyrate treatment resulted in substantial and persisting improvement of cardiomyopathy in these infants who were critically ill. D,L-3-hydroxybutyrate also improved hypotonia and feeding tolerance in a patient with MADD.[2] Administration of ketone bodies to human volunteers decreases lipolysis with decreased free fatty acids in plasma. End product administration not only restores a deficit, but also through feedback inhibition reduces formation of toxic precursors as indicated by decreased decanoylcarnitine.

Our observations and results of other studies suggest that treatment with D,L-3-hydroxybutyrate is safe and effective. It was not associated with adverse side-effects. D,L-3-hydroxybutyrate is an additional therapeutic option for cardiomyopathy and cerebral dysfunction in severe fatty-acid oxidation defects.

Contributors

J L K Van Hove and J V Leonard designed and implemented the study and wrote the report. J Jaeken and S Grünewald assisted in the clinical study and writing of the report. J E Deanfeld did the echocardiograms and managed the cardiomyopathy, P Demaerel did the brain MRI studies. P E Declercq, P Bourdoux, and K Niezen-Koning did the laboratory studies and the drug and metabolite measurements.

Conflict of interest statement

None declared.

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Control of encrustation and blockage of Foley catheters

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Urinary catheters often become encrusted and blocked by crystalline *Proteus mirabilis* biofilms. Results of experiments in a laboratory model of a Foley catheterised bladder infected with *P mirabilis* showed that when retention balloons were inflated with a solution of triclosan (10 g/L), the catheters drained freely for at least 7 days. Triclosan became impregnated throughout the silicone catheter material and completely inhibited the formation of crystalline biofilm, whereas catheters inflated with water became blocked in 24 h. Our observations suggest a way to control a common complication in patients with long-term indwelling bladder catheters.

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Many patients undergoing long-term bladder catheterisation experience encrustation of their catheters. The problem stems from infection by *Proteus mirabilis* or other urease-producing bacteria such as *Providencia* spp and *Morganella* spp. These organisms colonise catheter surfaces, forming biofilm communities embedded in a polysaccharide matrix. Urease generates ammonia and raises the pH of urine and biofilm. Under these conditions, crystals of magnesium and calcium phosphates form and become trapped in the organic matrix and can eventually block the catheter. This complication can seriously compromise patients' health and welfare.[1] There are no effective procedures for controlling this problem, to which all types of Foley catheter are vulnerable.[2]

Bibby and colleagues[3] suggested that to control catheter encrustation, the retention balloon should be inflated with an antimicrobial solution rather than with water. Thus, delivery of the agent to the urine might be achieved by diffusion through the balloon. In an in-vitro model, low concentrations of mandelic acid were shown to diffuse