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3-Hydroxydicarboxylic aciduria due to long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency associated with sudden neonatal death: protective effect of medium-chain triglyceride treatment

M. Duran[1], R. J. A. Wanders[2], J. P. de Jager[3], L. Dorland[1], L. Bruinvis[1], D. Ketting[1], L. Ijlst[2], and F. J. van Sprang[1]

[1] University Children's Hospital, 'Het Wilhelmina Kinderziekenhuis', Nieuwe Gracht 137, NL-3512 LK Utrecht, The Netherlands
[2] Department of Paediatrics, University Hospital Amsterdam, Amsterdam, The Netherlands
[3] Department of Paediatrics, Elkerliek Ziekenhuis, Helmond, The Netherlands

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Abstract. Two siblings were found to be affected by long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, one of which died suddenly and unexpectedly on the 3rd day of life suffering from extreme hypoketotic hypoglycaemia. The younger sibling started to have feeding problems, lowered consciousness, and liver dysfunction at the age of 5 months. Her urine contained large amounts of C_6–C_{14} 3-hydroxydicarboxylic acids and conjugated 3-hydroxyoctanoic acid, as verified by gas chromatography/mass spectrometry. Plasma long-chain acylcarnitine was increased. A clue to the diagnosis was given by the results of a phenylpropionic acid loading test. This revealed small, but significant amounts of conjugated 3-hydroxyphenylpropionic acid (phenylhydracrylic acid) in the patient's urine. Subsequently, the activity of long-chain 3-hydroxyacyl-CoA dehydrogenase was found to be deficient in cultured skin fibroblasts. Based on the findings obtained by a medium-chain triglyceride load, a diet enriched in this type of fat was prescribed. On this regimen the patient started to thrive, signs of cardiomyopathy disappeared, and her liver function normalized.

Key words: 3-Hydroxydicarboxylic aciduria – Sudden neonatal death – Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency – Medium-chain triglycerides

Offprint requests to: M. Duran

Abbreviations: ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; LDH = lactate dehydrogenase; MCT = medium-chain triglyceride

Introduction

Inherited defects of fatty acid β-oxidation have been recognized as potentially dangerous inborn errors of metabolism. The crucial hazardous phenomenon is the shortage of acetyl-CoA which leads to a decreased production of ketone bodies during prolonged starvation. As the human brain utilizes only glucose and ketone bodies as a fuel, the dramatic effect of a deficiency of the latter substrate can easily be understood. Accordingly, patients with defects of fatty acid β-oxidation present with hypoketotic hypoglycaemia. Symptoms of this disease may develop so rapidly and unexpectedly, that in several patients the diagnosis was originally missed by labelling their disease as sudden infant death syndrome [6].

β-Oxidation of fatty acids proceeds stepwise, via dehydrogenation, hydratation, dehydrogenation and thiolytic cleavage (Fig. 1). Multiple enzymes are involved for each step with different substrate specificity. The dehydrogenation of the various L-3-hydroxyacyl-CoA's (reaction 3) needs at least a short-chain and a long-chain enzyme.

So far six patients with long-chain acyl-CoA dehydrogenase deficiency and at least 150 patients with medium-chain acyl-CoA dehydrogenase deficiency have been reported [14]. Both conditions appear to be characterized by a specific pattern of urinary organic acids, mainly products of ω- and (ω-1)-oxidation of fatty acids. The other theoretically possible defects have not yet been described. Here we describe a family in which one child had a proven deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase and another child died suddenly and unexpectedly, probably due to the same defect. The pattern

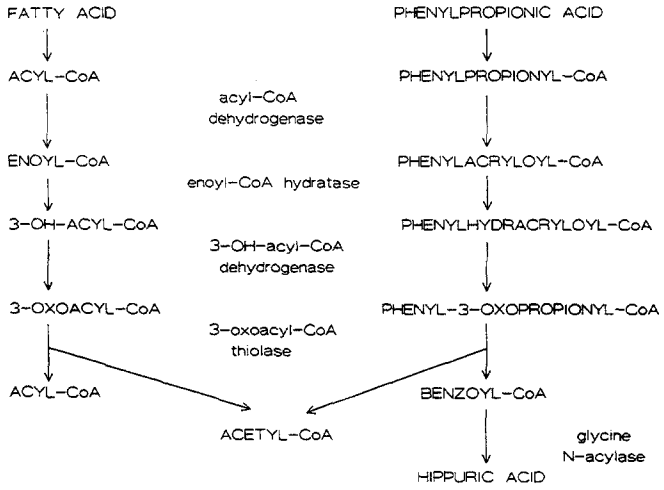

Fig. 1. Scheme of fatty acid β-oxidation showing the fate of orally ingested phenylpropionic acid. The dehydrogenation of phenylpropionyl-CoA is effected only by medium-chain acyl-CoA dehydrogenase

of plasma and urine organic acids was impressive, both in basal conditions and during provocative tests. Clinical observations with respect to treatment are reported. A brief report on this family has been published [16].

Case histories

Patient 1

A girl was the first child of healthy, non-consanguineous Caucasian parents. She was born at home in 1985 after an uneventful pregnancy with a birth weight of 3330 g. She was breastfed and received small amounts of extra dextrose-water. In the morning of the 3rd day she refused her feeds and became cyanotic with irregular breathing and comatose. She was immediately transported to hospital but was dead upon arrival. Autopsy showed an enlarged liver with fatty degeneration. Excess lipid deposits were also observed in the heart, pancreas, and lungs. There was hyperaemia of the lungs and a provisional diagnosis of Reye syndrome was made. The only material for biochemical investigations was a blood sample obtained immediately after death. This showed a profound hypoglycaemia with hypoketonaemia: plasma glucose 0.1 mmol/l, 3-hydroxybutyrate 0.47 mmol/l. Free carnitine was normal: 39 μmol/l and short-chain acylcarnitine was increased to 61 μmol/l. Plasma organic acid analysis revealed a highly unusual profile (see results section). Plasma lactate (12.8 mmol/l) was in the same order of magnitude as seen in other dying children.

The second girl in this family was born 1 year later. She has always been in good health and tolerated a 24 h fast at the age of 6 months without clinical or biochemical abnormalities (plasma organic acids).

Patient 2

The third girl was born after an uneventful 39 week pregnancy in March 1988 (birth weight was 3350 g; Apgar score after 5 min, 10). Because of the family history she was monitored very carefully during the neonatal period. She never had episodes of hypoglycaemia, not even when she was fasted 5 h in excess of her usual fasting interval in the 2nd month of life. A urine sample collected at that time contained 3-hydroxyadipic acid, a finding which could not then be pursued. One morning 5 months of age she was found lethargic, pale, with staring eyes. Her leucocyte count was 10.10^9/l; blood glucose and liver function tests were normal. The only abnormal laboratory findings at that time were an increased lactate (6.4 mmol/l) and pyruvate (133 μmol/l). Neurological and neurophysiological examinations gave normal results, but there were marked feeding difficulties. Two weeks later the child contracted gastro-enteritis whereon she again became lethargic and hypotonic. The following day she recovered clinically, but the next day she was hard to arouse, there was an enlarged liver and the EEG was suggestive of an encephalopathy. Glucose remained stable, but lactate was 6.3 mmol/l. Over a period of 24 h her clinical condition deteriorated and blood glucose fell to 2.6 mmol/l. She was given i.v. glucose and transferred to the University Children's Hospital.

Upon admission the following abnormal results of laboratory analyses were obtained: blood glucose 3.6 mmol/l, CSF glucose 2.8 mmol/l, blood pH 7.30, base deficit −5 meq/l, alanine aminotransferase (ALAT) 312 units/l, aspartate aminotransferase (ASAT) 400 units/l, lactate dehydrogenase (LDH) 2010 units/l, creatinine kinase 83 units/l later increasing to 217. No indications were found for viral or bacteriological infection: the leucocyte count had dropped to 8.10^9/l. Following the first results of metabolic investigations (see results section) the patient was put on a regimen with frequent, carbohydrate-rich feedings, which was changed to a medium-chain triglyceride (MCT) diet after the results of the in vivo loading tests became available. Treatment with riboflavin (3 × 25 mg/day) and carnitine (4 × 100 mg) was started earlier.

Clinically her condition improved gradually, although hypotonia persisted for several months. A cardiological examination at the age of 6 months revealed a left ventricular hypertrophy, which was interpreted as a first sign of cardiomyopathy. Plasma free carnitine was 23 μmol/l (controls 25–60) and long-chain acylcarnitine 8 μmol/l (controls < 5). Ten months later no cardiac abnormalities were apparent.

The patient's liver functions improved only slowly: 3 months after admission ALAT was 57 units/l, ASAT 64 units/l and LDH 377 units/l.

Feeding difficulties remained a major problem throughout the 1st year after the onset of symptoms. Even at times of hospitalization there were several bouts of gastro-enteritis, which seemed to coincide with attempts to lower the frequency of the meals. Detailed gastro-intestinal investigations failed to show causing factors other than the metabolic derangement. In order to protect the child from further decompensations she was put on gavage feeding, which is still continued. When the child was last seen at the age of 18 months growth and development were normal. Liver function tests had almost completely normalized: ALAT 22 units/l, ASAT 50 units/l, LDH 678 units/l, gamma glutamyl transpeptidase 9 units/l. Therapy with riboflavin (75 mg/day), and carnitine (4 × 100 mg/day) is still being continued.

Careful investigation of the family history has not revealed any peculiarities. Both parents underwent a brief fasting experiment, which was clinically well tolerated.

Materials and methods

Urine and plasma organic acids were analysed by capillary gas chromatography/mass spectrometry as described earlier [3]. Hydrolysis of conjugates was achieved by heating a 1:2 mixture of urine and 11 *M* NaOH at 100°C for 3.5 h. Under these conditions phenylhydracrylic acid was partially converted to phenylacrylic acid. The structure of plasma medium- and long-chain 3-OH-monocarboxylic acids was verified using authentic reference substances which were synthesized in our laboratory by means of the Reformatzky reaction. 3-Hydroxyadipic acid was synthesized from 3-oxoadipic acid by reduction with $NaBH_4$. It readily forms a lactone in acidic conditions. Urinary acylglucuronides were isolated by preparative thin-layer chromatography on silica plates in a system employing n-butanol/acetic acid/water (2:1:1 v/v) as a solvent [2]. Identification of these compounds was done both by electron impact and by ammonia chemical ionization mass spectrometry. Plasma bile acids

were analysed by capillary gas chromatography/mass spectrometry. Free carnitine and short-chain acylcarnitine were measured by a colourimetric method using dithio-bis-(nitrobenzoic acid). Long-chain acylcarnitine is co-precipitated with plasma proteins and can be quantitated after alkali treatment of the precipitate, thereby liberating carnitine [11].

Phenylpropionic acid was given to the patient in an amount of 25 mg/kg. Following this load urine was collected for 12 h.

Medium-chain acyl-CoA dehydrogenase activity was measured in the patient's lymphocytes by a gas chromatographic method according to Kolvraa et al. [10]. The formation of 3-hydroxyoctanoyl-CoA from octanoyl-CoA was checked by mass spectrometric analysis.

The activities of the various L-3-OH-acyl-CoA dehydrogenases were measured at 37°C in fibroblast homogenates using a spectrophotometric method. Fibroblasts were cultured and harvested as described previously [17]. As substrates we used 3-oxobutyryl-CoA, 3-oxo-octanoyl-CoA, and 3-oxopalmitoyl-CoA. Incubations were done in the following medium: 50 mmol/l 2-(N-morpholino)-ethanesulphonic acid, 100 mmol/l potassium phosphate, 0.1 mmol/l dithiothreitol, 0.1% (w/v) Triton X-100, 100 µmol/l NADH (final pH 6.16) and 25 µl fibroblast homogenate (approx. 75 µg/ml protein). The reaction was started by adding the 3-oxoacyl-CoA ester at a final concentration of 50 µmol/l. Absorbance changes were recorded at 340 nm.

The activity of 3-oxoacyl-CoA thiolase was measured by following the decrease in absorbance at 303 nm using the following conditions: 100 mmol/l Tris-HCl (pH 8.05), 10 mmol/l $MgCl_2$, 50 mmol/l KCl (if added), 50 µmol/l coenzyme A, 50 µmol/l acetoacetyl-CoA and fibroblast homogenate (150 µg protein/mg).

The activity of glutamate dehydrogenase was measured at 37°C by following the decrease in absorbance at 340 nm using the following assay medium: 50 mmol/l triethanolamine-HCl, 2.5 mmol/l EDTA, 100 mmol/l NH_4Cl, 1 mmol/l ADP, 0.3 mmol/l NADH, 0.1% (w/v) Triton X-100 (final pH 9.0). Reactions were started by adding 2-oxoglutarate at a concentration of 10 mmol/l.

All enzyme analyses were carried out on a Cobas-Centrifugal Analyser (Hoffmann-La Roche, Basel, Switzerland). Final volume was 250 µl; the absorbance was read every 20 s for a period of 10 min.

Table 1. Plasma and CSF organic acids in two siblings with a (presumed) deficiency of long-chain 3-OH-acyl-coenzyme A dehydrogenase. The sample obtained from patient 1 was a post-mortem sample. Concentrations are given in µmoles/l. Tr = trace; + = present, but not quantitated because of interferences.

Compound	Patient 1	Patient 2			
		13/9	13/9 CSF	19/9	10/10
Lactic acid	12800	4610	3917	2205	3918
Pyruvic acid	308	364	148	262	155
3-OH-butyric acid	467	400	114	147	842
3-Oxobutyric acid		177	83	76	383
3-OH-hexanoic acid		17	9	4	4
5-OH-hexanoic acid	29	18	6	4	
Adipic acid	184	48			
Unsat. adipic acid	27	32			
3-OH-adipic acid	183	+			
Octanoic acid		16	2		82
3-OH-Octanoic acid	18	34	16	Tr	1
Suberic acid	50	15			
Unsat. suberic acid	+				
3-OH-suberic acid	+				
Decanoic acid		31		11	52
'Decenoic acid'	13	30		Tr	3
3-OH-Decanoic acid	+		Tr		(+)
Sebacic acid		+	Tr		
Unsat. sebacic acid	+				
3-OH-Sebacic acid	26	24			
Total free fatty acids	436	2257		246	625
3-OH-Dodecanoic acid (+ unsat.)		+			
3-OH-Tetradecanoic acid (+ unsat.)		+			
3-OH-Hexadecanoic acid (+ unsat.)		+			

Results

Plasma organic acids of the two affected children showed distinct similarities (Table 1). The sample from patient 1 was taken immediately after death, whereas the first sample from patient 2 was taken during the acute episode of metabolic decompensation (blood glucose 2.6 mmol/l). Most notable are the differences in the amounts of adipic acid and 3-hydroxyadipic acid. These dicarboxylic acids appeared only in strikingly abnormal concentrations during life-threatening metabolic decompensation. All 3-hydroxymonocarboxylic acids with chain lengths from six to sixteen carbon atoms could be identified by comparing the mass spectra with those of the synthetic reference compounds (to be published). Quantitation of these acids was only possible for the C_8 and C_{10} homologues, which did not coincide with the corresponding higher free fatty acids in the gas chromatogram. The sample obtained from patient 2 (19/09) was during clinical remission, whereas that of 10/10 was taken at the start of the treatment with medium-chain triglyceride-enriched feedings. All plasma samples contained an unsaturated decanoic acid, indicated in Table 1 as "decenoic acid". Although its retention time and mass spectrum were identical to those of cis-4-decenoic acid, a characteristic metabolite of medium-chain acyl-CoA dehydrogenase deficiency [4], it is theoretically possible that another decenoic acid isomer accumulates in this condition.

Analysis of CSF revealed the same unusual 3-hydroxyalkanoic acids as in plasma, albeit in somewhat lower concentrations (Table 1). Surprisingly no dicarboxylic acids could be detected in CSF. CSF ketone body concentrations were even lower than those in plasma, possibly reflecting an enhanced utilization of these substrates in the brain. Plasma and CSF lactate and pyruvate were increased on all occasions, not only in the dying child, but also in the surviving sibling. The molar ratio of free fatty acids/3-hydroxybutyrate was most disturbed in patient 2 at the time of admission to the University Children's Hospital (5.64, controls <1). The first urine collected after admission at the age of 5 months showed a severe dicarboxylic and 3-hydroxydicarboxylic aciduria, involving all saturated and unsaturated homologues with chain lengths ranging from 6 to 14 carbon atoms. Ketonuria was negligible, as exemplified by the urinary 3-hydroxybutyrate concentration of only 0.21 mmol/g creat. In con-

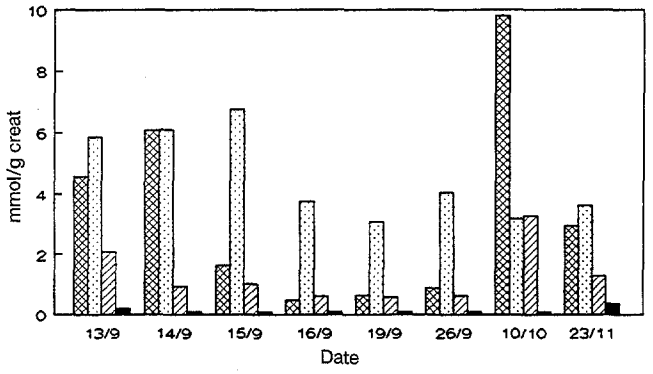

Fig. 2. Urinary excretion levels of selected organic acids in a patient with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. ▩ Adipic acid; ▨, 3 hydroxyadipic acid; ▩ 3-hydroxysebacic acid; ■ 3-hydroxybutyric acid. The patient was admitted to the University Children's Hospital on 13/09; treatment with MCT was started on 10/10

trast adipic acid was 4.6 mmol/g creat., 3-hydroxyadipic acid 5.9 mmol/g creat., suberic acid 1.5 mmol/g creat. and its unsaturated analogue 0.85 mmol/g creat.

Urinary organic acids were analysed serially in patient 2 (Fig. 2). During the 2 weeks following her admission the organic acid profile gradually improved. The only persisting abnormality was the abnormal excretion of 3-hydroxyadipic acid, which had also been observed in a random urine sample collected earlier in her life (Dr. A. H. van Gennip, personal communication). In all urine samples except the one collected just after the start of the MCT-diet (10/10) the concentration of 3-hydroxyadipic acid was higher than that of adipic acid. Although the patient improved slowly on the carbohydrate-enriched diet, the dicarboxylic aciduria did not disappear completely. As it was not clear whether the primary defect affected long-chain or medium-chain fatty acid oxidation, we decided to test the patient's capacity for oxidation of medium-chain fatty acids by administering MCT (1.5 g/kg; 80% C_8 and 20% C_{10}) orally together with phenylpropionic acid (25 mg/kg). Plasma samples were taken at 1, 2, and 3 h after administration of the load and urine was collected from 0–3 h, 3–6 h, and 6–12 h following the start of the test.

Peak plasma octanoate reached a level of 0.7 mmol/l after 3 h (control 0.5), whereas 3-hydroxybutyrate increased to 1.24 mmol/l (control 1.40 mmol/l, patient with medium-chain acyl-CoA dehydrogenase deficiency 0.6 mmol/l). Plasma 3-hydroxyhexanoate (12 μmol/l) was only detectable 3 h after loading. Urinary MCT metabolites included the usual dicarboxylic acids and, in addition, octanoylglucuronide and 3-hydroxyoctanoylglucuronide. The concentrations of these were 1.90 and 0.28 mmol/l in the urine which was collected 3–6 h after loading.

Phenylpropionic acid loading resulted in a peculiar excretion pattern of metabolites. The main urinary product was conjugated benzoate, its concentration being 20.9 mmol/l in the 3–6 h post loading sample, but there were 0.24 mmol/l phenylhydracrylate and phenylacrylate. Indirect evidence was obtained concerning the nature of the latter two conjugates: most probably they were glycine esters. Plasma organic acid analysis showed that phenylpropionic acid was absorbed rapidly, as it reached its peak plasma concentration of 102 μmol/l already 1 h after the administration of the test substance. At 3 h after the load its plasma concentration had dropped to 54 μmol/l.

The results of the treatment with an MCT-enriched diet were reassuring: although a control urine sample collected 6 weeks after the start of the treatment still showed dicarboxylic aciduria, this could be attributed at least for a part to the physiological dicarboxylic aciduria which is always observed after MCT-treatment (Fig. 2). Plasma contained only a trace of 3-hydroxyoctanoate (2 μmol/l) and the ratio of free fatty acids/3-hydroxybutyrate was virtually normal at 1.10. Moreover the plasma lactate had entirely normalized to 1.62 mmol/l.

In order to explore the possibility of a deranged bile acid metabolism, the concentrations of bile acids in plasma were measured. As the trihydroxycoprostanoic acid concentration was normal, it can be concluded that the peroxisomal beta-oxidation of bile acids functioned normally.

The results of the assay of the activities of L-3-hydroxyacyl-CoA dehydrogenase using substrates with various chain lengths are shown in Table 2. A marked deficiency of L-3-hydroxypalmitoyl-CoA dehydrogenase was established. The apparent residual enzyme activity was even lower in a mitochondrial membrane-bound enzyme preparation, which was free of the matrix short-chain 3-hydroxyacyl-CoA dehydrogenase. The presence of the latter enzyme was demonstrated by immunoblotting.

No abnormalities were found in β-ketothiolase, the final enzyme of the β-oxidation cycle, which was assayed both with and without stimulation by potassium ions.

Medium-chain acyl-CoA dehydrogenase in the patient's lymphocytes showed an activity of 3.27 nmol/min · mg protein (controls 3.46 ± 0.12; $n = 14$).

The total plasma (= free + short-chain acyl) carnitine of patient 2 on admission was rather low: 23 μmol/l. At the same time long-chain acylcarnitine was moderately increased at 8 μmol/l. The urinary excretion of free carnitine was decreased to 9 μmol/l (5 μmol/mmol creatinine). Following the addition of MCT to the diet, plasma long-chain acylcarnitine decreased to a normal level of less than 5 μmol/l. Subsequently, carnitine therapy was initiated, which led to a normalization of plasma free carnitine (47 μmol/l). Surprisingly, plasma long-chain acylcarnitine increased simultaneously to a value of 24 μmol/l.

The results of the family investigation can be summarized as follows. The second child of this family, was subjected to a short fasting test. She has developed normally and is now 3 years old. A urine sample from both parents was collected after a 17-h fasting period and analysed for organic acids. The father showed a normal ketonuria and only traces of dicarboxylic acid. However, the mother produced – in a concentrated urine sample – an appreciable amount of 3-hydroxyadipic acid and conjugated 3-hydroxyhexanoic acid. Following this finding she was subjected to a 24-h fasting test under clinical surveillance. A plasma sample taken at the end of the test did not contain a measurable amount of 3-hydroxy-

octanoate, and the free fatty acid/3-hydroxybutyrate ratio was normal (0.93). Urinary organic acids again included 3-hydroxyadipic acid, at a concentration of 213 μmol/l, which was 4 times as high as adipic acid. Furthermore the urine contained some conjugated 3-hydroxyhexanoic acid (49 μmol/l) again. Clinically she tolerated the fasting test well. Neither the parents, nor any of their relatives, have ever suffered from conditions associated with a disturbed energy homeostasis.

Discussion

Over the past few years several reports have appeared dealing with inborn errors of fatty acid β-oxidation in sudden infant death or in children suffering from a Reye-like syndrome. In the majority of cases which led to a positive diagnosis this concerned a deficiency of medium-chain acyl-CoA dehydrogenase [8], possibly one of the most frequent inborn errors of metabolism.

Infants who die unexpectedly from a defect in energy homeostasis usually suffer from a prodromal illness characterized by diarrhoea and/or vomiting lasting 1 or a few days [3]. Symptoms usually start around the 5th–6th month of life [14], although an earlier start has been noted occasionally. In this respect our patient 2 fits perfectly in this clinical pattern. In retrospect one can say that her metabolic decompensation was probably initiated by cessation of her late-evening meal 1 week before. However, no clinical abnormalities were observed in the days prior to her metabolic derangement. The initial results of laboratory investigations failed to show hypoglycaemia, hence the cerebral dysfunction has to be attributed to some other effect, possibly the toxic action of one of the metabolites, as has also been suggested in medium chain acyl-CoA dehydrogenase deficiency [4].

Similar beneficial effects of an MCT diet were reported by Glasgow et al. [7] in a patient with an apparent defect of long-chain fatty acid β-oxidation. This patient also accumulated long-chain acylcarnitine in muscle and plasma, as did our patient. Glasgow's patient (and her twin sibling) was recently shown to be affected by a deficiency of 3-hydroxyacyl-CoA dehydrogenase (D.E. Hale, to be published). The clinical presentation of these patients was very similar to our patients and included episodes of hypoketotic hypoglycaemia with concomitant hepatic dysfunction. Surprisingly, their patients were reported not to display an abnormal organic aciduria, which is in sharp contrast to the present patients. So far all defects of intra-mitochondrial components of the β-oxidation pathway have been found to be associated with dicarboxylic aciduria.

Patients having a defect located outside the mitochondrial matrix generally have no abnormal dicarboxylic aciduria, as demonstrated for carnitine palmitoyltransferase I deficiency [1] and systemic carnitine deficiency [15]. One of the explanations could be that formation of a carnitine ester is necessary prior to ω-oxidation. In the case of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency we think that L-3-hydroxyacyl-CoA's are transformed into carnitine esters by carnitine palmitoyltransferase II and leave the mitochondrial matrix. When these esters reach the microsomes they are ω-oxidised.

Table 2. Activities of L-3-hydroxyacyl-CoA dehydrogenase in cultured skin fibroblasts of a patient with 3-hydroxydicarboxylic aciduria. 3-Oxoalkanoyl-CoA esters were used as substrates. Glutamate dehydrogenase was assayed as a check of mitochondrial integrity

Enzyme	Substrate chain length	Activity[a]	
		Patient	Controls
L-3-OH-acyl-CoA dehydrogenase	C-4	91.2	77.8 ± 12.1 (5[b])
	C-8	32.0	51.8
	C-16	21.2	71.2 ± 6.5 (5[b])
Glutamate dehydrogenase		177	173 ± 50 (5[b])

[a] nmoles/min per mg protein
[b] Number of control cell lines

So far the dehydrogenation of L-3-hydroxyacyl-CoA has not been studied in great detail in human tissues. Several years ago it was shown that rat liver mitochondria possess two separate 3-hydroxyacyl-CoA dehydrogenases: a long-chain enzyme and a short-chain enzyme [5]. Our results in the present family as shown in Table 2 suggest a similar situation in man. Both the long-chain and the short-chain enzyme are supposed to have a rather broad specificity, as it was stated that the medium-chain substrate 3-hydroxyoctanoyl-CoA could be metabolized by both enzymes [5]. However, as our two siblings accumulated 3-hydroxyoctanoate in their plasma, one has to assume that the short-chain enzyme lacks sufficient activity for the complete breakdown of 3-hydroxyoctanoyl-CoA. On the other hand our patient produced a virtually normal amount of ketone bodies following an MCT load.

To date a few scattered reports on 3-hydroxydicarboxylic aciduria have appeared [9, 12, 13]. Although it is tempting to assume that all patients suffered from the same defect, the apparent clinical heterogeneity suggests that there may be secondary contributing factors which determine the final outcome of the disease. The patient described by Kelley and Morton [9] had developed liver cirrhosis at the age of 5 months, which possibly led to her early death. On the other hand the two French patients [12] recovered quite rapidly from their attacks of hypoketotic hypoglycaemia occurring at the age of 9, 11, and 36 months, respectively. Clinically they developed a peripheral neuropathy and pigmentary retinopathy. Liver dysfunction associated with 3-hydroxydicarboxylic aciduria was also a hallmark of the patients described by Pollitt et al. [13]. Both sibs died in their 1st year of life, one of them suddenly and unexpectedly at the age of 10 months.

In summary, we have shown that long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency is a life-threatening disorder, which at least in some patients can be treated effectively with an MCT-enriched diet. It is our opinion that this diagnosis should be considered in every child who presents with symptoms of deranged energy homeostasis in its 1st or 2nd year of life.

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