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Carnitine-acylcarnitine translocase deficiency: phenotype, residual enzyme activity and outcome

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Abstract Carnitine-acylcarnitine translocase deficiency is a rare and life-threatening mitochondrial fatty acid β-oxidation disorder. We describe a patient who, despite a severe clinical course and an extremely low carnitine-acylcarnitine translocase activity, is currently alive and in good health. We performed an extensive analysis of all previously published cases in order to evaluate the clinical features and prognostic factors. Reports on 21 patients with carnitine-acylcarnitine translocase deficiency were obtained. Only 5 out of the 21 patients survived early childhood. At least 20 siblings are reported to have died of sudden unexplained death in the neonatal period. Although phenotype and residual enzyme activity have been suggested to be related to outcome, we were not able to establish such a relationship.

Conclusion Phenotype and residual enzyme activity do not appear to be major prognostic factors. Vigorous work-up in order to reach an expedite diagnosis and prompt medical intervention during acute episodes, especially in the neonatal period, may prevent fatal complications.

Key word Carnitine-acylcarnitine translocase deficiency

Abbreviation *CAT* carnitine-acylcarnitine translocase

Introduction

Carnitine-acylcarnitine translocase (CAT) deficiency is a rare and life-threatening mitochondrial fatty acid β-oxidation disorder characterised by hypoketotic hypoglycaemia induced by fasting or infections, and acute dysfunction of fatty acid-dependent tissues, such as liver, heart and skeletal muscle, leading to liver failure, hypertrophic cardiomyopathy and myopathy, respectively. Most reported cases died within 3 years of age. So far, only 5 of the 21 reported patients with CAT deficiency are still alive [1, 8, 11, 15, 17]. We describe a patient with CAT deficiency who presented at an unusually late age, 6 months after birth. Despite having a severe clinical course and an extremely low CAT activity, our patient is currently alive and doing well at 2 years of age.

Case report

A boy was born to unrelated, healthy Japanese parents after a normal pregnancy. Breast-feeding was started immediately after

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birth. No problems were noted until the age of 6 months. At this time, the patient developed a 2 week history of diarrhoea. After a prolonged overnight fast the patient gradually became lethargic, for which he was referred to our hospital. On examination the patient was comatose. The liver was enlarged to 10 cm below the right costal margin.

Initial laboratory investigations showed severe hypoglycaemia (0.3 mmol/l) and only trace amounts of ketone bodies in the urine. After intravenous administration of glucose, his clinical condition improved rapidly. Other laboratory results included hyperammonaemia (154 μmol/l; normal <40 μmol/l), raised transaminases (alanine aminotransferase 143 U/l; normal <45 U/l, and aspartate aminotransferase 301 U/l; normal <60 U/l), elevated creatine kinase (142 U/l; normal <35 U/l), normal lactic acid concentration, as well as normal electrolytes, blood urea nitrogen, arterial blood gas and blood cell count. Urine organic acid analysis showed an excess of dicarboxylic and hydroxycarboxylic acids in absence of ketones. Acylcarnitine analysis in plasma, performed by gas chromatography mass spectometry [16], showed elevated concentrations of C16 carnitine (11.6 μmol/l; normal 0.073–0.227 μmol/l), C18 carnitine (0.95 μmol/l; normal 0.027–0.086 μmol/l) and C18:1 carnitine (4.61 μmol/l; normal 0.084–0.361 μmol/l). Plasma free carnitine concentrations were extremely low (<1 μmol/l; normal 27–49 μmol/l). Dietary treatment based on a medium-chain triglyceride-based formula with frequent diurnal meals and continuous nocturnal tube feeding was started, supplemented with L-carnitine (75 mg/kg body weight per day). During hospitalisation the patient developed respiratory insufficiency due to muscle hypotonia with associated pneumonia and lung compression due to hepatomegaly. Mechanical ventilation was required during 4 consecutive days. Repeated ultrasound examination of the heart showed no signs of hypertrophic cardiomyopathy. Enzyme studies performed on cultured fibroblasts showed a very low residual activity of CAT, confirming the diagnosis CAT deficiency. The CAT activity in digitonin-permeabilised fibroblasts was measured essentially according to Pande et al. [16].

He was briefly admitted twice to our hospital because of gastroenteritis at 9 and 10 months of age, respectively. The last intercurrent infection was also followed by a hypoglycaemic seizure. Currently, at 2 years of age, the infant shows normal growth and psychomotor development.

Methods

A Medline search for patients with CAT deficiency was performed. A total of 21 patients with CAT deficiency were identified, to which we added a case of our own. Clinical features, laboratory investigations and outcome were analysed. Phenotype and residual enzyme activity were studied and set out against the outcome of each individual patient. As in other fatty acid β-oxidation disorders, the phenotype was defined as severe when liver failure and myopathy, as well as hypertrophic cardiomyopathy, were present [2]. When cardiomyopathy was absent, the phenotype was defined as mild. Information on the current status of each patient reported alive was obtained directly from the authors of the case reports (personal information from Drs. Ozand [1], Dionisi-Vici [6], Smeitink [8], Morris [11], Olpin [15] and Parini [17]). Data were analysed using the χ^2 test. A P value <0.05 was considered statistically significant.

Results

The initial findings of hypoketotic hypoglycaemia, dicarboxylic aciduria and elevated plasma long-chain acylcarnitines suggested an underlying defect in the β-oxidation of long-chain fatty acids. Defects of long-chain hydroxyacyl-CoA dehydrogenase and carnitine palmitoyl transferases I and II were first excluded. Measurement of CAT activity by specific studies in the patient's cultured fibroblasts gave 0.5 versus 56 ± 26 pmol/min per mg protein for patient and controls respectively. Mean residual enzyme activity in our patient was $<1\%$.

Results of clinical features, laboratory investigations and outcome of all reported patients with CAT deficiency are summarised in Table 1. The overall mortality rate was 73% (16/22). Death occurred mainly before 3 years of age and only three times in the neonatal period. At least 20 siblings died of sudden unexplained death in the neonatal period. Results of the relation between phenotype, residual enzyme activity and outcome are presented in Table 2. Two patients with a mild phenotype and detectable residual enzyme activity had a benign clinical course and are currently alive and doing well [11, 15]. A patient with mild phenotype and detectable residual enzyme activity who was initially reported to be alive and well at 5 months of age, died 1 month later (personal information from Dr. Dionisi-Vici) [6]. Two patients with detectable residual enzyme activity had a fatal outcome [4, 7], as well as another patient with a mild phenotype [16]. Two patients with severe phenotypes are currently alive and doing well at respectively 6 months and 4.5 years of age [1, 17]. One of them also has an undetectable CAT activity [1]. Two other patients, including ours, are currently doing well despite an undetectable CAT activity [8].

Discussion

CAT deficiency is a recently recognised mitochondrial fatty acid β-oxidation disorder. Like all other forms of β-oxidation defects, CAT deficiency is an autosomal recessive disorder and is frequently associated with severe and often fatal disease. Currently, a total of 22 patients with CAT deficiency, including our patient, have been reported. Almost all patients presented directly after birth with acute episode of hypoketotic hypoglycaemia induced by fasting or infections. However, our patient presented at an unusually late age, 6 months after birth. Association with liver failure, cardiomyopathy and myopathy due to accumulation of triglycerides in liver and muscle is often reported. Besides hypoketotic hypoglycaemia, laboratory investigations usually show severe hyperammonaemia due to liver failure, hypocarnitinaemia, dicarboxylic aciduria and elevated acylcarnitines. Despite early diagnosis as well as specific dietary treatment, most patients die following acute metabolic decompensation often triggered by intercurrent infections. Although only three patients were reported to have died before 1 month of age, at least 20 siblings died of sudden unexplained death in the neonatal period (Table 1). As most of these siblings were probably also affected by CAT deficiency, the actual neonatal mortality rate may be much higher. High neonatal mortality rate is explained by the fact that

Table 1 Clinical features and outcome in 22 patients with CAT deficiency. (*NA* information not available, *ND* not detectable)

Reference	Neonatal onset	Phenotype	Residual enzyme activity (as % of mean of control values)	Survivors: age (last received information)	Deaths: Age (cause of death)	Neonatal deaths of siblings
[1]	Yes	Severe	< 1	6 months (3.1.1999)	–	NA
[3]	No	NA	NA	–	8 weeks (NA)	2
[4]	Yes	NA	4.5	–	2 days (NA)	0
[5]	Elective[a]	NA	ND	–	6 months (NA)	7
[6]	Yes	Mild	4.5	–	6 months (cardiac arrhythmias)	NA
[7]	Yes	NA	ND	–	6 months (croup)	NA
	Yes	NA	4	–	5 months (NA)	NA
[8]	NA	NA	ND	10 years (26.1.1999)	–	0
[9]	Yes	Severe	ND	–	8 weeks (cardio-respiratory distress)	2
[10]	Yes	NA	NA	–	6 months (cardiac arrhythmias)	NA
	Yes	NA	NA	–	3 weeks (cardio-respiratory arrest)	NA
[11]	Elective[a]	Mild	5	6 years (3.5.2000)	–	1
[12]	Yes	Severe	ND	–	2 years (NA)	1
[13]	Elective[a]	NA	NA	–	6 months (sepsis)	6
[14]	Yes	Severe	ND	–	8 weeks (multiorgan failure)	0
	Yes	Severe	ND	–	9 weeks (NA)	0
[15]	No	Mild	6	5 years (3.5.2000)	–	0
[16]	Yes	Mild	ND	–	8 days (pulmonary haemorrhage)	NA
[17]	Yes	Severe	3	5 years (5.5.2000)	–	0
[18]	Yes	Severe	< 1	–	3 years (aspiration pneumonia)	1
[19]	Yes	NA	NA	–	9 months (pneumonia)	0
This study	No	Mild	< 1	2 years (22.6.2000)	–	0

[a] Elective admission immediately after birth and treatment with glucose i.v because of abnormal family history

Table 2 Phenotype, residual enzyme activity and outcome in patients with CAT deficiency. (*ns* not significant)

	Phenotype			Residual enzyme activity		
	Severe	Mild	*P*	< 1%	> 3%	*P*
Survivors (%)	2/7 (29%)	3/5 (60%)	> 0.05 (ns)	3/11 (27%)	3/6 (50%)	> 0.05 (ns)
Deaths (%)	5/7 (71%)	2/5 (40%)	> 0.05 (ns)	8/11 (73%)	3/6 (50%)	> 0.05 (ns)

β-oxidation and ketogenesis are essential metabolic pathways for energy provision in newborn infants.

Two patients with a mild phenotype and detectable residual enzyme activity had a benign clinical course and are currently alive and doing well [11, 15]. Phenotype, residual enzyme activity and outcome have therefore been suggested to correlate with each other [11, 15]. However, we found that several other patients with a mild phenotype, with or without detectable residual enzyme activity, had a fatal outcome [4, 6, 7, 16]. Similarly, several patients with a severe phenotype, with or without undetectable residual enzyme activity, are currently alive and doing well [1, 8, 17]. Although a larger number of patients is obviously needed in order to be more conclusive, we could not establish a relation between phenotype, residual enzyme activity and outcome. Nevertheless, two important caveats must be taken into consideration before reaching a conclusion. Firstly, phenotype in patients with CAT deficiency has not yet been strictly defined and distinction between severe and mild phenotype may not always be obvious. Secondly, given the fact that CAT activities may have been measured by different methods, the results of enzyme studies may not be strictly comparable. Yet, even if these two factors influenced the correlation with outcome, the relationship between residual enzyme activity, phenotype and outcome is not unequivocal and would still need to be established. Other factors, such as genotype or prompt medical intervention during acute episodes, might be, hypothetically, more important prognostic factors. Finally and most importantly, since the period of follow-up is still relatively short, the prognosis for our patient remains highly uncertain.

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