Eur J Pediatr (2000) 159: 82–85

ORIGINAL PAPER

J.-M. Nuoffer · P. de Lonlay · C. Costa · C. R. Roe · N. Chamoles · M. Brivet
J. M. Saudubray

Familial neonatal SIDS revealing carnitine-acylcarnitine translocase deficiency

Received: 13 April 1999 / Accepted: 26 August 1999

Abstract A patient with a severe phenotype of carnitine-acylcarnitine translocase deficiency (CATR)(McKusick 212138) is reported. Prior to birth, a defect in β-oxidation was suspected because of neonatal death of six siblings. Dietary treatment during neonatal adaptation and the subsequent six months of life and a trial of carnitine supplementation are reported. The rapidity with which long chain fatty acid metabolites can accumulate and induce secondary carnitine deficiency within a few hours after birth in an infant with CATR is noteworthy.

Conclusion High rates of glucose suppressed neonatal lipolysis in this infant, but did not seem sufficient to avoid secondary carnitine deficiency as in severe forms of CATR. Therefore simultaneous use of insulin and glucose may be necessary to control neonatal lipolysis. Carnitine supplementation and the possible adverse effects of MCT systematically administrated, should be further assessed in patients with CATR.

Key words Long chain fatty acids · Medium chain fatty acids · Diet · Carnitine · Beta-oxidation

Abbreviations *CATR* carnitine-acylcarnitine translocase deficiency · *LCT* long chain triglycerides · *MCT* medium chain triglycerides · *LCFA* long chain fatty acid · *NEFA* non esterified fatty acids · *BW* body weight · *MRI* magnetic resonance imaging · *VEP* visual evoked potential · *ERG* electroretinogramm · *GGT* gamma glutamyl transferase

Introduction

Long chain fatty acid oxidation contributes substantially to energy homeostasis, therefore defects of mitochondrial LCFA oxidation are serious, multisystemic and life-threatening disorders. The clinical relevance of secondary carnitine deficiency and the question of carnitine substitution in LCFA oxidation still remains controversial [17]. Besides its use for conjugating acyl-groups, carnitine-acylcarnitine translocase has a central role in the so called "carnitine cycle" allowing acylcarnitine esters to cross the inner mitochondrial membrane for β-oxidation [17]. We report on a patient with CATR defect, in whom a β-oxidation disorder was highly suspected prior to birth because of the neonatal death of six

J.-M. Nuoffer (✉)[1] · P. de Lonlay · J. M. Saudubray
Departments of Metabolic Disease and Pediatrics,
Hôpital Necker – Enfants, Malades, Paris, France

C. Costa · M. Brivet
Laboratoire de Biochimie, Hôpital Bicêtre,
Le Kremlin Bicêtre, France

C. R. Roe
Institute of Metabolic Disease,
Baylor University Medical Centre, Dallas, Texas, USA

N. Chamoles
Enfermedades Neurometabolicas, Buenos Aires, Argentina

Present address:
[1] Department of Endocrinology and Metabolic Disease,
Childrens University Hospital,
Freiburgstrasse, 3010 Bem, Switzerland
Tel.: (41) 31 632 21 11; Fax: (41) 31 63 24 772

The work was supported by a grant from the Swiss national science foundation

siblings and describe the evolution and dietary treatment from birth to death at 6 months of age. We also emphasize the rapidity with which LCFA metabolites accumulate at birth inducing secondary carnitine deficiency within a few hours. Further we discuss a trial with intravenous and oral carnitine supplementation.

Case report

The girl, was the eighth child, of healthy gypsy parents who are first cousins. Only one girl is alive and healthy. Four children died unexpectedly before day three and were considered SIDS. One child died on day one with a hemorragic syndrome and severe refractory bradycardia. Another sibling died following an overnight fast at 24 h of life. Investigations revealed hypoketotic hypoglycemia, hyperammonemia, C6–C10-dicarboxylic aciduria, 5-OH-hexanoic acid excretion and auriculo-ventricular block. Necropsy showed a liver steatosis in both siblings.

A defect in β-oxidation was strongly suspected prior to birth in the present patient, because of the suggestive family history. A postnatal transfer to the pediatric hospital was planned. The child was born at 38 weeks of gestation; with a birth weight of 2800 g, length of 46 cm, head circumference of 33.8 cm. There was a mucocutaneous bleeding syndrome; clinical examination was otherwise normal. Glucose infusion and continuous gastric drip feeding with glucose enriched skimmed milk, providing 14 mg/kg/min glucose, in order to block lipolysis, was started at 4 hours of life, after the child had received blood platelets. At arrival in our department at 10 hours of age laboratory studies revealed: lactate 6 mmol/l (N: 0.63–2.44), ammonia 128 μmol/l (N: < 40 μmol/l), NEFA 0.64 mmol/l (N: 0.3–0.7 mmol/l), creatine kinase 574 IU/l (N: < 300 U/I). Plasma and urine amino acid as well as urine organic acid analyses and blood glucose were normal. Cardiac investigation showed mild abnormalities of repolarisation and moderate left ventricular hypertrophy with good systolic function. On day three the CATR defect was confirmed and laboratory studies showed: normal glucose, lactate, ammonia and very low NEFA (< 0.02 mmol/l), suggesting indeed a total suppression of lipolysis. On day four a MCT based formula (Portagen, Mead Johnson) was delivered by continuous nasogastric tube feeding, supplying in total 60 g carbohydrates (15 mg/kg/min), 5 g protein, 4.5 g MCT and 0.5 g LCT providing 120 kcal/kg BW. At 2 weeks an accidental fast, due to an interruption of the continuous nasogastric tube feeding of 14 hours, occurred. The child presented with hypothermia, hypotonia, pallor and coma, hypoglycemia, lactacidemia (5.4 mmol/l), hyperammonemia (117 μmol/l). Organic acid analyses showed C6 to C10-dicarboxylic acids, 4-hydroxy phenyllactic and 4-hydroxy phenylpyruvic acid excretion without ketones. EKG and echocardiography remained normal. The clinical and biochemical abnormalities normalized within 48 hours. Further complications were the mucocutaneous bleeding syndrome, oesophagitis, repeated bacterial infections and unexplained arterial hypertension controlled by nifedipin. An exhaustive hematological investigation (coagulation, in vitro platelet aggregation test, ADP release, platelet membrane receptors for VWF and fibrinogen) pointed to a platelet aggregation disorder. Glanzmann thrombasthenia, known in this family, was excluded, because she was found to be heterozygous. The diet was regularly maintained, keeping glucose intake at 10–13 mg/kg/min, protein 2 g/kg/d, MCT 2–3 g/kg/d, providing 100–120 kcal/kg/d, without carnitine supplementation for the first two months. Adequate feeding was ensured by gastrostomy and a port-a-cath. Repeated attempts to divide continuous nasogastric tube feeding into individual meals failed, causing ileus-like symptoms. At two months, plasma carnitine was very low (total 6 μM and free 3 μM) and a trial with iv carnitine (200 mg every 8 hours for four days) was started, because of the suspected relation of low carnitine and feeding intolerance. Later on, oral carnitine was maintained at the same dosage, without improvement of feeding tolerance. At five months psychomotor development, brain MRI, VEP, ERG and cardiac function were normal and growth followed the 10th centile. Hepatomegaly developed after five months, with a slight elevation of alkaline phosphatase (300–700 U/L), GGT (40–250 U/L), and conjugated bilirubin (3–50 μmol/l). The patient died unexpectedly at 6 months of age from a staphylococcal port-a-cath septicemia with exacerbation of the hemorrhagic mucocutaneous syndrome. Necropsy was refused by the parents.

Methods

Overall β-oxidation, carnitine-acylcarnitine translocase, carnitine acetyltransferase and the pyruvate oxidase system were measured in lymphocytes and fibroblasts [3, 5, 15]. Acylcarnitines were regularity monitored from blood samples on standard Guthrie cards by tandem mass spectrometry [11]. Samples from day 1 to 76 were analyzed (Ch Roe and DS Millington) at Duke University, USA and samples from day 85 on (N Chamoles) in Buenos Aires, Argentina.

Results

Overall β-oxidation of palmitate in lymphocytes and fibroblasts was severely depressed, CATR was profoundly deficient with almost no residual activity (Table 1). Mutation analysis revealed a homozygous C558T transition in the CATR cDNA, resulting in a premature stop codon (R166X) [8]. Selected acylcarnitine profiles of

Table 1 β-oxidation flux and translocase activity

	Lymphocytes		Fibroblasts	
	Patient	Controls (n = 40) (Range)	Patient	Controls (n = 25) (Range)
Flux from [1-^{14}C]octanoate*	2.42	3.53 ± 0.81 (2.23–6.37)	6.30	4.89 ± 1.74 (2.25–8.89)
Flux from [9,10-^{3}H]palmitate†	0.29	6.12 ± 1.28 (4.00–9.20)	0.30	9.39 ± 1.70 (6.75–13.4)
Translocase activity§	0.025	1.16 ± 0.16 (0.82–1.49)	0.00	1.47 ± 0.20 (0.93–2.00)

Pyruvate oxidase and carnitine acetyl transferase activities were normal (data not shown). Values for control subjects are mean ± SD, with ranges in parenthesis

* Values are expressed as nmol of $^{14}CO_2$ released/hour/mg of protein

† Values are expressed as nmol of $^{3}H_2O$ released/hour/mg of protein

§ Values are expressed as nmol/minute/mg of protein

interest are depicted (Figure 1). At birth the profile showed grossly increased palmitoylcarnitine which normalized on day four as did other signs of metabolic decompensation. Changes in carnitine concentration during the neonatal period, at MCT introduction and on iv and oral carnitine are shown in Figure 1. On iv carnitine short-, medium- and long-chain acylcarnitine increased twenty, thirty and sevenfold respectively. Off carnitine, secondary carnitine deficiency developed within a few days.

Discussion

CATR deficiency is a disorder of LCFA β-oxidation. Most reported patients were seen within 2 days after birth with hypoglycemia, hyperammonia, heart beat disorder or sudden death [3, 4, 6, 9, 12–15, 18]. In the present reported family, six siblings died within the first days of life, four were considered as neonatal SIDS. Although the term SIDS [20] is not entirely appropriate, one should be aware that patients with defect in β-oxidation are easily mistaken for SIDS if no histologic examination of liver and cardiac muscle is done [1]. As energy metabolism in neonates is mostly based on high palmitate flux and fatty acid β-oxidation [2], the degree of neonatal lipolysis may be an important determinant of clinical outcome in severe forms of CATR deficiency.

Despite glucose infusion started at 4 hours of life, our patient presented slight signs of biochemical decompensation, while free fatty acids were 0.64 mmol/l. The carbohydrate enriched, LCT free diet however further suppressed neonatal lipolysis, resulting in prompt normalization of lactate, ammonia and palmitoylcarnitine within the first days of life. An even better control of neonatal lipolysis may be achieved with simultaneous use of insulin and glucose. Plasma carnitine deficiency developed within few days despite continuous gastric drip feeding and very low NEFA. Carnitine deficiency is an usual finding in β-oxidation deficient patients. Carnitine supplementation in LCFA oxidation defects remains however controversial [17]. Arrhythmogenesis induced by experimental myocardial ischemia has been shown to be related to long-chain acylcarnitine accumulation [7], however this observation has been more recently questioned [10]. On the other hand esterification with carnitine of potentially toxic acyl-CoA intermediates resulting from lipolysis and MCT enriched diet may be the only way of detoxification. Indeed there is some evidence that in CATR decanoyl (C10) and dodecanoyl (C12) oxidation is also reduced [17]. This may be due to the substrate specificity of long chain acyl-CoA synthase ranging from C10–C20 saturated fatty acids [19]. Since this enzyme is located at the outer mitochondrial membrane, C10- and C12-CoA will not be able to enter the mitochondria in the absence of CATR. As in MCT oil the fatty acid moieties C10 or longer account for 41.5% of total fatty acids, MCT supplementation may lead to the accumulation of C10–C12 acyl-CoA. Although C10–C12 oxidation was not directly investigated in the present patient, a deficient oxidation was indirectly sug-

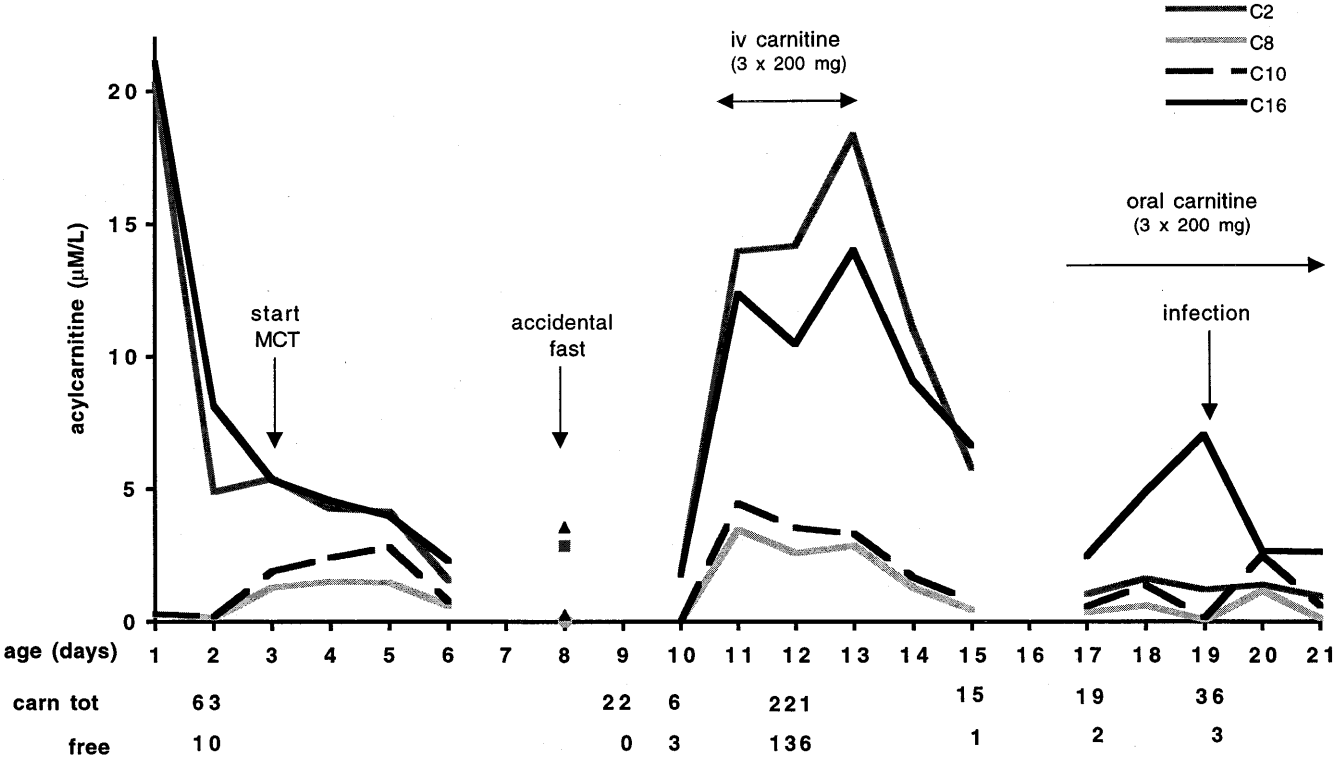

Fig. 1 Special events are indicated with an arrow. C2 = acetylcarnitine, C8 = octanoylcarnitine, C10 = decanoylcarnitine, C16 = palmitoylcarnitine. Carn tot and free = total and free plasma carnitine concentrations in μM measured by conventional method

gested by the increase of C10/C8 acylcarnitine ratio from 1 to 1.6. Similarly as in organic aciduria, this could be a rational for carnitine substitution [16]. Indeed carnitine supplementation was well supported with no cardiac side effects as already observed in 2 previously treated CATR patients [14, 18]. Intravenous carnitine supplementation rose all acylcarnitine species and free carnitine to supraphysiological concentrations as it is observed after carnitine substitution in carnitine depleted states (Roe, personal communication). High rates of glucose did suppress neonatal lipolysis but did not avoid carnitine depletion in our patients. Carnitine supplementation should be systematically tried and further assessed in patients with CATR. In addition the usefulness and the safety of MCT supplementation in CATR deficiency should be carefully investigated. The early neonatal presentation with sudden unexplained death in previous patients and our observation further underline the importance of prenatal diagnosis for families at risk.

References

1. Boles RG, Buck EA, Blitzer MG, Platt MS, Covan TM, Martin SK, Yoon H, Madsen JA, Reyes-Mugica M, Rinaldo M (1998) Retrospective biochemical screening of fatty acid oxidation in postmortem livers of 418 cases of sudden death in the first year. J Pediatr 132:924–933
2. Bougneres PF, Karl IE, Hillmann LS, Bier DM (1982) Lipid transport in the human newborn. Palmitate and glycerol turnover and the contribution of glycerol to neonate hepatic glucose output. J Clin Invest 70(2):262–270
3. Brivet M, Slama A, Millington DS, Roe CR, Demaugre F, Legrand A, Bouton A, Poggi F, Saudubray JM (1996) Retrospective diagnosis of carnitine-acylcarnitine translocase deficiency by analysis in the proband Guthrie card and enzymatic studies in the parents. J Inher Metab Dis 19:181–184
4. Brivet M, Slama A, Ogier H, Bouton A, Demaugre F, Saudubray JM, Lemonnier A (1994) Diagnosis of carnitine acylcarnitine translocase deficiency by complementation analysis. J Inher Metab Dis 17:271–274
5. Brivet M, Slama A, Saudubray JM, Legrand A, Lemonnier A (1995) Rapid diagnosis of long chain and medium chain fatty acid oxidation disorders using lymphocytes. Ann Clin Biochem 32:154–159
6. Chalmers RA, Stanley CA, English N, Wigglesworth JS (1997) Mitochondrial carnitine acylcarnitine translocase deficiency presenting as sudden neonatal death. J Pediatr 131:220–225
7. Corr PB, Creer MH, Yamada KA, Safitz JE, Sobel BE (1989) Prophylaxis of early ventricular fibrillation by inhibition of acylcarnitine accumulation. J Clin Invest 83:927–936
8. Costa C, Costa JM, Nuoffer J-M, Slama A, Boutron A, Saudubray JM, Legrand A, Brivet M (1999) Identification of the molecular defect in a severe case of carnitine acylcarnitine carrier deficiency. J Inher Metab Dis 22:267–270
9. Dionisi Vici C, Garavaglia B, Bartuli A (1995) Carnitine acylcarnitine translocase deficiency: benign course without cardiac involvement. Ped Res 37 abstract 869
10. Madden MC, Wolkowicz PE, Pohost GM, McMillin JB, Pike MM (1995) Acylcarnitine accumulation does not correlate with reperfusion recovery in palmitate-perfused rat hearts. Am J Physiol 268:pH2505–2512
11. Millington DS, Kodo N, Norwood DL, Roe CR (1991) Tandem mass spectrometry: a new method for acylcarnitine profiling with potential for screening for inborn errors of metabolism. J Inher Metab Dis 13:321–324
12. Morris AAM, Olpin SE, Brivet M, Turnbull DM, Jones RAK, Leonard JV (1998) A patient with mild carnitine-acylcarnitine translocase deficiency with a mild phenotype. J Pediatr 132:514–516
13. Niezen-Koning J, Van Spronsen FJ, Ijlist L, Wanders RJ, Brivet M, Duran M, Reijngoud DJ, Heymans HS, Smit GP (1995) A patient with lethal cardiomyopathy and a of carnitine acylcarnitine translocase deficiency. J Inher Metab Dis 18:230–f232
14. Olpin SE, Bonham JR, Downing M, Manning NJ, Pollit RJ, Sharrard MJ, Tanner MS (1997) Carnitine-acylcarnitine translocase deficiency – a mild phenotype. J Inher Metab Dis 20:714–715
15. Pande SV, Brivet M, Slama A, Demaugre F, Aufrant C, Saudubray JM (1993) Carnitine-acylcarnitine translocase deficiency with severe hypoglycemia and auriculo ventricular block. Translocase assay in permeabilized fibroblasts. J Clin Invest 91(1):1247–1252
16. Roe CR, Millington DS, Maltby DA, Bohan TP, Kahler SG, Chalmers RA (1985) Diagnostic and therapeutic implications of medium chain acylcarnitines in medium chain acyl coA dehydrogenase deficiency. Pediatr Res 19(5):459–466
17. Stanley CA (1995) Disorders of fatty acid oxidation. In: Femandes J, Saudubray JM, van den Berghe G (eds) Inborn Metabolic Diseases – Diagnosis and therapy. Springer Verlag, Berlin, pp 133–143
18. Stanley CA, Hale DE, Berry GT, Deleeuw S, Boxer J, Bonnefont JP (1992) A deficiency of carnitine-acylcarnitine Translocase in the inner mitochondrial membrane. N Engl J Med 372:19–23
19. Waku K (1992) Origins and fates of fatty acyl CoA esters. Biochem Biophys Acta 1124:101–111
20. Willinger M, James LS, Catz C (1991) Defining the sudden infant death syndrome (SIDS): deliberation of an expert panel convened by the National Institute of Child Health and Human Development. J Pediatr 124:677–684