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METABOLIC DISEASES

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Succinyl-CoA:acetoacetate transferase deficiency: identification of a new patient with a neonatal onset and review of the literature

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Abstract We describe the clinical symptoms and biochemical findings of a patient with succinyl-CoA:acetoacetate transferase deficiency who presented in the neonatal period and review the current literature on this subject. Our patient was initially suspected to have distal renal tubular acidosis, and subsequently, a fasting test revealed severe metabolic ketoacidosis with normal blood glucose after 13 h which suggest a defect in ketolysis. In his cultured skin fibroblasts succinyl-CoA:acetoacetate transferase was deficient (residual activity 15%). Treatment in the acute phase consisted of sodium bicarbonate. At the present age of 9 years, psychomotor and physical development are within normal limits.

Conclusion Defects of ketolysis probably are underdiagnosed disorders and should be considered in infants and young children with persistent ketosis.

Key words Ketolytic defect · Ketone bodies · Ketoacidosis

Abbreviations FFA free fatty acids · KB ketone bodies

Introduction

During metabolic crisis ketoacidosis can be one of the presenting abnormalities in a number of metabolic and

endocrinological diseases (for review see [7]) including some defects of glycogenolysis, gluconeogenesis, disorders of branched-chain amino acid metabolism, diabetes, partial insufficiency of the adrenal gland, growth hormone deficiency, defects of ketolysis and congenital lactic acidosis due to multiple carboxylase deficiency or pyruvate carboxylase deficiency [2].

Upon fasting, the rate at which ketone bodies are generated from fatty acids by the liver is strongly increased. Ketone bodies (KB) (acetoacetate and 3-hydroxybutyrate) produced in the liver are important for peripheral tissues as oxidative substrates and lipogenic precursors. They are used by different tissues, particularly the brain, to generate ATP [7]. The 'glucose-sparing' effect of KBs is regarded to be important, as the use of muscle protein to supply amino acids for gluconeogenesis is restricted during fasting.

Increased concentrations of plasma KBs are due to an increased production, a decreased consumption or an alteration of a specific regulatory process in KB metabolism. Hyperketotic states due to ketolytic defects are mainly caused by decreased KB utilization in peripheral tissues [9]. When a patient presents in the neonatal period with a severe ketoacidosis, in combination with a blood glucose varying between slightly below to slightly above normal, low or normal lactate and ammonia concentrations in plasma, defects in ketolysis at the level of acetoacetyl-CoA thiolase or succinyl-CoA:acetoacetate transferase should be suspected [10].

Succinyl-CoA:acetoacetate transferase (EC 2.8.3.5) is a mitochondrial enzyme which forwards the transfer of Coenzyme A from succinyl-CoA to acetoacetate. Subsequently, mitochondrial acetoacetyl-CoA thiolase (EC 2.3.1.9) converts acetoacetyl-CoA to acetyl-CoA, which can be oxidized in the Krebs cycle.

A limited number of patients with a defect of succinyl-CoA:acetoacetate transferase, an autosomal recessive disorder, has been described so far [4–6, 8, 9, 11, 12]. We present a patient with succinyl-CoA:acetoacetate transferase deficiency with a presentation early in life and a review of the literature.

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Case report

A boy, first child of healthy unrelated parents, was born after a pregnancy that was complicated by toxemia in the 32nd week. After an induced delivery at 38 weeks (Apgar 9/10) he presented at 3 days of age with respiratory insufficiency. On admission in another hospital he was intubated and ventilated. Turgor and peripheral circulation were poor, he was hypotonic and liver and spleen were not enlarged. He showed no dysmorphic features.

Biochemically the patient presented with a severe metabolic acidosis (pH 6.88; $p\text{CO}_2$ 24 mm Hg; $p\text{O}_2$ 75 mm Hg; BE -30; HCO_3^- 4 mmol/l; O_2 sat 97%), anion gap 38 (normal range: 8–16 mmol/l), marginal hypoglycaemia (glucose 2.1 mmol/l) and ketonuria; urinary pH and bicarbonate were not measured. Blood chemistry (haemoglobin 11.3 mmol/l, haematocrit 41.7%, total protein 55 g/l, Na^+ 157; K^+ 3.1; Cl^- 118; urea 14.7 mmol/l and creatinine 69 $\mu\text{mol/l}$) indicated hypernatraemic dehydration.

He was referred to our hospital where additional laboratory investigations in blood showed normal concentrations of ammonia (50 $\mu\text{mol/l}$) and lactate (2.16 mmol/l). Initially, the patient was suspected of having distal renal tubular acidosis. Intravenous fluid and electrolyte therapy including a constant sodium bicarbonate infusion (8.4%) resulted in improvement of blood chemistry and pH (pH 7.31; $p\text{CO}_2$ 18 mm Hg; $p\text{O}_2$ 76 mm Hg; HCO_3^- 9 mmol/l; O_2 sat 87%), urinary pH 6.1; urinary HCO_3^- 7 mmol/l. After recovery and discharge he was hospitalized four times during the 1st year of life with attacks of relatively mild metabolic acidosis and ketoacidemia, due to intercurrent infections.

Extensive metabolic screening revealed only slightly elevated plasma concentrations of glutamine, glycine, valine, leucine, tyrosine, ornithine and lysine. Urinary organic acid analysis showed increased concentrations of 2-hydroxy- and 3-hydroxybutyrate, acetoacetate and lactate.

At the age of 1 year, because of persistent ketonuria between attacks also in the fed state, a fasting test was performed. During fasting he showed a metabolic acidosis with a normal blood glucose (3.5 mmol/l) and increased KB concentration (4.1 mmol/l) resulting in a low ratio of free fatty acids (FFA) vs KB (FFA/KB ratio: 0.13) after 13 h. After 17 h of fasting blood glucose was normal (3.4 mmol/l), KB increased (6.6 mmol/l) and the ratio FFA/KB low (0.24). Carnitine concentrations in blood were decreased (free 8.2 $\mu\text{mol/ml}$ and total 15.0 $\mu\text{mol/ml}$). These results are in agreement with a defect in ketolysis [1].

The enzyme activity of both acetoacetyl-CoA thiolase and succinyl-CoA:acetoacetate transferase in cultured fibroblasts, showed a deficient activity of succinyl-CoA:acetoacetate transferase.

Treatment was started with sodium bicarbonate (16.3 mmol/kg/day). The protein intake of the diet was 1.5 g/kg/day, which was moderate in view of the age of the patient. At his present age of 9 years psychomotor and physical development are within normal limits. His treatment consists of sodium bicarbonate (1.3 mmol/kg/day) and a moderate protein-restricted diet (1.5 g/kg/day).

Methods

Plasma lactate, glucose, ammonia, pyruvate, 3-OH butyrate and acetoacetate were determined by standard enzymatic methods. Analysis of organic acids in urine, as their trimethylsilyl derivatives, was done by gas chromatography and gas chromatography-mass spectrometry.

Skin fibroblasts from the patient were cultured and harvested cells were frozen at -80°C for subsequent assay of the ketolytic enzymes.

Succinyl-CoA:acetoacetate transferase activity was determined as acetoacetyl-CoA removal (acetoacetyl-CoA 40 $\mu\text{mol/l}$) [3]. Acetoacetyl-CoA thiolase was assayed in the presence and absence of K^+ (KCl 50 mmol/l) [13].

Results

Table 1 shows normal values for acetoacetyl-CoA thiolase activity but a deficient activity of succinyl-CoA:acetoacetate transferase amounting to 15% of mean control levels.

In Table 2 the clinical and biochemical findings of ten patients with an established succinyl-CoA:acetoacetate transferase deficiency are summarized.

Discussion

This defect of ketolysis apparently presents early in life: eight out of the ten known patients presented in the 1st year of life (Table 2). Although, an apparent life-threatening event was not mentioned, two patients and four siblings of index patients have died (Table 2).

Tildon and Cornblath [12] described a patient with a neonatal onset form of succinyl-CoA:acetoacetate transferase deficiency who died at the age of 6.5 months. This patient suffered from several episodes of severe ketoacidosis especially during acute infections. No measurable residual succinyl-CoA:acetoacetate transferase enzyme activity could be demonstrated in cultured skin fibroblasts from the patient. The first patient with a neonatal onset presenting a rather uncomplicated clinical course has been described by Pérez-Cerdá et al. [5]. This patient (age 4 years) showed a normal psychomotor and physical development and an uncomplicated clinical course, except for some episodes of minor ketosis, vomiting and tachypnoea related to infections. The

Table 1 Enzyme activities^a in fibroblasts from the patient

	Succinyl-CoA:acetoacetate transferase	Acetoacetyl-CoA thiolase			
		-K ⁺	+K ⁺	ratio $\pm$ K ⁺	3-ketohexadecanoyl-CoA thiolase
Patient	2.0	8.30	14.7	1.77	23.4
Control ^b	13.5 $\pm$ 3.4 (n = 11)	6.32 $\pm$ 2.48 (n = 38)	13.33 $\pm$ 4.73 (n = 38)	2.20 $\pm$ 0.64 (n = 38)	23.6 $\pm$ 5.3 (n = 14)

^a Activities are expressed in nmoles $\cdot$ min⁻¹ $\cdot$ mg⁻¹ protein, mean of duplicates

^b Mean $\pm$ SD

Table 2 Clinical findings and biochemical features in ten patients with Succinyl-CoA:acetoacetate transferase deficiency

Number of case analysed	10	
Males/females	7/3	
Parameter studied/investigated	Incidence	(%)
Clinical findings:		
Consanguinity of the parents:	3/10	(30)
Age of first presentation:		
0–6 months	5/10	(50)
7–12 months	3/10	(40)
13–18 months	0	(0)
19–24 months	1/10	(10)
> 25 months	0	(0)
Siblings of described index patients:		
– alive	6/10	(60)
– dead	4/10	(40)
Apparent life-threatening event	0	(0)
Presenting symptoms:		
– tachypnoea	6/10	(60)
– hypotonia	3/10	(30)
– coma	4/10	(40)
– cardiomegaly	2/10	(20)
Clinical status between attacks:		
– no specific abnormalities	8/10	(80)
– permanent ketonuria/aemia	8/10	(80)
Present status:		
– alive	8/10	(80)
– dead	2/10	(20)
Treatment:		
– oral bicarbonate	3/10	(30)
– relative low protein diet	6/10	(60)
Normal psychomotor development	10/10	(100)
Biochemical features:		
Metabolic acidosis	10/10	(100)
Blood glucose:		
– high	1/9	(11)
– normal	8/9	(89)
– low	0/9	(0)
Blood lactate:		
– normal	8/8	(100)
Blood ammonia:		
– normal	7/7	(100)
Free carnitine:		
– low	1/1	(100)
ratio 3-OH butyrate/acetoacetate		
– normal	1/6	(17)
– abnormal	5/6	(83)
ratio FFA/KB		
– abnormal	3/3	(100)

residual succinyl-CoA:acetoacetate transferase enzyme activity which could be demonstrated in cultured skin fibroblasts from the patient was 23% of control value.

Our patient also presented early in life. After instalment of the appropriate treatment he showed a normal psychomotor and physical development without episodes of severe ketoacidosis up to his present age of 9 years. His clinical picture was rather mild as compared to the two patients described by Spence et al. [11] and Tildon and Cornblath [12], respectively. This difference may be related to the fact that the residual enzyme activity of succinyl-CoA:acetoacetate transferase is 15% and not so severely deficient as in the other patients mentioned above [11, 12]. Furthermore, our therapeutic measures apparently were of benefit for our patient. The moderately protein-restricted diet might prevent stimulation of ketogenesis via the isoleucine or leucine pathway. Follow up of this patient during the coming years

will give insight into whether or not this treatment must be kept life-long.

The marginal hypoglycaemia together with a severe ketoacidosis in our patient was misleading at first presentation. At present we think these symptoms are very suggestive for a defect of ketolysis.

Our patient showed all the clinical and biochemical symptoms at first presentation including tachypnoea, coma and metabolic acidosis (Table 2). However, based on the blood and urinary pH values the initial clinical diagnosis was distal renal tubular acidosis. Extended investigations at age 1 year pointed towards a defect of ketolysis, in which ketonaemia/uria and normal blood lactate concentrations were found.

Most of the patients show a permanent ketonuria/aemia between metabolic crises. Blood glucose, lactate and ammonia are in almost all cases normal. Carnitine status of these patients was not mentioned (Table 2). We

found decreased blood concentrations of free (8.2 $\mu\text{mol/ml}$) and total (15.0 $\mu\text{mol/ml}$) carnitine. Carnitine therapy was not started because of the suspected enhancement of ketogenesis leading towards further deterioration of the patient.

The prevalence of defects of ketolysis is still not known. One can speculate that especially patients with mild defects are probably underdiagnosed. Therefore, we would suggest that whenever severe ketoacidosis is present in combination with blood glucose varying between slightly below to slightly above normal, low or normal lactate and ammonia concentrations in blood, a defect in ketolysis has to be taken into account and the respective enzymes of ketolysis measured.

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