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Case report

Valproic acid triggers acute rhabdomyolysis in a patient with carnitine palmitoyltransferase type II deficiency

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Abstract

A 47-year-old man suffering from a bipolar disorder and intermittent myoglobinuria presented with acute rhabdomyolysis with renal failure after starting therapy with valproic acid. On morphological examination, skeletal muscle revealed increased lipid storage. Biochemically, decreased enzyme activity of carnitine palmitoyltransferase (CPT) type II with carnitine levels in the lower limit was found. Genetic analysis detected the common Ser113Leu substitution on one allele of the CPT2 gene. We conclude that valproic acid should be avoided in patients with CPT type II deficiency. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Carnitine; Carnitine palmitoyltransferase deficiency; Rhabdomyolysis; Valproic acid

1. Introduction

Valproic acid is a branched-chain fatty acid and is normally used as an antiepileptic drug with an expanding spectrum of medical indications. It is also applied in the therapy of bipolar disorders and migraine prophylaxis. In addition to the well-known benign side effects, valproic acid can cause toxic hepatitis, pancreatitis, hyperammonemia and a hepatocerebral syndrome similar to Reye's Syndrome. It has been proposed that valproic acid should be avoided in patients with mitochondrial diseases and with defective fatty acid oxidation as it may induce mitochondrial oxidative impairment by depletion of cytochrome aa3, inhibition of fatty acid oxidation and trapping of mitochondrial CoA [1–4].

Long-chain fatty acids constitute the major source of energy production in humans during prolonged fasting or exercise. In order to be metabolized in mitochondria, long-chain acyl CoA esters must cross the inner mitochondrial membrane by means of carnitine palmitoyltransferase (CPT) type I and II. CPT type II catalyzes the reesterification of acylcarnitines to form acyl-CoA esters within the inner mitochondrial membrane [5]. Classical CPT type II deficiency, which affects mostly young adults, is characterized by episodic rhabdomyolysis with paroxysmal myoglobinuria [6]. We here report for the first time the occurrence of acute rhabdomyolysis triggered by valproic acid in a patient with CPT type II deficiency.

2. Case report

On admission, a 47-year-old man presented with acute rhabdomyolysis and renal failure. He had a history of myoglobinuria with episodes of dark urine, muscle pain and stiffness after physical work starting at age 18. On laboratory testing, myoglobinuria was diagnosed at age 23. Two years later he developed a bipolar disorder and was treated with lithium until age 40. The depressive symptoms recurred after a symptom-free interval of 7 years and medication with valproic acid was initiated in a dose of 100 mg three times a day. In the following days he experienced increasing weakness, vomiting, myalgias, cough and apathy. On the fourth day after starting medication with valproic acid, he had brown-coloured urine and fever up

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to 39°C; the medication was stopped. No focal neurological deficit could be detected, but there was generalized muscle tenderness. White blood cell count was 9.5×10^9/l. Creatine kinase was 49200 U/l (normal <80), serum creatinine was 5.7 mg/dl (normal <1.2), BUN was 138 mg/dl (normal <80), potassium was 5.5 mmol/dl and serum myoglobine was elevated to 36490 μg/ml (normal <90). Chest X-ray showed no infiltrates. The patient received extracorporal hemodialysis for 13 days and was treated with dopamine and forced solute-alkaline diuresis without substitution of carnitine. His condition stabilized over the next 2 weeks. Two weeks prior to the acute episode, the patient caught a mild cold with no residual complaints. No other influencing factors like physical efforts, fasting or emotional stress were apparent in the days preceding the acute attack. The patient was reexamined 2 months later. He reported no further episodes. Neurological examination was normal. At that time, needle EMG revealed no myopathic changes of the quadriceps femoris muscle except a borderline myopathic result in the interference pattern analysis.

A muscle biopsy was taken 2 weeks after the acute episode. Routine stains showed a fairly normal architectural pattern with normal enzymatic stains but increased lipid droplets were apparent adjacent to mitochondria, possibly as a consequence of the impaired metabolism by valproic acid. Total carnitine in skeletal muscle was in the lower limit of the normal range (23.9 μmol/g; normal 21.0–43.1), with low-normal free carnitine (19.9 μmol/g; normal 19.5–35.1) and a normal concentration of short-chain acylcarnitine (4.0 μmol/g; normal 0.5–13.4). CPT type II activity was severely decreased (1.6 U/g; normal 6.7–17.4). Additional genetic testing revealed the common C439T mutation (Ser113Leu substitution) on one allele of the CPT2 gene [7]. Determination of acylcarnitines by tandem mass spectrometry revealed a characteristic pattern with elevation of C16- and C18:1-long chain acylcarnitines [8].

3. Discussion

Carnitine palmitoyltransferase deficiency type II and more rarely the long-chain and short-chain acyl-CoA dehydrogenase deficiencies are associated with intermittent rhabdomyolysis in mitochondrial fatty acid disorders of the adult-onset type. In the present case, the clinical history was typical of a CPT type II deficiency in line with the common mutation (Ser113Leu) frequently detected in adult CPT type II-deficient patients. The disease manifests most often after fasting, physical exertion or infection (for overview see Roe [6]). In the present case, an infection-mediated exacerbation of the disease can almost be ruled out, since the patient had only a mild cold 2 weeks prior to his acute episode, with a symptom-free interval. No other influencing factors like physical exertion, fasting or emotional stress were apparent in the days preceding the acute attack. In contrast, valproic acid medication was started 5 days prior to the deterioration, indicating the closest temporal coincidence of possible factors leading to the disease.

Valproic acid tends to decrease the plasma carnitine levels and the level of muscle carnitine [9]. Carnitine concentrations in skeletal muscle, usually within the normal range in patients with CPT type II deficiency, were within the lower limits of the normal range in our patient. Clinical and biochemical data suggest that tissue carnitine levels have to exceed critical threshold values by 10–20% of normal to become clinically evident [10]. Therefore the deterioration in this patient can not be explained by carnitine depletion. A direct influence of valproic acid on CPT type II activity has also to be considered, however, experiments on isolated rat liver mitochondria fractions of valproic acid-treated rats revealed a clear increase of enzyme activity [11]. In our patient, the CPT type II activity was 24% of normal. As discussed by Demaugre [12], residual enzyme activities of CPT type II of 25% become rate-limiting for metabolisation of long-chain fatty acids in skeletal muscle. An important physiopathological factor might be the inhibition of β-oxidation by valproic acid and its metabolite 2-n-propyl-4-pentenoic acid. This inhibition has been shown in rat liver and could also lead to decreased function of β-oxidation in muscle tissue [13]. CPT type II has been shown to be involved in the export of toxic metabolites out of the mitochondrial matrix, so that a decreased enzyme activity could lead to an accumulation of these products [14].

We conclude that valproic acid can cause acute rhabdomyolysis in patients with CPT type II deficiency by severe impairment of fatty acid β-oxidation. Symptoms like episodes of brown urine should be taken into consideration prior to starting valproic acid treatment in both adult and pediatric patients. In these cases systemic evaluation of free carnitine and acylcarnitines in serum by tandem mass spectrometry may be also helpful to detect a CPT type II deficiency prior to starting valproic acid treatment [8].

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