

Case reports

Recurrent post-infectious rhabdomyolysis in muscle CPT-II deficiency caused by a novel missense mutation

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Abstract

A case is reported of a 39-year-old woman with recurrent rhabdomyolysis caused by minor *S. pyogenes* tonsillitis. She was diagnosed with the adult form of CPT-II deficiency. Molecular analysis revealed compound heterozygosity for a common c.338C > T (p.Ser113Leu) mutation in exon 3 and a most likely pathogenic c.200C > G (p.Ala67Gly) variant in exon 2. Here we discuss the case, along with a clinical review of rhabdomyolysis and adult CPT-II deficiency. When a patient presents with recurrent episodes of rhabdomyolysis, especially when provoked by minor causes, a thorough work-up for a possible metabolic myopathy is mandatory.

Key words : Rhabdomyolysis ; carnitine palmitoyltransferase II deficiency.

Introduction

Rhabdomyolysis is a clinical syndrome caused by generalized muscle breakdown. The classic triad of symptoms consists of muscle weakness, pain and reddish-brown urine. Important etiologies are trauma, myotoxins or excessive exercise. Sometimes, an underlying metabolic myopathy can be identified. The most common hereditary cause of recurrent rhabdomyolysis is muscle carnitine palmitoyltransferase II (CPT-II) deficiency. CPT-II mediates the transfer of long-chain fatty acids across the inner mitochondrial membrane. Various genetic mutations have been reported and a common mutation, p.Ser113Leu, is present in approximately 60% of pathologic alleles (Bonfont *et al.*, 2004).

We report a case of a woman with recurrent rhabdomyolysis, at least once preceded by a minor *S. pyogenes* tonsillitis. She was found to have a molecular proven adult form of CPT-II deficiency. The case is discussed, along with a review of rhabdomyolysis in the context of defects of fatty acid oxidation, in particular CPT-II deficiency.

Case history

CLINICAL AND BIOCHEMICAL FINDINGS

A 39-year-old Norwegian woman presents to the emergency department because of generalized muscle weakness. About three days before admission she developed a sore throat and a moderate flu-like illness, as did several of her family members. Upon admission, she complains of generalized muscle weakness that started the same morning and made it impossible to walk without help. Both arms felt heavy and tired. She noticed an uncomfortable dull pain in her lower back and over the chest as well as pain in the proximal muscle groups upon moving arms or legs. There were no other symptoms, in particular no sensory disturbances, no abdominal or urinary symptoms, no cough or dyspnoea.

The patient's medical history includes hip dysplasia at birth, which was operated on at 18 years of age. She had a similar episode of muscle weakness preceded by tonsillitis seven years before which had resulted in a hospitalisation for a couple of weeks. According to her, no precise diagnosis was found at that time.

On further inquiry, she describes recurrent weakness after prolonged exercise, mainly during childhood. She remembers how she had to be carried home by her parents after an afternoon of cross-country skiing. These problems were always attributed to the hip dysplasia.

There is no history of drug or alcohol abuse, the patient doesn't smoke, takes no prescribed medications and cannot remember recent insect bites. She works for a publishing company and sometimes travels within Europe. She goes to fitness regularly. There is no relevant family history.

On physical examination her temperature was 38,1°C but other vital signs were normal. Heart and lung auscultation were normal, as was abdominal examination. Inspection of the skin did not reveal

abnormalities. The pharynx was red, with swollen white tonsils.

On neurologic examination, there was a marked symmetric weakness of both arms and legs, with inability to raise the legs (MRC scale 2/5) and difficulty abducting the shoulders (3/5). Strength more distally in knees, feet and hands was relatively spared, although still weaker than normal (4 to 4+/5). Palpation of muscles was not painful. There were no sensory disturbances. Deep tendon reflexes were intact, with bilateral plantar flexor responses.

The hematological and biochemical laboratory values throughout the course of the hospital stay are shown in table 1. We noticed a raised white-cell count with a relative increase of the neutrophil population and CRP up to 14,72 mg/dl suggesting bacterial infection. Most striking however was the marked increase of creatin kinase (CK) to 8336 U/liter, which together with the elevated levels of aspartate aminotransferase and lactate dehydrogenase, but normal liver function tests and troponin-I, points to major breakdown of striated muscle or rhabdomyolysis.

A chest radiograph and an electrocardiogram did not reveal any abnormality. Specimens of blood and urine were collected for culture but remained negative, as did extensive viral serologic examination and screening for *Borrelia* and Syphilis. Swab culture of the tonsils revealed *Streptococcus pyogenes* (Group A beta-hemolytic).

Vigorous intravenous hydration was started and we prescribed antibiotic therapy (amoxicillin-clavulanate) to treat the throat infection.

Over the following days there was an increase in CK, which peaked one day after admission (table 1) and afterwards decreased progressively. There were minor disturbances in electrolyte concentrations: initially for example relatively high potassium, but low calcium or phosphate levels, and later an increase in urea caused by the degradation of proteins. No renal failure developed. Urinalysis three days after admission revealed a normal myoglobin level (532 µg/l).

Electrophysiologic examination at day 3 showed normal nerve conduction studies and myography.

SPECIAL STUDIES

The repeated episodes, all of them provoked by relatively minor causes prompted us to investigate genetic and metabolic disorders after informed consent.

An open quadriceps muscle biopsy was performed at day 6. The muscle biopsy specimen was processed for light microscopy and enzyme histochemistry according to established techniques (Engel, 2004). Type II muscle fiber atrophy and increased fat droplets in type I and to a lesser extent in type II muscle fibers was found. Muscle

biochemistry showed a CPT content of 1,48 nmole/min/g (normal: 11,3 ± 4,3) and a carnitine level of 3,44 µmole/g (normal: 3,22 ± 0,85). Respiratory chain enzyme activities determined by spectrophotometry on muscle homogenate were normal.

DNA was isolated from peripheral lymphocytes using Chemagic blood10K kit on Chemagic magnetic separation module (Chemagen). Molecular analysis of the CPT-II gene was performed by PCR amplification and direct sequencing of all coding exons. Primer sequences for PCR amplification are available on request. Sequence analysis was performed on an ABI3130xl Genomic analyzer.

Molecular analysis of all CPT-II coding exons revealed the presence of a common c.338C > T (p.Ser113Leu) mutation in exon 3 of the CPT-II gene and a c.200C > G (p.Ala67Gly) variant in exon 2, each on a different allele. The second mutation has not been described before.

Discussion

Rhabdomyolysis is a pathological syndrome that results from acute necrosis of striated muscle fibers. The clinical presentation can be quite heterogeneous. More than half of the patients do not mention classical symptoms such as pain or weakness and the urine discoloration often is not noticed. Many patients complain of general symptoms such as malaise, fever, tachycardia, nausea and vomiting or present with severe acute renal failure and hypovolemic shock (Sauret *et al.*, 2002; Huerta-Alardin *et al.*, 2005). Therefore, alertness to the clinical syndrome is essential for prompt diagnosis.

Diagnosis can be made by detecting various muscular constituents that leak into the circulation, the most relevant are the muscular form of CK, myoglobin and various electrolytes (Giannoglou *et al.*, 2007). It is myoglobin with its heme moiety that causes the dark discoloration of urine. Detection of myoglobin in plasma or urine is pathognomonic for the syndrome, but as it gets readily cleared by the kidneys during the first 12 to 24 hours, it is often missed, as was the case in our patient. CK on the other hand peaks in the plasma during the first 24 to 36 hours and only returns to baseline levels 3 to 5 days after cessation of the injury. Therefore, elevation of CK, in the absence of cardiac muscle injury, is considered the most reliable marker for detecting rhabdomyolysis and for following the degree of muscle damage (Allison and Bedsole, 2003; Giannoglou *et al.*, 2007).

The most feared and common complication of rhabdomyolysis is acute renal failure (ARF). It occurs in 15 to 46% of patients (Melli *et al.*, 2005) and might account for 10 to 15% of all ARF-cases (Zager, 1996), although frequency reports vary probably depending on the underlying cause and the way patients are selected. The exact mechanisms of

Table 1
Laboratory values

	<i>normal values</i>	Day 0	Day 1	Day 2	Day 3	Day 4	Day 8
<i>Hematology results</i>							
Sedimentation 1 hour (mm)	2-20		57		51	33	
Hemoglobin (g/dl)	11,0-14,4	14,4	13,9	12,9	11,4	11,7	
Erythrocytes (milj/mm ³)	3,65-4,59	4,82	4,66	4,34	3,9	4,01	
White-cell count (/mm ³)	3,5-9,8	12 200	16 100	14 700	13 700	13 100	
<i>Biochemical results</i>							
C-reactive protein (mg/dl)	0,00-1,00	6,86		14,6	6,21	2,21	
Ureum (mg/dl)	15-36	21	16	17	28	34	
Creatinine (mg/dl)	0,70-1,20	0,61	0,56	0,49	0,6	0,69	
Uric acid (mg/dl)	2,50-7,00	3,37		2,15	2,27		
Sodium (mmol/l)	135-145	132	135	135	135	136	
Potassium (mmol/l)	3,60-5,00	4,69	4,22	4,24	4,51	3,77	
Chloride (mmol/l)	101-111	94	96	96	98	94	
Bicarbonaat (mmol/l)	22,0-30,0	28,3		29,1		34,8	
Calcium (mg/dl)	8,40-10,20	8,73				8,81	
Phosphate (mg/dl)	2,50-4,50	3,57				2,31	
Aspartate aminotransferase (U/l)	14-36	151		877		196	
Alanine aminotransferase (U/l)	9-52	60		417		396	
Gamma GT (U/l)	12-43	11		11		20	
Alkaline phosphatase (U/l)	38-126	77		70		69	
Lactate dehydrogenase (U/l)	313-618	698		3485		3874	
Creatin kinase (U/l)	30-135	8336	38364	26663	9042	2181	227
Creatin kinase-MB (U/l)	0,0-4,6	170	381	159	58	17,4	2,9
Troponin I	< 0,012	< 0,012		< 0,012	< 0,012	< 0,012	

ARF in rhabdomyolysis are not completely understood. It is generally accepted that tubular myoglobin precipitation and cast formation is an important contributing factor (Zager, 1996 ; Van Holder *et al.*, 2000).

Other complications are mostly related to the various electrolyte disturbances seen after muscle injury (Sauret *et al.*, 2002). These include hyperkalemia, hypo- and later hypercalcemia and metabolic acidosis, eventually causing cardiac arrhythmia and further impairing renal function. Hepatic dysfunction may result from inflammation induced by proteases released from damaged muscle (Akmal and Massry, 1990). A dangerous complication is the compartment syndrome caused by swelling and inflammation of muscles within a tight fascia. This might lead to further muscle injury and provoke irreversible paralytic damage to peripheral nerves (Van Holder *et al.*, 2000).

The danger of rhabdomyolysis lies not necessarily in the muscle injury that usually leads to reversible disability, but rather in the large amounts of toxic substances released in the circulation. In order to prevent most complications, prompt treatment with adequate intravenous volume expansion

is mandatory. Guidelines vary, but five or even up to ten liters of 0,45% or 0,9% saline per day should be administered. To avoid metabolic acidosis, half of the salt can be administered as sodium bicarbonate (Van Holder *et al.*, 2000 ; Sauret *et al.*, 2002). The use of mannitol as an osmotic agent and free radical scavenger is controversial (Sauret *et al.*, 2002 ; Huerta-Alardín *et al.*, 2005). Close cardiac and laboratory monitoring of the patient is necessary and if renal failure does develop, extracorporeal hemodialysis should immediately be started.

RECURRENT RHABDOMYOLYSIS – IN PURSUIT OF AN UNDERLYING CAUSE

The etiologies of rhabdomyolysis are numerous and can be subdivided into traumatic, exercise-induced, toxic, environmental, metabolic, infectious, immunologic and inherited causes. The most important causes are myotoxins (prescribed or illicit drugs), trauma or crush injury, prolonged immobility with compression of muscle groups and excessive muscle activity such as in marathon-running or epilepsy (reviewed in Allison and Bedsole, 2003 ; Huerta-Alardín *et al.* 2005).

The various etiologies of rhabdomyolysis all result either in rupture of the muscle fiber membrane or in depletion of energy within the muscle cell. Both cause an increase of the intracellular calcium concentration which, through a final common pathogenic pathway, ultimately leads to apoptosis and necrosis (reviewed in Giannoglou *et al.*, 2007).

Of note, in about 60% of cases multiple concomitant etiologic factors are required for rhabdomyolysis to develop (Melli *et al.*, 2005). However, when the cause is single, obscure or minor, when recurrent episodes of rhabdomyolysis are reported, or when multiple systems are involved, an underlying myopathy should be considered (Löfberg *et al.*, 1998 ; Melli *et al.*, 2005).

Our patient presented because of a minor throat infection and described a similar episode several years ago. The medical records of that time indeed describe rhabdomyolysis, preceded by a throat infection with white swollen tonsils, but no causative agent could be identified then. Also, during childhood she had several similar episodes. Swab culture of the tonsils now revealed *S. pyogenes* and we suppose this provoked the rhabdomyolysis. Infection indeed is an important etiologic factor, but only sporadic cases of Group A Streptococci provoking rhabdomyolysis are described, mostly in the course of a toxic shock syndrome (Yuen *et al.*, 1999 ; Bagnulo and Rodríguez, 2001). One similar case of rhabdomyolysis from streptococcal pharyngitis was described in a child (Huyn *et al.*, 2007). The absence of a toxic shock syndrome makes direct invasion of muscle by bacteria or bacterial toxins less likely. Therefore, we believe the fever-mediated increase in muscle metabolic activity, probably together with the effect of circulating cytokines were, although minor, direct causative factors for developing rhabdomyolysis in these patients (Allison and Bedsole, 2003 ; Giannoglou *et al.*, 2007).

The major hereditary disorders predisposing to rhabdomyolysis are listed in table 2, except for the many mitochondrial myopathies that often present with a distinct, multisystemic picture (Löfberg *et*

al., 1998 ; Darras and Friedman, 2000b ; Sauret *et al.*, 2002). All of them are relatively rare genetic diseases and mainly involve deficiencies of enzymes directly or indirectly participating in the catabolism of various energy molecules (e.g. glycogen, fatty acids or purines). Some clinical and laboratory findings may already point to a particular type of deficiency, although further investigations are needed for a definitive diagnosis to be made. These include electromyography, a forearm ischemic exercise test and nuclear magnetic resonance spectroscopy. When carefully performed, muscle biopsy also might help to further differentiate between different types of metabolic defects and in fact is mandatory to exclude inflammatory myopathies or muscular dystrophies (Löfberg *et al.*, 1998 ; Darras and Friedman, 2000a ; Melli *et al.*, 2005). These results together eventually guide advanced metabolic and genetic testing for particular enzyme defects. However, in only a quarter of children and half of the adults with recurrent rhabdomyolysis, a specific biochemical abnormality will be identified (Löfberg *et al.*, 1998 ; Darras and Friedman, 2000a).

CARNITINE PALMITOYLTRANSFERASE-II DEFICIENCY

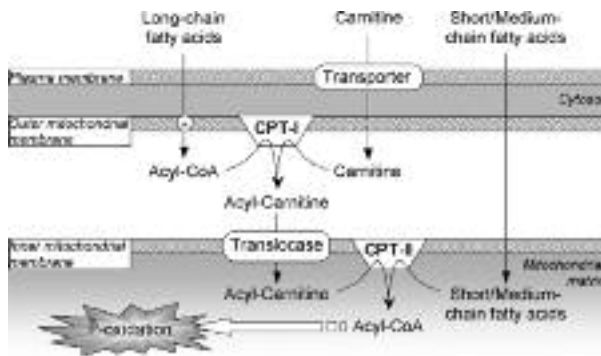
Carnitine palmitoyltransferase (CPT) deficiencies are among the most common disorders of mitochondrial fatty acid oxidation and are an important cause of inherited recurrent rhabdomyolysis (Löfberg *et al.*, 1998 ; Deschauer *et al.*, 2005). The CPT-system consists of two distinct enzymes, CPT-I and CPT-II, located in the outer and inner mitochondrial membranes respectively (Fig. 1) (Bonfont *et al.*, 2004).

CPT-I exists in different isoforms across different tissues, but to date only deficiencies affecting the liver have been described (Bonfont *et al.*, 2004). CPT-II in contrast, exists only in one isoform across various tissues. The CPT-II gene is mapped to chromosome 1p32 and consists of 5 exons coding for a 658 amino acid protein. More than 40 different mutations have been reported until now ; two of

Table 2

Main genetic causes of rhabdomyolysis

<i>Glycogen metabolism</i>	
	Myophosphorylase deficiency (McArdle's disease)
	Phosphorylase kinase deficiency
	Phosphofructokinase deficiency (Tarui's disease)
	Phosphoglycerate mutase deficiency
	Lactate dehydrogenase deficiency
<i>Fatty acid metabolism</i>	
	Carnitine palmitoyl transferase I and II deficiency
	Carnitine deficiency
	Short-, medium- and (very) long-chain acyl-coenzyme A dehydrogenase deficiency
<i>Various</i>	
	Myoadenylate deaminase deficiency
	Muscular dystrophies



Short- and medium-chain fatty acids can cross the mitochondrial membrane by passive diffusion. Long-chain fatty acids first are activated to their CoA-esters by CoA synthetase (*), then cross the outer mitochondrial membrane and are linked to carnitine by carnitine palmitoyltransferase 1 (CPT-I). This acyl-carnitine form is transferred to the mitochondrial matrix by a translocase in the inner mitochondrial membrane. All fatty acids are activated to CoA-esters by CPT-II and eventually undergo β -oxidation, ultimately resulting in ATP.

FIG. 1. — Transport of fatty acids across the mitochondrial membrane.

them, c.338C > T and c.149C > A, with an allele frequency of 60% and 6,5% respectively, are regarded as common mutations (Taroni et al, 1993 ; Thuillier et al, 2003 ; Bonnefont *et al.*, 2004).

Next to this common c.338C > T mutation in exon 3, molecular analysis of the CPT-II gene of our patient detected a new c.200C > G (p.Ala67Gly) variant in exon 2. This substitution has not been described before and was not detected in our control population (> 100 chromosomes). The alanine residue on position 67 of the CPT-II gene is highly conserved between several species (human-mouse-drosophila) and theoretical predictions (SIFT, Polyphen) also predict this variant to be pathogenic.

According to age and presentation, three different phenotypes of CPT-II deficiency are distinguished (Bonnefont *et al.*, 2004), which to a certain extent are correlated to particular genetic mutations (Deschauer *et al.*, 2005 ; Corti *et al.*, 2008). There is a lethal neonatal form and a lethal infantile form. A third and most common form starts in childhood or adulthood. This group of patients presents with recurrent rhabdomyolysis. Between the attacks, persistent muscle weakness is uncommon and CK levels return to normal, as opposed to for example McArdle's disease, the second most common metabolic myopathy (Deschauer *et al.*, 2007). A similar division in three groups, based on presentation and genotype, was proposed for defects of very long chain acyl-CoA dehydrogenase (VLCAD), the enzyme involved in the initial rate-limiting step of fatty acid β -oxidation. The adult form of this condition presents with an indistinguishable clinical picture from adult CPT-II deficiency (Andresen *et al.*, 1999).

Forearm ischemic testing depicts a normal lactate response and electromyographic studies are normal or show mild myogenic signs. Muscle biopsy shows a normal glycogen content and no, or only a slight lipid excess in type 1 fibers (Darras and Friedman, 2000b ; Corti *et al.*, 2008).

It was suggested that a high-carbohydrate, low-fat and low-protein diet, with frequent meals can prevent episodes of rhabdomyolysis and increase exercise tolerance. Prolonged aerobic exercise, fasting and cold-exposure should be avoided (Darras and Friedman, 2000b ; Orngreen *et al.*, 2003). However, in contrast to what is generally believed, pre-exercise oral glucose loading might not improve exercise tolerance (Orngreen *et al.*, 2002).

Conclusion

We present a case of a 39-year-old woman presenting with recurrent episodes of rhabdomyolysis. At least two of the episodes were provoked by minor tonsillitis. One of these was caused by Group A - hemolytic streptococci, without the development of a toxic shock syndrome, in contrast to most reported cases. A CPT-II enzyme deficiency was found. Next to a common mutation on one allele, we identified a novel c. 200C > G (p.Ala67Gly) variant on the other allele, which is most likely pathogenic.

It is important to stay alert for the clinical syndrome of rhabdomyolysis and react appropriately in order to prevent serious complications such as renal failure or death. When patients repeatedly present with muscle breakdown, certainly when triggered by minor causes, a thorough work-up for a possible underlying metabolic myopathy should be started. In some cases, this might result in an adequate treatment but it especially will help the patient and his or her environment to put the symptoms in a context and accept the minor or major consequences for everyday life.

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