

Emotional distress induced rhabdomyolysis in an individual with carnitine palmitoyl-transferase deficiency

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ABSTRACT

A 48-year-old male patient with under-lying CPT II enzyme deficiency is described. Emotional stress appeared to precipitate recurrent myalgias, rhabdomyolysis and reversible renal impairment over a 40-year period. Our search of the English literature indicates this to be the first time that the emotional stress has been documented to precipitate the CPT II syndrome. Although the pathogenesis of this syndrome has yet to be established, existing knowledge is briefly reviewed and the likely metabolic and neuroendocrine mechanisms which link emotional stress to muscle metabolism are examined. These mechanisms influence the extent of lipolysis or glycolysis that occurs during the process of muscle ATP generation. It is suggested that neuroendocrine and other stress related changes which favour lipolysis over glycolysis adversely affect muscle energy metabolism in patients whose mitochondria are deficient in CPT II enzyme.

Possible treatment strategies are those that favour glycolysis over fatty acid metabolism and include a variety of ways of modulating sympathetic and parasympathetic tone. The use of carbohydrate supplementation, β -blockers and anxiolytic agents is discussed.

Introduction

Recurrent myalgia, cramps, rhabdomyolysis, myoglobinuria and associated acute renal impairment due to partial deficiency of carnitine palmitoyl transferase (CPT) deficiency was first reported in 1973 (1). Since then, almost 100 cases have been reported. The syndrome can be precipitated by physical activity, fasting, high fat intake, febrile illness, cold exposure and sleep deprivation (2). Less common manifestations of the syndrome, associated with more severe enzyme deficiencies, include respiratory failure (3), recurrent pancreatitis (4), status epilepticus (5), hypoketotic hypoglycaemia, arrhythmia, sudden death and chronic myopathy (6).

This report documents, for the first time (Medline 1973 - December 2000), a case of CPT deficiency syndrome

precipitated by emotional stress. Given the frequent clinical observation of emotional stress aggravating musculoskeletal pain, this report also provides insights into the possible neuroendocrine and biochemical mechanisms for such observations.

Case report

A 48 year old Australian male of Sicilian parentage was referred for further investigation of a 40-year history of recurrent attacks of severe muscle pain, tenderness, cramps, mild dyspnoea and the passage of dark urine. He claimed involvement of most muscle groups including the jaw, but excluding the ocular and other facial muscles. There was no history of dysphonia, dysphagia or sphincter dysfunction. Symptoms were usually provoked by feelings of annoyance, irritability or anger at a situation where the patient was being manipulated into an unfavourable agreement, or being coerced to perform physical activity which he perceived as threatening or where there was a significant probability of failure. Alternatively, if he enjoyed the physical activity or he agreed with the purpose behind it, he tolerated the activity without difficulties and "would not even be tired at the completion of it". Some of the examples described by the patient are as follows:

(a) Between the ages of 11-15 he was involved in boxing - some 25-30 fights of which he lost approximately 25%. During the immediate pre-bout confrontations with his opponents, he recalled development of myalgias, particularly when his opponents appeared to be bigger or otherwise more threatening. Where the opponents seemed more manageable and hence less threatening, there would be no muscle pains.

(b) He recalled playing football at school which, at times, aggravated his symptoms. When the coach would direct him to enter a field of aggressive play he generally did so, as he found it embarrassing to admit to myalgias, but afterwards his symptoms would be severe especially if he played against his unspoken wishes.

(c) Cane cutting is physically very demanding, yet he claimed the ability to match the other cane cutters' "efficien-

cy" throughout the cane cutting season. If he were challenged to a cane cutting competition by an opponent who seemed likely to beat him, the anxiety about possibly losing would provoke the muscle symptoms. If, on the other hand, his cane cutting competitor was not a threat, he would have no complications from such an event.

(d) In relation to family confrontations, he found symptoms to be provoked at times of unmanageable emotions.

(e) Walking through a difficult terrain and discovering an unexpected obstacle or complication could be a trigger for annoyance and anxiety, and subsequently he would be likely to develop disabling myalgias. Without such adverse influences the symptoms would not occur.

The muscle groups generally affected were those most in use at the time of the stressful event - usually the lower limb muscles. The initial symptoms of muscle tightness and tiredness were followed by generalised myalgias within 30-60 minutes. Rest in bed with "knees flexed and hands behind the head" was usually the most comfortable position. During such rest any movements were acutely painful with mobility gradually returning to normal within 7-14 days. Milder attacks lasted shorter periods of time. On average, the patient described 6 relapses per year and claimed to be completely normal between the attacks. During the 40-year period he had at least 15 severe relapses, each warranting hospitalisation for an average of 7-10 days. During these hospitalisations, elevated serum creatine kinase (CK) and myoglobinuria were documented. His condition had been previously attributed to McArdle's syndrome although no definite diagnostic studies were performed. There was no history of symptom aggravation by fasting, alcohol intake, sleep deprivation or febrile illness. He had one general anaesthetic at age 20 for an appendectomy without complications. Over the years he learned to curtail his interactions with threatening environmental and interpersonal situations. Otherwise he had not used any other therapies. Overall, his quality of life, were significantly disrupted by

these symptoms.

The patient was a non-smoker and consumed an average of 15 g of alcohol per day. There was no history of toxin exposure or allergies. There was no significant medical illness in his family. He was not regularly involved in heavy or prolonged physical activity, but previously worked as a cane farmer and currently as a busy property developer. His past medical history was unremarkable.

On the occasion leading up to the present admission he developed severe myalgias during a 5-10 minute verbal confrontation with a builder. There was no physical violence. His symptoms started as the builder was walking out and progressed in the usual, but more florid manner with the patient requiring admission to a local hospital (3 days after the confrontation) with myoglobinuria and rhabdomyolysis [CK level 78, 100 U/L (reference range: 30-210)], complicated by acute renal failure [serum creatinine peaked at 1.8 mmol/L (reference range: 0/06-0.12)]. Renal biopsy at the time showed evidence of chronic interstitial nephritis. Renal function rapidly normalised following rehydration. Because of the severity of this illness, he was referred to a tertiary hospital for further evaluation. The patient was asymptomatic at the time of admission.

On examination, he was of above average intelligence, 171 cm tall and weighed 85 kg. There was no evidence of muscle weakness, fasciculation or tenderness. Physical examination was otherwise unremarkable. Laboratory analysis of haematology profile (including platelet and white cell differential counts), erythrocyte sedimentation rate, biochemistry profile (including indices of renal and liver function), CK, antinuclear antibodies, thyroid function tests were all normal. In addition, electrocardiography, electromyography, echocardiography and chest x-ray were all normal. Left triceps muscle biopsy was of normal morphology under light microscopy, with normal staining for the oxidative enzymes myophosphorylase and phosphofructokinase. There was no evidence of excess glycogen or lipid storage. Biochemical

studies of muscle tissue revealed normal phosphorylase but a marked deficiency of CPT - 0.01 3 U/g (reference range: 0.13-0.31 U/g).

Discussion

Two clinically and biochemically distinct forms of CPT enzyme deficiency syndromes have been identified *viz* CPT I, predominantly "hepatic" variant and the more common CPT II, "muscular" variant (7). Such biochemical characterisation was not feasible in the case reported above, but the clinical presentation is consistent with the CPT II deficiency variant. Such patients usually present with episodic severe myalgia, muscle cramps and myoglobinuria with or without transient renal impairment (2). Although one case of chronic myopathy has been reported (6) the CPT II syndrome is usually not progressive. The diagnosis is frequently made in young adulthood, and usually after evidence of pigmenturia and/or rhabdomyolysis. Prolonged rather than strenuous exercise is a common precipitant. There is frequently a delay in making a diagnosis, with the patient's symptoms being dismissed as psychosomatic (2).

CPT II enzyme deficiency has an autosomal recessive inheritance. It involves the substitution of leucine for serine at position 113 on chromosome 1p11-p13 (8). The clinical syndrome is not usually manifest if there is more than 25% CPT II residual enzyme activity (7). Liver, leucocytes, fibroblasts and skeletal muscle are the target tissues in which CPT II deficiency has been demonstrated. However, only muscle tissue has been shown to be involved pathologically and as such, is the tissue on which the definitive test for CPT II deficiency is performed. Both sexes are equally affected with a male:female ratio of clinical disease of 5.5: 1.0 (2). Although usually considered uncommon, CPT II deficiency was found to be the most common cause of myoglobinuria in one survey of 77 patients (9). Other investigations which are usually unremarkable are electromyography and venous lactate production after ischaemic exercise. Muscle biopsy between attacks is frequently normal to

light microscopy. Lipid accumulation, acute muscle fibre necrosis and glycogen store depletion may be prominent findings in biopsies taken during clinical relapses (2). Type I muscle fibres are more commonly affected. The main alternative diagnosis is McArdle's syndrome, which is characterised by myalgia, myoglobinuria and rhabdomyolysis after episodes of strenuous muscular activity, due to myophosphorylase deficiency (10).

CPT enzymes facilitate active transport of fatty acids (FA) into mitochondria where their subsequent β -oxidation generates ATP. CPT I and CPT II are bound to the mitochondrial outer and inner membranes respectively. Palmitoyl CoA (derived from folic acid metabolism in the muscle sarcolemma and cytoplasm) is not capable of diffusing across the lipophilic mitochondrial membrane, but CPT I facilitates the formation of palmitoyl carnitine which freely crosses the membrane beyond (or internal to) which CPT II reforms palmitoyl CoA, thus making it available for β -oxidation in the mitochondrial matrix (11). Deficiency of the CPT II enzyme, especially in situations when folic acid is the principal energy substrate, would thus impair mitochondrial ATP generation. Energy crisis, especially in Type I muscle fibres, which are known to have a high oxidative metabolism, could thus explain the muscle damage. However, the exact mechanism of muscle fibre necrosis has yet to be elucidated in view of the frequent findings of vascular occlusions and histological changes consistent with localised muscle ischaemia (12).

The ATP generation in the skeletal muscle largely depends on either glucose or FA as substrates. The predominant availability of either carbohydrate or FA will inhibit the utilisation of the other (11). Thus in patients with CPT II deficiency, conditions favouring folic acid availability over carbohydrate would be expected to predispose to clinical disease. Catecholamines, cortisol, growth hormone, ACTH, glucagon, TSH and serotonin are known to mobilise FA through the activation of triglyceride lipase (11). Activities such as fasting, cold exposure, prolonged

submaximal exercise, sleep deprivation, and circulatory shock are also known to favour folic acid utilisation, while post-prandial states and "quick-burst" exercise are known to favour carbohydrate use.

Additionally, cholesterol-lowering agents such as HMG-CoA reductase inhibitors may incite rhabdomyolysis, but there is no evidence to suggest that this occurs more frequently in patients with CPT deficiency. The precise mechanism whereby HMG-CoA reductase inhibitors induce myolysis remains unclear, but current research suggests that those agents do this by inhibiting the production of ubiquinone (co-enzyme Q) (13). This mitochondrial membrane component serves as an electron carrier and plays an important role in the production of adenosine triphosphate (ATP). Thus, decreased production of co-enzyme Q by HMG-CoA reductase inhibitors may lead to reduced formation of ATP, resulting in cell death and subsequent rhabdomyolysis.

Emotional stress has been shown to produce quantitative changes in both sympathetic and corticotropin responses. A subsequent rise in FA in plasma in association with this state has been demonstrated in the laboratory (14). If the metabolic state of lipolysis is to be avoided in favour of glycolysis in patients with CPT II deficiency, the treatment strategies would need to be: (a) stress avoidance, which worked well for our patient, (b) attenuation of sympathetic responses and enhancement of parasympathetic tone through relaxation and conditioning techniques such as repetitive role playing in artificial stressful situations in preparation for real life stress. The use of physical exercise, which enhances the vagal tone and reduces sympathetic activity, has a potentially complicated effect - short bursts of intensive training (which usually utilise the available glycogen stores) would not be contraindicated, but prolonged submaximal exercise (which promotes lipolysis) may precipitate bouts of the illness. Ingestion of simple carbohydrates during predicted periods of prolonged exercise may be helpful, but may not be benefi-

cial in situations of emotional stress in which FA excess rather than carbohydrate depletion exists (11). Exercise has also been shown to increase the activity of mitochondrial enzymes and potentially this could improve the level of CPT activity (14), (c) use of β -blockers to reduce sympathetic activity is theoretically beneficial, but in a study of animals undergoing stress, metoprolol failed to inhibit corticosterone release mediated by the hypothalamic pituitary-adrenal response despite there being evidence of a reduction in catecholamine drive (14); levels of FA were not, however directly assessed in this study, (d) anxiolytic drugs potentially have a role, although their effect on FA has not been studied and the sedative effect on the quality of life would need to be considered (15).

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