Myoglobinuria: the importance of reaching a firm diagnosis – a patient with defective fatty acid oxidation

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Summary: A 52 year old man presented with myoglobinuria-induced acute renal failure requiring dialysis. Despite renal biopsy, the cause of the myoglobinuria was not established until he re-presented a year later with a milder episode. At this stage investigations, including a muscle biopsy, demonstrated a defect in fatty acid oxidation amenable to dietary and lifestyle advice. This report emphasizes the importance of reaching a definitive diagnosis in myoglobinuria.

Introduction

We report a patient with a rare muscle disorder (defective fatty acid oxidation) who presented with two episodes of myoglobinuria-induced acute renal failure before the correct diagnosis was made. This condition requires dietary treatment and this report highlights the importance of making an accurate diagnosis in such a patient.

Case report

A previously well 52 year old engineer presented following a 10-day history of myalgia, vomiting and ‘chocolate-coloured’ urine. Examination was normal. Mid-stream urine revealed no casts, infection or visible myoglobin, renal ultrasound was normal, urea 52 mmol/l (3.0–6.5 mmol/l), creatinine 1224 µmol/l (60–125 µmol/l), aspartate transaminase > 450 IU/l (5–42 IU/l), potassium 5.5 mmol/l (3.5–5.0 mmol/l). Two days later the aspartate transaminase had fallen to 103 IU/l when the creatine kinase was 4880 IU/l (25–195 IU/l), suggesting a higher peak value of creatine kinase before admission. Peritoneal dialysis followed by haemodialysis was required before the acute renal failure resolved. Renal biopsy showed marked tubular damage and a moderate interstitial infiltrate, with immuno-peroxidase evidence of tubules containing red-brown material, compatible with myoglobin.

The patient remained well and the following year he obtained a postman’s job in his rural area, which involved 5 miles of walking and cycling daily. After 2 days, he was re-admitted with leg muscle cramps and red-brown urine. Investigations revealed visible myoglobinuria (laboratory confirmed), urea 8.8 mmol/l, creatinine 138 µmol/l, potassium 3.8 mmol/l, aspartate transaminase > 300 IU/l, creatine kinase > 36 000 IU/l. With bed rest, the symptoms and biochemistry returned to normal.

Further history at this stage indicated several episodes during his life of exercise-induced severe muscle cramps, including one as a young army recruit when he had to drop out of an exercise march. Having excluded other commoner causes of myoglobinuria (see discussion), a muscle enzyme defect was suspected. An ischaemic forearm test showed a normal rise of lactate after anaerobic exercise – lactate levels: pre-test 1.3 mmol/l (0.6–2.4 mmol/l), immediately post-test 8.0 mmol/l, 20 minutes post-test 2.0 mmol/l – and a provisional diagnosis of a defect in fatty acid oxidation was made. Muscle biopsy was performed 6 months later (when the muscle would have regained its normal histology) and confirmed this diagnosis.

Methods and results

Mitochondria isolated from a quadriceps muscle tissue obtained by needle biopsy demonstrated a decreased oxidation of palmitoyl carnitine, 0.02 µmol min⁻¹·g tissue⁻¹ (normal 0.73 ± 0.17 s.e.m., n = 9). Oxidation of pyruvate and the activity of succinate cytochrome reductase and cytochrome oxidase were all normal in the same biopsy.

The accumulation in the muscle of short chain fatty acid carnitine esters 15.3 µmol, g protein⁻¹ (normal 0.8–4.0) and of long chain fatty and

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carnitine esters 1.17 μmol g protein−1 (normal 0.1–0.7) is consistent with the restricted metabolism of these fatty acid intermediates. This could arise from a deficiency of carnitine palmitoyl transferase (CPT) or in β-oxidation (see below). Organic acid investigations on both urine and plasma were normal without any abnormal dicarboxylic acids.

He was advised to have a low fat diet and to follow a more sedentary life-style, both treatments reported to prevent further rhabdomyolysis in this condition,2 and he remains well a year later.

Discussion

Rhabdomyolysis is the syndrome resulting from skeletal muscle injury, with the release of muscle cell contents into plasma. These include enzymes of which creatine kinase is the most sensitive indicator of rhabdomyolysis3 and myoglobin. Myoglobinuria occurs at the low serum concentration of 1.5 mg/dl. However, the distinctive brown colouration only becomes visible to the naked eye once the myoglobin concentration exceeds 100 mg/dl. There are many causes of myoglobinuria: toxins (especially alcohol), infections, drugs, muscle trauma (including epilepsy), metabolic disorders and immunological diseases (e.g. polymyositis) being among the more common.4 Exercise-induced myoglobinuria may result from defective glycerogen utilization with enzyme abnormalities such as myophosphorylase deficiency (McArdle’s disease) or muscle phospho-fructokinase deficiency (Tauri’s disease) in the carbohydrate pathway. Similarly, deficiencies in lipid metabolism may cause an energy (adenosine triphosphate: ATP) deficit resulting in muscle breakdown.5

Depending upon the metabolic state, skeletal muscle uses variable proportions of glucose or free fatty acids and ketone bodies as fuel. Integrity of both the lipid and carbohydrate metabolic pathways is therefore essential for normal muscle function. Normally more than 50% of the energy requirement of resting skeletal muscle is supplied from the oxidation of lipids, but this quantity increases during fasting when glucose is spared. During short bursts of strenuous activity skeletal muscle predominantly uses muscle glycogen.6

Figure 1 demonstrates these enzyme defects in the pathways of lipid and carbohydrate metabolism. A simple test to distinguish between defects in the 2 pathways is the ‘ischaemic forearm test’ but it carries some risk of contracture formation in defects of carbohydrate metabolism. In this the forearm is cuffed at above systolic blood pressure, and a vigorous hand-squeezing exercise is performed. Venous samples show a normal rise of lactate after anaerobic exercise with the lipid pathway defects (as in our patient), but not with an enzyme deficiency in glycoenolysis.7 There are 2 distinct currently recognizable deficiencies concerned with the transfer of fatty acids into mitochondria. In myopathic carnitine deficiency, only the skeletal muscle tissues contain low concentrations of L-carnitine. The clinical symptoms in this condition are those of muscle weakness, and muscle biopsy shows a gross lipid storage myopathy.

Two carnitine palmitoyl transferase (CPT) enzymes have been recognized; CPT-I located on the inner face of the outer mitochondrial membrane and CPT-II located on the inner face of the inner mitochondrial membrane. Carnitine palmitoyl transferase deficiency can cause exercise-induced muscle cramps and myoglobinuria,8 worsened by fasting, cold or high fat diet; myopathy is not usually a feature.9

Carnitine palmitoyl transferase deficiency was first reported by Di Mauro and Bank and colleagues10.11 who found 2 brothers with the condition. Cases previously described as ‘paroxysmal myoglobinuria’ or the ‘Meyer–Betz syndrome’ were probably also due to carnitine palmitoyl transferase deficiency.12 The genetic basis of inheritance is unclear, and although autosomal recessive with differing expression is likely, sub-groups do seem to exist.13.14 Fewer examples of genetic defects in the beta-oxidation pathway have been described.

It is likely that the patient reported here is
CPT-II deficient but further investigations would be required to establish whether the defect in this patient is in the CPT-II enzyme or in the beta-oxidation of long chain fatty acids. More accurate diagnosis would not alter treatment but this report emphasizes the need to make an accurate diagnosis in any patient with myoglobinuria, at least as far as determining whether there is a defect in oxidation of carbohydrates and fatty acids. Such metabolic defects render the patient at risk of recurrent myoglobinuria and repeated episodes of acute renal failure, yet may respond well to appropriate preventive therapy.

References

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