Myopathic causes of exercise intolerance with rhabdomyolysis

ROS QUINLIVAN1,2 | HEINZ JUNGBLUTH3,4

1 MRC Centre for Neuromuscular Diseases, Institute of Neurology, National Hospital, London; 2 Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London; 3 Clinical Neuroscience Division, IOP, King’s College, London; 4 Department of Paediatric Neurology – Neuromuscular Service, Evelina Children’s Hospital, Guy’s and St Thomas’ NHS Foundation Trust, London, UK.

Correspondence to Dr Ros Quinlivan at MRC Centre for Neuromuscular Diseases, Institute of Neurology, National Hospital, Queen Square, London WC1N 3BG, UK. E-mail: r.quinlivan@ucl.ac.uk

Leg pains and exercise intolerance are common complaints in children and young adults. In most cases the cause will be considered benign and idiopathic, especially when symptoms occur only at night-time, after unaccustomed intense exercise, or in the course of an intercurrent viral illness. The differential diagnosis of any young person presenting with leg pains is wide and includes benign joint hypermobility syndrome, spinal disease such as spondylolisthesis and spinal stenosis, musculoskeletal causes such as hip and skeletal dysplasia and chondromalacia patellae, metabolic causes such as rickets, hypothyroidism, and iron deficiency, juvenile rheumatoid arthritis, and neoplasms such as leukaemia. Specific neuromuscular causes include hereditary neuropathies and muscle diseases. The scope of this article will be to focus primarily on those conditions presenting with muscle cramps as the predominant symptom and in which there is a high risk of recurrent rhabdomyolysis or progressive muscle weakness even though clinical examination may be normal.

Myopathic disorders presenting with leg cramps carry a risk of either acute rhabdomyolysis or progressive muscle weakness and can easily be missed. Acute rhabdomyolysis is a serious, life-threatening complication often requiring critical care; it has many causes, including acute infections, systemic disease, toxins, trauma, and inherited muscle disorders. Milder episodes of rhabdomyolysis presenting with myoglobinuria (a red–black discoloration of the urine) can go unnoticed or be mistaken for haematuria and investigated by nephrologists, leading to a delay in the correct diagnosis. When a history of ‘dark urine’ in association with muscle aches is given, biochemical assessment of urine during an episode is essential to confirm myoglobinuria. Figure 1 provides a diagnostic algorithm for myalgia and recurrent myoglobinuria and Table I provides a more detailed summary of the key conditions.

MUSCULAR DYSTROPHIES

The muscular dystrophies are a diverse group of conditions resulting in progressive muscle atrophy and weakness. In forms of muscular dystrophy associated with defects of membrane stability and repair, serum creatine kinase levels are usually significantly raised (more than 10× normal) and muscle biopsy shows dystrophic features. Histochemical staining for the muscle sarcolemmal proteins will point to a specific protein defect in most cases and the diagnosis can be confirmed with DNA analysis. In most cases the diagnosis of muscular dystrophy may be obvious because the child presents with muscle weakness, but sometimes exercise-induced cramps may be the only presenting symptom in the absence of any clinical signs, and in these patients muscle histopathology may show only minor changes.

The dystrophinopathies are sex-linked disorders ranging in severity from the severe form of Duchenne muscular dystrophy (DMD) to Becker muscular dystrophy (BMD), which has a milder phenotype. Affected individuals will have a deletion, duplication, or point mutation in the dystrophin gene at Xp21. In males with DMD, cramps and myoglobinuria are not typical presenting features but may become prominent...
following treatment with corticosteroids, probably secondary to the increase in physical activity as a consequence of treatment. Muscle aches usually occur after, but not during, exercise, and myoglobinuria is usually mild, requiring no specific treatment other than an increase in oral fluid intake. In BMD, exercise-induced muscle cramps and myoglobinuria can be the only presenting symptom occurring before the onset of muscle weakness. Affected individuals typically present between early childhood and adolescence with leg pains occurring both during and after exertion. The precise relationship of pain to exercise can be vague and inconsistent, with myalgia occurring sometimes within minutes and at other times after a more prolonged period of exercise. Following unaccustomed physical activity, leg pains occurring during the night-time are a frequent complaint. Myoglobinuria following exercise is usually mild and rarely requires hospitalization for treatment. On examination the child may be noted to be toe walking and there is usually calf hypertrophy. In the early stages, muscle weakness is either absent or mild, affecting only the pelvic extensor muscles. In most affected individuals, serum creatine kinase is significantly elevated and muscle biopsy demonstrates a dystrophic picture with reduced dystrophin staining. Molecular genetic analysis confirms the diagnosis by finding a deletion, duplication, or nonsense mutation in Xp21. The diagnosis of an underlying dystrophinopathy in an otherwise asymptomatic male presenting with exertional myalgia and/or myoglobinuria is important with a view to the long-term follow-up, as an associated cardiomyopathy is a relatively common complication that does not correlate with the degree of muscle weakness. The leg cramps may respond to massage, heat pads, and physiotherapy, but their frequency and severity usually subside spontaneously as the condition progresses.

Exertional myalgia and rhabdomyolysis may also be a presenting feature in female carriers of X-linked dystrophinopathies; for example, two unrelated females seen by the authors, one aged 5 and one aged 7 years, who presented with a history of calf pains following excessive exertion were subsequently found to be manifesting carriers of DMD. Examination showed asymmetrical calf hypertrophy in the absence of muscle weakness. This finding initially led clinicians at the referring hospitals to consider a diagnosis of acute myositis – the muscle hypertrophy was thought to be due to muscle swelling. In both females serum creatine kinase was raised (between 4000IU/L and 5000IU/L) and the karyotype was normal. Muscle biopsies taken from vastus lateralis showed dystrophic features with a mosaic pattern of dystrophin staining. Molecular genetic studies showed deletions in Xp21 in both females, confirming them to be manifesting carriers of DMD. Accurate diagnosis in these two individuals led to appropriate genetic counselling and cardiac surveillance.

Limb girdle muscular dystrophy type 2I (LGMD2I) is one of the most common autosomal recessive limb girdle muscular dystrophies presenting in childhood. Affected individuals may be initially paucisymptomatic, and exertional myalgia and/or rhabdomyolysis may be the only presenting feature. An 11-year-old female known to one of the authors presented to the accident and emergency department with severe leg pains following, but not during, exertion. Clinical examination was normal apart from muscle hypertrophy of calves and deltoids; there was no muscle weakness. Her serum creatine kinase was

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**What this paper adds**

- This article provides a summary of the important differential diagnosis of exercise intolerance and rhabdomyolysis. It has been written to guide clinical assessment and investigation of such patients and includes features of clinical cases.

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**Figure 1:** Diagnostic algorithm for investigations of rhabdomyolysis. aFor fatty oxidation studies and bfor respiratory chain enzyme studies. cRecurrent R50X/G205S mutation should be excluded in European patients; muscle biopsy should be performed before PYGM sequencing. dXp21 dystrophies. LPIN1, lipin 1 gene; PYGM, myophosphorylase gene; RYR1, skeletal muscle ryanodine receptor gene.
markedly elevated (15 000IU/L), but blood spot for acylcarnitine by mass tandem spectroscopy, free carnitine, and lactate were normal. Muscle biopsy was virtually normal apart from a very small number of basophilic fibres, but histochemical stains showed a reduction of alpha-dystroglycan. The diagnosis of LGMD2B was subsequently confirmed by finding homozygous C826A mutation in the dysferlin gene, resulting in complete or almost complete deficiency; CCD, central core disease; MmD, multi-minicore disease; AD, autosomal dominant; MH, malignant hyperthermia.

Another limb girdle muscular dystrophy which appears to be frequently associated with exertional myalgia is LGMD2B, secondary to recessive mutations in the dysferlin gene (DYSF), often with a marked inflammatory component as evidenced both on muscle biopsy and muscle magnetic resonance imaging (MRI). In LGMD2B exertional myalgia may be the presenting feature and is often prominent, probably reflecting the fact that some affected individuals are quite athletic before the onset of overt muscle weakness. Some patients may thus present with features of a ‘pseudometabolic’ myopathy, and not infrequently a misdiagnosis of polymyositis is made at presentation. The authors have clinical experience of a 14-year-old female presenting with prominent exertional myalgia and a markedly elevated creatine kinase (>15 000IU/L) in whom, based on MRI and muscle biopsy findings, an inflammatory myopathy had been suspected before the correct genetic diagnosis of LGMD2B was established. Although not previously reported in LGMD2B, exertional rhabdomyolysis has been documented in Miyoshi myopathy, an allelic condition due to mutations in the DYSF gene.

In addition, rhabdomyolysis has been reported in individuals presenting with beta- and gamma-sarcoglycanopathies, as well as in patients harbouring mutations in the PYGM gene, resulting in complete or almost complete absence of the enzyme muscle glycogen phosphorylase. From early childhood affected individuals report symptoms of

### Table 1: Diagnostic algorithm for investigations of rhabdomyolysis

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<tr>
<th>Disorder</th>
<th>Genetics</th>
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<th>Diagnostic investigations</th>
<th>Comments</th>
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<tr>
<td>Muscular dystrophies</td>
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<td>DMD/BMD</td>
<td>DYS</td>
<td>X-linked</td>
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<td>AR</td>
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<td>AR</td>
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<td>McArdle disease</td>
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<td>AR</td>
<td>Exercise within minutes</td>
<td>Severe (ARF)</td>
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<tr>
<td>Tarui disease</td>
<td>PFKAB</td>
<td>AR</td>
<td>Exercise within minutes</td>
<td>Severe (ARF)</td>
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<td>Disorders of fatty acid metabolism</td>
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<td>Exercise (prolonged), fasting, fever</td>
<td>Severe (ARF)</td>
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<td>ACADVL</td>
<td>AR</td>
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<td>Severe (ARF)</td>
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<td>AR</td>
<td>Variable</td>
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<td>AR</td>
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<td>Core myopathies (CCD, MmD)</td>
<td>RYR1</td>
<td>AD, AR</td>
<td>Exercise</td>
<td>Moderate</td>
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</tbody>
</table>

DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; IHC, immunohistochemistry; DG, Dystroglycan; LGMD, limb girdle muscular dystrophy; AR, autosomal recessive; ARF, acute renal failure; CPTII, carnitine palmitoyl transferase II; VLCAD, very long-chain acyl-CoA dehydrogenase; CCD, central core disease; MmD, multi-minicore disease; AD, autosomal dominant; MH, malignant hyperthermia.
muscle fatigue followed by discomfort in the first few minutes of aerobic activity, and they are particularly vulnerable to muscle damage (rhabdomyolysis) following eccentric (isometric) muscle activities such as squatting, lifting heavy weights, or tensing muscles. They are unable to perform strenuous exercise and usually cannot run.

Symptoms are almost always present from a very young age, with many individuals reporting their school years as being particularly miserable. In many cases, childhood muscle symptoms are labelled as ‘growing pains’, resulting in delay in diagnosis until adulthood. In McArdle disease, exercise typically induces muscle fatigue and cramping within 3 to 5 minutes, and symptom intensity reaches a peak by about 6 to 8 minutes. If the intensity of activity is maintained despite symptoms, a severe cramp or contracture occurs, which can last for a prolonged period and is followed by severe muscle pain, swelling, and myoglobinuria. Severe episodes of contracture involving multiple muscles will lead to severe rhabdomyolysis and acute renal failure necessitating critical care admission. However, if the intensity of exercise is reduced or stopped as soon as symptoms occur, myalgia subsides rapidly, and after 8 to 10 minutes the individual may experience a second wind phenomenon whereby exercise can continue safely. Thus, obtaining a history of a second wind is essential in any patient presenting with exercise intolerance. Clinical examination is usually normal although some patients exhibit muscle hypertrophy in the lower limbs. Muscle wasting and weakness occurs in about 30% of patients, is confined to the upper limbs and axial muscles, and is rare in those below the age of 40 years. Serum creatine kinase is almost always raised (mean 2000–3000IU/L), but the level is dependent upon physical activity and varies between occasions. Muscle biopsy shows complete, or almost complete, absence of the enzyme muscle phosphorylase and there may be subsarcolemmal blebs containing glycerogen. Molecular genetic analysis for mutations in PYGM will confirm the diagnosis; 75% of British patients will be homozygous for mutations at R50X. Testing for this common mutation can be a useful screening test in this population.

There is no specific treatment for McArdle disease, but preventing episodes of rhabdomyolysis is essential to prevent episodes of acute renal failure and the need for critical care. Limited evidence suggests that regular aerobic exercise is safe and can benefit patients by conditioning their muscles for fatty acid oxidation. Ingesting a glucose load immediately before planned exercise can help patients to enter a second wind and improve exercise capacity, although the benefit has to be weighed against the potential for significant weight gain.

Tarui disease is a very rare disorder caused by the absence of the glycolytic enzyme AB phosphofructokinase (PFKAB). The enzyme is also absent in red blood cells, and some affected individuals may also exhibit a mild haemolytic anaemia. A rare fatal infantile form associated with fetal akinesia and arthrogryposis has been reported, but most individuals present with severe exercise intolerance and a progressive myopathy. As with McArdle disease, exercise-induced fatigue and cramping occur within minutes of initiating an activity, and there may be myoglobinuria and episodes of acute renal failure due to rhabdomyolysis. However, in contrast to individuals with McArdle disease, one study failed to demonstrate a second wind in a small number of patients with Tarui disease. The diagnosis is made by finding raised serum creatine kinase and in some cases raised bilirubin. Muscle biopsy shows complete absence of the enzyme phosphofructokinase, and molecular genetic studies should be performed to confirm homozygous mutations in the PFKAB gene.

Other extremely rare glycogenoses presenting with similar symptoms include phosphorylase B kinase deficiency (which can be associated with liver disease), phosphoglycerate kinase deficiency (which can be associated with learning difficulty and haemolytic anaemia), phosphoglycerate mutase deficiency, beta enolase deficiency, and lactate dehydrogenase deficiency. Six individuals with aldolase A deficiency have been reported, in whom exercise intolerance and rhabdomyolysis are present in association with haemolytic anaemia and in some cases learning difficulty.

**DISORDERS OF FATTY ACID OXIDATION**

Disorders of fatty acid oxidation are rare and often present in infancy with episodes of hypoglycaemia and liver and cardiac involvement, but milder cases present in adolescents and young adults with myalgia and exercise intolerance.

Carnitine palmitoyl transferase II (CPTII) deficiency presenting in adolescents and young adults is characterized by recurrent myoglobinuria, muscle aching, and stiffness induced by prolonged aerobic exercise, fasting, infections, emotional stress, and cold. The condition may appear silent until the first episode of rhabdomyolysis, which characteristically follows an episode of prolonged aerobic exercise, often with fasting. Patients report that pain and cramping begins in the legs and then spreads to involve the paraspinal and arm muscles. The cramping is so severe that there may be difficulty in walking. There is usually severe rhabdomyolysis with myoglobinuria and serum creatine kinase is often above 100 000IU/L. In these circumstances, intensive care admission for renal dialysis is often required. However, between attacks the patient may have few symptoms and the clinical examination and serum creatine kinase may be normal. Muscle biopsy is often normal, although in a minority of cases there may be mild myopathic changes with an increase in intracellular lipid. A blood acylcarnitine profile is the best first-line investigation and can show increased long-chain acyl carnitines (C16, C18, C18:1, C18), although sometimes it may be normal in a non-fasted patient. The diagnosis is confirmed by measuring CPTII activity in leukocytes and cultured fibroblasts followed by gene sequencing. However, screening for the common mutation (c.338C>T, p.Ser113Leu) may be a useful first-line investigation as it may yield a positive diagnosis in 60% of patients.

Very long-chain acyl-CoA deficiency (VLCAD) has a similar presentation to CPTII deficiency. Neonatal screening with acylcarnitine profiles revealed an incidence of 1:50 000 neonates in Germany. It is caused by homozygous mutations in the ACADVL gene. Severe infantile forms presenting with hypoglycaemia occur together with a late-onset
form presenting with exercise intolerance. Children surviving the severe infantile form will later develop an ‘adult phenotype’ with exercise intolerance. As with CPTII deficiency, symptoms are provoked by prolonged exercise, fasting, cold, and emotional stress. Between attacks clinical examination is normal and serum creatine kinase may be normal or raised. Muscle biopsy may show increased lipid in type 1 fibres, but this is not a universal finding and the muscle biopsy may be normal. First-line investigation includes screening blood acyl carnitines by tandem mass spectroscopy, which may show abnormal long-chain acyl carnitines with tetracosanoylcarnitine (C_{24:1}), although, as with CPTII deficiency, acyl carnitines can be normal between attacks. The diagnosis is confirmed by genetic analysis to look for homozygous mutations in the ACDAYL gene.

Patients with CPTII deficiency and VLCAD should avoid fasting and prolonged exercise. There may be improvement in their symptoms with a low-fat–high carbohydrate diet and/or medium chain triglyceride (MCT) oil supplements. Glucose supplements before, during and after planned aerobic exercise should also be recommended. A recent pilot study in adults with CPTII deficiency suggested that bezafibrate may be beneficial.

Mitochondrial trifunctional protein (MTP) deficiency presents with heterogeneous clinical manifestations including a severe encephalopathy with liver disease, cardiomyopathy with retinopathy, and progressive axonal sensory motor peripheral neuropathy. However, episodes of rhabdomyolysis can be induced by exercise, fasting, or illness, and can be life-threatening. The combination of rhabdomyolysis with peripheral neuropathy should lead the paediatrician to suspect a deficiency of long-chain co-acyl dehydrogenase (LCHAD) or MTP (combined) deficiencies. Muscle biopsy may sometimes show reduced respiratory chain enzymes with decreased activity of complex I and sometimes complexes II and III, although there is not usually evidence of increased intracellular lipid. When the child is stable, the blood acylcarnitine profile may be normal, but during episodes of rhabdomyolysis long-chain hydroxyacyl carnitines will be abnormal. Genetic studies will confirm a mutation in either the HDHLA or HDHB gene.

A newly identified cause of recurrent myoglobinuria in childhood is phosphatidic acid phosphatase deficiency caused by mutations in LPIN1 encoding lipin-1. Children typically present between 15 months and 7 years with recurrent episodes of myoglobinuria precipitated by intercurrent infections and fever. Serum creatine kinase is markedly elevated during attacks, but total and free carnitine, acyl carnitine, and organic acids are normal. Muscle biopsy may show increased lipid droplets but can also be normal. Diagnosis is confirmed by molecular genetic studies.

CONGENITAL MYOPATHIES

Autosomal dominant and autosomal recessive mutations in the skeletal muscle ryanodine receptor gene (RYR1) are an important cause of the malignant hyperthermia susceptibility (MHS) trait and various congenital myopathies including central core disease (CCD), distinct subgroups of multi-minicore disease (MmD), and centronuclear myopathy (CNM). Exertional myalgia as a prominent feature in CCD was recognized soon after the original description of this disorder and is common in many myopathies due to RYR1 mutations, particularly those causing a ‘hyperactive’ RYR1 channel. Exercise intolerance/rhabdomyolysis in association with MHS has been described in several case reports and appears to be closely associated with an increased risk of heat stroke. Heat stroke is a syndrome of hypercatabolism that occurs during physical exertion in hot and humid climates and is particularly common in soldiers, in whom it can lead to exertional rhabdomyolysis and acute renal failure. Mutations in RYR1 are becoming increasingly recognized and may be an important cause of exercise intolerance and rhabdomyolysis.

MANAGEMENT OF MYOglobinurIA AND RHABDOMYLosis

Mild instances of myoglobinuria, presenting with a mild reddish discoloration of urine without systemic symptoms, can be managed at home by increasing oral fluid intake and resting sore muscles. More severe episodes require admission to hospital and typically include ‘flu-like’ symptoms with severe muscle aches and fever. There may also be nausea and vomiting. Urine will be ‘cola’ coloured and strongly positive for blood on Haemostix but negative for red blood cells on microscopy. Management includes vigorous intravenous rehydration with 6- to 12-hourly monitoring of serum creatine kinase, blood gases, coagulation, electrolytes, and calcium. Cardiac rhythm, blood pressure, and urine output must be carefully monitored. Hypocalcaemia and hyperkalaemia should be treated promptly. Analgesia is important as muscle pain can be severe. About 30 to 40% of patients will develop acute renal failure requiring dialysis. In very severe episodes, the patient may present following acute collapse and even cardiac arrest due to hyperkalaemic acidosis and there may be disseminated intravascular coagulation. During an episode of acute rhabdomyolysis there is severe muscle damage, but any diagnostic muscle biopsy should be deferred until recovery is complete, which could be up to 12 weeks after the episode. The overall mortality from acute rhabdomyolysis is up to 8%; thus, early diagnosis with appropriate exercise and dietary advice is essential to prevent these episodes from occurring.

SUMMARY

Leg pain is a common symptom with many causes; however, myalgia associated with exercise intolerance may be the presenting feature of an underlying metabolic or myopathic disorder with potentially serious consequences. A careful history and examination will dictate the most appropriate first-line investigations (Fig. 1). All children presenting with leg pains should have their serum creatine kinase checked. Blood acylcarnitine profile and ‘hotspot’ genetic tests for McArdle disease and CPT2 deficiency can be useful and cost-effective first-line investigations. Second-line investigations will depend upon the history and results of first-line investigations and will include either skin or muscle biopsy followed by identification of the
causative genetic defect (Table I). Accurate diagnosis is important to provide appropriate long-term surveillance including prevention of rhabdomyolysis and genetic counselling.

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