Scottish Muscle Network

Investigation of exercise – related myalgia in adults

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Introduction

The aim of this document is to identify **significant exertional myalgia** in adults and how to investigate further. This document should not be used if there has been a significant episode of rhabdomyolysis. In this instance, please use the "Single Episode of Rhabdomyolysis Investigation Pathway" guideline.

Myalgia is the symptom of muscle ache and discomfort and is common in the general population. It is not usually indicative of an underlying metabolic muscle disorder. It may occur in association with biochemical abnormalities such as elevation of creatine kinase (CK) levels. In its extreme form, rhabdomyolysis results from significant skeletal muscle injury and breakdown.

It is important to distinguish exercise-related pain/myalgia caused by underlying muscle pathology from nonspecific chronic aches and pains, usually caused by myofascial pain or joint problems.

Summary of distinguishing clinical features

Fatty acid oxidation defects	Mitochondrial disorders	Glycolytic defects
• Can manage endurance exercise e.g. marathons if adequately "fuelled" • Crisis occurs during unaccustomed endurance exercise or with an additional physiological trigger, e.g. fasting, dehydration or if unwell with a fever • Muscle contractures occur if exercise continues	• Longstanding exercise intolerance • Exercise precipitates headache, nausea, pre/syncope • Multi-system features, e.g. short stature, ptosis, ocular dysmotility, diabetes, migraine, hearing loss • Crisis occurs when fasting, dehydrated, running fever	• High-intensity exercise intolerance e.g. running upstairs, shovelling snow • Unable to carry out endurance exercise • Second-wind phenomenon pathognomonic for • McArdle's • Out of wind phenomenon (eating before exercise exacerbates symptoms) in Tarui's

Detailed description of distinguishing features

1) **Pain that occurs at rest.** This would be atypical for metabolic myopathies, as there is no metabolic demand when at rest. Pain at rest may be due to fibromyalgia (diffuse tender points, innocuous stimuli elicit pain out of proportion to the stimulus, fatigue and brain fog, insomnia, and low mood). Hypermobile joints and a long history of ligamentous and joint laxity can also cause chronic daily pain.

2) **Cramps.** Cramp is common, especially in sedentary individuals. Patients often describe this as 'muscle spasms'. Ask about exercise regimes and life-style, the type of work they do (sedentary versus manual work) as well as their daily physical activity e.g. gardening, DIY etc. Ask about dietary habits, including caffeine intake, and intake of fizzy drinks.

3) **Presence of spontaneous movements (e.g. twitching).** Pain associated with cramps and fasciculations are characteristic of Isaac's Syndrome. Rippling of muscles is associated with caveolin-related myopathies – on examination look for percussion-induced muscle mounding or percussion-induced rapid contractions (PIRCs).

4) **Stiffness and/or contractures**: Contraction of the muscle under stress can occur in metabolic myopathies, especially McArdle's disease (GSD V). Muscle stiffness is characteristic of myotonia. There may be signs of myotonic dystrophy on examination, and you can elicit grip or percussion myotonia. Also think of myotonia congenita and paramyotonia congenita.

5) **Timing of myalgia:** when does the myalgia occur in relation to exercise? Is this affected by fuelling (eating) before or during exercise? A detailed clinical history of the symptoms associated with exercise often points to a specific type of metabolic myopathy. Glycogen Storage Disorders result in intolerance of **high-intensity exercise**. Fatty Acid Oxidation Defects and the mitochondrial myopathies manifest predominately during **endurance type-activity** or when exercising fasted or during other metabolically stressful conditions (such as intercurrent viral illness). A detailed physiological explanation can be found in Appendix A.

6) **"Second wind" phenomenon**: myalgia occurs after a few minutes of exercise. However, slowing down or resting for a short period (30 seconds or so) allows for the blood borne delivery of glucose from the liver so exercise can subsequently continue at a lower intensity. This is classical for McArdle's Disease (GSD V). Eating / drinking sugary snacks or drinks approximately 20 minutes before exercise can encourage the second wind phenomenon and allow people with McArdle's to exercise for longer. In McArdle's, symptoms of myalgia, cramp and pigmenturia are brought on by sudden sharp higher intensity exercise e.g. climbing upstairs, sprinting for a bus, shovelling snow, opening a stiff jar lid. The baseline CK is almost always elevated.

7) **"Out of wind" phenomenon**: in Tarui Disease (GSD VII) defective phosphofructokinase activity blocks muscle glycolysis, so the consumption of

high sugar / high carbohydrate food or drink before exercise exacerbates exercise intolerance and myalgia.

8) **Symptoms from childhood:** exercise tolerance in many metabolic myopathies may date from childhood, but not always. **Mitochondrial disorders** usually cause symptoms from childhood, often with headaches, nausea and vomiting and presyncopal symptoms induced by exercise. Be careful not to overinterpret these symptoms, as severely deconditioned individuals may experience similar. Ask about family history (not only maternal). Look for red flags on examination (ptosis, ocular dysmotility, short stature, hearing aids/loss). It is useful to check their lactate levels (but beware of false-positives: diabetics with high blood sugars will have low-level high lactate levels or individuals who take a sugary drink prior to blood testing will transiently raise their lactate) – so it has limited utility and low sensitivity. If carrying out an exercise test in your department also be aware that deconditioned individuals can raise their lactates to very high levels with exercise.

9) **Prior or intermittent episodes of myoglobinuria / dark red urine**, characteristic of previous episodes of rhabdomyolysis. Ask patients whether they have experienced coca-cola coloured / tea coloured / maroon urine to distinguish between the normal colour changes seen with dehydration.

Investigations for exertional myalgia

Acyl carnitine profile will detect defects of fatty acid oxidation. Acyl carnitine profile can be normal if patients are not decompensated and well fuelled / fed. Fasting acyl carnitine profiles are more sensitive, but could risk precipitating a potentially lifethreatening metabolic decompensation, so should only be considered in special circumstances / under specialist advice.

Creatine kinase – if high repeat; enquire if this was taken after exercise in which case repeat after a period of abstaining from exercise. If persistently elevated (>2 ULN) with a significant history of exercise-induced myalgia and exercise intolerance, then consider genetic testing for metabolic myopathies using the rhabdo gene panel.

Thyroid function

Electrolytes

Vitamin D

Lactate (ideally taken when the patient has not exercised or had any food/drinks for 3h prior to having blood test)

Uric acid – if suspecting GSD – frequently high and compensatory for flux through the myoadenylate deaminase system– ask for a history of gout. **Urine organic acids** (spot urine - usually most helpful in an acute event)

ECG with ECHO if ECG abnormal

EMG is usually unhelpful for metabolic myopathies but is helpful if you elicited fasciculations, neuromyotonia or myotonia on examination.

Muscle MRI is usually unhelpful in metabolic myopathies unless a pseudometabolic presentation is being considered, e.g. if there is weakness on examination, contractures etc and you think this is more likely to be a type of muscular dystrophy.

Have a low threshold for requesting **muscle biopsy** if there is weakness with high CK and/or if muscle MRI shows focal fatty infiltration.

Genetic testing
Consider sending DNA for storage.
If a mitochondrial disorder is likely, send blood-derived DNA and early urine morning samples to be tested for the common mitochondrial mutations e.g. mt.3243 A>G etc.
Criteria for testing on a multi-gene rhabdomyolysis/metabolic myopathy panel are any ONE of the following:

- Characteristic biochemistry: acyl carnitine profile or urine organic acids suggestive of a specific metabolic disorder (e.g. VLCAD, CPT2, MADD)
- Clear ‘second wind’ phenomenon
- Glycogen or lipid accumulation in muscle (in the absence of multisystem disease)
- CK persistently elevated >2x ULN (ULN- Upper limit of normal. It should be borne in mind that CK levels vary with age, sex, ethnic origin, and muscle conditioning, and reference ranges may vary between laboratories. Highest CK levels would be in fit
- Afro-Caribbean males, in whom CK may be twice that of Caucasian males)
- Cases not fulfilling the above criteria may be agreed for testing on an individual basis through discussed with the Glasgow DNA laboratory geneticlaboraties@ggc.scot.nhs.uk.
- Please note that patients with suspected RYR1-related congenital myopathies would usually be more appropriately tested on congenital myopathy panels and can be discussed with/referred to Clinical Genetics.

Any patient with abnormal metabolic biochemistry should be referred to the Scottish IMD Service for advice / input.