Scottish Muscle Network

Investigation Pathway: Single episode of Rhabdomyolysis 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.

Definition

Rhabdomyolysis (rhabdo for short) is a potentially life-threatening disorder caused by the breakdown of skeletal muscle, resulting in the release of various intracellular contents into the circulation. Clinically the patient presents with acute muscle pain, with or without muscle weakness, and has an elevated CK (>1000 IU/L). Often the patient reports pigmenturia. There are numerous causes of rhabdomyolysis, all of which result in the same common pathway of myocyte destruction. **Genetic causes of rhabdomyolysis are rare** but are more likely if there are recurrent episodes.

Causes

The most common causes of rhabdomyolysis are listed below:

1. **Exertion:** exertional rhabdo occurs as a physiological response to unaccustomed, prolonged, repetitive exercise with eccentric characteristics causing muscle tension, strain and injury. This is an area of litigation in the military, where rhabdomyolysis happens not infrequently in the context of training under extreme conditions (including heat stress, and/or with limited access to food / hydration).

2. **Ischemia and Trauma:**
    i. Falls
    ii. Prolonged muscle compression e.g. immobilisation after a fall or lying unconscious on a hard surface during illness or after taking drugs or alcohol
    iii. Crush injuries
    iv. Status epilepticus
    v. Electrical shock injury
    vi. Third degree burns
    vii. Lightning strike
    viii. Venom from snake or insect bite

3. **Drugs and Toxins:**
    i. Alcohol, carbon monoxide, anti-retroviral drugs, opiates, benzodiazepines, ecstasy, amphetamines, heroin, ask also about over the-counter remedies and herbal remedies. Green tea supplements when taken in excess can cause rhabdomyolysis due to the effect of polyphenols on kidney and liver function
    ii. Statins
    iii. Neuroleptics (2/10,000 people experience neuroleptic malignant syndrome)

4. **Temperature extremes exacerbated by dehydration**

5. **Infection:** common infectious precipitants include Influenza A, Coxsackie B virus, HIV and seroconversion, EBV and CMV and bacterial infections such as Streptococcal infection and Salmonella etc.

6. **Endocrinopathies and electrolyte disturbances:**
    i. Thyroid disease
    ii. Diabetes mellitus
    iii. Diabetes insipidus
    iv. Pituitary dysfunction
    v. Diabetic ketoacidosis
    vi. Profound hyokalemia eg in renal tubular dysfunction
    vii. Adrenal pathology
    viii. Hyponatremia and hypernatremia

7. **Connective tissue disorders:** including dermatomyositis, necrotising myopathy.

History

A detailed history is important, with particular focus on the **drug history,** including any over the counter remedies. Information on dose, quality and source (e.g. purchased from the internet) should be obtained. Check the purity of commercially sourced supplements or remedies. Ask specifically about recreational drugs, alcohol consumption and diet, particularly hydration and caffeine consumption.

It is important to identify if this is the first episode of rhabdomyolysis or whether they have had other episodes. Ask if they have ever passed dark (maroon/tea coloured/coca-cola coloured) urine in the past.

Enquire about their **usual fitness regime** and whether they experience any muscle symptoms, including exercise intolerance with myalgia, cramp or weakness, or muscle fatigue or swelling during or after exercise. Ask about their performance in relation to their peers, especially during childhood. Ask specifically about **second wind** phenomenon (myalgia with exercise that improves after brief rest). This is characteristic of **McArdle's Disease (GSD V)**. In contrast, **out of wind** phenomena – the exacerbation of symptoms after eating high carbohydrate snacks before exercise – would point you towards a rarer metabolic disorder called **Tarui's Disease (GSD VII)** caused by phosphofructokinase deficiency. Rhabdomyolysis in **CPT2 (carnitine palmitoyl transferase type 2) Deficiency** is often extreme and does not occur after brief bursts of exercise but usually occurs after prolonged, moderate - intense exercise and often in the context of fasting, dehydration or concurrent illness.

Ask about **family history**: maternal diabetes, deafness, cardiac disease (in mitochondrial disease) and/or muscle disease or critical illness in the neonatal period in siblings (in FAODs)

Examination

It is crucial to detect muscle **weakness** that persists 3-4 months after the event, and to elicit other signs such as **muscle hypertrophy/atrophy** and early **contractures**. Ask about symptoms such as **muscle twitching** and **muscle rippling** (suggestive of Caveolinopathies). Look specifically for ptosis, ocular dysmotility, and for specific features such as short stature, diabetes, migraine, epilepsy, hearing loss – which would suggest mitochondrial disorders. Such features should trigger testing for the common mitochondrial disorders in blood- and urine-derived DNA. If DNA studies are normal yet there are red flags on examination and history, request for a muscle biopsy. Other multi-system features, including signs / symptoms of malabsorption and/or GI dysmotility, premature menopause, osteoporosis and retinal pigmentation, may also indicate mitochondrial cytopathies.

In the context of a suspected underlying connective tissue disorder, look for systemic inflammation, with rash, nail changes, and skin changes and ask about arthralgia, joint swelling, fever, night sweats, malaise, anorexia and weight loss. This is the only time it would be justified to obtain a muscle biopsy on presentation, as an inflammatory aetiology would mean steroid treatment may be indicated.

When connective tissue disorders are not suspected, you should defer muscle biopsy for at least a month, and up to 6 months, after the rhabdomyolysis event. If taken too early the pathology is likely to show necrotic features, masking the true underlying pathology.

When to consider genetic causes for rhabdomyolysis:
Genetic causes of rhabdomyolysis are rare, but important to diagnose as they may have specific treatments or management strategies to reduce the risk of recurrence.

Consider the acronym '**RHABDO':**

- **RECURRENT**
- **HIGH CK PERSISTS (>500 IU/L) – 4 months after event.**
- **ABSENT UNACCUSTOMED EXERCISE**
- **BLOOD CK >50X NORMAL (>10,000 IU/L during rhabdo episode)**
- **DRUGS (ARE NOT INVOLVED)**
- **OTHER (FAMILY MEMBERS ARE AFFECTED)**

Genetic Causes of rhabdomyolysis include:

1. Deficiencies of glycol (geno) lytic enzymes (glycogen storage disorders)
2. Disorders of lipid metabolism (fatty acid oxidation defects)
3. Myopathies and dystrophies including dystrophinopathies, limb-girdle myopathies (including calpain-3, dysferlin, ANO-5, Caveolin-3)
4. Mitochondrial disorders
5. Multiple acyl CoA dehydrogenase deficiency (riboflavin responsive myopathies)
6. Myoadenylate deaminase deficiency
7. RYR-1 gene associated exertional myalgia/rhabdomyolysis

When to consider the Rhabdomyolysis Gene Panel:

- If there are **red flags** indicative of an underlying metabolic disorder e.g. features of second-wind, exercise intolerance predating the event, objective weakness on examination >4 months after rhabdomyolysis, history characteristic of intermittent metabolic decompensations, family history of rhabdomyolysis, or biochemistry suggestive of a specific metabolic disorder. If no pathogenic variants are detected, the patient should be referred to the local specialist neuro-muscular / neuro-muscular genetics clinic.

- If there was **no clear trigger** precipitating rhabdomyolysis, or the degree of rhabdomyolysis was out of keeping with the trigger, AND the **CK rose >10,000 IU/L**. If no pathogenic variants are detected AND the CK fails to normalise (<2x ULN 4 months after the rhabdo episode) refer to the local specialist neuro-muscular / neuro-muscular genetics clinic for further evaluation.

The Rhabdomyolysis Gene Panel is <u>not</u> indicated:

- If the patient has had a single episode of rhabdo with a recognised trigger and CK normalises or is less than 2x ULN (ie <500 IU) 4 months after the event. This scenario is common, is unlikely to recur and no further investigation is indicated. Patients should be advised to return to regular physical activity and avoid deconditioning. This should be phased in gradually, first with stretching based exercise, e.g. pilates, before returning to gym-work and running.

- If there are features indicative of a mitochondrial cytopathy (see above). In this instance, test for the common mitochondrial mutations in blood and urine (samples are tested in the genetics laboratory in Dundee). If normal, then refer to the neuro-muscular / neuro-muscular genetics clinic for further evaluation. Further genetic testing or a muscle biopsy may be required to establish the molecular diagnosis.

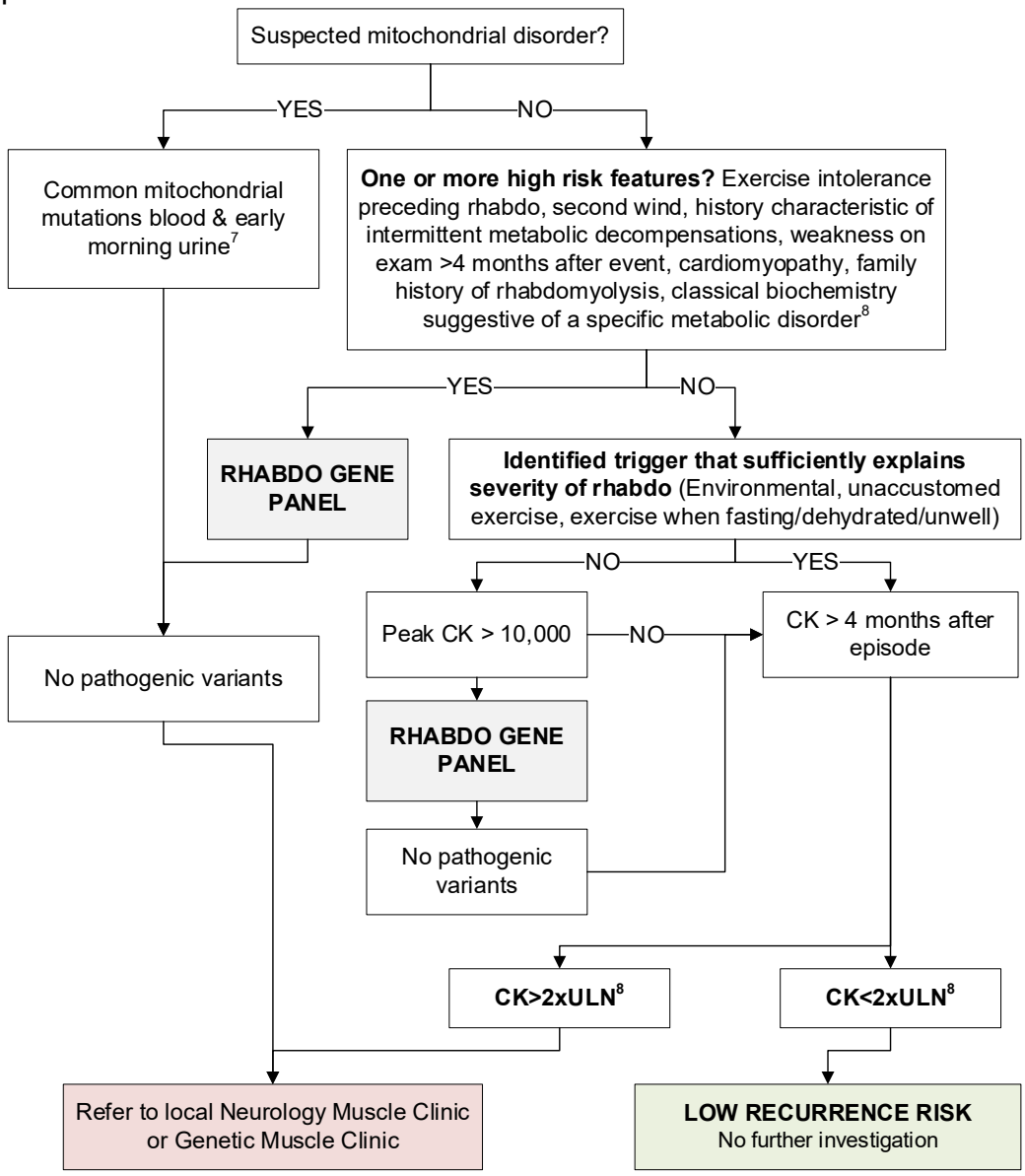
Single Episode Rhabdomyolysis[1] in Adults Pathway

History:

- Environmental triggers - illness, infection, HIV seroconversion, trauma, drugs including recreational, heat, alcohol, diet, hyperemesis
- Exercise context - unaccustomed (too much, too fast, too hard, too soon) or in context of fasting/dehydration/illness
- Personal and family history- exercise intolerance, weakness, second wind, mitochondrial features[2]

Examination:
>4/12 after acute event for weakness, muscle hypertrophy. If ptosis or progressive external ophthalmoplegia suspect mitochondrial disorder

Consider Investigations:
Hepatitis screen, HIV, thyroid function, ANA, double stranded DNA, acylcarnitine profile[3], urinary organic acids[4], DNA storage/testing[5], ECG, Echo, If on statin, check HMG CoA reductase antibodies[6], consider myositis-specific antibodies when appropriate[6]



Single Episode Rhabdomyolysis[1] Pathway- Appendix

1. Rhabdomyolysis definition **–** Documented CK>1000 IU/L associated with acute muscle pain
2. Mitochondrial features include deafness, diabetes, seizures, other endocrinopathies, premature menopause, ptosis (remember to ask about prior surgery), eye movement disorders, ataxia, cognitive difficulties, swallowing difficulties and gut disorders including malabsorption or history of obstruction
3. Acylcarnitine profile - Either send dry blood spot sample (if card available) and/or >5ml blood in lithium heparin tube to local biochemistry. *NB Discussion required on fasting when taken outside acute event as per podcast- Practical Approach to the Metabolic Myopathies; Diagnosis and Treatment-FAOD and Mitochondrial Myopathies by Mark A. Tarnopolsky*
4. Urinary organic acids - Spot urine collection to local biochemistry laboratory
5. DNA storage - 5ml blood in EDTA to Regional genetics laboratory for storage only. Lab details at https://www.sglc.scot.nhs.uk/?page_id=85
6. Antibodies – 5ml in serum tube, via local immunology lab
7. Common mitochondrial mutations- 5ml blood in EDTA and early morning spot urine in universal container to Regional genetics laboratory. Lab details at https://www.sglc.scot.nhs.uk/?page_id=85
8. Biochemical features of common metabolic myopathies.
   - Biochemistry will usually comment where observed patterns are suggestive of an underlying metabolic disorder. Mild non-specific abnormalities are not uncommon and can be discussed with biochemistry, but are not on their own an absolute indication for genetic testing. Repeat testing may confirm whether abnormality is significant or not
   - Most detected disorders are CPT2 deficiency, VLCAD and MADD
     - **VLCAD -** Onset childhood/early adulthood. Myalgia provoked by exercise and fasting. Look for episodes of hypoglycaemia.
     - **CPT2 deficiency -** Onset usually later; triggered by exercise in context of fasting, illness, low carbohydrate diet; can tolerate long distance exercise/marathons if they maintain hydration and focus on increasing carbs pre-exercise.
     - **MADD -** Crisis often triggered by prolonged fasting or limited diet; often develop fixed myopathy if not recognised early.
9. 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.