ACUTE RHABDOMYOLYSIS - INVESTIGATION AND MANAGEMENT - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Rhabdomyolysis can be due to a number of genetic and non-genetic causes, and may be associated with an acute life-threatening risk of electrolyte imbalance and/or acute renal failure. Early recognition, investigation and emergency management is vital.
- This document provides a protocol for the evaluation and management of patients suspected of or at risk of having rhabdomyolysis, and should be used in consultation with the Genetic Metabolic Diseases Service, the Nephrology Department and PICU. It covers the following areas:
  - Patient history
  - Tests to confirm rhabdomyolysis
  - Investigations to monitor treatment
  - First line diagnostic investigations
  - Complex diagnostic investigations
  - Acute and long term management

CHANGE SUMMARY

- New genetic cause of rhabomyolysis identified.
- Clinical Features and Causes section changed – *LPIN1* mutations as a cause added.
- Investigation (Special Tests) section changed – mutation testing for *LPIN1* added.

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READ ACKNOWLEDGEMENT

This document should be read by medical staff who are likely to be involved in the diagnosis and management of children presenting with clinical or biochemical features suggestive of acute rhabdomyolysis.

Medical staff who are likely to encounter children in an acute medical or surgical setting should be aware of this document.

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1 Introduction

Rhabdomyolysis can be defined as the breakdown of skeletal muscle cells, with the subsequent release of their contents into the circulation[1]. It is characterised by a rise of plasma creatine phosphokinase (CPK) by fivefold or more[2]. Some of the major consequences of clinical significance include[3]:

- the leakage of myoglobin into the systemic circulation, with a risk of renal vasoconstriction and acute renal failure[4]
- the leakage of potassium into the systemic circulation, with potentially life-threatening acute hyperkalaemia
- hyperuricaemia due to release of purines from disintegrating cell nuclei
- hyperphosphataemia may be due to efflux from damaged muscle cells with potential metastatic calcification and hypocalcaemia
- metabolic acidosis and aciduria

Whilst the risk of acute renal failure is associated with higher CPK levels, the absolute level is not an accurate predictor of the risk. However, a CPK level of 10,000U/L or more should be regarded as a potentially dangerous level.

2 Clinical Features and Causes

Clinically, patients may complain of muscle stiffness, weakness and myalgia, with or without fever[3]. In addition, there may be other disease-specific symptoms and signs related to the underlying condition. Some of the more important causes of acute rhabdomyolysis include:

Drugs and Toxins

- Neuroleptic malignant syndrome – idiosyncratic reaction associated with the use of neuroleptic drugs, e.g. phenothiazines, droperidol.
- Other drugs (including statins, fusidic acid, colchicine, extremely high dose pyridoxine (one report)[5], MDMA (ecstasy)[6], ethanol, toluene, naltrexone).
- Carbon monoxide poisoning.
- Multiple wasp or hornet stings[7].
- Snake venom.

Traumatic

- Crush syndrome, trauma to multiple areas of the body, or coma with immobility for prolonged periods with resultant muscle compression.

Vascular Compromise

- Ischaemia.
- Heat stroke.

Severe Infections

- Bacterial or viral.

Excessive Muscle Activity

- Seizures.
- Strenuous exercise.

Autoimmune Inflammation

- Polymyositis/dermatomyositis.
- SLE
- Polyarteritis nodosum.

Inborn Errors of Metabolism

- Fatty acid oxidation defects[8, 9] (precipitated by prolonged exercise, fasting or infection; no "second wind" phenomenon):
    - Carnitine palmitoyltransferase II deficiency.
    - Very long chain acyl-CoA dehydrogenase deficiency.
    - Others less common (eg long chain fatty acid oxidation disorders, carnitine – acylcarnitine translocase deficiency, medium chain ketoacyl-CoA thiolase deficiency).
- Mitochondrial respiratory chain defects[10, 11].
- Glycogen storage diseases[12]:
    - Myophosphorylase deficiency (type V; McArdle disease):
        - Painful muscle contractures with exercise.
        - Unusual to have symptomatic presentation before puberty.
        - If stop activity as soon as pain starts and rest briefly, can then resume activities again ("second wind" phenomenon).
    - Muscle phosphofructokinase deficiency (type VII; Tarui disease) – similar to type V, but:
        - Exercise intolerance is more obvious in childhood.
        - Also have compensated haemolytic anaemia.
        - Exercise intolerance worse after high carbohydrate meals.
    - Debrancher deficiency (type III; Cori disease) – seen in some adults.
    - Phosphorylase b kinase deficiency (type IX) – some patients have a muscle-specific form.
- Glycolytic defects[12]:
    - Phosphoglycerate kinase deficiency (seizures, intellectual disability, haemolytic anaemia; X-linked).

- Phosphoglycerate mutase deficiency (clinically like GSD VII).
- Fructose-1, 6-bisphosphate aldolase deficiency (also with haemolytic anaemia).
- Lactate dehydrogenase deficiency.
- Pyruvate kinase deficiency.

- Myoadenylate deaminase deficiency.
- X-linked adrenoleukodystrophy (a consequence of an Addisonian crisis)[13] .

Muscular Dystrophies

- Nemaline myopathy[14].
- Becker muscular dystrophy[15].
- Other congenital muscular dystrophies[16].

Other Genetic Disorders

- *LPIN1* deficiency[17]:
  - Encodes Lipin-1, a phosphatidic acid phosphatase, which plays a prominent role in triglyceride metabolism.
  - Usually precipitated by intercurrent febrile illnesses.
  - During acute episodes CPK is often in excess of 100,000U/L.
  - Second most common cause, after fatty acid oxidation disorders, of severe early onset rhabdomyolysis[18].
  - Up to a third of individuals may die during an acute episode, usually due a cardiac arrhythmia[18].
- Malignant hyperthermia – autosomal dominant pharmacogenetic disorder due to abnormal skeletal muscle calcium regulation, with mutations in the skeletal muscle ryanodine receptor (*RYR1*) in over 50%[19].
  - Provoked by volatile anaesthetics (e.g. halothane) and depolarising muscle relaxants (e.g. suxamethonium).
  - Muscle contractions, tachycardia, metabolic acidosis, hyperthermia.

Central core myopathy – is allelic with malignant hyperthermia[20].

3 Investigation

3.1 History

Questions to ask:

- Drug ingestion.
- Nature and severity of recent trauma.
- History of recent excessive exertion.
- Provoking/relieving factors e.g. infection, fasting, emotional stress, cold, anaesthetics.
- History of recurrences.
- Careful family history.
- "Second wind" phenomenon (GSD V, GSD IX) [The patient rests when myalgia and stiffness first become evident. On resumption of activity, symptoms do not recur. This is thought to be the result of increased delivery of glucose and free fatty acids to muscle because of a hyperdynamic circulation.]
- "Out of wind" phenomenon (GSD VII) [Extra ingested glucose leads to a reduction in work ability. This is because there is a reduced delivery of free fatty acids and ketone bodies to muscle, which are the preferred substrates in this disorder.]
- Associated haemolytic anaemia (GSD VII, phosphoglycerate kinase deficiency, fructose-1, 6-bisphosphate aldolase deficiency).

3.2 Confirm the Rhabdomyolysis

- Plasma CPK.
- Urine myoglobin.

3.3 Baseline Investigations to Monitor Treatment

- Serial CPK, electrolytes (especially potassium, calcium and phosphorus), acid-base status, uric acid, urea and creatinine measurements.

3.4 Baseline Diagnostic Investigations

- Urine amino and organic acid screens.
- Plasma carnitine and acylcarnitines.
- Blood lactate and pyruvate.
- ESR, serology for investigation of autoimmune causes.
- Bank DNA (5 – 10 ml EDTA blood) in anticipation of possible future genetic testing.

3.5 Special Tests

(depending on clinical indications, should only be performed in consultation with the Neurology or Metabolic teams)

- Forearm ischaemic exercise test (see[1, 21]).
- Non-ischaemic forearm test may be considered as an alternative to the forearm ischaemic test[22].
- *In vitro* contracture test (malignant hyperthermia).
- White blood cell (CPT II deficiency) or fibroblast fatty acid oxidation studies.
- Muscle biopsy for histopathology.
- Other specific enzyme studies (tissues to be tested may include liver, muscle, cultured skin fibroblasts, or red blood cells).
- Mutation analysis (*LPIN1* gene, especially if CPK is >100,000U/L, and in particular if the onset is in early childhood.
- Other gene testing as appropriate.

3.6 Specific Muscle Histopathological Features

- GSD III, V, IX – mild-moderate accumulation of glycogen.
- GSD VII – amylopectin-like polysaccharide accumulation (PAS positive, diastase resistant).
- Fatty acid oxidation defects – micro- or macrovesicular lipid accumulation.
- Autoimmune disorders – inflammatory changes.

4 Management

4.1 Acute Management

It is important to note that early consultation with the Renal Team is vital so that management can be planned appropriately. Much of the experience with regards to acute management is based on experience with crush syndrome victims[4, 23, 24].

- Attend to and stabilise the ABCs. In particular monitor cardiac rhythm, blood pressure, urinalysis and record a strict fluid balance.
- Baseline and regular biochemistry and metabolic tests (as above).
- Consult the Genetic Metabolic Diseases and Nephrology teams as soon as diagnosis is suspected.
- Consult PICU if there are severe electrolyte disturbances, trauma, renal impairment or any concerns about patient stability.

- "Compartment syndrome" represents a true surgical emergency, and urgent involvement of the general or orthopaedic surgeons to measure limb compartment pressures with possible subsequent fasciotomies, is essential and can be limb-saving.
- Maintenance of adequate preload and urine output are important management principles and may require consideration of various strategies being mindful of renal function. [24]
- Maintenance fluid at 2 – 3 x normal requirements.
- Alkalinisation of urine, (sodium bicarbonate 1 – 3mmol/kg/day (IV or orally depending on the clinical status of the patient), given as doses every 4 – 8 hrs) to protect against myoglobin-induced renal failure[25]. Aim to keep urinary pH above 6.5. If metabolic alkalosis develops (pH > 7.45) there is a theoretical risk of enhancing metastatic calcification[24]. It has been suggested that acetazolamide could be given as this can improve metabolic alkalosis by increasing renal clearance of bicarbonate[3, 23, 24]. This is best discussed with the Nephrology Team if the above measurements do not preserve renal function.
- Haemodialysis or CVVH may be necessary for acute renal failure. CVVH is very effective in clearing myoglobin[26], however it remains unknown whether it would alter or shorten the course of acute renal failure once it has developed[27].
- Acute disease-specific caloric support (e.g. MCT oil for long-chain fatty acid oxidation defects).
- Dantrolene or bromocriptine using established protocols (malignant hyperthermia and neuroleptic malignant syndrome)[1].

4.2 Long-term Management

- Avoidance of triggering agents.
- Prevention of catabolic episodes.
- Provision of preferred energy substrates.
  - Low fat-high carbohydrate diet: - fatty acid oxidation defects.
  - MCT oil - CPT II, VLCAD, trifunctional protein defect, translocase.
  - Carbohydrate supplementation - GSD V, IX ***but not*** VII).
  - Triheptanoin is an emerging potential therapy for long chain fatty acid oxidation disorders and CPT II deficiency[28-30].

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