RHABDOMYOLYSIS PROTOCOL IN THE EMERGENCY DEPARTMENT (Unknown patient)

Priority patient: must not be kept waiting in the emergency department

1 DEFINITION AND SYMPTOMS

Acute rhabdomyolysis is the sudden destruction of skeletal muscle fibres, characterised by elevated CPK during acute episodes. It can be associated with acute cardiac involvement. The presence of myoglobinuria indicates an elevation of CPK to at least > 15,000 IU/L (N < 250 IU/L), and therefore severe rhabdomyolysis.

The clinical signs of rhabdomyolysis may include:

- Classically, myalgia = muscle pain (which may precede CPK elevation), muscle fatigability
- Sometimes, diffuse poorly-defined pain (in the back or neck), or inability to walk / stand, prostration
- Arrhythmias, heart failure
- Impaired consciousness
- Hypovolaemic shock
- Myoglobinuria (sign of severe rhabdomyolysis)

Refer to the **Emergency section** on

Differential diagnosis Guillain- Barré syndrome (pain in the legs), myelitis, transient synovitis of the hip, myasthenia (muscle fatigability), acute hepatitis, hepatic cytolysis

2 EMERGENCY TREATMENT TO BE IMPLEMENTED

Rhabdomyolysis with CPK >10,000 IU/L is always an emergency, as the intensity of the episode over the following hours cannot be predicted.

- **If signs of hypoperfusion, rehydrate** with Ringer Lactate or NaCl 0.9% at **10ml/kg** (maximum 500 ml) if no cardiac signs; reassess and repeat if needed.
- Start specific treatment for any intercurrent infection.
- **If CPK < 20,000 U/L:** Infusion for **IV hydration**
  - **G10% (10% glucose) + NaCl 6g/L WITHOUT POTASSIUM.** Intake **2L/m²/day** (maximum flow rate 150 ml/hr). **Do not use ready-made potassium-containing solutions** (balanced electrolyte solutions such as Glucidion, Bionolyte etc.) [BSA = (4W+7)/(W+90)]
- **If CPK >20,000 U/L <u>or immediately if myoglobinuria:</u>** arrange **transfer to HDU/ICU** and, as soon as possible, start **aggressive IV hydration**, with approval from the intensive care doctor:
  - Volume **3L/m²/day**
  - Preparation for 1 litre of solution: 200 mL/kg 30% glucose solution + 400 mL bicarbonate 14‰ + 400 mL NaCl 0.9%
    No potassium or calcium
- Potential specific treatments:
  - **Short-term corticosteroid therapy may be considered** (for the inflammatory component of rhabdomyolysis. Especially useful in rhabdomyolysis due to LPIN1 mutation): **Methylprednisolone 1 to 2 mg/kg/day for 3 to 5 days**, after consultation with a metabolic physician, neurologist or internal medicine specialist.
  - **Levocarnil** 20-50 mg/kg/day by continuous IV, not exceeding 6g/24h for adults; if there is suspected fatty acid oxidation disorder or carnitine transporter deficiency (see overleaf - In this case, the intake of glucose must be reassessed - see protocol for fatty acid oxidation disorder - G2M website). Contraindicated if there is cardiac rhythm disorder or suspicion of *TANGO2* deficiency.
  - Consider **Dantrolene IV** if *RYR1* mutation is suspected (see overleaf).

3 SIGNS OF SERIOUS ILLNESS = Specialist opinion/transfer to intensive care

- **CPK > 20,000 IU/L** (after starting the above infusion)
  - **Consider renal replacement therapy** if potassium level > 5mmol/L despite correctly performed aggressive IV hydration, if there is any ECG abnormality, if anuria/oliguria and positive fluid balances contraindicate continuation of high-volume IV hydration, or if there is kidney injury (creatinine results do not reflect the severity of the kidney impairment, as it is released by muscle breakdown; urea is more reliable).
  - **Monitoring in ICU:** blood glucose**,** Na and K every 2 hours during the first 24 hours, complete electrolyte panel with Ca, P, Mg, urea, creatinine, CPK every 6 hours. Hourly monitoring of urine output > 2ml/kg/h, urine pH and urine specific gravity < 1005. Fluid balance assessment every 3 hours to adjust aggressive IV hydration. ECG in place, hourly trace. Echocardiogram.
- **Cardiac rhythm disorders**, **ECG signs** of hyperkalaemia, **hyperkalaemia > 7 mmol/L**
- **Oliguria / anuria, port wine-coloured urine, kidney failure**
- **Neurological disorders, prostration** (risk of hyperosmolar coma)

4 MONITORING (except for severe rhabdomyolysis > 20,000 IU/L in ICU)

- **Check CPK, electrolytes, Ca, Ph, diuresis and urine colour** every 4 h. Adjust potassium supplementation according to serum potassium levels and renal function (if not included in the infusion there is also a risk of hypokalaemia).
- **Vital signs monitor, ECG every 4 hours**

5 AETIOLOGIES

Acute rhabdomyolysis can be triggered by a viral cause (particularly influenza virus , Covid-19), fever, fasting, anaesthesia, and physical effort. The challenge is to recognise an underlying genetic cause, which could account for recurrent attacks. The search for an aetiology can be guided by the patient's history: acute or chronic nature of the myolysis (return of CPK levels to normal or persistence of elevated CPK some time after the acute episode), severity of the acute episode (very severe if CPK > 50,000 U/L), age of onset, associated signs (neurological, muscular, cardiac etc.). Non-exhaustive list.

- **Possible causes of acute rhabdomyolysis:**
  - **Endocrine causes: cortisol deficiency, hypothyroidism.**
  - **Inflammatory myositis /** dermatomyositis: inflammatory syndrome (+/-), skin rashes, joint involvement, sometimes with no functional deficits, painless. Note that CRP is often normal. **Specific therapeutic emergency: seek specialist opinion.**
  - **Toxic or traumatic causes**
  - **Fatty acid oxidation disorder**: episode can be associated with hypoketotic hypoglycaemia, hyperammonaemia, liver damage, Reye syndrome, myocardial damage / rhythm disorder.
  - ***LPIN1* deficiency**: acute rhabdomyolysis which is often very severe, with early onset (under 6 years of age). Sometimes moderate chronic CPK elevation and muscle fatigability (see specific emergency protocol).
  - **Calcium channel abnormalities (mutations in *RYR1*** and related genes): most often triggered by anaesthesia or physical exertion, associated with malignant hyperthermia, dominant inheritance (family history of rhabdomyolysis should be investigated) (see specific emergency protocol).
  - ***TANGO2* mutations**: associated neurological signs (intellectual disability, encephalopathy, epilepsy) and/or extra-neurological signs (cardiac, with long QT syndrome/Brugada/ventricular rhythm disorders, hypothyroidism), contraindication to many treatments and anaesthetic agents (see specific emergency protocol).
- **Possible causes of chronic rhabdomyolysis include:**
  - **Myopathies and muscular dystrophies:** assess for proximal muscle weakness, calf hypertrophy and sometimes cognitive impairment
  - **Some types of glycogen storage disease**: which can be accompanied by liver damage with hypoglycaemia (Glycogen storage diseases type III, VI, IX), or muscle involvement alone (glycogen storage disease type II (Pompe disease), type V (McArdle disease): "second-wind" phenomenon). Deficiency of glycolysis.

6 TESTS TO DETERMINE AETIOLOGY

Tests to be performed in all cases of acute rhabdomyolysis <u>when starting treatment in ED:</u>

- Blood gases, electrolytes, venous blood lactate, calcium, phosphate, urine dipstick and electrolytes.
- Liver function tests (AST, ALT, GGT, ALP, Bilirubin), PT, factor V, blood ammonia, glucose.
- Inflammation panel (CRP, CBC) with additional tests following specialist advice if suspicion of myositis or dermatomyositis.
- Cortisol. Thyroid function tests
- Acylcarnitine profile: 1 green heparin tube
- Urinary organic acid chromatography: collect the first urine samples after the episode, minimum 2 mL of urine to freeze
- Anti-myositis antibodies: 1 dry red tube (6 mL) without anticoagulant (e.g. at La Pitié: PL7, PL12, EJ, SRP and anti-HMG-CoA reductase antibodies)
- Cardiology investigations: ECG, echocardiogram

Give the patient a prescription for follow-up check of CPK some time after the episode. Complete the 8 hr cortisol test, thyroid function tests and echocardiogram if not already done.

Refer the patient to inborn errors of metabolism specialists at the Necker hospital who will oversee the subsequent **metabolic and/or neuromuscular investigations,** in collaboration with **doctors at the neuromuscular reference centre,** for example:

- If CPK level returns to normal: metabolic panel: blood uric acid level, redox state, consider tests for genes specific to metabolism and calcium.
- If chronic myolysis: neuromuscular specialist opinion, consider autoantibodies specific to dermatomyositis/necrotising myopathy: 1 dry red tube (6mL) with no anti-coagulant (for example at the Pitié-Salpétrière hospital), acid maltase activity, muscle glycogen storage diseases (metabolic panel) and myopathies/dystrophies/myotonia: ENMG +/- muscle biopsy, neuromuscular panel. Consider rarer causes: PGM1-CDG, mitochondrial respiratory chain disorders etc.

If death occurs: - 5 mL blood in EDTA tube at ambient temperature for gene panels.

- Skin biopsy for fibroblast culture (kept in culture medium or sterile physiological saline at ambient temperature).
- Muscle biopsy for histology and western blot (fresh muscle in physiological saline at ambient temperature), myoblasts (as for fibroblasts - biobank laboratory) and frozen muscle sample (liquid nitrogen). Seek specialist opinion during working hours to sent the samples.

6/2S16

Élévation des enzymes musculaires chez l'enfant

Increased creatine phosphokinase in pediatric population

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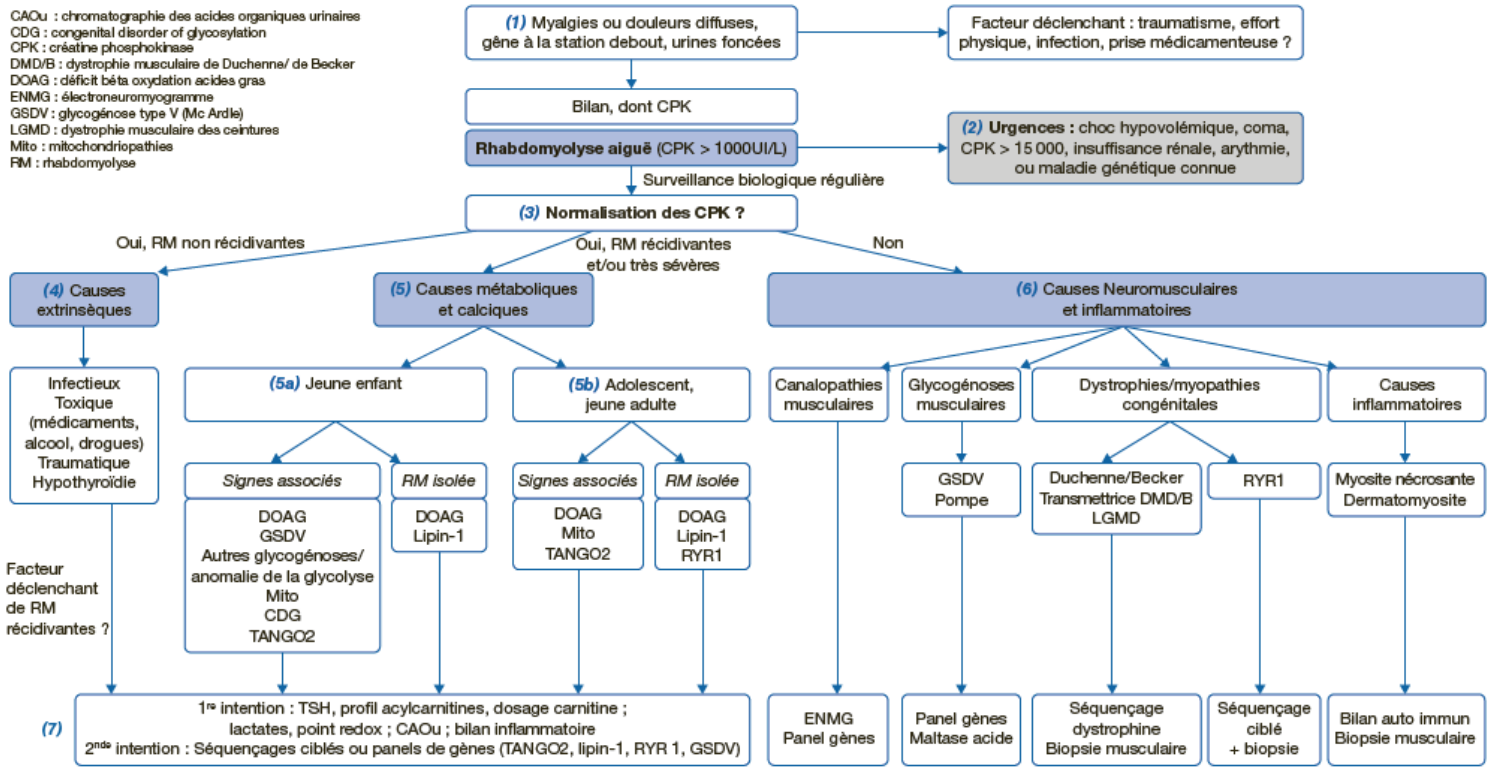
CAOu : chromatographie des acides organiques urinaires
CDG : congenital disorder of glycosylation
CPK : créatine phosphokinase
DMD/B : dystrophie musculaire de Duchenne/ de Becker
DOAG : déficit béta oxydation acides gras
ENMG : électroneuromyogramme
GSDV : glycogénose type V (Mc Ardle)
LGMD : dystrophie musculaire des ceintures
Mito : mitochondriopathies
RM : rhabdomyolyse



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NUMBERS AND MEDICAL SPECIALISTS

On-call telephone numbers for metabolic emergencies:

At night, only medical teams can call in emergency situations, and only if the emergency certificate has not been understood or if the clinical state or test results are worrying. Whenever possible, calls should be made before nightfall.
Secretarial issues must be dealt with via the medical secretariat during the week, or by email addressed to the patient's metabolic medicine specialist.
Certificate issued on Dr