RHABDOMYOLYSIS PROTOCOL FOR A&E (New patient)

Priority patient: must not be kept waiting in A&E

1 DEFINITION AND SYMPTOMS

Rhabdomyolysis (RM) is the sudden destruction of skeletal muscle fibres, characterised by an increase in CPK levels at the time the acute attack occurs. It can be associated with acute cardiac damage. The presence of myoglobinuria indicates an increase in CPK level to > 20 000 IU/L (N <250 U/L) and hence severe rhabdomyolysis.

The clinical signs of rhabdomyolysis include:

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

Look up the **emergency**

Differential diagnosis Guillain-Barré syndrome (pain in the legs), myelitis, transient synovitis of the hip, myasthenia (muscle fatigue), acute hepatitis, hepatocellular injury

2 TREATMENT TO BE STARTED URGENTLY

Acute rhabdomyolysis with CPK > 5000 U/L is always an emergency situation, because it is impossible to predict how severe the attack will become in the following hours.

- **If signs of hypo-perfusion, rehydrate** with Ringer Lactate or NaCl 0.9% at **10ml/kg** (maximum 500 ml) if no cardiac signs; reassess and continue if necessary.
- Start specific treatment for any intercurrent infection.
- **If CPK <20 000 U/L:** Infusion for **IV fluid therapy**
  - **G10% (10% glucose) + NaCl 6g/L WITHOUT POTASSIUM.** Intake **2L/m²/day** (maximum flow rate 150 ml/hr). **Do not** use ready-made solutions containing potassium (polyionic, Glucidion, Bionolyte etc.) [body surface area = (4W+7)/(W+90)]
- **If CPK >20 000 U/L or immediately if myoglobinuria:** arrange **transfer to HDU/ICU** and, as soon as possible, start **hyperhydration**, after getting agreement from intensive care doctor: Volume **3L/m²/day** (maximum flow rate 150 ml/hr)
  - Preparation for 1 litre of fluid: 200 ml of G30% (30% glucose) + 400 ml of Bicarbonate 14 ‰ + 400 ml of NaCl 0.9% No potassium or calcium
  - Provided that there is no infection, and after obtaining the opinion of a specialist in metabolic disease, neurology or internal medicine, consider a short period of **corticosteroid therapy** before transfer to HDU/ICU (rationale: inflammatory component of RM. Will be useful if there is a LPIN1 mutation*)* **Methylprednisolone 1 to 2mg/kg/day for 3 to 5 days**.
- Potential specific treatments:
  - **Levocarnil** 20-50 mg/kg/day by continuous IV, not exceeding 6g/24 hrs for adults; if there is suspected fatty acid oxidation or carnitine transporter deficiency (see over - In this case, the intake of glucose must be reassessed - see protocol for fatty acid oxidation deficiency - G2M web site). Contraindicated if there is cardiac rhythm disorder or suspicion of *TANGO2* deficiency.
  - Consider **Dantrolene IV** if *RYR1* mutation is suspected (see over).
  - If there are underlying neurological abnormalities, known hypothyroidism or long QT, TANGO2 deficiency should be suspected (see drug contraindications in the specific emergency protocol)

3 SIGNS OF SEVERITY = seek advice / transfer to ICU

- **CPK > 20 000 IU/L** (change infusion as indicated above only if transfer to HDU/ITU: Volume **3L/m²/day**(maximum flow rate 150 ml/hr)
  - **Consider extra-renal purification** if potassium level > 5mmol/L despite correctly performed hyperhydration, if there is any ECG abnormality, if anuria/oliguria with serum electrolyte results contraindicating continuation of hyperhydration, or if there is kidney injury (creatinine levels do not reflect the severity of kidney injury, because it is released following muscle necrosis; 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 hrs. Hourly monitoring of urine output > 2ml/kg/hr, urine pH and density < 1005. Blood electrolytes every 3 hrs to adjust hyperhydration. ECG in place, trace per hour. Echocardiogram.
- **Cardiac rhythm disorders**, **ECG signs** of hyperkalaemia, **hyperkalaemia > 7 mmol/L**
- **Oliguria / anuria, port wine-coloured urine, kidney failure**
- **Neurological disorders, exhaustion** (risk of hyperosmolar coma)

4 MONITORING (except for severe rhabdomyolysis CPK > 20 000 U/L in ICU)

- **CPK, electrolytes, Ca, P, urine output and colour** 4 hrs later, then every 4 hrs to 8 hrs depending on the subsequent course of CPK levels. Adjust potassium intake according to potassium level and renal function (if there is no potassium in the infusion, there is **also a risk of hypokalaemia**). **Continuous cardiac monitoring, ECG at 4 hrs, then once a day; Monitoring of cardiac function (clinical and ultrasound).**

5 AETIOLOGY

Acute rhabdomyolysis can be triggered by a viral cause (particularly influenza virus , Covid-19), a 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

- **The causes of acute rhabdomyolysis** (with subsequent normalisation of CPK levels) **include**:
  - **Endocrine causes: cortisol deficiency, hypothyroidism.**
  - **Inflammatory myositis /** dermatomyositis: inflammatory syndrome (+/-), skin rashes, joint involvement, sometimes with no functional deficits, painless. Check that there is no inflammatory syndrome. **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 chronic moderate elevation of CPK with muscle fatigue (see specific emergency protocol).
  - **Calcium channel abnormalities (including mutation of *RYR1*** and related genes): most often triggered by anaesthesia or physical exercise, associated with malignant hyperthermia, dominant transmission (look for family history of rhabdomyolysis or anaesthetic incidents) (see specific emergency protocol).
  - ***TANGO2* mutations:** associated neurological signs (mental retardation, dystonia, encephalopathy, epilepsy) and/or non-neurological signs (cardiac signs e.g. long QT / Brugada syndrome / ventricular rhythm disorders; hypothyroidism). Numerous anaesthetic agents contraindicated (see specific emergency protocol).
- **Among the causes of chronic rhabdomyolysis** (no subsequent return of CPK levels to normal):
  - **Myopathies and muscular dystrophies**: clinically, look for proximal muscle weakness, calf hypertrophy and sometimes cognitive abnormalities.
  - **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 ency of glycolysis.

6 TESTS TO DETERMINE AETIOLOGY

Tests to be performed in all cases of acute rhabdomyolysis <u>when starting treatment in A&E:</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, FBC) 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
- 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 inherited metabolic disease 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). Enquiries relating to dispatch of samples to be made during working hours

NUMBERS AND MEDICAL SPECIALISTS

On-call telephone numbers for metabolic emergencies:

At night, only medical teams can call in emergency situations, and <u>only</u> if the emergency certificate has not been understood or if the clinical state or test results are worrying. As far as possible, make calls before nighttime.

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