TANGO 2 deficiency

Priority patient: must not wait in A&E

Label

If presents with vomiting, diarrhea, high temperature or not eating:

Risk of irregular heartbeat, heart failure, rhabdomyolosis, hypoglycaemia, neurological impairment

Do not wait for signs of decompensation, in all cases initiate management as set out below

1 EMERGENCY WORKUP

Electrolyte test with **serum potassium, magnesium, CPK,** GDS, lactate, liver function test, PT, factor V, **Capillary blood glucose, venous blood glucose,** NH3, lipase, amylase, TSH + work-up depending on the context and the intercurrent illness triggering the crisis. Must not delay treatment.

SYSTEMATIC ECG, BNP, Troponin +/- heart ultrasound depending on clinical findings (look for long QT interval >500 msec or Brugada appearance in leads V1, V2 or other cardiac rhythm disorders).

2 TREATMENT TO BE STARTED URGENTLY, without waiting for test results

- **In cases of hypoglycemia <60mg/dL (3.3mmol/L)**: raise blood sugar with **1ml/kg of 30% glucose orally** (max 30ml) or **2-3ml/kg of 10% glucose** by direct IV and start the glucose infusion below
- **Systematic drip if there is food intolerance or hypoglycemia: G10%** serum glucose infusion with standard electrolyte additions* (not pure 10% glucose). **/!\ Volumes proposed to be adjusted depending on the hydration status and cardiac function**

Age	0-24 months	2-4 years	4-14 years	> 14 years / adult	MAX FLOW RATE
Polyionic 10% glucose	5ml/kg/h (8mg/kg/min)	4ml/kg/h (7 mg/kg/min)	3.5ml/kg/h (6mg/kg/min)	2.5ml/kg/h (4mg/kg/min)	**120ml/h (3L/24h)**

e.g.: Polyionic, Bionolyte, B45, Glucidion, etc. if no solutes available, 10% glucose + 4 to 6g/L of NaCl (70-100 meq/L) and 2g/L of KCl (27 meq/L)

If it is not possible to infuse the patient => Nasogastric tube or gastrostomy: prepare the IV fluids listed above and pass them through the tube at the same rates

- Supplement with **magnesium** if rhythm disorder, without waiting for the magnesium level results
- **No** lipid infusions. No carnitine.
- **Continue** with normal oral or IV drug treatments (particularly possible treatment of hypothyroidism and vitamin therapy)
- Specific treatment of a possible intercurrent infection. Specific hyperNH3 treatment (see hyperammonemia protocol)
- **If severe rhabdomyolysis (CPK > 10 000 IU/L or from the outset if myoglobinuria/muscle pain):** Serum Glucose **G10% + NaCl 6g/L WITHOUT POTASSIUM.** Intake **2L/m²/d** (maximum flow 150 ml/h). **Do not use pre-prepared solutes containing potassium** (polyionic, Glucidion, Bionolyte, etc.) [body surface area = (4P+7)/(P+90)]. See rhabdomyolysis certificate for adjustments

If cardiac rhythm disorders: cardiology consultation. See back for drug contraindications

- These patients are at risk of **long QT syndrome (>500msec)** and **Brugada syndrome**
- **CORDARONE and SOTALOL ARE CONTRAINDICATED** (lengthen QT and risk of ventricular rhythm disorder). Verapamil: its efficacy has not been demonstrated for rhythm disorders in patients with long QT or Brugada syndrome.
- **In acute phase of rhythm disorders** (torsades de pointes for long QT, arrhythmic storm for Brugada): **ISUPREL** (isoproterenol) ESIV effective in acute phase, in both long QT and Brugada (also used for AV blockage).
- **Magnesium** supplements
- **If it persists: CEE and discuss ECMO option.** Transfer to an Intensive Care unit with cardiologist and heart rhythm specialists present.
- **If long QT: propose Beta blocker other than Sotalol** (preference for Corgard if no left ventricular impairment, otherwise Bisoprolol). To be introduced for all long QT on ECG or holter ECG, to prevent or avoid recurrence of ventricular rhythm disorders (this is not a problem if associated with Brugada).

3 SEVERITY SIGNS = Consult / transfer to Intensive Care

- **Coma** or **worsening**of the clinical neurological state
- **QTc > 500 msec or rhythm disorders:** Mg IV. Transfer to a centre or ECMO option. See above
- **Rhythm disorders:** Type 1 Brugada syndrome, ventricular extrasystoles (treatment with Isuprel = Isoproterenol). See above
- **Heart failure**
- **Rhabdomyolysis: CPK > 10 000 IU/L. NH3 > 150 µmol/L**

4 MONITORING under treatment

- Electrocardioscope
- ECG at least daily; Monitoring of cardiac function (clinical and ultrasound).
- Biology: as per initial assessment. Check after 24 hrs as a minimum electrolytes, K+ especially if infused without potassium, liver function (signs may be secondary)

PATHOPHYSIOLOGY:

Patients with *TANGO2* gene mutations present with chronic disorders: neurological impairment (psychomotor retardation, dystonia, cerebellar syndrome, epilepsy, deafness, etc.), hypothyroidism, sometimes long QT syndrome, etc.,
and are at risk of "metabolic crises" that **decompensate with fasting, infections and possibly excess amounts of lipids, mimicking a generalised fatty acid oxidisation disorder (FAOD).** Therefore, in all circumstances where there is a risk of catabolism (fever, gastroenteritis, fasting), they require strict emergency treatment with a glucose infusion.
A recommendation has been recently introduced to administer vitamin therapy by B5 and B9 (5mg of each) for these patients.

CIRCUMSTANCES IN WHICH THERE IS A RISK OF DECOMPENSATION:

° Intercurrent infectious disease, high temperature, weight loss, vomiting, surgery, **or any fasting state, calorie deficiency, wasting or catabolism**.
° **Excess lipids, maybe carnitine administration**
° **Drugs that prolong the QT interval, some anaesthetics**
° **In all these cases, the patient will be kept in hospital. This is an emergency situation:** treat the patient in A&E before transferring them for hospitalisation and apply the protocol on the previous page.

CLINICAL SIGNS OF DECOMPENSATION: Do not wait for these signs!

- Acute neurological degradation, ataxia, loss of consciousness, coma
- **Heart rhythm issues: Life-threatening system due to arrhythmia** specific to this deficiency where **Brugada Syndrome** is associated with a **long QT interval** (which can be observed even without deterioration)
- **Cardiomyopathy:** Caution, the **onset of cardiac signs may occur out of sync** with the metabolic decompensation.
- Severe acute rhabdomyolysis
- Lactic acidosis, hyperammonemia
- Severe hypoglycaemia with prolonged fasting, Reye's syndrome
- Some rare cases of pancreatitis and adrenal insufficiency have been described.

Consult the **Emergency page** on

DRUG CONTRAINDICATIONS / GENERAL ADVICE:

Prohibited drugs:
- salicylic acid, valproic acid
- glucagon in cases of hypoglycaemia (in long fasting hypoglycaemia, glucagon is not useful and delays the treatment)
- any drugs based on lipids in prolonged administration (propofol, medialipids or intralipids, etc.)
- Levocarnil (L-carnitine)
- Drugs that prolong the QT - **Check QTc before using any drug which may interfere with this -** can be consulted on the following website (list is regularly updated, you can access it by creating an account): https://clicktime.symantec.com/3ATrKXhQ5VosjsWtJh372ni6H2?u=https%3A%2F%2Fcrediblemeds.org%2Findex.php%2Fdrug search. For example: some antiarrhythmics (**amiodarone, procainamide, sotalol, quinidine, etc.)** Phenothiazines (Tercian, Largactil, etc.), Erythromycine, Lidocaine IV, Ondansetron, Droperidol, Haloperidol, Atropine, Hydroxyzine (Atarax)
- Drugs that are contraindicated for Brugada Syndrome: list on https://www.brugadadrugs.org
- certain anaesthetics (see below)

- **Extended fasting contraindicated: never leave the patient without a glucose supply for long periods** (infusion or CEF)
- All vaccinations are recommended (particularly influenza).

SURGERY / ANAESTHETICS

- CAUTION: **Never leave a patient in a fasting state without glucose** (drip protocol above) Continue with usual treatments, including vitamins B5 and B9.
- Wherever possible, plan the surgery in a hospital with a cardiology department with experts in heart rhythm and intensive care. Check for presence or absence of long QT interval and cardiac function.
- **ABSOLUTE CONTRAINDICATIONS**: succinylcholine (depolarizing curare: promotes muscle contractions, thus rhabdomyolysis and hyperkalaemia); Propofol under prolonged administration (excess lipids). Sevoflurane and other halogens (myocardium depressors)
- **For the induction**: give preference to **Ketamin and morphinics** +/- non-polarizing curares if needed. (e.g.: rocuronium)
- **For maintenance:** give preference to **morphine and benzodiazepines.** Propofol contraindicated for extended use. If curarization (non-depolarizing curares): Monitoring+++ before intubation (TOF)
- As in RYR1 deficiency, discuss the availability of Dantrolene in the operating theatre (IV anti-calcium agent, as rhabdomyolysis due to calcium release). See the SFAR recommendations: http://sfar.org/recommandations-dexperts-pour-le-risque-dhyperthermie-maligne-en-anesthesie-reanimation/

REFERENCE DOCTORS AND CONTACT DETAILS

To be completed by each department

At night, only the 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. As far as possible make calls before night time.
Secretarial issues must be dealt with via the medical secretariat during the week or by email addressed to the patient's referring metabolic doctor.

Certificate issued on Dr