Patient with CDG syndrome 1A (PMM2-CDG)

Priority patient: must not wait in A&E

Patient label

Patient under treatment for CDG type_____ Usual haemostasis tests: AT III: %, Factor XI: %

Risk of thrombosis including cerebral / haemorrhage / stroke-like episodes / seizures

1 IF ACUTE / UNUSUAL NEUROLOGICAL SIGNS

- Patients at risk of: stroke-like episodes, stroke (thrombotic or haemorrhagic), seizures, migraine (usually in a context of fever or head injury)
- **Laboratory workup:** FBC, **PT, aPTT**, **Antithrombin III, Factor XI,**
  add if possible: Protein C, protein S and factors I, II, V, VII, VIII, IX, X. Liver function tests + other relevant tests if needed
  Note: results of the haemostasis tests will be compared to the usual results for the patient (see above)
- **Brain MRI** with **diffusion** sequence and **T1, T2, FLAIR** and **perfusion sequences (ASL)** to investigate a **stroke-like episode,** cerebral **thrombosis** and/or **haemorrhage**, or another differential diagnoses (including **migraine**)
- EEG to investigate **status epilepticus** (differential diagnosis)

2 SPECIFIC MANAGEMENT IN CASE OF ACUTE EVENTS

A. In case of thrombotic event

- Anticoagulation with **LMWH** or **UFH** following current recommendations.
- **Anti-Xa monitoring is essential** due to the potential deficiency of antithrombin (target range 0.5-1 IU/ml (for LMWH) or 0.3-0.7 (for UFH) 4h after the 2nd or 3rd SC injection for children).
  If AT < 70% and reduced by 20% from baseline level: potential difficulty in balancing anticoagulants. Administration of **human antithrombin (Aclotine ®)** (target after infusion: ATIII at baseline level, check 12 to 24 h after administration). Do not wait for this result or for the infusion before starting anticoagulation, which is urgent!
- Relay with anti-vitamin K or oral anticoagulants after assessment of haemorragic risk.
- If bleeding risk on anticoagulation: FFP is not contraindicated if the procoagulant factors are low.

B. In case of stroke-like episode: (MRI diagnosis with T2/FLAIR sequences, diffusion and perfusion ASL)

- **FFP: if disturbed hemostasis** (reduction by more than 20% from patient's baseline levels and AT < 70% and/or factor XI < 40%)
- **Avoid Aclotine ®** (human antithrombin) : risk of hemostatic imbalance
- **Corticosteroid therapy**: if impaired consciousness / headache, consider methylprednisolone orally or IV with dose of 2mg/kg of body weight/day for 3 to 5 days to reduce vasogenic oedema and intracranial hypertension

C. In case of haemorrhagic event

- Administer **FFP**
- If the haemorrhagic manifestations are not controlled despite administration of FFP, administration of human prothrombin complex concentrates (PCC) can only be considered after checking clotting factors, and only with medicinal products containing protein C and protein S such as Confidex ® or Octaplex ®. Post-infusion objectives: get closer to the patient's baseline levels and refer to a clinical hemostasis team.

WARNING: in all cases, administration of Hemoleven® (factor XI concentrate) or Novoseven® is contraindicated due to the risk of thrombosis associated with this product.

D. If seizures or status epilepticus

- Standard management following local protocol

E. If migraine

- Symptomatic: **Paracetamol.** Consider **NSAIDs if no portal hypertension.** Maintenance therapy to be discussed.

F. If consumptive coagulopathy (DIC)

- Administration of **FFP**
- Human antithrombin (Aclotine®) to be considered depending on the context and if the level of ATIII is reduced by 20% compared to baseline level.

3 IN CASE OF EMERGENCY CONSULT FOR ANOTHER REASON

- **In cases of head injury or fever:** Risk of neurological adverse event, which may be delayed in onset. **Clinical monitoring essential,** either as outpatient or in hospital depending on the context.
- **If significant inflammatory syndrome and increased haemostasis anomalies**: do not hesitate to use **PFC**, and discuss **preventive anticoagulation** if risk factors for thombosis (bed rest, puberty, worsening AT deficiency, inflammatory sd, hypoalbuminemia…).
- **If repeated vomiting: Do not hesitate to set up an infusion** in order to maintain normal hydration (thrombotic risk if dehydration). Usual fluids: no specific infusion, glucose if past history of hypoglycaemia.

PATHOPHYSIOLOGY:

CDG syndrome patients have coagulation disorders with mainly a risk of thrombosis or sometimes bleeding. The levels of several coagulation proteins can be lowered (both pro- and anti-coagulant factors), particularly antithrombin and factor XI, but also protein C, protein S and factor IX.
There are also long-term neurological affections (developmental delay, cerebellar syndrome), and a risk of acute neurological disorders (particularly stroke-like episodes, epilepsy and migraine).
Liver involvement with moderate elevation of transaminases can occur, and should not raise fears of liver failure or Reye's syndrome (very rare).

DRUG CONTRAINDICATIONS / GENERAL ADVICE:

Drug contraindications: Oestrogens, Hemoleven® (factor XI concentrate) or Novoseven® due to risk of thrombosis.
If portal hypertension: avoid salicylates and non-steroidal anti-inflammatory drugs (NSAIDs).

All vaccinations are recommended (particularly influenza).

IN CASE OF SURGERY: potential bleeding and thrombotic risk

- No contraindication to anaesthetics
- At the anesthesia consult, order: FBC, PT (if prothrombin ratio < 70% or INR >1.2, test factors II, V, VII, X), aPTT, factors VIII, IX, XI (even if aPTT normal), ATIII.
- Prophylactic administration of FFP, +/- aclotine depending on the clotting factor deficits, the risk of bleeding during surgery, and the risk of post-operative thrombosis.
- Post-operatively: In the event of post-operative bleeding complications: repeat transfusion of FFP. LMWH prophylaxis discussed on a case-by-case basis once the hemostasis work-up has been stabilized and after assessment of the patient's bleeding/thrombotic risk ratio and the surgical procedure. In the event of prolonged immobilization, compression stockings, hyperhydration and preventive anticoagulation are recommended.

PREVENTION OF THROMBOSIS IN AT-RISK SITUATIONS (bedridden, plaster, extended trip, etc.):

- Before puberty: compression stockings, hyperhydration; discuss preventive anticoagulation on a case-by-case basis, assessing the thrombotic/hemorrhagic risk ratio.
- If LMWH started: **Anti-Xa monitoring is essential** due to the potential deficiency of antithrombin (target: 0.2-0.4 IU/mL 4h after the 3rd SC injection for children). If the anti-Xa target is difficult to attain: consider administration of Aclotine (target: return to baseline ATIII levels, check 12 - 24 h after administration).

IN CASE OF FEVER :

- Systematically give antipyretics and systematically look for a treatable infection, as fever or infections favor acute neurological episodes.
- If significant inflammatory syndrome and increased haemostasis anomalies: do not hesitate to use **PFC**, and discuss **preventive anticoagulation** if risk factors for thombosis (bed rest, puberty, worsening AT deficiency, inflammatory sd, hypoalbuminemia…).

ASSISTANCE WITH PRACTICAL ADMINISTRATION OF TREATMENTS:

Usual dose regimens recommended:

FFP: 10-20mL/kg of body weight, slow IV drip
Human antithrombin (Aclotine): 50 IU/kg of body weight/24h or 48h, by slow IV over 30 min to 1 hour
PPSB: 30 IU/kg of body weight, by direct IV injection
LMWH: usual dose regimens depending on the situation: 100 IU/kg/day to prevent the risk of thrombosis or 100 IU/kg/12h for curative treatment
Corticosteroid therapy: Methylprednisolone orally or IV, 2mg/kg in a single dose (max 60mg)
Standard management of status epilepticus following local protocol

REFERENCE DOCTORS AND CONTACT DETAILS

On-call telephone numbers for metabolic emergencies of:

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