

Patient with CDG syndrome 1A (PMM2-CDG)

Priority patient: must not wait in A&E

Label

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

Risk of thrombosis including cerebral / haemorrhage / stroke-like episodes / epilepsy**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, if possible: Protein C, protein S and factors I, II, V, VII, VIII, IX, X. Liver function tests + other relevant investigations if intercurrent infection.
- NB: the results of the haemostasis tests will be compared to the usual results for the patient (see above)
- **cmRI** with **diffusion** sequence and **T1, T2, FLAIR** sequences and **perfusion sequence (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**

- Anticoagulant treatment with **LMWH** or **UFH** following current recommendations.
- The target anti-Xa level depends on the site of the thrombosis. **Anti-Xa monitoring is essential** due to the potential deficiency of antithrombin (obj 0.5-1 IU/ml (for LMWH) or 0.3-0.7 (for UFH) 4h after the 3rd SC injection in children). If difficulty in achieving the anti Xa target: discuss administration of human antithrombin (Acclotone®) (objective after infusion: AT at basal level).
- **If AT < 70% and reduced by 20% of baseline level:** potential difficulty in balancing anticoagulants. Administration of **human antithrombin (Acclotone®)** (target after infusion: ATIII at the baseline level for the patient, check 12 - 24 h after administration). Do not wait for this result or for the infusion before starting anticoagulation, which is urgent!
- May be possible to replace with anti-vitamin K after assessment of the patient's risk of bleeding
- If bleeding risk on anticoagulation: FFP is not contraindicated if all the factors are low

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

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

C. In case of haemorrhagic event

- Administration of **FFP**
- If the haemorrhagic manifestations are not controlled despite administration of FFP, administration of human prothrombin complex (PPSB) 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 get closer 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 (Acclotone®) to be considered depending on the context and if the level of ATIII is reduced by 20% compared to baseline level

3 IF ATTENDANCE AT A&E IS 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 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 history of hypoglycaemia.

PATHOPHYSIOLOGY:

Patients with CDG syndrome present coagulation disorders which mainly expose them to a risk of thrombosis, but also sometimes to a risk of bleeding. The levels of several coagulation proteins can be reduced (both pro- and anti-coagulant factors), particularly antithrombin and factor XI, but also protein C, protein S and factor IX.

There is also long-term neurological damage (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 (which are very rare).

DRUG CONTRAINDICATIONS / GENERAL ADVICE:

Drug contraindications: Oestrogens, Hemoleven® (factor XI concentrate) or Novoseven® due to risk of thrombosis.

All vaccinations are recommended (particularly influenza).

IN CASE OF SURGERY: potential bleeding and thrombotic risk**- No contraindication to anaesthetics**

- At the anaesthetic consultation, carry out: 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, +/- aprotine depending on the clotting factor deficiencies, 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 PFC. 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, in plaster etc.):

- Prepubertal child: 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 in the child). If the anti-Xa target is difficult to attain: consider administration of Aprotine (target after perfusion: ATIII at the patient's baseline level, 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.

ASSISTANCE WITH PRACTICAL ADMINISTRATION OF TREATMENTS:**Usual dose regimens recommended:**

FFP: transfusion 10-20ml/kg

Human antithrombin (Aprotine): 50 IU/kg/24h or 48h, by slow IV over 30 min to 1 hour

PPSB: 30 IU/kg 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