

CDG syndrome Ia (PMM2-CDG)

Priority patient: must not wait in A&E / ED

Patient Label

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

Risk of thrombosis including cerebral / bleeding / 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 enzymes + other relevant investigations if intercurrent infection.
- NB: the results of the hemostasis tests will be compared to the patient's usual results (see above)
- **Brain MRI with diffusion, T1, T2, FLAIR, perfusion (ASL)** sequences to investigate a **stroke-like episode, thrombosis** and/or **hemorrhage**, or another differential diagnoses (including **migraine**)
- EEG to investigate **status epilepticus** (differential diagnosis or associated symptom)

2 SPECIFIC MANAGEMENT IN CASE OF ACUTE EVENT

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.
- **If ATIII < 70% and reduced by 20% of baseline level:** potential difficulty in balancing anticoagulants. Administration of **human antithrombin (Aclotine®)** (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!
- Possible to switch to **viamine K** antagonists after assessment of the patient's bleeding risk.
- 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, diffusion and perfusion ASL sequences)

- **FFP: if abnormal hemostasis** (reduction by >20% of patient's baseline levels and AT < 70% and/or factor XI < 40%)
- **Avoid Aclotine®** (human antithrombin) : risk of hemostase imbalance.
- **Corticosteroids:** if impaired consciousness / headache, consider methyl/prednisolone orally or IV 2mg/kg/day for 3 to 5 days to reduce vasogenic oedema and intracranial hypertension

C. In case of hemorrhagic event

- Administrate **FFP (Fresh frozen plasma)**
- If hemorrhagic manifestations are not controlled despite administration of FFP, administration of human prothrombin complex concentrate (PCC) can only be considered after checking clotting factors, and only with drugs containing protein C and protein S such as Confidex® or Octaplex®. Targets after administration: Factor XI > 40% and approaching patient's baseline level. Consult 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 IF EMERGENCY CONSULT FOR ANOTHER REASON

- **In case of head injury or fever:** risk of neurological adverse event, which may be delayed. **Clinical monitoring essential**, either as outpatient or in hospital depending on 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 hypoglycemia.

PATHOPHYSIOLOGY:

Patients with CDG (congenital disorder of glycosylation) 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 (both pro- and anti-coagulant factors) can be low, 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 progress to 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.

All vaccinations are recommended (particularly influenza).

IN CASE OF SURGERY:

- **No contraindication to anesthetics.**

- At the anesthetic 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 +/- a clotting factor depending on the clotting factor levels, the risk of bleeding during surgery, and the risk of post-operative thrombosis.

- **Post-operatively:** consider LMWH prophylaxis on a case-by-case basis once the hemostasis results have stabilised and after assessing the balance of bleeding vs thrombosis risks relating to the patient and the surgical procedure.

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

- Prepubertal child: **consider on a case-by-case basis**, assessing the balance of risk of thrombosis vs. bleeding.

- If LMWH initiated: **anti-Xa monitoring is essential** due to the potential deficiency of antithrombin (target: 0.1-0.3 IU/mL 4h after the 3rd SC injection for children). If the anti-Xa target is difficult to attain: consider administration of Aclotine® (target after perfusion: ATIII at the patient's baseline level, check 12-24h after administration).

ASSISTANCE WITH PRACTICAL ADMINISTRATION OF TREATMENTS:**Usual recommended doses:**

FFP: transfusion 10-20mL/kg

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

PCC: 30 IU/kg by direct IV injection

LMWH: usual dose regimens depending on the situation: 100 IU/kg/day for thrombosis prophylaxis or 100 IU/kg/12h for curative treatment.

Corticosteroids: Methylprednisolone oral or IV, 2mg/kg in a single dose (max 60mg).

Standard management of status epilepticus following local protocol.

REFERENCE PHYSICIANS 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 the outpatient office during the week or by email addressed to the patient's referring metabolic physician.

Certificate issued on :

Dr