:: Classic Homocystinuria

- *This document is a translation of the French recommendations drafted by Professor Pascale De Lonlay and Dr Gilles Bagou, reviewed and published by Orphanet in 2007.*
- *Some of the procedures mentioned, particularly drug treatments, may not be validated in the country where you practice.*

Synonyms:

homocystinuria due to cystathionine beta synthase deficiency

Definition:

Cystathionine beta synthase is an enzyme that breaks down methionine. A deficiency of this enzyme leads to a build-up of toxic homocysteine in the body. Classic homocystinuria consists of chronic intoxication, without acute decompensation except for **vascular accidents and acute psychiatric episodes**, where the diversity of clinical manifestations makes diagnosis difficult and often delays it until late childhood or adulthood. The associated clinical picture is made up of a combination of disorders, affecting the bones (Marfan syndrome, osteoporosis, ligamentary hyperlaxity) and the eyes (lens subluxation, myopia, cataract) and resulting in learning difficulties, sometimes psychiatric problems, and a serious risk of thromboembolic arterial or venous vascular accidents.

Further information:

See the Orphanet abstract

Pre-hospital emergency care recommendations
Call for a patient suffering from classic homocystinuria

Synonyms

- cystathionine-ß-synthase deficiency

Mechanisms

- deficiency of cystathionine-ß-synthase, an enzyme that breaks down methionine, leading to a build-up of homocysteine, which is toxic to the body (particularly endothelial lesions)

Emergency situations

- venous or arterial thrombosis
- acute psychiatric problems

Commonly used long-term treatments

- vitamin B6
- low-protein (no animal protein, in particular) or methionine-free diet

Complications

- be wary of an acute psychiatric picture in any affected patient
- be wary of forms that are resistant to vitamin B6
- be wary of thrombosis, for which anaesthesia creates the right conditions

Specific pre-hospitalisation medical care

- symptomatic treatment
- vitamin B6 (100mg/kg/d) if the patient has some and if resistance is absent or not known

Further information

- CLIMB National Information Centre for Metabolic Diseases: http://www.climb.org.uk
- Please visit www.orpha.net and type the name of the disease → in the summary page click on “Expert centres” on the right tab → select “United Kingdom” in the “Country” field in the Expert centres page.

Recommendations for hospital emergency departments

Emergency situations

Thrombo-embolic accidents

The **risk of decompensation** is associated primarily with surgery, where there is a very high risk of venous or arterial thrombosis **if the plasma homocysteine level exceeds 50 µmol/L**.

- **Immediate diagnostics**:
  - **Emergency investigations**
    - full clinical examination
    - vascular examination: arterial pulses, check for phlebitis
    - neurological examination, level of consciousness
  - **Confirm the diagnosis**: abnormal presence of homocysteine and homocysteine-cysteine mixed disulfide in the blood (and urine), raised plasma methionine concentrations.
    - request a **total homocysteine and factor VII assay**. The **specimen needs to be stored under perfect conditions** for the plasma homocysteine assay **(immediate deproteinisation**)
    - carry out chromatography screening for urinary organic acids, to make sure that there is no methylmalonic acid in the urine (**rule out an alternative metabolic deficiency**)
  - **Assess severity**: severity is indicated by acute accidents: vascular venous or arterial accidents, for which the right conditions are created by all vascular risk factors and anaesthesia; severity is also indicated by disorders affecting the organs listed above and by the absence of a response to vitamin B6 treatment.

- **Immediate treatment**:
  - **Try to establish whether the patient is sensitive or resistant to vitamin B6**; if there is any doubt, prescribe some routinely: vitamin B6 100 mg/K/d. Do not exceed a dosage of 1g per day
  - **Treat the vascular accident**
    - protein-free, energy-rich diet, in the form of carbohydrates and lipids:
    - oral emergency diet of which the family will be aware
    - otherwise, infuse 10 % dextrose plus lipids for energy-rich dietary intake
    - do not give protein. Give a mixture of methionine-free amino acids if the patient takes them
    - betaine (100 mg/K/d, p.o.) if possible, plus folic acid (10 mg/d, p.o.)
  - If there are vascular complications or psychiatric problems, or if anaesthesia is planned, get in touch immediately with one of the Expert Centres

Anaesthesia

- **Anaesthesia is contra-indicated if the total plasma homocysteine level is > 50 µmol/L.**
- **If surgery is planned**, ask the specialist Biochemistry laboratory (e.g. Necker Biochemistry B) for an emergency plasma homocysteine level during working hours, also for clotting factor VII.
- **Anticoagulation**, at an isocoagulant dosage, needs to be discussed after the procedure, depending on an assessment of the patient's metabolic function and vascular risk factors.

Additional therapeutic measures and hospitalisation

Feeding

In forms that are resistant to vitamin B6, **protein restriction** is designed to eliminate all free homocysteine and to achieve a total homocysteine level of ‹ 50 µmol/L, the threshold beyond which the risk of thrombosis can be ruled out.

- **Strict diet** in which methionine is restricted to 150 to 200 mg / day (methionine accounts for 3 % of proteins).
- **All animal proteins are ruled out from the diet** and also certain types of food, such as dry vegetables, flour and oleaginous fruits, that are too rich in vegetable protein.
- **Make up for the loss of energy** from foodstuffs that have been removed as a result of the low-protein diet: pasta, rice, semolina, cakes, bread, biscuits.
- **Prescribe a mixture of methionine-free amino acids** (refer to the patient's prescription or contact the Reference Centre; this diet will have to be lifelong).
- **Limits to the strict diet:**
  - **in cases of established learning difficulties ("the harm has already been done")**
  - **in late childhood (difficulty in setting up this change in dietary habits)**
- **In cases of surgery**, this diet remains essential in view of the risk of thrombosis.
- **If vitamin B6 treatment fails**, betaine (100 mg/K/d p.o.) and folic acid (10 mg/d p.o.) are prescribed along with the low-protein diet.

Organ donation

– The disease does not allow organ donation

Emergency telephone numbers

- Please visit www.orpha.net and type the name of the disease → in the summary page click on “Expert centres” on the right tab → select “United Kingdom” in the “Country” field in the Expert centres page.

Documentary resources

- Sriver CR, Beaudet AL, Sly WS, Valle D eds: The Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, New York, 8th edn., 2001.
- Fernandes J, Saudubray JM, Van Den Berghe G eds: Inborn Metabolic diseases. Springer-Verlag, Berlin Heidelberg New York. 3° ed, 2006.

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