WHEN TO CONSIDER HOMOCYSTINURIA CAUSED BY CYSTATHIONINE BETA-SYNTHASE (CBS) DEFICIENCY.

Association and severity of symptoms vary depending on patients
Spectrum of clinical manifestations ranging from paucisymptomatic to severe forms with 4 main types of impairment

Neonatal screening in France since 1st January 2023: most of these symptoms should no longer be seen in children born in France after January 2023 who have been screened[1]

Clinical signs

Inconstant ophthalmological
Age of onset: primarily during childhood

Rapidly progressing myopia
(Sub)luxation of the lens
Microspherophakia
Glaucoma

Central nervous system

Neurological impairment
Age of onset: from childhood

Intellectual disability
Learning / neurodevelopmental / autistic spectrum disorders
ADHD
Epilepsy

Psychiatric disorders
Age of onset: adolescence/adulthood

Personality disorders, Anxiety-depressive syndrome, Psychotic episodes, etc.

Bones and skeleton
Age of onset: childhood

Marfan-like body type
Dolichostenomelia, Arachnodactyly

Bone deformities
Genu valgum, flat feet, kyphosis, scoliosis, pectus excavatum

Osteoporosis

Sometimes dysmorphia
Ogival palate, poorly rooted teeth

Vessels
Possible impairment starting in childhood, but onset may occur later in adolescence or adulthood

Most frequent cause of morbidity and mortality, and possible telltale sign for the disease, with no other associated signs

Risk of thromboembolism
Venous and arterial vascular thrombosis (stroke, pulmonary embolism, thrombosis in the limbs or digestive, etc.)

Specialist workup

Additional tests

Total plasma homocysteine (Hcyt)

Normal → **Differential diagnoses**
Marfan syndrome
Other genetic causes

Abnormal = Hyperhomocysteinaemia

- **Moderate increase (14-30 µmol/l)**
- **Intermediate increase (30-100 µmol/l)** **OR** **Severe hyperHcyt (>100 µmol/l) Probable CBS deficiency**

Homocystinuria caused by CBS deficiency?

Workups should be done before any vitamin supplements are given (B12, B6, Folates)

Tests to assess vitamin status
CBC, reticulocytes, B12, Folates, methylmalonic acid in the plasma

Additional metabolic assessments[2]

Abnormalities indicating an inherited metabolic disease

- **YES** → **Confirmatory genetic analysis** to be carried out subsequently by a specialist centre
- **NO** → **Secondary causes of hyperhomocysteinaemia**

Folate and/or B12 deficiency due to:
- Dietary shortfall
- Acquired malabsorption
- Hereditary malabsorption
- Iatrogenic medication (PPI)

Kidney failure, diabetes, cancer

Hypothyroidism

Toxic: repeated use of nitrous oxide (for medical reasons or due to addiction), chemotherapy

Seek specialist advice quickly from a Centre of Excellence: Rare Disease Centre of Reference / Competence: https://www.filiere-g2m.fr/annuaire/
Initial assessment and specialist treatment to be coordinated by the Centre of Excellence, specific treatment to be rapidly implemented

Genetic counselling, family screening in a specialist centre

For more information: PNDS: French National Authority for Health - Homocystinuria caused by cystathionine beta-synthase (CBS) deficiency (has-sante.fr) **and emergency protocol:** https://www.filiere-g2m.fr/urgences

Specialist medical opinion and reference laboratory

Maladies rares Héréditaires du Métabolisme
Filière nationale de santé

[1] Neonatal screening (https://depistage-neonatal.fr/) **makes it possible to identify affected neonates and initiate treatment at an early stage to prevent the onset of clinical symptoms. However, false negatives can occur in the screening (especially in B6-sensitive forms) and it is worth investigating this disease if the patient has telltale symptoms.**

[2] **Plasma: amino acid chromatography, methylmalonic acid, Urine: organic acid chromatography, methylmalonic acid.**