WHEN TO CONSIDER COBALAMIN C (CblC) DEFICIENCY

Age at onset, type and severity of symptoms vary depending on patients, with inevitable worsening if the specific treatment (=Hydroxocobalamin) is not administered

MOST FREQUENTLY ASSOCIATED NEUROLOGICAL/HAEMATOLOGICAL/OPHTHALMOLOGICAL/RENAL SYMPTOMS
MOST FREQUENTLY DIAGNOSED EARLY (PARTICULARLY IN THE FIRST MONTHS OF LIFE. SOMETIMES ANTENATALLY), AND SOMETIMES LATER IN CHILDREN AND ADOLESCENTS/ADULTS

Clinical signs

Neurological impairment

The earlier the onset occurs, the greater the severity, of variable intensity

Neonates, first months of life

Possible microcephaly, hypotonia, progressively worsening encephalopathy with lethargy, possible convulsions, and frequently **associated damage to internal organs**[1]
Sometimes hydrocephalus

Children

Sometimes acquired microcephaly, **psychomotor development disorder,** hypotonia, epilepsy, **intellectual disability, demyelinating neuropathy**

Adolescents/adults

Progressive encephalopathy with cognitive decline, trouble walking due to ataxia, and peripheral neuropathy linked to **subacute combined degeneration of the spinal cord**
Thromboembolic complications
Neuro-psychiatric symptoms: behavioural issues, psychosis, dementia

Haematological diseases

Normalisation under treatment, especially in early forms and in children
Megaloblastic macrocytic anaemia, cytopaenia

Vascular damage

Arterial and/or venous thrombosis (in all regions), especially in adolescents/adults
Pulmonary arterial hypertension

Inconstant ophthalmological

Possible telltale clinical sign, especially found in early forms and in children
Nystagmus secondary to **maculopathy,** with the potential to progress to**retinal degeneration** and optical atrophy

Kidney involvement

Sometimes isolated and a telltale clinical sign (adolescents/adults), may be reversible with B12
Atypical haemolytic uraemic syndrome (aHUS)
Glomerulopathy, tubulointerstitial nephropathy

Metabolic decompensation

Rare and prevented by treatment, but a potential telltale clinical sign in neonates/infants[1]
Progressive altered consciousness up to**coma,** hypotonia, polypnoea

Other

Feeding difficulties
(early forms)
Unusual growth:intrauterine **growth restriction** (IUGR) or post-natal delay
Cardio-pulmonary failure:
congenital cardiopathy,
foetal cardiomyopathy
(dilated, left ventricular noncompaction), interstitial pneumopathy
Oral conditions:
stomatitis, glossitis

Additional tests

Laboratory:
Macrocytic anaemia, thrombocytopaenia and/or neutropaenia with normal B12 and folate levels, sometimes kidney disease (HUS)
Metabolic acidosis with high anion gap, +/- hyperlactataemia and +/- hyperammonaemia[2] in neonates and infants
Brain MRI with spectroscopy: possibility of cerebral atrophy, leukoencephalopathy, damage to basal ganglia (Leigh Syndrome-type), lactate peaks; MRI may be normal

Specialist workup

Cobalamin C deficiency?

Specialist workup in collaboration with a centre of excellence
at the same time as looking for other potential differential diagnoses

Methylmalonic acid (blood +/- urine), Total plasma **homocysteine**: high
Plasma amino acid chromatography: low **methionine**
Plasma acylcarnitine profile: high C3 +/- C4DC

Confirmatory genetic analysis if biochemically oriented, to be carried out subsequently by a specialist centre

Specialist advice from a Centre of Excellence: Rare Disease Centre of Reference / Competence, *: https://www.filiere-g2m.fr/annuaire/*

Initial assessment and specialist treatment coordinated by the Centre of Excellence, specific treatment to be rapidly implemented

Genetic counselling, family screening in a specialist centre

For more information: emergency protocols for each symptom and/or disease: https://www.filiere-g2m.fr/urgences

Specialist medical opinion and reference laboratory

[1] Neurological damage often associated with growth issues (sometimes IUGR), feeding difficulties and multiorgan damage (renal, haematological, ophthalmological, etc.) and metabolic issues, risk of death if specific treatment by hydroxocobalamin is not initiated rapidly.
[2] Pay attention to sample-taking conditions. Always perform tests but do not necessarily wait for test results to start treatment.
Standard norms (may vary depending on the laboratories): Neonates: ammonia <100 µmol/L, Non-neonates: ammonia <50 µmol/L, see: emergency protocol for hyperammoniaemia: https://www.filiere-g2m.fr/urgences.

Maladies rares Héréditaires du Métabolisme
Filière nationale de santé