WHEN TO CONSIDER A BIOTINIDASE OR HOLOCARBOXYLASE SYNTHETASE (HCS) DEFICIENCY.

Most frequently revealed when **associated with neurological or dermatological symptoms,**
from the neonatal period or the first weeks or months of life (HCS deficiency, severe biotinidase deficiency) or in later childhood or adulthood, and sometimes only by acute episodes triggered by intercurrent infections.
The age of onset, and association and severity of symptoms vary depending on patients and the type of deficiency.

Specific treatment with biotin to prevent/reverse some symptoms or slow their progression; greater effect when introduced at an early stage.

Clinical signs

Neurological impairment

Early-onset forms

Epilepsy (myoclonic, generalised or focal seizures)
Psychomotor development disorder: hypotonia, language delay, ataxia
Sensorineural hearing loss (biotinidase deficiency only)
Optical atrophy

In children / adolescents / adults

Potential symptoms of early forms that are identified later on
Progressive or sub-acute spastic paraparesis associated with **myelopathy**[1]
Progressive or sub-acute **optical neuropathy**[1]
Progressive or sub-acute peripheral neuropathy[1]
MS-like clinical pictures[1]

Dermatological conditions

Erythematous, scaly skin eruptions, often around orifices and skin folds, reminiscent of seborrheic dermatitis or ichthyosis

Alopecia sometimes involving eyebrows and eyelashes

Recurrent viral or fungal infections

Inconstant ophthalmological

Recurrent **keratoconjunctivitis**

Damage to vision linked to **optical neuropathy** with optical atrophy

Acute metabolic decompensation

Triggered by intercurrent diseases or catabolism, sometimes the only signs in some partial deficiencies
May be absent in older child or adult forms

Vomiting, feeding problems
Altered consciousness, lethargy
Metabolic acidosis: **tachypnoea,** Kussmaul breathing, apnoea, stridor
Potentially progressing to **coma** and death if untreated

Additional tests

Laboratory:
Workup may be normal, or show (fluctuating) **Hyperlactataemia**, and during acute metabolic decompensation: **lactic acidosis** with **ketosis,** sometimes **hyperammonaemia**[2]

Brain and medulla MRI with spectroscopy: abnormality around the 3rd ventricle with restricted diffusion, potential abnormality in myelin and lactate peak **Cervical spinal cord:** non-specific myelin abnormalities with **T2 hypersignal.** Distribution abnormalities are generally bilateral and symmetrical.

There are forms of optical neuromyelitis such as NMOSD (neuromyelitis optical spectrum disorder) with hypersignal of the optical nerves and/or abnormalities in the mammillary bodies and restricted diffusion

Specialist workup

Biotinidase deficiency or holocarboxylase synthetase deficiency?

Specialist workup in collaboration with a Centre of Excellence
at the same time as looking for other potential differential diagnoses[3]

Plasma acylcarnitine profile, urinary organic acid chromatography: telltale abnormalities

Measurement of enzyme activity: serum biotinidase activity +/- holocarboxylase synthetase on fibroblasts

Confirmatory genetic analysis to be carried out subsequently by a specialist centre

Specialist advice froma Centre of Excellence: Rare Disease Centre of Reference / Competence: https://www.filiere-g2m.fr/annuaire

Initial assessment and specialist treatment coordinated by a 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] Possible (sub-acute or chronic) neurological presentations with no previous episodes of acute metabolic decompensation.
[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): Neonate: ammonia <100 µmol/L, Non-neonates: ammonia <50 µmol/L, see: emergency protocol for hyperammoniaemia: https://filiere-g2m.fr/urgences
[3] Other metabolic diseases, biotin deficiency, acrodermatitis enteropathica, other causes of epilepsy, hearing loss, optical atrophy.
Demyelinating inflammatory conditions of the nervous system, optical neuromyelitis.

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