WHEN TO CONSIDER ACID SPHINGOMYELINASE DEFICIENCY

THREE MAIN PHENOTYPES: THE MOST COMMON CHRONIC VISCERAL FORM, AND THE 2 RARER NEUROVISCERAL FORMS[1]

The chronic visceral form is characterised by visceral damage with no neurological damage *and onset may be in childhood or adulthood, with symptoms varying greatly in their severity*
There is an early onset for the chronic infantile visceral form in the first few months of life, and the visceral and neurological progression is rapid
The chronic neurovisceral form is an intermediate phenotype that begins in children, *with both internal organ and neurological* ***damage,*** *which most often progresses slowly*

Maladies rares Héréditaires du Métabolisme
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Clinical signs

Organ impairment is the most prominent sign

Organomegaly

Variable severity and age at onset, frequently the 1st symptom

From 3 months of age in the infantile neurovisceral form

Splenomegaly, sometimes massive

Hepatomegaly

Lung damage [2]

Interstitial damage[3], dyspnoea, **frequent infections**, possible progression to pulmonary fibrosis and **respiratory failure**

Liver damage [2]

Moderate increase in transaminases

Possible progression to **fibrosis** and **cirrhosis, possibly** with **portal hypertension (PHT)**

Sometimes **signs of hepatocellular insufficiency and ascites**

Other organ impairments

Skeletal damage and growth retardation

Possible growth retardation and/or **puberty delay**
Osteopenia, osteoporosis
Frequent bone/joint pain , **fractures**

Haematological diseases

Thrombocytopaenia, other signs **of hypersplenism**
Haemorrhagic syndrome(nosebleeds and bleeding gums, petechiae, etc.)

Cardiovascular damage (chronic forms)

Early coronary artery disease, coronary artery calcifications
Valvulopathy
Abnormalities in the **lipid profile (pro-atherogenic profile)**

Inconstant ophthalmological

Possible in all forms but occurs more frequently in the neurovisceral infantile form
"Cherry red" mark on the retinal macula[4]

Other

Sometimes disabling **asthenia**, **Digestive** symptoms (abdominal pain, diarrhoea), Association with MGUS (chronic forms)
Sometimes dysmorphia (crude features) (forms with neurological damage)

Neurological impairment

Only in neurovisceral forms, rarer

Infantile neurovisceral form

Onset at around 6 months, fairly stereotypical progression, associated with severe internal organ damage starting at around 3 months of life

Hypotonia, stagnation followed by regression of psychomotor development, signs of neuropathy, progressing towards disability and death in the early years of life (often <3 years)

Chronic neurovisceral form

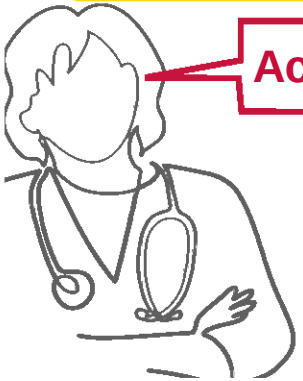
Onset during childhood, variable depending on the patient
Intellectual disability, neuropathy, cerebellar syndrome, extra pyramidal damage, psychiatric symptoms

Additional tests

Non-specialist laboratory workup: results that may indicate this diagnosis:

Sometimes **thrombocytopaenia** (hypersplenism), possible **cytolysis** (most often transaminases <3N) and elevated bilirubin (rarer), and **sometimes signs of hepatocellular insufficiency (coagulation factor abnormalities)**
Abnormal lipid profile: Low HDL-C, hypertriglyceridemia and high LDL-C
Overload cells on myelogram (if this has already been performed, but not recommended in the diagnostic procedure)
Thoracic imaging (X-ray, scan): apparent interstitial syndrome 3, possible lung calcifications
Abdominal ultrasound: hepatomegaly and splenomegaly (sometimes nodular), liver calcification (rare but more specific than lung calcifications), adrenal calcifications, adrenal hypertrophy, PHT and cirrhosis (monitored)

Specialist workup



Acid Sphingomyelinase deficiency?

Specialist workup
in collaboration with a centre of excellence, and at the same time as looking for other potential differential diagnoses[5]

Acid sphingomyelinase enzymatic activity assay:
a deficit of activity supports the diagnosis

Confirmatory genetic analysis for (*SMPD1 gene*)

Specialist advice from a Centre of Excellence specialising in lysosomal diseases: Rare Disease Centre of Reference / Competence: https://www.filiere-g2m.fr/annuaire/

Initial assessment (including biomarker assays), specialist care, specific treatments (indication, initiation) to be coordinated by a Centre of Excellence

Genetic counselling, family screening in a specialist centre

For more information: **PNDS under preparation:** French National Authority for Health
French National Diagnosis and Treatment Protocols (PNDS) (has-sante.fr)
and the **Lysosomal disease treatment assessment committee** website (CETL) **www.cetl.net**

Specialist medical opinion and reference laboratory

[1] Previously known as Niemann Pick Disease Type B (chronic visceral form), type A (infantile neurovisceral form) and Type A/B (chronic neurovisceral form)
[2] Main causes of Morbidity/Mortality in forms where there is chronic visceral impairment.
[3] Sometimes the abnormalities are initially solely radiological with no clinical implications.
[4] To be determined by a dedicated clinical examination, because it does not lead to loss of visual acuity.
[5] Main differential diagnoses: haemopathy, other metabolic disease (especially Gaucher disease, see diagnosis help sheet: https://www.filiere-g2m.fr/banque-nationale-de-donnees-maladies-rares).