WHEN TO CONSIDER ALPHA-MANNOSIDOSIS

PROGRESSIVELY WORSENING MULTISYSTEM DISORDER

Association and severity of symptoms vary depending on patients 2 main phenotypes:
Severe form in infants: rapid progression, death in infancy: *neurological damage, organomegaly, frequent infection is the most prominent sign*
More moderate, slowly-evolving form:
skeletal damage, hearing loss in early years, intellectual disability, ataxia is the most prominent sign in adulthood

Maladies rares Héréditaires du Métabolisme
Filière nationale de santé

Clinical signs

Morphological abnormalities
becoming more marked with age

Facial dysmorphia (similar to that found in patients with mucopolysaccharidosis):

heavy features, frontal bossing, **enlarged skull,** marked nasal bridge, **wide, upturned nostrils, gapped teeth, prognathism, possible early height** gain

Early, often major

Thoracic-lumbar **kyphosis**
Deformed sternum, pectus carinatum,
genu valgum,
Hip dysplasia
Joint stiffness and limitations

Neurological impairment
with a severity that can vary between patients

Severe forms: early hypotonia, limited learning
Milder forms:
Language delay, intellectual disability
Developmental delay, sometimes late to walk
Clumsy gross and fine motor skills
Possibility of spastic paraplegia
Psychiatric symptoms with psychosis, behavioural issues
Sometimes hydrocephalus

ENT damage

Constant neuro-sensory or mixed**hearing loss** beginning in childhood,
Chronic **nasopharyngeal congestion**

Immune disorder

Frequent bacterial infections
(ENT, primarily pulmonary)

Other possible impairments

Frequent moderate hepatosplenomegaly
Inguinal, umbilical and hydrocele hernias

Ophthalmological damage:
eye refraction problems (hypermetropia, myopia, astigmatism), corneal haze, cataracts, glaucoma, damaged retinas

Cardiac impairment: possible thickening of the heart valves with failure or stenosis, possible decrease in ejection fraction

Specialist workup

Additional tests

X-Rays (Spine, thorax, pelvis, hand): spinal (platyspondyly, rostrum, ovoid) and costal deformities, thoracic-lumbar kyphosis, scoliosis, coxa valga, femoral and acetabular dysplasia, multiple dysostosis, epiphyseal changes, focal lytic lesions, delayed bone age, osteonecrosis, osteopenia

Additional tests

Brain MRI:
Cortico-subcortical atrophy (predominantly in the region of the vermis) and white matter abnormality

Laboratory: CBC: presence of vacuolated lymphocytes

Alpha-mannosidosis?

Seek specialist neuro-metabolic advice

Specialist workup
In collaboration with the centre of excellence, at the same time as looking for other potential differential diagnoses[1]

Measurement of α-D-mannosidase activity: low activity supports the diagnosis
+/- Analysis of oligosaccharides in the urine
Confirmatory genetic analysis (*MAN2B1* gene)

Seek specialist advice quickly from a Centre of Excellence: Rare Disease Centre of Reference / Competence:
https://www.filiere-g2m.fr/annuaire/

Initial assessment, specialist care, specific treatment (indications, initiation) to be coordinated by a Centre of Excellence

Genetic counselling, family screening in a specialist centre

For more information: **CETL website** (Lysosomal disease treatment assessment committee: www.cetl.net).

Specialist medical opinion and reference laboratory

[1] **Other lysosomal storage diseases (mucopolysaccharidoses), see the diagnosis help sheet:** https://filiere-g2m.fr/diagnostic/les-fiches-diagnostiques **or other neurological/metabolic diseases, constitutional bone disease, other genetic syndromes, depending on the presentation**