DISCOVER
Alpha Mannosidosis

Alpha-mannosidosis

Recognising “red flags” to aid early diagnosis

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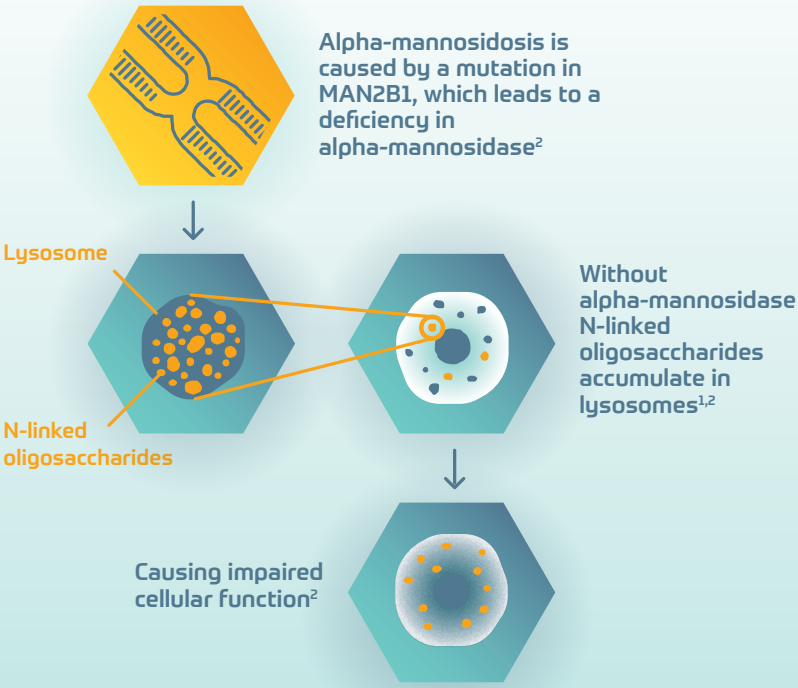
Chiesi
global rare diseases

What is alpha-mannosidosis?

Alpha-mannosidosis is a rare lysosomal storage disorder caused by the deficiency of alpha-mannosidase, leading to accumulation of mannose-rich oligosaccharides in all tissues and resulting in impaired cellular function and apoptosis.[1,2]

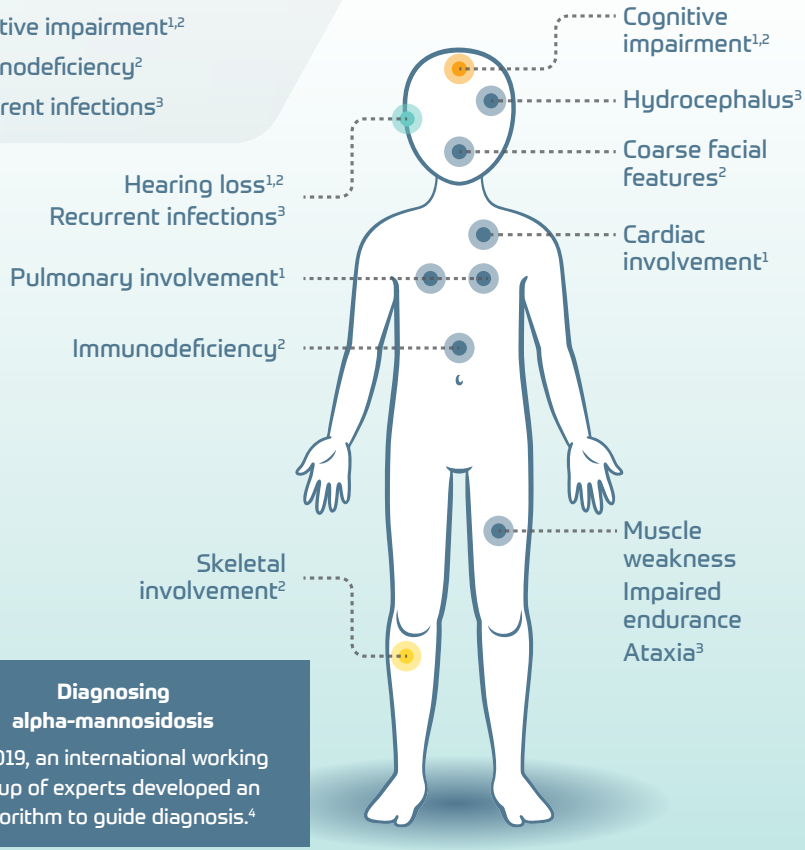


Clinical presentation of alpha-mannosidosis

Alpha-mannosidosis presents with broad heterogeneity of symptoms.[1–3]

Some of the main features are:

- Hearing loss[1,2]
- Skeletal involvement[2]
- Cognitive impairment[1,2]
- Immunodeficiency[2]
- Recurrent infections[3]



Diagnosing alpha-mannosidosis

In 2019, an international working group of experts developed an algorithm to guide diagnosis.[4]

Hearing loss in alpha-mannosidosis

Patients with alpha-mannosidosis suffer from a combination of conductive and sensorineural hearing loss.[1]

- In a natural history study evaluating clinical and surrogate parameters of 43 alpha-mannosidosis patients:[1]

100%

of patients over the age of 3 years had significant hearing loss and had to wear hearing aids.[1]

How important is hearing loss when diagnosing alpha-mannosidosis?

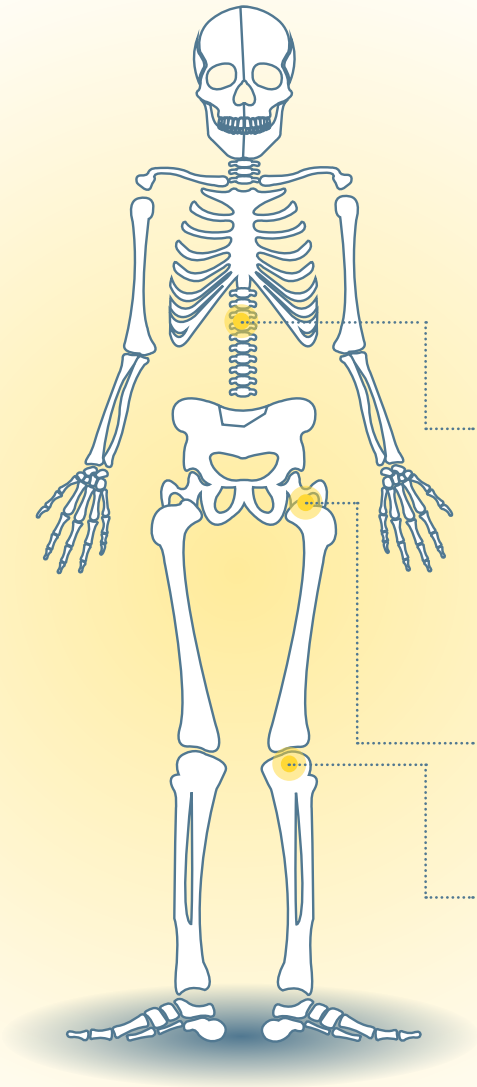
Hearing loss is an important and early manifestation of alpha-mannosidosis.[5]

In 2019, Lehalle and colleagues reported cases of 7 patients referred to clinical geneticists for syndromic hearing loss and moderate cognitive impairment that were diagnosed with alpha-mannosidosis.[5]

The authors suggest that hearing loss, especially when associated with learning or cognitive difficulties, with or without dysmorphic features, should raise a possible diagnosis of lysosomal storage disorder – in particular, alpha-mannosidosis.[5]

The broad phenotypic spectrum of alpha-mannosidosis combined with the molecular heterogeneity of genetic deafness highlight the value of exome sequencing for establishing early diagnoses of rare disorders.[5]

Skeletal involvement in alpha-mannosidosis



Bone anomalies are one of the most common manifestations of alpha-mannosidosis, as reported by Zielonka and colleagues in a quantitative analysis of published cases.[6]

62% of patients <18 years and **92%** of patients ≥18 years have skeletal abnormalities, such as **joint contractures, scoliosis, genua valga** and **hip dysplasia**[1]

Study design: Natural history study evaluating clinical and surrogate parameters of 43 alpha-mannosidosis patients

90% of patients show clinical or radiographic signs of **mild-to-moderate dysostosis multiplex**[3]

From the **second to the fourth decade of life**, patients may develop destructive polyarthropathy, including coxarthrosis and gonarthrosis[3]

Cognitive impairment in alpha-mannosidosis

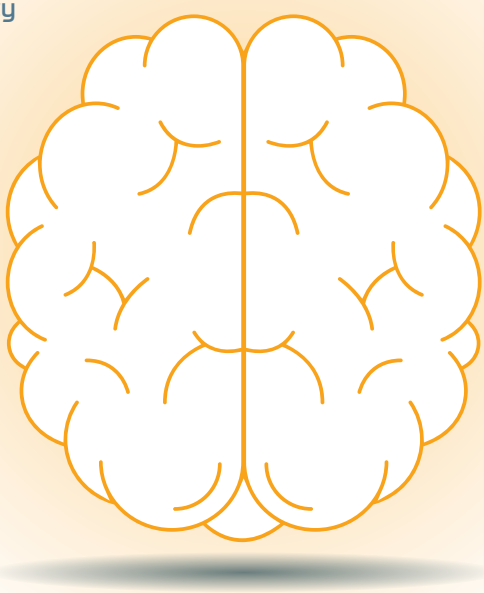
Cognitive impairment is one of the most common manifestations of alpha-mannosidosis.[1]

In a clinical study of 8 patients with alpha-mannosidosis:[3]

- Symptoms typically began with delayed development of speech or motor or mental functions.[3]
- All patients showed mild or moderate mental retardation, with an IQ of 60–80 and a declining tendency over later decades.[3]

Patients with alpha-mannosidosis are also at an increased risk of **psychiatric symptoms**, with 25% of patients affected.[7]

- First onset of symptoms usually occurs in late puberty to early adolescence.[7]
- Episodes generally last 3–12 weeks and may be recurrent.[7]
- Symptoms include confusion, hallucinations, anxiety and depression.[7]



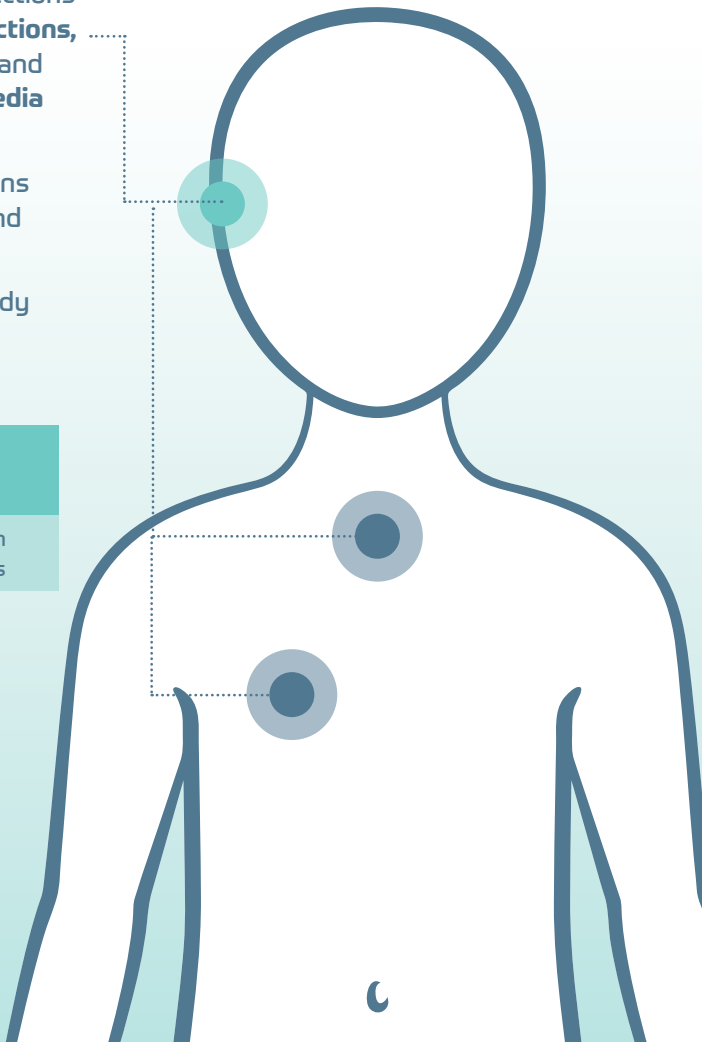
Recurrent infections

Patients with alpha-mannosidosis frequently have recurrent infections, especially in the first 10 years.[7]

- The most common infections are: **upper airway infections, pulmonary infections** and **acute/serous otitis media infections**[7]
- The number of infections diminishes in the second and third decades[7]
- In a natural history study of 111 patients with alpha-mannosidosis:[6]

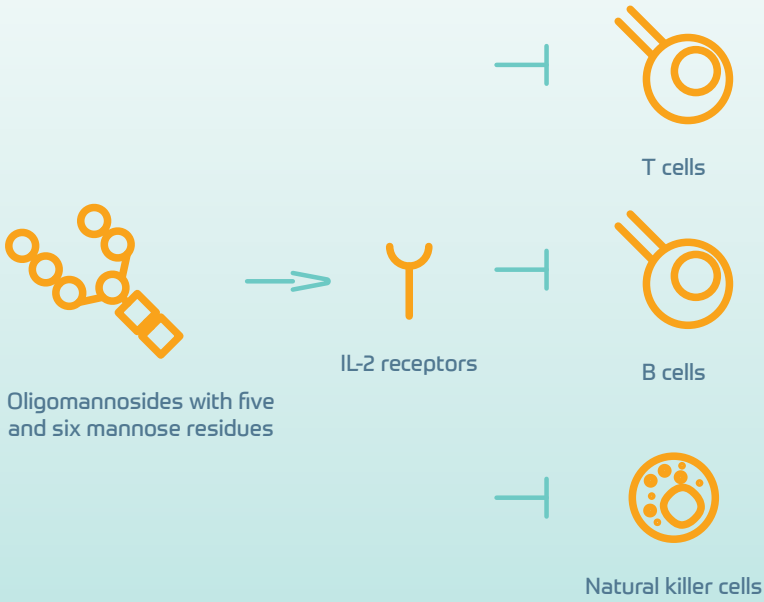
53%

of patients presented with respiratory tract infections



Immunodeficiency

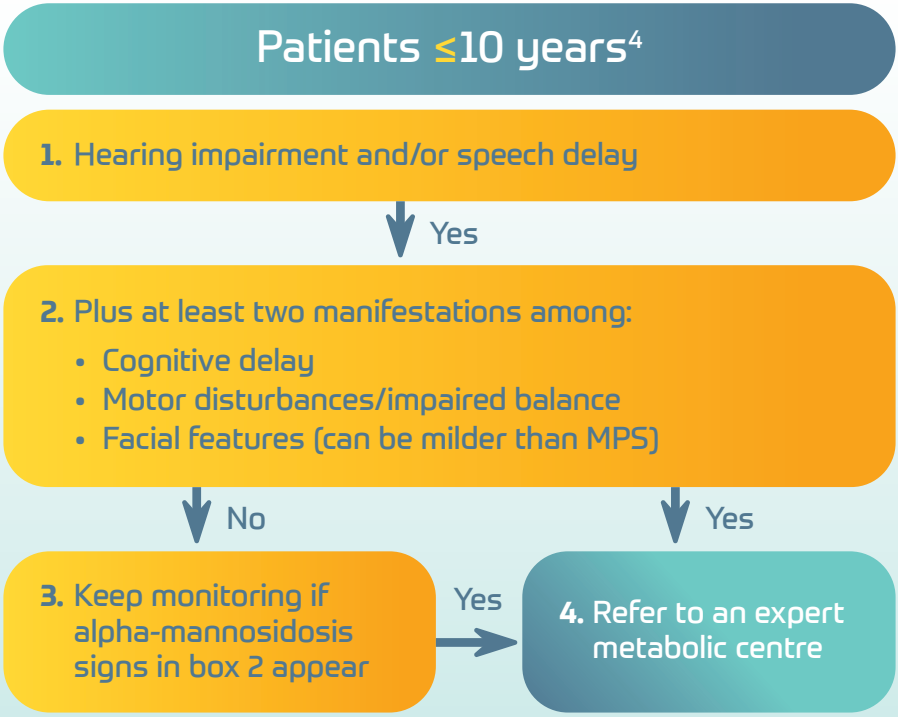
- Alpha-mannosidosis patients have increased levels of oligosaccharides in plasma. These are able to bind to interleukin-2 (IL-2) receptors, disturbing IL-2-dependent activation of T cells, B cells and natural killer cells. Blockage of this receptor may be the mechanism behind immunodeficiency in alpha-mannosidosis.[3]
- In a comparison of six alpha-mannosidosis patients to six age- and sex-matched healthy controls, post-immunisation antibody levels were lower in patients, showing decreased antibody production in response to antigen presentation.[3]
- Evidence of reduced phagocytosis and impaired leukocyte chemotaxis has also been found in alpha-mannosidosis patients.[3]



Diagnosing alpha-mannosidosis

≤10 years

In 2019, with no internationally recognised guidelines for early group of experts met to establish an algorithm to help general achieve early diagnosis and initiate adequate treatment as



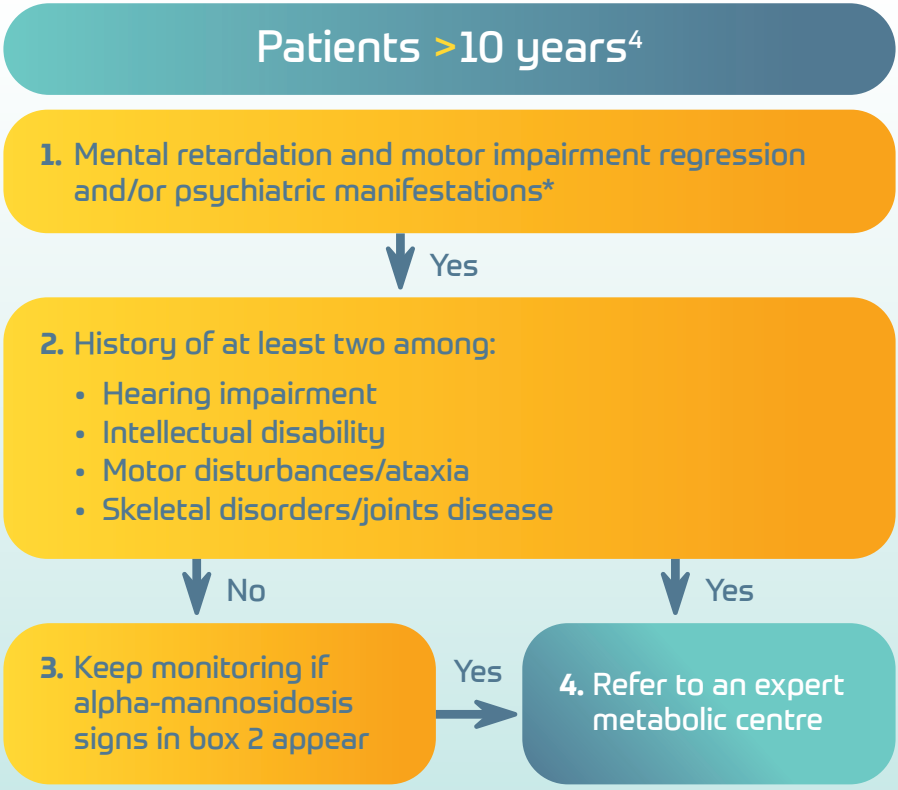
Adapted from Guffon et al. 2019.[4]

MPS = mucopolysaccharidosis.

Diagnosing alpha-mannosidosis

>10 years

diagnosis of alpha-mannosidosis, an international working practitioners and specialists (metabolic and non-metabolic) soon as possible.[4]



Adapted from Guffon et al. 2019.[4]

*Includes acute psychotic events.

References

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2 Borgwardt L et al. *Orphanet J Rare Dis* 2015;10:70.
3 Malm D and Nilssen Ø. *Orphanet J Rare Dis* 2008;3:21.
4 Guffon N et al. *Mol Genet Metab* 2019;126(4):470–474.
5 Lehalle D et al. *Am J Med Genet A* 2019;179(9):1756–1763.
6 Zielonka M et al. *J Inherit Metab Dis* 2019;42(5):975–983.
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