DISCOVER
Alpha Mannosidosis

Hearing impairment in alpha-mannosidosis and mucopolysaccharidosis

A key symptom for suspicion of rare and ultra-rare metabolic diseases

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Chiesi
global rare diseases

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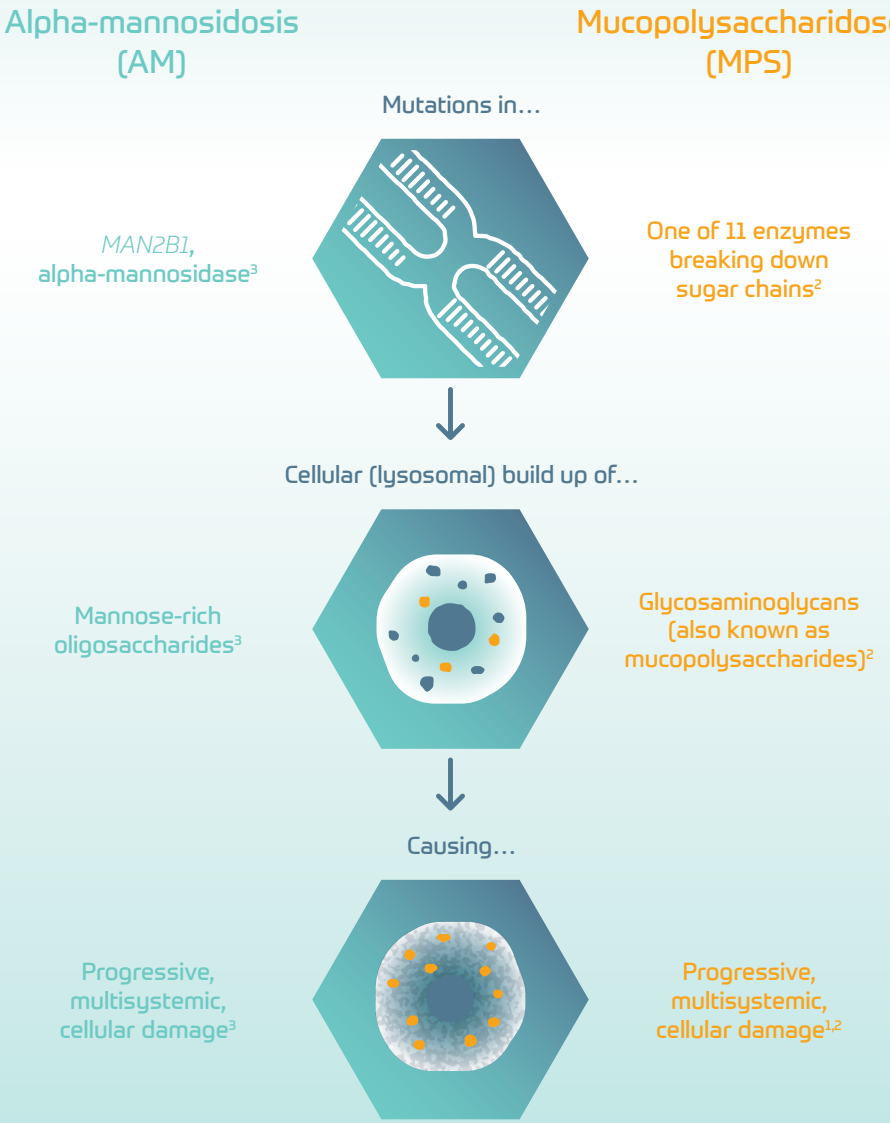
MPS = mucopolysaccharidosis.

Lysosomal storage disorders

Mucopolysaccharidoses and alpha-mannosidosis belong to the larger group termed 'lysosomal storage disorders' – conditions in which large numbers of molecules that normally break down inside lysosomes instead accumulate in harmful amounts in the body's cells and tissues.[1,2]



Alpha-mannosidosis

- Alpha-mannosidosis is a rare lysosomal storage disorder caused by the deficiency of alpha-mannosidase[2,3]
- Alpha-mannosidosis is caused by a mutation in *MAN2B1*, encoding lysosomal alpha-mannosidase. Without alpha-mannosidase, N-linked oligosaccharides progressively accumulate in lysosomes of all tissues[3]
- This results in impaired cellular function and apoptosis[3]

Mucopolysaccharidoses

- Mucopolysaccharidoses are a group of rare lysosomal storage disorders caused by the absence or malfunctioning of enzymes that break down glycosaminoglycans (formerly known as mucopolysaccharides)[2]
- People with a mucopolysaccharidosis disorder have a deficiency in one of the 11 enzymes required to break down these sugar chains, resulting in build-up in cells (e.g., skin, cartilage, vascular tissue, liver, spleen)[2]
- This results in progressive cellular damage[1,2]

MPS = mucopolysaccharidosis.

Alpha-mannosidosis and MPS

The presentation of alpha-mannosidosis and MPS diseases is heterogeneous; early clinical manifestations can be non-specific and similar to other common conditions. Symptom overlap leads to a wide variety of differential diagnoses, causing potential delay in patients receiving a specific diagnosis and treatment.[1,2]

The clinical characteristics of patients with various lysosomal storage disorders were evaluated using the medical records of specifically diagnosed individuals aged 1–70 years (N=188).

- This study showed a high degree of overlap between the clinical signs of alpha-mannosidosis and MPS, particularly Type I and Type II

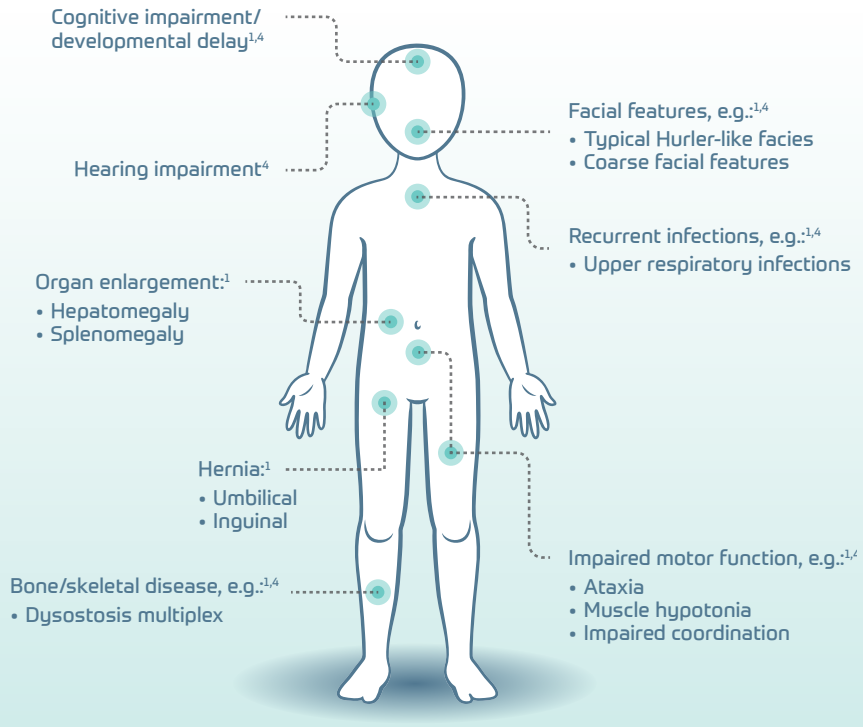
Disease	No.	Delay in diagnosis	Clinical signs										
		Mean, years	H	S	C	O	R	N	RE	HE	HM	OI	HY
MPS Type I	7	5.54±5.2	+	+	+	+	+	±	–	+	–	+	+
MPS Type II	23	2.9±2.88	+	+	+	+	+	±	–	+	–	+	+
MPS Type III	8	3.81±3.55	+	+	+	+	+	+	–	+	–	+	+
MPS Type IV	6	3.2±2.67	+	+	+	+	+	–	–	+	–	+	+
MPS Type VII	1	11.60	+	+	+	+	+	+	–	+	–	+	+
Alpha-mannosidosis	2	9.62±9.72	+	+	+	+	+	±	–	+	–	+	+

Adapted from Alkhzouz C, et al. 2021.[1]

C = cardiac involvement; H = hepatomegaly; HE = hernia; HM = haematological impairment; HY = hypoacusia; MPS = mucopolysaccharidosis; N = neurological impairment; O = osteoarthropathy; OI = ophthalmological impairment; R = respiratory involvement; RE = renal impairment; S = splenomegaly.

Hallmark symptoms of alpha-mannosidosis and MPS

Patients with lysosomal storage disorders are often asymptomatic at birth – the combination of particular signs and symptoms, especially early manifestations, should prompt suspicion of alpha-mannosidosis or MPS:[1,4]



Two key symptoms for differentiating a person with MPS from a person with alpha-mannosidosis are short stature and contractures – those with MPS present with these, while those with alpha-mannosidosis likely do not.[4]

Hearing impairment in alpha-mannosidosis and MPS

Patients with alpha-mannosidosis and MPS can present with any type of hearing impairment (sensorineural, conductive or mixed)[5–7]

- In alpha-mannosidosis, patients are primarily diagnosed with **sensorineural hearing impairment** but can also experience the mixed or conductive forms[5]
- In MPS, patients primarily present with **conductive hearing impairment** but many patients also experience a sensorineural component[6,7]

In a long-term, observational study following 12 patients with alpha-mannosidosis:[8]

83%

of patients presented with hearing loss – importantly, this was not progressive but congenital, with patients requiring audiological management from birth.[8]

In a descriptive, cross-sectional study of 53 patients with mucopolysaccharidosis:*[7]

96%

of patients demonstrated hearing loss, with over 60% classed with at least a moderate degree of loss.[7]

Hearing impairment is an important early manifestation of alpha-mannosidosis and MPS[4–6,9]

Clinical suspicion of a lysosomal storage disorder should be triggered by **particular clusters of signs and symptoms** that are unlikely to appear in an unaffected child, but that often occur together in a child with alpha-mannosidosis or MPS[1,4]

Suspect alpha-mannosidosis or MPS when you see:

- Hearing impairment[6,8–10]
- Learning/cognitive difficulties[8–10]
- Coarse facial features[6,8–10]
- Motor disturbances/ataxia[8,10]
- Recurrent infections[6,8–10]
- Hepatomegaly[6,8,10]
- Hernia (inguinal or umbilical)[6,8,10]
- Respiratory disorders[6,9]
- Bone abnormalities[6,8–10]

For example:

- In case reports from Lehalle and colleagues (2019), 7 individuals were referred to clinical geneticists for etiologic **exploration of syndromic hearing loss, associated with moderate learning disabilities**. These individuals were subsequently diagnosed with alpha-mannosidosis.[9]

*Including patients with MPS type I, II, III, IV and VI.[7]
ENT = ear, nose and throat; MPS = mucopolysaccharidosis.

Diagnostic algorithm for alpha-mannosidosis

In 2019, with no internationally recognised guidelines for early diagnosis of alpha-mannosidosis, an international working group of experts met to establish an algorithm to help general practitioners and specialists (metabolic and non-metabolic) **achieve early diagnosis and initiate adequate treatment as soon as possible**.[10]

This guideline recognises **hearing loss** as one of the most prominent symptoms for the suspicion of alpha-mannosidosis in both very young (≤10 years old) and older patients (over 10 years old).[10]

Patients ≤10 years[10]

1. Hearing impairment and/or speech delay

↓ Yes

2. Plus at least two manifestations among:

- Cognitive delay
- Motor disturbances/ impaired balance
- Facial features (can be milder than MPS)

↓ No → **3.** Keep monitoring if alpha-mannosidosis signs in box 2 appear → Yes → **4.** Refer to an expert metabolic centre

↓ Yes → **4.** Refer to an expert metabolic centre

Adapted from Guffon N, et al. 2019.[10]

As an ultra-rare condition, alpha-mannosidosis has a high potential for challenging differential diagnosis, and its incidence may be underestimated in the general population.[11]

Symptomology, including hearing impairment, should prompt suspicion and testing for alpha-mannosidosis.[10,11]

Patients >10 years[10]

1. Mental retardation and motor impairment regression and/or psychiatric manifestations*

↓ Yes

2. History of at least two among:

- Hearing impairment
- Intellectual disability
- Motor disturbances/ataxia
- Skeletal disorders/joints disease

↓ No → **3.** Keep monitoring if alpha-mannosidosis signs in box 2 appear → Yes → **4.** Refer to an expert metabolic centre

↓ Yes → **4.** Refer to an expert metabolic centre

Adapted from Guffon N, et al. 2019.[10]

For example:

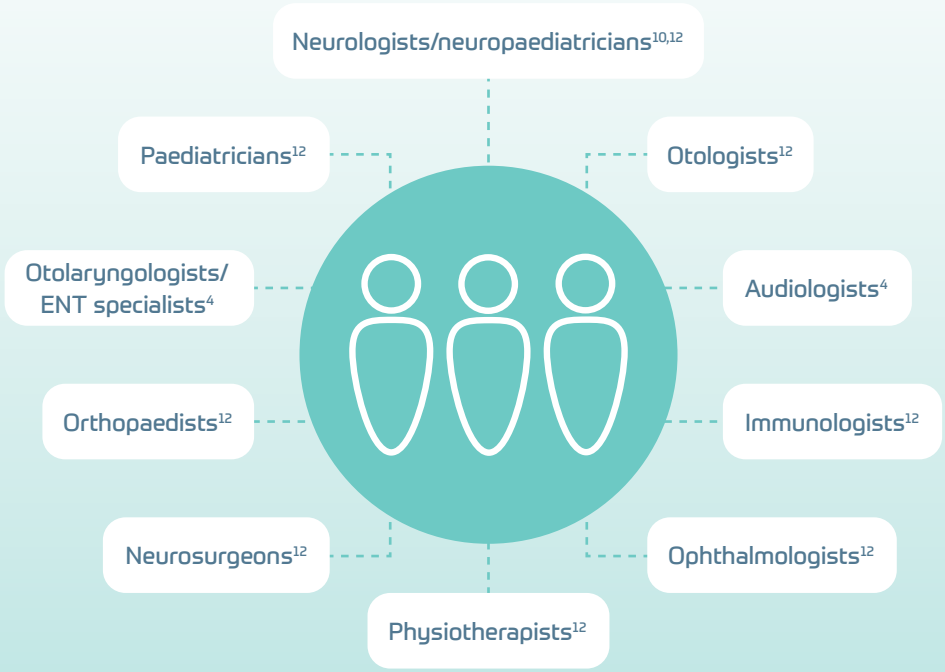
- In a study analysing enzyme activity and genetics of dried blood spot samples from 1,010 individuals clinically suspicious for MPS, **4 cases** were confirmed to have alpha-mannosidosis (a ratio of 1:253 in those with MPS-like phenotype)[11]

*Includes acute psychotic events.
MPS = mucopolysaccharidosis.

The importance of multidisciplinary care

As alpha-mannosidosis and MPS affect multiple systems,[1,4] patients should be managed by a **multidisciplinary team** to achieve diagnosis as early as possible, optimise quality of life and prevent complications related to disease progression.[10,12]

The multidisciplinary team could involve, but is not limited to:[4,10,12]



Diagnostic tests for alpha-mannosidosis

The diagnosis of lysosomal storage disorders relies on a combination of biochemical analyses, with disease confirmation by genetic analysis to identify specific mutations.[10,13]

Biochemical assessments

- **Peripheral blood examination**[4,14]
  Light or transmission electron microscopy demonstrates vacuoles in bone marrow smears or lymphocytes from peripheral blood in most affected individuals
- **Oligosaccharides in urine**[4,14]
  Elevated urinary excretion of mannose-rich oligosaccharides can be demonstrated by thin-layer chromatography or by HPLC
- **Alpha-mannosidase enzyme activity assay (most reliable method)**
  Fluorometric assays using leukocytes or other nucleated cells[14] *and MS/MS analysis of dried blood spots can be used to determine alpha-mannosidase activity levels*[11]

Genetic testing

- **Molecular testing of the patient and their parents should be performed as a confirmatory step and for family investigations**[4,10]
- **If gene panels are used in the diagnostic process, it is important that alpha-mannosidosis is included in screening panels for disease-relevant manifestations**[10]

ENT = ear, nose and throat; MPS = mucopolysaccharidosis.

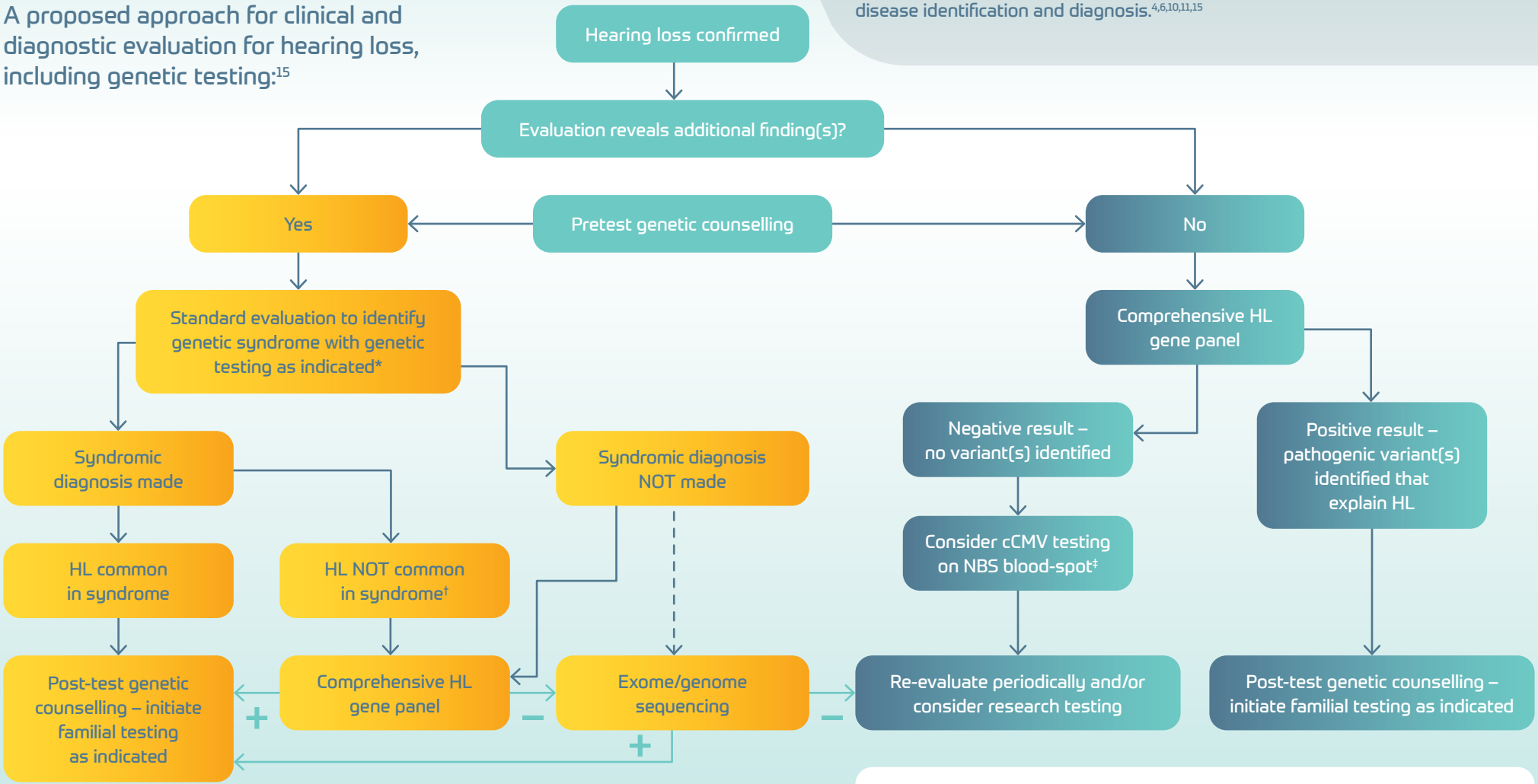
HPLC = high performance liquid chromatography; MPS = mucopolysaccharidosis; MS/MS = multiplex tandem mass spectrometry.

Genetic testing for hearing loss

Hearing loss is a common and complex condition that can occur at any age, can be inherited or acquired, and features in a wide variety of disease presentations. More than 400 genetic syndromes include hearing loss as a feature, with hearing loss transmitted as an autosomal recessive, autosomal dominant, X-linked or matrilineal trait.[15]

Hearing loss is an important early manifestation of both alpha-mannosidosis and MPS and, through standard or NGS genetic testing/screening, could lead to prompt disease identification and diagnosis.[4,6,10,11,15]

A proposed approach for clinical and diagnostic evaluation for hearing loss, including genetic testing:[15]



Adapted from Li MM, et al. 2022.[15]

The symbol + indicates positive. The symbol – indicates negative.[15]
*Genetic testing could include single-gene tests, multigene panels, chromosome analysis, or microarray depending on clinical findings.[15]
†If genetic syndrome identified is not typically associated with HL, proceed to evaluate for secondary cause of HL.[15]
‡US state of birth may screen newborns for cCMV.[15]
cCMV = congenital cytomegalovirus; HL = hearing loss; MPS = mucopolysaccharidosis; NBS = newborn screening; NGS = next-generation sequencing.

Investigations for alpha-mannosidosis and MPS should be included in high-risk population screening programmes, especially hearing panels, to support early disease identification, diagnosis and treatment[4,11]

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