CAN YOU RECOGNIZE ALPHA-MANNOSIDOSIS?

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Global Rare Diseases

Alpha-Mannosidosis

- Alpha-Mannosidosis is a rare lysosomal storage disorder caused by mutations affecting alpha-mannosidase lysosomal enzyme.
  Alpha-mannosidase is an exoglycosidase, that cleaves α-linked mannose residues of N-linked oligosaccharides.[1]

- Impaired function of alpha-mannosidase causes a block in the degradation of glycoproteins and thereby a progressive lysosomal accumulation of mannose-rich oligosaccharides in all tissues, resulting in impaired cellular function and apoptosis (figure 1).[2]

- Prevalence is estimated of one in 1.000.000 live births.[1,3,4]

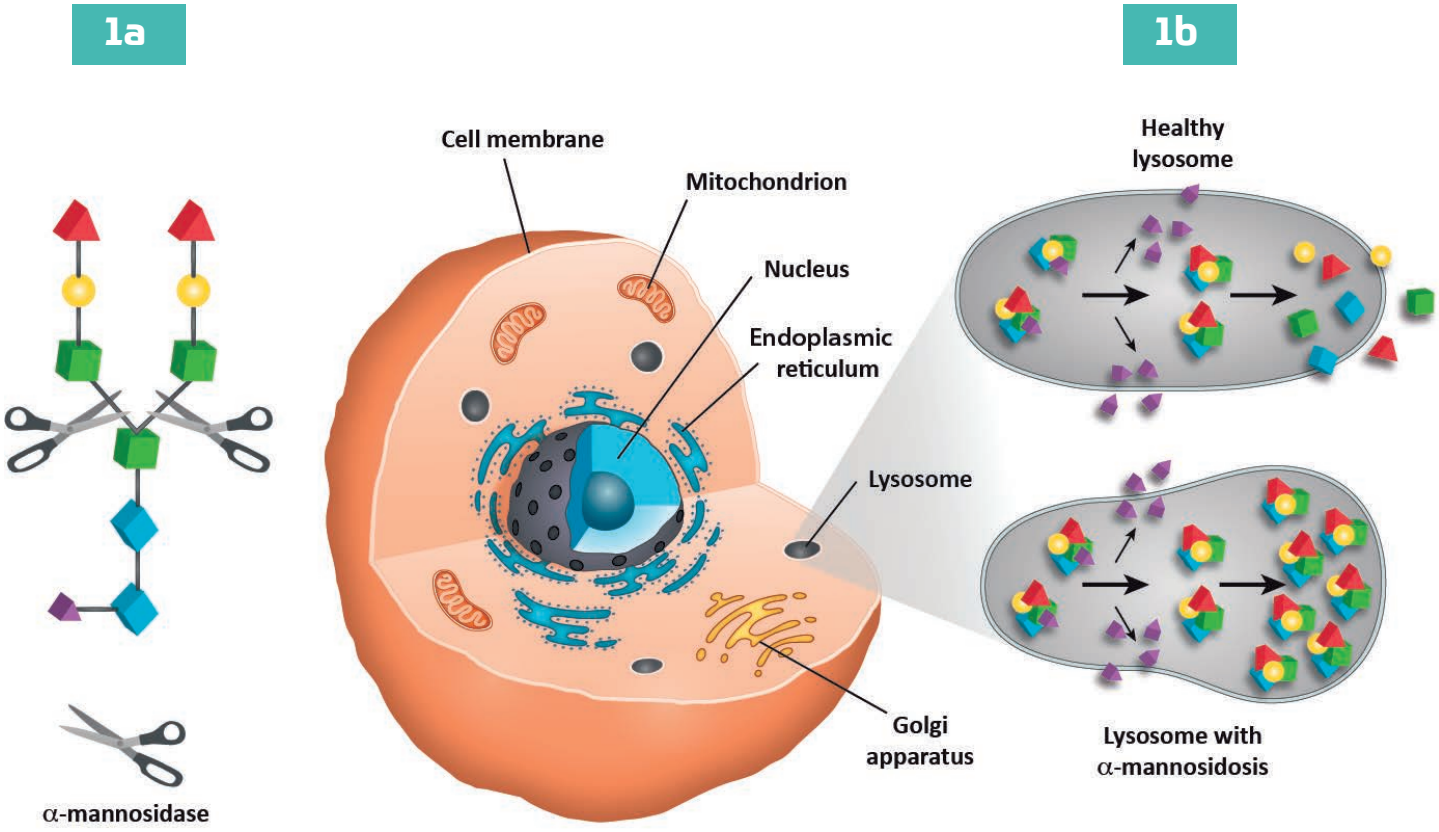
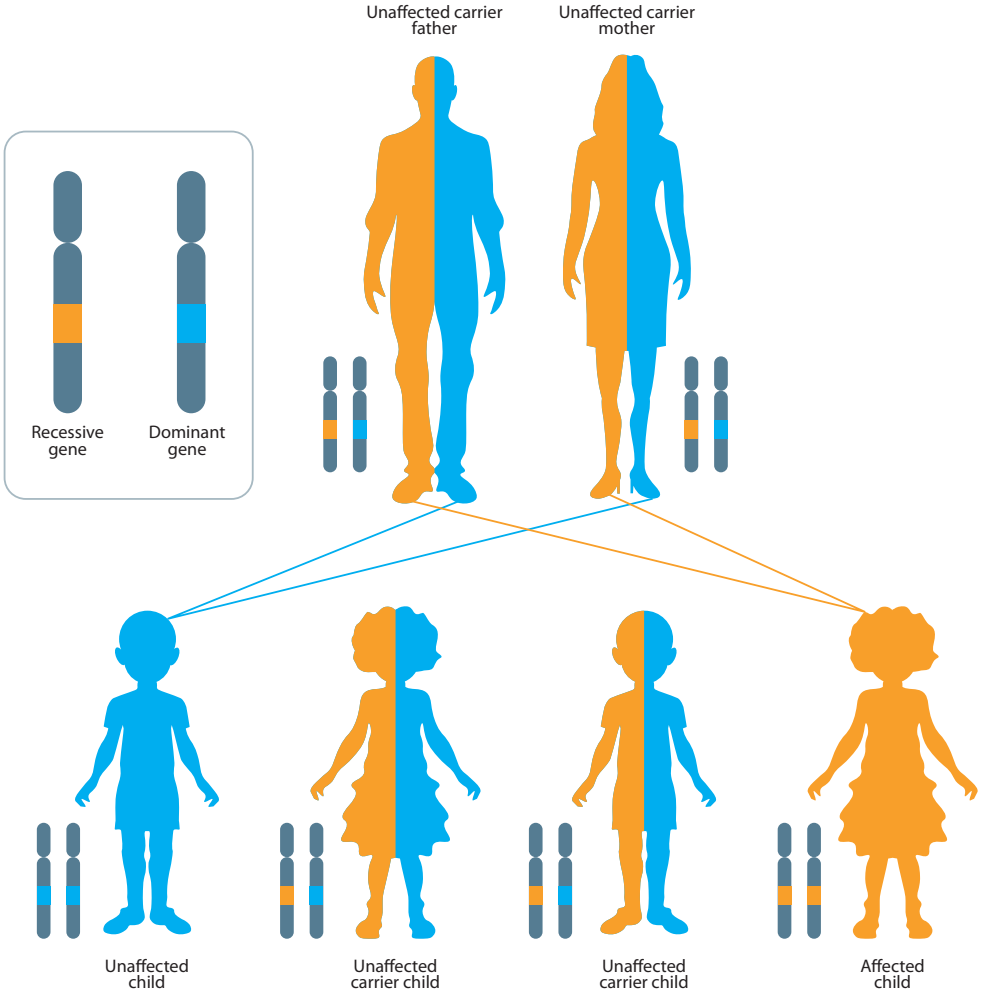


Figure 1a. α-mannosidase cleaves the alpha-linked mannose residues of N-linked oligosaccharides.[1,2]

Figure 1b. In healthy cells, α-mannosidase in the lysosomes acts in the sequential degradation of complex glycoproteins. Smaller breakdown products leave the lysosome. In α-mannosidosis accumulation of α-mannosyl rich N-linked oligosaccharides leads to lysosomal engorgement and disruption of normal cell function.[1,2]

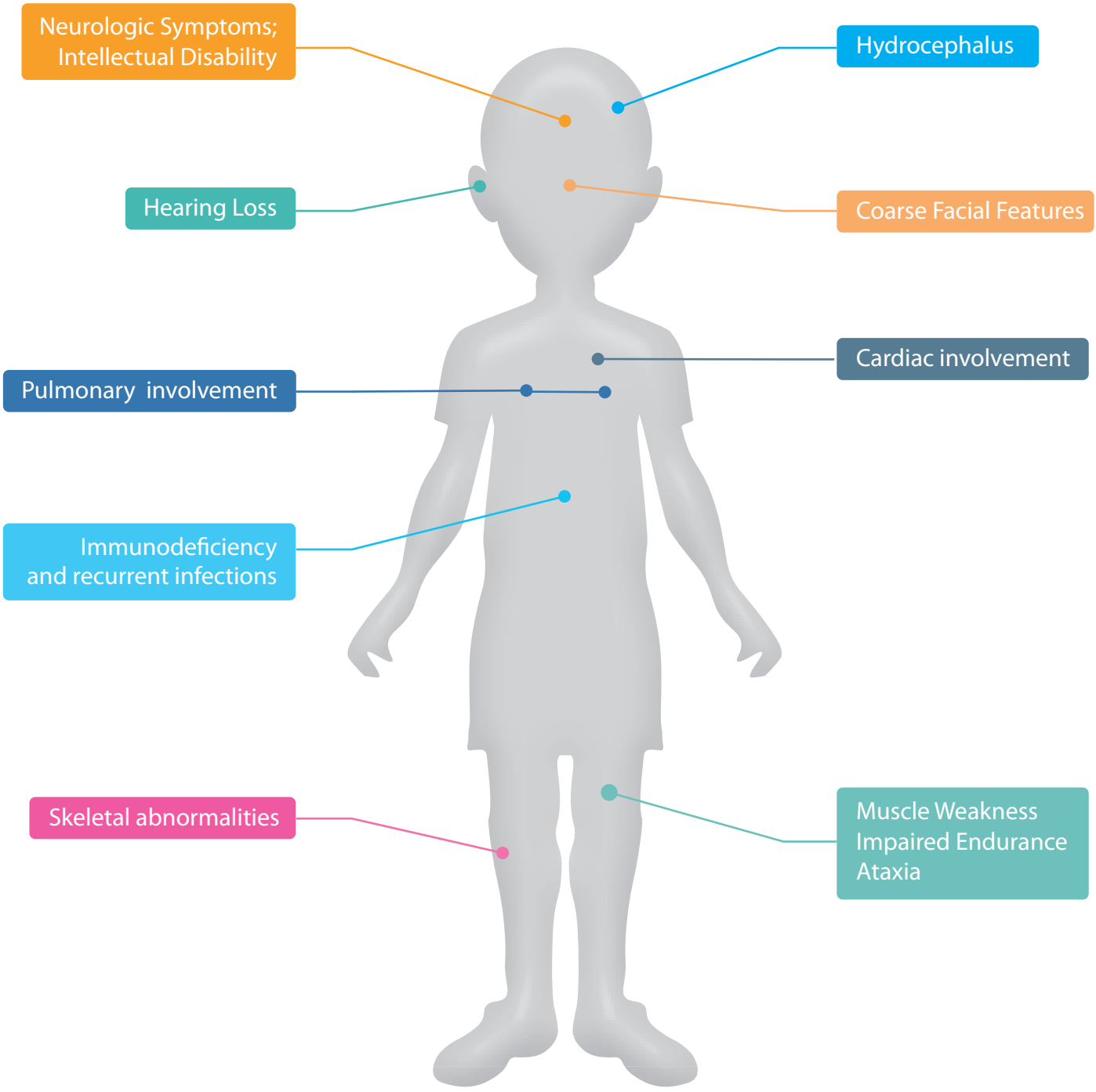
Alpha-mannosidosis inheritance

- Alpha-mannosidosis is inherited in an autosomal recessive fashion, caused by mutations in the gene MAN2B1 located on chromosome 19.[1]
- A total of 127 MAN2B1 mutations associated to alpha-mannosidosis have been described so far, with most of them being private.[2]
- The phenotypic variability is high, even between siblings with identical genotypes.[2]



A multi-systemic disease

- Alpha-Mannosidosis presents with broad heterogeneity of symptoms:[1,2,4]



Disease presentation

- The disease encompasses a continuum of clinical findings from a perinatal-lethal form to one that is not diagnosed until adulthood. In general, phenotypes of patients with alpha-mannosidosis are not considered "clearly distinguishable" and the prediction of the clinical course for an individual patient is very challenging[5]

- The typical clinical phenotype encompasses a broad range of findings, including facial coarsening, intellectual disability with varying degrees of CNS impairment, motor function disturbances, hearing impairment, impaired speech, immunodeficiency and recurrent infections, psychiatric symptoms and skeletal abnormalities.[1,4,5]

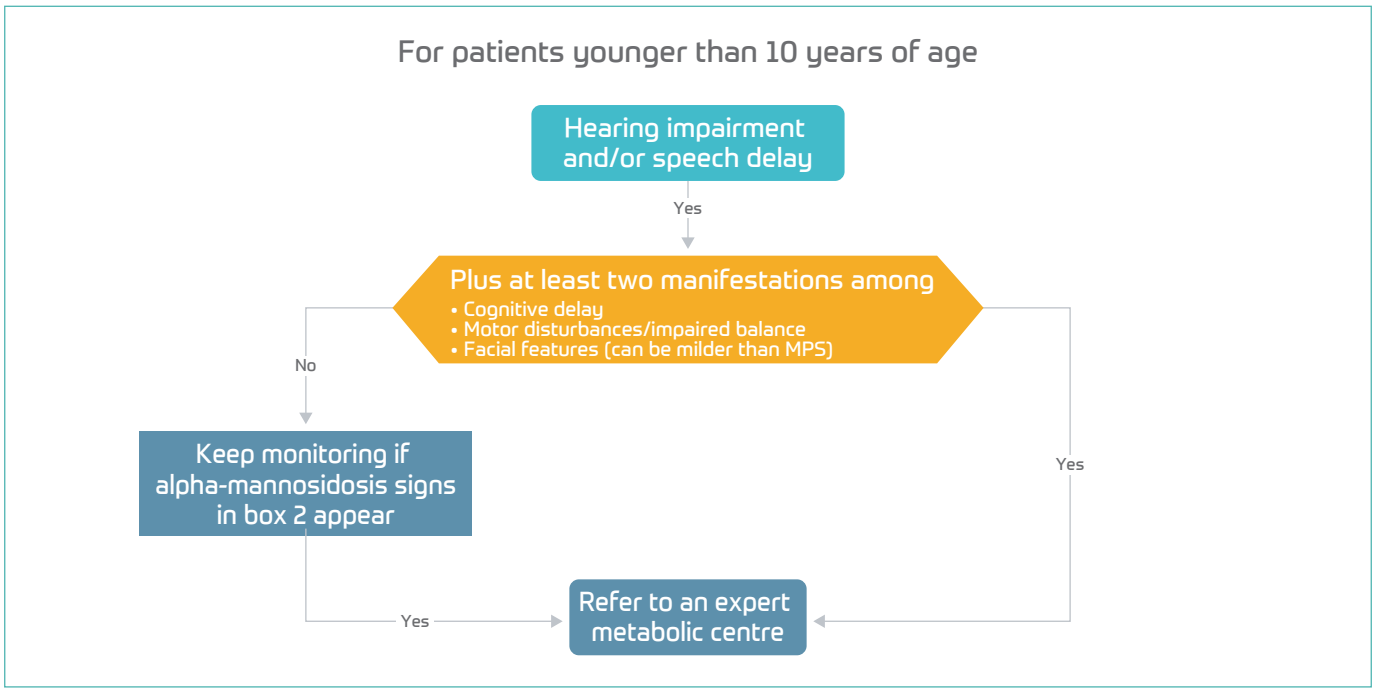
- Literature on longevity in alpha-mannosidosis is lacking.

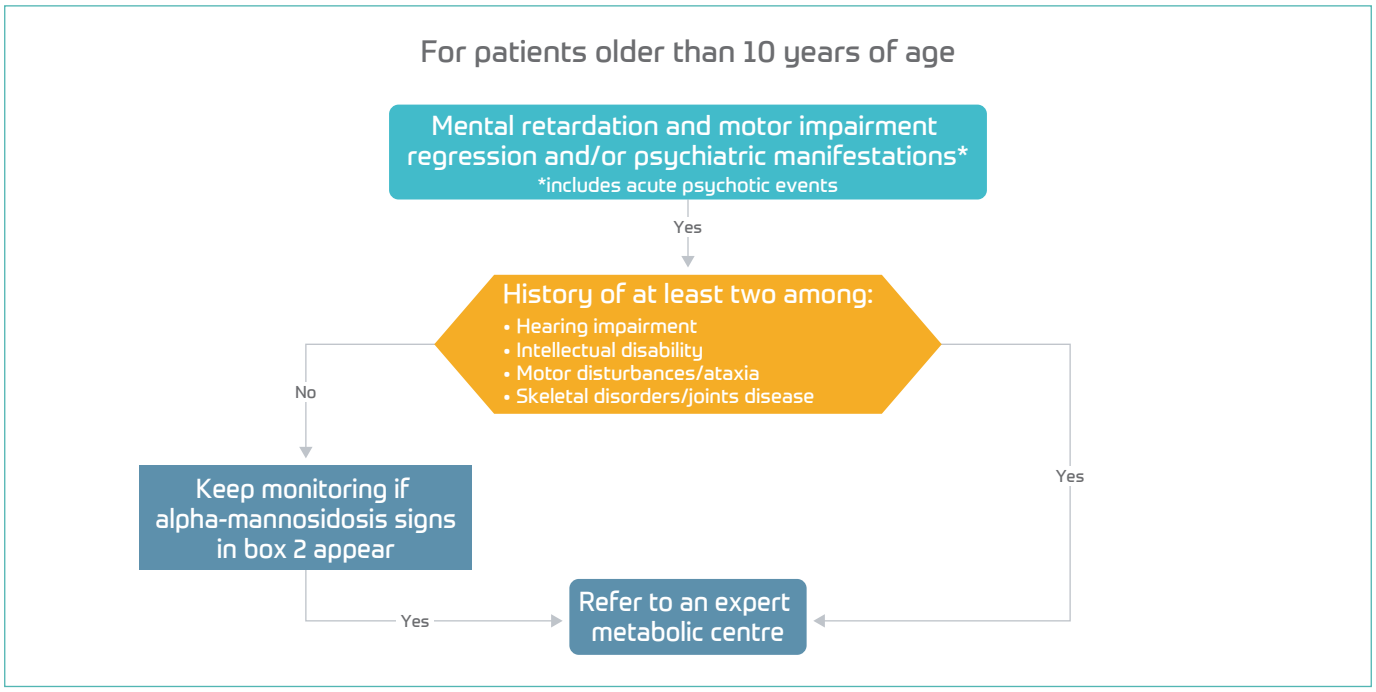
How to diagnose Alpha-Mannosidosis?

- A preliminary investigation may be run by measuring mannose-rich oligosaccharides concentration in urine.[1]
- Measurement of residual alpha-mannosidase activity in leucocytes is the most reliable diagnostic method, along with genetic testing.[1]

Diagnostic algorithm for alpha-mannosidosis

- An international working group of experts has developed a diagnostic algorithm to guide the diagnosis of alpha mannosidosis[6]





Adapted from Guffon N, Tylki-Szymanska A., Borgwardt L. et al (2019) Recognition of alpha-mannosidosis in paediatric and adult patients: Presentation of a diagnostic algorithm from an international working group. Mol Genet Metab 126: 470-474

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6. Guffon N, Tylki Szymanska A, Borgwardt L et al. (2019) et al., Recognition of alpha-mannosidosis in paediatric and adult patients: Presentation of a diagnostic algorithm from an international working group Molecular, wGenetics and Metabolism 126 (2019) 470-474

Notes:

For more information on Alpha Mannosidosis please visit www.alphamannosidosis.com

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