Mucopolysaccharidosis type I (Hurler's syndrome)

What is Mucopolysaccharidosis Type I?

The mucopolysaccharidoses are a group of inherited disorders caused by a lack of specific lysosomal enzymes involved in the degradation of glycosaminoglycans (GAGs).

Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive inherited disease, caused by deficiency of the enzyme α-L-iduronidase, resulting in accumulation of the glycosaminoglycans (GAGs) dermatan and heparan sulfate in organs and tissues. If untreated, patients with the severe phenotype die within the first decade of life.[1]

Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes including Hurler's (severe), Scheie's (mild) and Hurler-Scheie (intermediate) syndromes. It is now widely accepted that overlap in clinical features and severity exists among these subtypes.[2]

The genetic defect involves a mutation in the gene IDUA that encodes alpha-L-iduronidase on chromosome 4.[3]

How common is Mucopolysaccharidosis Type I? (Epidemiology)

- The estimated incidence of MPS I is 1 in every 100,000 live births.[2]
- The mode of inheritance is autosomal recessive.[3] Genotype-phenotype correlation is poor.[4]

Symptoms[4] [5]

The characteristic clinical features include:

- General learning disability.
- Short stature.
- Coarse facies and enlarged tongue.
- Corneal clouding.
- Hearing impairment.
- Umbilical hernias and inguinal hernias.
- Joint stiffness and skeletal deformities.
- Cardiomyopathy and coronary heart disease.
- Hepatosplenomegaly.
- Dysostosis multiplex: enlarged skull, enlarged but shortened bones, malformed pelvis, and other skeletal defects.

Mucopolysaccharidosis I-Hurler (MPS I-H)

Mucopolysaccharidosis I-Hurler (MPS I-H) is the most severe form MPS . It causes multisystem morbidity including progressive neurological disease, upper airway obstruction, skeletal deformity and cardiomyopathy.

Affected children appear normal at birth but usually develop the characteristic appearance within the first year of life. The median age of onset of symptoms is 6 months.[2] Maximum functional development is reached when the child is aged between 2 and 4 years. Typical features include:

- Dysostosis multiplex, seen in severe variants of MPS I. The hypoplastic odontoid puts these patients at high risk of cervical cord damage.
- MPS I-H causes a spinal 'gibbus' deformity, persistent nasal discharge, middle ear effusions and frequent upper respiratory infection.
- Other features include 'coarse' facial features, and an enlarged tongue. Progressive upper airway disease leads to obstructive sleep apnoea.
- Corneal clouding and cognitive impairment develop, as well as cessation of growth, causing short stature. Joint stiffness and contractures limit mobility.

- Cardiac disease affects all children with MPS I-H. Death occurs before the age of 10 years.

Scheie's syndrome

Scheie patients tend to be diagnosed as teenagers with hepatomegaly, joint contractures, cardiac valve abnormalities and corneal clouding . Prolonged survival with considerable disability without cognitive impairment is usual.

MPS Hurler-Scheie (I-H/S)

MPS Hurler-Scheie (I-H/S) is normally diagnosed by 6.5 years, with variable skeletal and visceral manifestations without cognitive involvement. Joint stiffness, corneal clouding, umbilical hernia, abnormal facies, hepatomegaly, joint contractures, and cervical myelopathy occur. Death tends to be in their 20s.

Differential diagnosis

- Other mucopolysaccharidoses: Hunter's syndrome (mucopolysaccharidosis type II) has no corneal clouding and progression is slower.
- Other causes of general learning disability and short stature.

Investigations [3] [4]

Diagnosis:

- The urine GAGs pattern, confirmed by iduronidase enzyme assay, is diagnostic.
- Lymphocytes examined in blood smears may show abnormal cytoplasmic inclusions.
- Definitive diagnosis is established by alpha-L-iduronidase enzyme assay using artificial substrates in cultured fibroblasts or isolated leukocytes.
- Carrier testing can be performed by differentiating normal enzyme activity from half-normal levels of enzyme activity.

- Prenatal diagnosis: using cultured amniotic fluid cells or chorionic villus biopsies.
- Molecular diagnosis: difficult because of genetic heterogeneity.

Assessment of complications will include:

- Echocardiogram and MRI brain scan.
- In severe cases, radiography of the skeleton (especially the spine) may detect a gibbus deformity of the lower spine. A mild form of dysostosis multiplex may be seen on X-ray.
- Ultrasound imaging of the ophthalmic nerve sheath and sclera is a useful technique for assessing the presence of morphological changes.[6]

Mucopolysaccharidosis Type I treatment and management[5]

Currently approved treatments consist of enzyme replacement therapy (ERT) and/or haematopoietic stem cell transplantation (HSCT). Patients with attenuated disease are often treated with ERT alone, while the recommended therapy for patients with Hurler syndrome also consists of HSCT.[7]

Allogeneic hematopoietic stem cell transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the gold standard for the treatment of MPS I-H in patients diagnosed and treated before 2-2.5 years of age, having a high rate of success. However, because of the difficulties and potential complications associated with HSCT, it is not recommended for less severe forms of MPS I.

Enzyme replacement therapy

Lifelong enzyme replacement therapy (ERT) with human recombinant laronidase has also been demonstrated to be effective in ameliorating the clinical conditions of pre-transplant MPS I-H patients and in improving HSCT outcome, by peri-transplant co-administration. [8]

Other treatments

- Orthopaedic surgery for joint contractures and skeletal deformities. Other surgical procedures may include myringotomy, hernia repair and adenoidectomy/tonsillectomy.[9]
- Corneal transplants may be required.
- Gene therapy may present treatment possibilities in the future.[10]

Complications

- Orthopaedic complications lead to pain and immobility.
- Upper airways obstruction; progressive airway, craniofacial and skeletal abnormalities may make both ventilation and intubation difficult.[11]
- Increased susceptibility to respiratory tract infections.

Prognosis

- There is a high morbidity and mortality, causing in many cases severe neurological and somatic damage in the first years of life.[12]
- As stated above, the survival for MPS I is very variable, depending on the severity of the condition.[4]
- Common causes of death include upper airways obstruction, cardiac insufficiency and respiratory tract infections.

Considerable residual disease occurs in the majority of transplanted patients with MPS-IH, but with high variability between patients.

Preservation of cognitive function at HSCT and a younger age at transplantation are associated with better cognitive development following transplant.

The long-term prognosis of patients with MPS-IH receiving HSCT can be improved by reducing the age at HSCT through earlier diagnosis, as well as using exclusively non-carrier donors.[13]

Further reading

- Sakuru R, Bollu PC; Hurler Syndrome. StatPearls, Jan 2023.
- Bay L, Amartino H, Antacle A, et al; New recommendations for the care of patients with mucopolysaccharidosis type I. Arch Argent Pediatr. 2021 Apr;119(2):e121-e128. doi: 10.5546/aap.2021.eng.e121.

References

1. Hampe CS, Eisengart JB, Lund TC, et al; Mucopolysaccharidosis Type I: A Review of the Natural History and Molecular Pathology. Cells. 2020 Aug 5;9(8):1838. doi: 10.3390/cells9081838.
2. Beck M, Arn P, Giugliani R, et al; The natural history of MPS I: global perspectives from the MPS I Registry. Genet Med. 2014 Oct;16(10):759-65. doi: 10.1038/gim.2014.25. Epub 2014 Mar 27.
3. Mucopolysaccharidosis Type IH, MPS1-H; Online Mendelian Inheritance in Man (OMIM)
4. Wraith JE, Jones S; Mucopolysaccharidosis type I. Pediatr Endocrinol Rev. 2014 Sep;12 Suppl 1:102-6.
5. Parini R, Deodato F, Di Rocco M, et al; Open issues in Mucopolysaccharidosis type I-Hurler. Orphanet J Rare Dis. 2017 Jun 15;12(1):112. doi: 10.1186/s13023-017-0662-9.
6. Schumacher RG, Brzezinska R, Schulze-Frenking G, et al; Sonographic ocular findings in patients with mucopolysaccharidoses I, II and VI. Pediatr Radiol. 2008 May;38(5):543-50. Epub 2008 Feb 26.
7. Hampe CS, Wesley J, Lund TC, et al; Mucopolysaccharidosis Type I: Current Treatments, Limitations, and Prospects for Improvement. Biomolecules. 2021 Jan 29;11(2):189. doi: 10.3390/biom11020189.
8. Jameson E, Jones S, Remmington T; Enzyme replacement therapy with laronidase (Aldurazyme((R))) for treating mucopolysaccharidosis type I. Cochrane Database Syst Rev. 2019 Jun 18;6(6):CD009354. doi: 10.1002/14651858.CD009354.pub5.
9. Arn P, Wraith JE, Underhill L; Characterization of surgical procedures in patients with mucopolysaccharidosis type I: findings from the MPS I Registry. J Pediatr. 2009 Jun;154(6):859-64.e3. Epub 2009 Feb 12.
10. Hurt SC, Dickson PI, Curiel DT; Mucopolysaccharidoses type I gene therapy. J Inherit Metab Dis. 2021 Sep;44(5):1088-1098. doi: 10.1002/jimd.12414. Epub 2021 Jul 9.
11. Gurumurthy T, Shailaja S, Kishan S, et al; Management of an anticipated difficult airway in Hurler's syndrome. J Anaesthesiol Clin Pharmacol. 2014 Oct;30(4):558-561.
12. Campos D, Monaga M; Mucopolysaccharidosis type I: current knowledge on its pathophysiological mechanisms. Metab Brain Dis. 2012 Jun;27(2):121-9. doi: 10.1007/s11011-012-9302-1. Epub 2012 Apr 14.

13. Aldenhoven M, Wynn RF, Orchard PJ, et al; Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. Blood. 2015 Mar 26;125(13):2164-72. doi: 10.1182/blood-2014-11-608075. Epub 2015 Jan 26.

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