

# Mucopolysaccharidosis I

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## Abstract

*Mucopolysaccharidosis type I (MPS I) is caused by the deficiency of the lysosomal enzyme  $\alpha$ -L-iduronidase. In the severe form (Hurler disease) skeletal deformities and a delay in motor and mental development are the leading symptoms. Radiological examination of the skeleton reveals a characteristic pattern that is called dysostosis multiplex. Patients with the adult form (Scheie disease) are of almost normal height and do not show mental retardation. Typical symptoms are stiff joints, corneal opacities, carpal tunnel syndrome and mild skeletal changes. In most cases also the heart is involved in the storage process. Some patients with  $\alpha$ -iduronidase deficiency exhibit symptoms that are intermediate between Hurler and Scheie disease. The different phenotypes are caused by allelic mutations of the  $\alpha$ -iduronidase (IDUA) gene. Mucopolysaccharidosis I is a rare lysosomal storage disorder, its prevalence being about 1:100 000. Besides palliative treatment bone marrow transplantation can be performed, that, however, is associated with several risks (for example graft-versus-host-reaction). In addition, an enzyme preparation (Laronidase, Aldurazyme<sup>R</sup>) is available that in clinical trials led to improvement of the lung function and joint-mobility, whereby long-time experience is still missing.*

## Keywords

mucopolysaccharidosis type I, mucopolysaccharidosis type I-H, mucopolysaccharidosis type I-S, mucopolysaccharidosis type I-HS, Hurler disease, Scheie disease, Hurler/Scheie disease, dysostosis multiplex, Heparan sulphate, Dermatan sulphate, enzyme replacement, gene therapy.

## Disease names

Mucopolysaccharidosis type MPS I  
 Alpha-L-Iduronidase Deficiency  
 IDA Deficiency  
 IDUA Deficiency  
 Hurler Syndrome  
 Scheie Syndrome  
 Hurler-Scheie Syndrome

Mucopolysaccharidosis type VI

## Diagnostic criteria

Progressive lysosomal storage disorder characterized by skeletal dysplasia, coarse facial features and mental retardation.

## Differential diagnosis

Mucopolysaccharidosis type II  
 Mucopolysaccharidosis type VI

## Excluded diseases

Mucopolysaccharidosis type II

## Prevalence

The prevalence has been calculated to be 1: 111 000 births (Australia, Meikle *et al.*, 1992) to 1: 84 000 (Netherlands, Poorthuis *et al.*, 1999).

## Clinical description

In Hurler disease (MPS IH), the severe form of  $\alpha$ -iduronidase deficiency, first symptoms such as a delay in mental development, deformities of the skeleton (gibbus) and inguinal hernias arise at the age of about 8 months. Later on, hepatosplenomegaly and coarsening of facial features with a depressed nasal bridge are seen. The skin is thickened, the tongue enlarged. There is an hearing impairment, that is due to a combination of conductive and neurosensory problems. Eye examination reveals corneal clouding. The children often have pulmonary infections that are caused by obstruction of the upper and lower respiratory tract. Further symptoms include disproportionate dwarfism and joint stiffness. By echocardiography thickening of the aortic and mitral valve and cardiomyopathy are found (Wippermann *et al.*, 1995). Progressive ventricular enlargement that leads to increased intracranial pressure is not uncommon. Most of the affected children die by ten years of age by respiratory infections or cardiac complications. Radiographic changes seen in Hurler disease are called *Dysostosis multiplex* and are a hallmark of all mucopolysaccharidoses (and glycoprotein storage disorders): There is a large skull with thickening of the calvarium, enlarged and J-shaped sella, deformities of the spine and pelvis and shortness of the metacarpals and the phalanges. In patients with the adult form of  $\alpha$ -iduronidase deficiency (Scheie disease, MPS IS), who are mentally normal, predominantly the skeleton, the heart and the eyes are involved. Corneal clouding, glaucoma and retinal degeneration are often observed. Carpal tunnel syndrome, resulting from compression of the median nerve, is not uncommon. Sleep apnea, caused by obstructive airway disease, necessitates tracheostomy in some patients. Diffuse thickening of the dura in the cervical region may lead to compressive myelopathy (Boor *et al.*, 2000). Patients with an intermediate phenotype (Hurler/Scheie syndrome, MPS I H/S) are characterized by progressive somatic involvement with little or no mental retardation. But, indeed Hurler and Scheie disease are just the endpoints of a broad phenotypic spectrum of  $\alpha$ -iduronidase deficiency.

## Treatment

Until recently only palliative treatment was available for MPS I patients. Corneal transplantation may become necessary in MPS IS (Scheie disease). Hearing aid may improve audition. Adenotomy and

drainage of the middle ear are necessary in most patients with Hurler disease. A release operation is recommended in the carpal tunnel syndrome. Hydrocephalus, observed in some cases of mucopolysaccharidosis I (Hurler disease), has to be relieved by a shunt operation. Replacement of the aortic valve may be helpful in patients with Scheie disease (MPS IS). Bone marrow has been transplanted to a great number of patients with mucopolysaccharidosis type I (Peter *et al.*, 1998). After successful engraftment leucocyte enzyme activity normalized, organomegaly decreased and joint mobility increased. Whether the brain function can be improved in patients with mental retardation remains questionable. Some patients maintained their learning capability or intelligence quotient, while others continued to deteriorate. The high morbidity and mortality of this procedure and low availability of compatible donors and transplantation facilities limit broad application of this therapy. Correction of the metabolic defect by the administration of the missing enzyme has been successful in animal models (Kakkis *et al.*, 1996). In a clinical trial with recombinant human  $\alpha$ -L-iduronidase the following results have been seen: The patients showed large reductions in liver volume and urinary glycosaminoglycan level. The lung function improved, and there was an increase of joint range of motion (Clarke *et al.*, 2002). Based on these results, the enzyme Laronidase (Aldurazyme<sup>R</sup>) has got the approval in the United States and in Europe. However, long-term results of enzyme replacement therapy are still missing. Gene transfer using retroviral vectors corrected the metabolic defect in bone marrow cells of MPS I patients (Baxter *et al.*, 2002).

## Etiology

Mucopolysaccharidosis type I is caused by a deficiency of the lysosomal enzyme  $\alpha$ -iduronidase, which is involved in the breakdown of dermatan and heparan sulphate. The coding gene is located on chromosome 4p16. A great number of mutations has been detected that explains the broad phenotypic heterogeneity of the disease (Beesley *et al.* 2001).

## Diagnostic methods

The clinical diagnosis of mucopolysaccharidosis type I (Hurler and Scheie disease) is supported by the detection of increased urinary excretion of dermatan- and heparan sulphate. To confirm the diagnosis, measurement of  $\alpha$ -iduronidase activity in leukocytes or cultured fibroblasts is necessary.

## Antenatal diagnosis

Antenatal diagnosis can be done by enzymatic assay in cultured chorionic or amniotic cells.

## References

- Baxter MA, Wynn RF, Deakin JA, Bellantuono I, Edington KG, Cooper A, Besley GT, Church HJ, Wraith JE, Carr TF, Fairbairn LJ: Retrovirally mediated correction of bone marrow-derived mesenchymal stem cells from patients with mucopolysaccharidosis type I. *Blood* 99 (2002) 1857-1859.
- Beesley CE, Meaney CA, Greenland G, Adams V, Vellodi A, Young EP, Winchester BG. Mutational analysis of 85 mucopolysaccharidosis type I families: frequency of known mutations, identification of 17 novel mutations and in vitro expression of missense mutations. *Hum Genet* 109 (2001) 503-511.
- Boor R, Miebach E, Bruhl K, Beck M: Abnormal somatosensory evoked potentials indicate compressive cervical myelopathy in mucopolysaccharidoses. *Neuropediatrics* 31 (2000) 122-127.
- Clarke LA, Muenzer J, Kolodny EH, Pastores GM, Beck M, Wraith JE: RhIDU enzyme replacement therapy for MPS I: 24-week extension study. *Am J Hum Genet* 71 (Suppl) (2002) 581.
- Kakkis ED, McEntee MF, Schmidtchen A, Neufeld EF, Ward DA, Gompf RE, Kania S, Bedolla C, Chien SL, Shull RM: Long-term and high-dose trials of enzyme replacement therapy in the canine model of mucopolysaccharidosis I. *Biochem Mol Med* 58 (1996) 156-167.
- Meikle PJ, Hopwood JJ, Clague AE, Carey WF: Prevalence of lysosomal storage disorders. *JAMA* 281 (1999) 249-254.
- Peters C, Shapiro EG, Anderson J, Henslee-Downey PJ, Klemperer MR, Cowan MJ, Saunders EF, deAlarcon PA, Twist C, Nachman JB, Hale GA, Harris RE, Rozans MK, Kurtzberg J, Grayson GH, Williams TE, Lenarsky C, Wagner JE, Krivit W: Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. The Storage Disease Collaborative Study Group. *Blood* 91 (1998) 2601-2608.
- Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, Niezen-Koning KE, van Diggelen OP: The frequency of lysosomal storage diseases in The Netherlands. *Hum Genet* 105 (1999) 151-156.
- Wippermann CF, Beck M, Schranz D, Huth R, Michel-Behnke I, Jungst BK: Mitral and aortic regurgitation in 84 patients with mucopolysaccharidoses. *Eur J Pediatr* 154 (1995) 98-101.