Ocular Changes in Patients With Mucopolysaccharidosis I Receiving Enzyme Replacement Therapy

A 4-Year Experience

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Objective: To describe the progression of ocular changes in patients with mucopolysaccharidosis I receiving enzyme replacement therapy.

Methods: Three male and five female patients with mucopolysaccharidosis I were followed up for 4 years while undergoing enzyme replacement therapy with α-L-iduronidase (Aldurazyme). Visual acuity, corneal clouding, intraocular pressure, ophthalmoscopy, and optic disc measurements were performed yearly.

Results: Vision remained stable in 5 patients and deteriorated by at least 2 Snellen lines in 3 patients. Deterioration in 2 of these patients was related to progressive corneal clouding. Visual acuities improved in 1 patient after bilateral penetrating keratoplasties. In the third patient, deterioration was related to increasing papilloedema. All patients had typical corneal stromal opacities, however, to a variable extent. Two patients had already undergone corneal transplantation before recruitment in the study. Their grafts remained clear throughout follow-up. Of 2 patients with an elevated intraocular pressure, 1 developed intraocular pressure-related optic nerve damage. Vision remained stable in a patient with bilateral optic atrophy.

Conclusions: Ocular findings remain stable in most patients with mucopolysaccharidosis I receiving enzyme replacement therapy. However, enzyme replacement therapy does not seem to prevent progression of corneal or optic disc changes and, thus, the related worsening of visual function.

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Mucopolysaccharidoses (MPSs) are a heterogeneous group of inherited lysosomal storage diseases characterized by intracellular accumulation of glycosaminoglycans (mucopolysaccharides) within various tissues and excretion of undegraded or partially degraded glycosaminoglycans in the urine.1-4

About 11 distinct subtypes of MPSs have been identified based on the specific enzyme deficiency and the glycosaminoglycan substrate(s) affected.2 Clinically, the MPSs are characterized by varying degrees of skeletal dysmorphism, joint stiffness, mental retardation, and respiratory, cardiac, and ocular abnormalities. The ocular features include corneal clouding, optic nerve swelling, optic atrophy, glaucoma, and retinal pigment epithelium degeneration.3,6 Electroretinographic abnormalities have been reported and may be significant even when the retina does not show a striking morphologic abnormality.7 The disease runs a progressive course, with increasing disability and debilitation.1-5 Without treatment in severe cases, death often results within the first decade.

Mucopolysaccharidosis I is seen as a clinical spectrum composed of 3 disease entities that differ mainly in the severity of clinical manifestations. Hurler syndrome is the most severe form, and Scheie syndrome is at the mild end of the spectrum; patients with the Hurler-Scheie syndrome are in between these 2 extremes. Mucopolysaccharidosis I is characterized by a deficiency of α-L-iduronidase, the enzyme responsible for hydrolyzing the terminal α-L-iduronic acid residues of dermatan and heparan sulfate.1 It is inherited as an autosomal recessive trait.1,3 According to McKusick, the 2 extremes of the disease spectrum are believed to represent allelic forms of a mutation at the p16.3 locus on chromosome 4.1,3 As holds true for severity of systemic disease manifestation, corneal clouding and retinal pigment epithelium degeneration are more frequent and occur at an earlier age in patients with Hurler syndrome or with Hurler-
Scheie syndrome than in those with Scheie syndrome. To our knowledge, only 1 patient with Scheie syndrome featuring optic nerve pathological features has been described in the literature, whereas optic nerve involvement is a typical finding in patients with the other subtypes of MPS I.

The enzyme α-L-iduronidase has been purified and characterized. With the aid of recombinant DNA technology, recombinant α-L-iduronidase has been synthesized and enzyme replacement therapy (ERT) has been approved for patients with MPS I. Treatment of patients with MPS is mainly symptomatic. However, specific treatments, such as hematopoietic stem cell transplantation and bone marrow transplantation (BMT), and, more recently, ERT, are targeted at prolonging and improving the quality of life. Published literature exists regarding ocular changes in patients following BMT. Two separate reports found an improvement of visual acuity (VA) in 3 of 10 patients after 1 year and in 3 patients after 5 years of ERT. There was no effect on corneal clouding.

In December 2000, a phase 3 double-masked, placebo-controlled, multicenter trial was initiated to assess the safety and efficacy of treatment with recombinant α-L-iduronidase (Aldurazyme [BioMarin Pharmaceutical Inc, Novato, California; and Genzyme Corporation, Cambridge, Massachusetts]) in those with MPS I. In this trial, 45 patients were enrolled at 5 sites in the United States, Europe, and Canada. At each study site, institutional ethic committee approval was obtained. The enzyme (α-L-iduronidase) or placebo was administered intravenously once each week for 26 weeks at a dosage of 0.58 mg/kg body weight. At the end of the double-masked phase, all 45 patients entered an open-label extension study. Patients enrolled in the study had MPS I with less than 10% iduronidase activity and were at least aged 5 years and able to perform the primary efficacy assessments. To be included, forced vital capacity had to be less than 80% of the predicted normal value and patients had to be able to perform a 6-minute walk test. At the study site in Mainz, 9 patients were included. Assignment of the patients to the MPS I subtypes (Scheie, Hurler-Scheie, or Hurler) was based on clinical findings. An 8-year-old patient died during the study period because of myocarditis unrelated to ERT. His data are not included in the present report. The remaining 3 male and 5 female patients (mean age: 25 years at study enrollment; age range: 7-43 years) were followed up with ERT for 4 years. Ophthalmological assessments were performed annually. However, patients with visual complaints were seen as required. The examination included most oculomotor assessment of best-corrected and uncorrected VA using Snellen charts, measurement of intraocular pressure by either Goldmann applanation tonometry or digital palpation, slitlamp examination of the anterior segment (model BQ 900; Haag Streit, Kôniz, Switzerland), and direct and indirect ophthalmoscopy. Corneal clouding, if present, was graded as mild, moderate, or severe. In a few patients, static 30° perimetry was performed (Octopus G2 perimeter; Interzeag AG, Schlieren, Switzerland).

The table summarizes the ophthalmological data of all the patients. We did not detect any difference in outcome between those patients who received ERT during the 26 weeks before entering the open-label study and those who did not receive ERT. Best-corrected VA remained stable in 5 patients (patients 2, 4, and 6-8). In patient 6, best-corrected VA seemed to improve in the right eye, from 0.4 to 0.8. However, this most probably was related to inadequate refraction initially, because the better acuity at the end of follow-up was obtained by contact lens correction. Best-corrected VA deteriorated by at least 2 Snellen lines in 3 patients (patients 1, 3, and 5). In patients 1 and 3, visual decline was because of increasing corneal clouding. Penetrating keratoplasty was performed in May 2002 and May 2003 in the right and left eyes of patient 3, respectively. Despite 2 episodes of endothelial graft rejection reactions in her right eye, keratoplasty led to a sustained improvement of vision. Mild elevation of intraocular pressures following topical corticosteroid treatment (administered for graft rejection) resolved with discontinuation of the corticosteroids. There was no evidence of optic nerve or retinal pathological features. In patient 1, keratoplasty was not considered because of poor general health. As ophthalmoscopy was impossible because of corneal clouding throughout the study period, we cannot rule out the possibility that impaired visual function might also have been because of additional optic nerve and/or retinal pathological features.

Two patients (patients 6 and 7) had undergone keratoplasty outside the study location and before the study period. In patient 7, keratoplasty had been performed in 1992 and 1995 in the left and right eyes, respectively. Both corneal grafts remained clear during the study period. The same held true for patient 6, who had undergone penetrating keratoplasty in her right eye in 1997 and lamellar keratoplasty in her left eye in 1999. In this eye, the macula exhibited a subre pigment membrane, although the patient did not experience any metamorphopsia.

Patient 2 had already been diagnosed as having glaucoma and had begun taking antiglaucoma medication before enrolling in the study. He was poorly compliant with his eyedrops at the outset. His optic disc exhibited glaucomatous cupping at the end of follow-up, while his visual fields remained stable.

Optic disc abnormalities were present in 2 additional patients. One (patient 4) had early optic atrophy, evidenced by bilateral temporal disc pallor and depression of sensitivity on central visual field testing, while the other (patient 5) had chronic bilateral papilloedema but no persistent gross field defects. In the latter patient, VA decreased by 2 Snellen lines during follow-up, although this patient did not subjectively complain of deterioration.

Retinal pigment epithelium dysfunction was strongly suspected in patients 2, 7, and 8, because we noted severe concentric narrowing of visual fields. Only in patient 7 did this correlate with the typical pigmentary fundus changes.

Objective refraction with an autorefractor (Retinomax K-plus; Nikon Co Ltd, Tokyo, Japan) revealed moderate degrees of hyperopia and astigmatism in most patients examined (7 of 8 patients). The mean spherical equivalent was 5.75 and 6.00 diopters in the right and left eyes, respectively. All 8 patients completed 4 years of evaluation.
### Table. Characteristics of the Patients With MPS I Receiving ERT

<table>
<thead>
<tr>
<th>Patient No./Sex/Type</th>
<th>Visual Acuity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Objective Refraction&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Cornea&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Optic Nerve</th>
<th>Indirect Ophthalmoscopy</th>
<th>Visual Field&lt;sup&gt;f&lt;/sup&gt;</th>
<th>IOP&lt;sup&gt;i&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, ya</strong></td>
<td><strong>Initial</strong></td>
<td><strong>Final</strong></td>
<td><strong>C/D Ratio</strong></td>
<td><strong>Visual Field</strong></td>
<td><strong>Visual Field</strong></td>
<td><strong>Visual Field</strong></td>
<td><strong>Visual Field</strong></td>
</tr>
<tr>
<td>1/F/10</td>
<td>H Right</td>
<td>0.1 (20/200)</td>
<td>0.005 (20/4000)</td>
<td>6.50 - 15.00 to 165°</td>
<td>+ +</td>
<td>No view</td>
<td>No view</td>
</tr>
<tr>
<td>2/M/17</td>
<td>H-S Right</td>
<td>0.32 (20/63)</td>
<td>0.4 (20/50)</td>
<td>6.75 - 4.00 to 170°</td>
<td>+ +</td>
<td>No view</td>
<td>No view</td>
</tr>
<tr>
<td>3/F/30</td>
<td>S Left</td>
<td>0.63 (20/32)</td>
<td>0.5 (20/40)</td>
<td>8.75 - 4.75 to 177°</td>
<td>+ +</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>4/F/7</td>
<td>S Right</td>
<td>0.3 (20/60)</td>
<td>0.8 (20/50)</td>
<td>6.75 - 4.00 to 120°</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5/F/24</td>
<td>S Left</td>
<td>0.4 (20/50)</td>
<td>0.8 (20/25)</td>
<td>ND</td>
<td>+</td>
<td>Papilloedema</td>
<td>N</td>
</tr>
<tr>
<td>6/F/28</td>
<td>S Right</td>
<td>0.6 (20/30)</td>
<td>0.8 (20/25)</td>
<td>ND</td>
<td>+</td>
<td>Papilloedema</td>
<td>N</td>
</tr>
<tr>
<td>7/M/44</td>
<td>S Left</td>
<td>0.5 (20/40)</td>
<td>0.8 (20/25)</td>
<td>9.25 - 2.75 to 37°</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8/M/40</td>
<td>S Right</td>
<td>0.6 (20/30)</td>
<td>0.8 (20/25)</td>
<td>7.75 - 1.75 to 14°</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Abbreviations:** C/D, cup-disc; ERT, enzyme replacement therapy; H, Hunter syndrome; H-S, Hunter-Scheie syndrome; IOP, intraocular pressure; ITx, lamellar keratoplasty (performed before the study); MPS, mucopolysaccharidosis; N, normal; ND, not done; pTx, penetrating keratoplasty (performed before the study); Ret deg, retinal pigmentary degeneration; S, Scheie syndrome; +, mild; + +, moderate; + + +, severe.

<sup>a</sup>Age at study enrollment is given.

<sup>b</sup>Best-corrected visual acuity at study enrollment (initial) and after 4 years of ERT (final). Data are expressed using the decimal notation (or decimal scale), with corresponding values on the traditional Snellen scale in parentheses.

<sup>c</sup>Cycloplegic refraction obtained by use of tropicamide.

<sup>d</sup>Optic nerve curvature (constriction).

<sup>e</sup>Analysis performed by static perimetry (described in the "Methods" section).

<sup>f</sup>Normal IOP is an IOP of 21 mm Hg or lower; increased IOP is an IOP of 22 to 30 mm Hg.

<sup>g</sup>This patient had additional fine subepithelial punctuate opacifications.

<sup>h</sup>This patient underwent penetrating keratoplasty during follow-up because of progressive visual decline.

<sup>i</sup>This patient had amblyopia due to divergent squint.

This study examined the progression of ocular changes during ERT in patients during a 4-year period. Our findings suggest that, in most patients, ocular abnormalities remain stable or progress slowly during ERT.

It is controversial whether the treatment of the systemic disease alters the course of ocular changes in patients with MPS. Bone marrow transplantation was associated with a reduction in corneal clouding and conjunctival cytoplasmic inclusions, resolution of optic nerve swelling, and improved or stabilized retinal function. Longer follow-up data confirmed improvement of VA and reduction of corneal clouding in about one-third of patients, while electroretinography showed a decline after the first year after BMT. Indeed, some patients developed new ocular complications (eg, cataracts) from the adjuvant therapy accompanying BMT, including irradiation and corticosteroids, while retinal function seemed to decline. No changes in corneal opacity were observed by Kakkis and coworkers in 10 patients undergoing ERT for 1 year, although 3 of their patients exhibited some improvement of VA. Similarly, Wraith was unable to demonstrate any effect of 5 years of ERT on corneal clouding, as documented by photographs. Some improvement in photophobia was noted in 3 patients who had reduced visual function at baseline.

While most of our patients had stable ocular signs, progression of corneal clouding and optic nerve pathological features was seen during follow-up in individual patients. Remarkably, optic nerve pathological features, which have not been regarded as typical features of the so-called attenuated variant of MPS I, Scheie syndrome, were seen in 2 patients. One patient with disc swelling had a slow decline...
in VA, although the patient did not notice any difference in her sight. The reduced acuity probably signals the onset of secondary atrophy, which is attributed to the accumulation of acid mucopolysaccharides (glycosaminoglycans) within the dura, sclera, or ganglion cells, resulting in optic nerve compression. The other patient had optic atrophy with temporal disc pallor. Vision was poor but remained stable. In both patients with optic nerve involvement, there was no evidence of increased intracranial pressure as detected by clinical investigation and imaging.

In patient 3, worsening of VA was related to increasing corneal opacity and prompted corneal transplantation. Despite repeated immunogenic graft rejections, this patient showed significantly improved VA, from 0.3 to 0.8, in both eyes. Two of our patients underwent keratoplasty before ERT. In these patients, no change in the corneal transplantations was seen during the study period. Whether this is because of a possible beneficial effect of ERT on graft survival or whether it reflects the natural course remains a matter of debate. Clear corneal grafts up to 2 and 5 years after keratoplasty in patients with MPS VI16 and MPS VII,17 respectively, have been reported. Uçakhan et al18 documented a 13-year graft survival in a patient with MPS VI who underwent BMT. Moreover, clearing of stromal opacity in the host corneal stroma adjacent to the donor cornea in individual patients with MPS VI-A16 and Hurler-Scheie syndrome has been reported. Kämnn-Kellner et al,19 on the other hand, have noted an unfavorable prognosis of keratoplasty in patients with MPS IV and have raised the issue of increased risk of graft reopacifications in those MPS types featuring an accumulation of keratan sulfate.

In our study population, we cannot confirm the association between increased corneal opacity and high intracocular pressure, as reported by Ashworth and associates. However, our retinal findings were in keeping with previous reports. The fact that no marked change in ocular symptoms was observed during this 4-year observation of ERT may be because enzyme therapy began in relatively older patients, in whom the disease process and its complications were already established. It is possible to speculate that earlier commencement of ERT, in infancy or the neonatal period, may prevent the development of some of these complications. Moreover, most (6 of 8) of our patients have the so-called attenuated MPS1Scheie subtype, in whom the ocular changes are less severe. Thus, it is less likely to detect a possible beneficial effect of ERT. Our findings suggest that keratoplasty should be considered in patients with MPS I because it may be associated with a good outcome.

In conclusion, ERT did not seem to significantly improve or worsen the ocular complications of patients with MPS I. We speculate that earlier commencement of ERT, in infancy or the neonatal period, may prevent the development of some of these complications. This requires further study.

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REFERENCES