Ocular Complications of Mucopolysaccharidoses

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ABSTRACT

Purpose: To study the extent of ocular involvement among children with mucopolysaccharidoses (MPS) at The Children's Hospital at Westmead, Sydney, Australia.

Methods: This study consists of a retrospective consecutive case series, with review of medical records of children with confirmed diagnosis of MPS from 1997 to 2009.

Results: Forty-five children had MPS but only 29 had a record of previous formal ocular assessment. Of these, more than half had documented ocular involvement, including corneal clouding, common among the MPS I subtypes and MPS VI (Maroteaux-Lamy) patients. Posterior segment changes, including pigmentary retinopathy, epiretinal membranes and optic disc changes were more common in MPS II (Hunter). Two children with MPS VI were also noted to have epiretinal membranes and this is likely to be a previously unrecognised association of MPS VI. Only 7 out of 18 children with MPS III (Sanfilippo) were examined, and clinically none were found to have retinopathy. Among those who were cooperative for vision assessment, four were found to see 6/12 or better, while the majority had best corrected vision between 6/15 and 6/60. Three patients had documented disease progression leading to blindness. All four MPS VI patients receiving enzyme replacement therapy (ERT) had stable visual acuity with no ocular progression (6.5 years mean follow-up). However progression of corneal clouding was noted in the only MPS I patient receiving ERT.

Conclusion: Ocular involvement in MPS may cause significant vision impairment. Formal ophthalmic review is important for early detection and treatment to help achieve the best visual outcome.

Keywords: mucopolysaccharidoses, Hurler, Scheie, Hunter, Sanfilippo

INTRODUCTION

The mucopolysaccharidoses (MPS) are a group of inborn errors of metabolism resulting from a deficiency of specific lysosomal enzymes necessary to break down complex carbohydrates called glycosaminoglycans (GAG). As a result glycosaminoglycans and other substances including glycosphingolipids, accumulate within various tissues and organs of the body. The most common MPS disorders are Type I (encompassing the severe Hurler and the attenuated Hurler-Scheie and Scheie spectrum), Type II (Hunter), Type III (Sanfilippo), Type IV (Morquio) and Type VI (Maroteaux-Lamy). Affected patients typically have coarse facial features, skeletal dysplasia, joint contractures and hepatosplenomegaly. Some will have significant cardiac and respiratory disease, intellectual impairment and neurological involvement. Ocular deposition leads to corneal clouding, glaucoma, pigmentary retinopathy and optic nerve involvement. These findings can result in significant vision impairment.[1]

There have been recent advances in the treatment of MPS. Although bone marrow transplantation (BMT) has known mortality and morbidity, in its current regimen as haematopoietic stem cell transplantation (HSCT) it is an increasingly effective treatment for some MPS disorders. It is a particularly effective treatment for children with MPS I (Hurler syndrome) transplanted less than two years of age. Successful engraftment replaces the relevant deficient enzyme, allowing for biochemical and clinical improvement and increased lifespan.[2,3] More recently, enzyme-replacement therapy (ERT) has been shown to decrease the level of urinary GAG, decrease hepatosplenomegaly and increase joint mobility.[4,5] Combined ERT/HSCT have been reported as efficacious therapy for young patients with MPS I (Hurler) with much reduced mortality and morbidity[6] and is now the treatment of choice. ERT alone is now available for MPS I (Hurler-Scheie), MPS II (non-neurological) and MPS VI of intermediate or milder type. Whether or not these treatment modalities alter long-term ocular progression remains uncertain. The full extent of ocular and visual morbidity from MPS disorders is not well documented. The

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objective of this study was to review the extent of ocular complications among children diagnosed and treated for MPS at a tertiary paediatric hospital.

METHODS

We conducted a retrospective review of the medical records of children diagnosed with MPS who received treatment at The Children's Hospital from July 1997 to June 2009. Diagnosis of the MPS subtypes was confirmed through their clinical phenotypes and biochemical assays. The children who underwent formal ophthalmic assessment within the study period were included. All ocular findings and conditions noted in the medical records were documented including visual acuity, presence of corneal clouding, glaucoma, pigmentary retinopathy and optic nerve changes. Progression of ocular complications during the course of follow-up and refractive status were also assessed. Visual outcome was determined by the best corrected visual acuity in the better eye (if unequal) at the most recent eye review, to reflect the child's functional vision. Institutional Ethics Committee approval was obtained for this study.

RESULTS

A total of 45 children (ranging from 0 - 18 years) were diagnosed with MPS during the 12-year study period, with MPS III being the most common (40%) followed by MPS I (24.5%), MPS II (24.5%), MPS VI (9%) and MPS IV (2%). Only twenty-nine children (64%) received formal ophthalmic review, of whom 18 (62%) children had significant ocular involvement. Table 1 summarises the number of children with each type of MPS and their ocular findings.

Table 1. Distribution of MPS patients and their ocular complications

MPS types N (%)	Those who underwent ocular examination	Those with ocular involvement	Corneal clouding	Glaucoma	Pigmentary retinopathy	Optic nerve involvement	Epiretinal membrane
MPS I 11 (24.5%)	8	8	8	0	2	2	0
MPS II 11 (24.5%)	9	5	0	0	2	3	2
MPS III 18 (40%)	7	0	0	0	0	0	0
MPS IV 1 (2%)	1	1	1	0	0	0	0
MPS VI 4 (9%)	4	4	4	1	0	1	2

Ocular findings in MPS I

Eight out of eleven children with MPS I sub-types underwent ophthalmic review. All of these children had significant ocular involvement with corneal clouding, which varied in severity according to the subtype present, being most advanced in the Hurler phenotype and least advanced in the Scheie phenotype. Pigmentary retinopathy was noted in two patients with one confirmed by an abnormal electroretinogram (ERG). One child had papilloedema whereas another child had marked elevation of the optic discs without evidence of raised intracranial pressure (pseudopapilloedema).

Ocular findings in MPS II

Five out of the nine MPS II children reviewed had significant ocular involvement. Posterior segment involvement was more commonly seen in the children with MPS II compared to other types of MPS. Pigmentary retinopathy and epiretinal membranes were found in two children, papilloedema in one and optic atrophy in two. In one boy the optic atrophy was associated with marked thickening of the posterior sclera on ocular ultrasound. No MPS II children were diagnosed with corneal clouding, as expected.

Ocular findings in MPS III

Eighteen children were diagnosed with MPS III, however, only seven underwent formal ophthalmic examination. None of them were known to have night blindness or were diagnosed with ocular involvement including the anticipated pigmentary retinopathy.[1] Unfortunately, none of these children underwent ERG.

Ocular findings in MPS IV

One child was diagnosed with MPS IV and was noted to have mild corneal clouding which did not significantly affect vision. Fundoscopy did not show any evidence of retinopathy or optic disc changes.

Ocular findings in MPS VI

All four children diagnosed with MPS VI underwent ophthalmic examination. All had corneal clouding of varying degrees, with one severe enough to warrant a corneal graft. None of the MPS VI children had pigmentary retinopathy; this was supported by a normal ERG in one child. Papilloedema was noted in one child. Interestingly, epiretinal membranes were also found in two children with MPS VI. One patient was documented to have glaucoma,

with intraocular pressures medically controlled by topical anti-glaucoma medication.

Visual acuity status

Visual acuity was assessed in 20 children using an age and intellectually appropriate vision test, including Teller Acuity Cards, Kay Picture test or the Snellen chart. Four children had a visual acuity of 6/12 or better while the majority (11 children) had vision between 6/15 and 6/60, and five had vision less than 6/60. Analysis of visual acuity over time showed most children's vision remained relatively stable. Unfortunately, three children (two with MPS I, one with MPS II) showed significant visual deterioration leading to severe vision impairment (defined as visual acuity worse than 6/60) during the study period. One MPS I child had severe hydrocephalus and optic atrophy associated with no perception of light in one eye and perception of light only in the fellow eye. In the other MPS I child the cause of the severely impaired vision was progression of corneal clouding. The MPS II child suffered from hydrocephalus with resulting optic atrophy and optic nerve compression from posterior scleral thickening around the optic nerve.

Refractive status

Cycloplegic refraction was successfully performed in 20 children. Seven had normal refraction for their age, while the remaining thirteen had refractive errors. Eight children had significant hypermetropia, three had myopia and two had myopic astigmatism. Glasses were prescribed for four children in whom the refractive error was considered to be the main cause of reduced vision.

Bone marrow transplant, enzyme replacement therapy and ocular findings

Two MPS I children underwent BMT, with one child receiving ERT prior to BMT. Both had no documented progression of their ocular findings over a mean follow-up period of 6.5 years. Vision remained stable (6/12 equivalent) in one child and stable at 6/75 in the other due to pigmentary retinopathy. Neither child developed severe dry eye (keratoconjunctivitis sicca) or cataract as a consequence of BMT. However, one child with MPS I (Hurler-Scheie subtype) experienced a deterioration of vision due to the progression of corneal clouding despite ERT (5 years follow-up). Four children with MPS VI received ERT and had stable vision and ocular findings whilst undergoing therapy, with a mean follow-up period of 6.5 years.

DISCUSSION

Ocular findings in MPS are frequent and may lead to significant vision impairment due to corneal clouding, glaucoma, pigmentary retinopathy and optic nerve involvement. Similar to previous studies, corneal clouding in this study was more common in the MPS I subtypes and MPS VI[1]; no children with MPS II or MPS III in this study showed corneal clouding. A favourable prognosis for corneal transplant has been previously documented in MPS disorders, including MPS VI.[7,8,9,10,11] In our study, the one child who underwent corneal transplant for severe corneal clouding had MPS VI. The donor cornea remained clear for a three-year follow-up period with best corrected vision of 6/20.

Glaucoma in MPS results from GAG accumulation within the anterior segment structures of the eye, including the trabecular meshwork, causes narrowing of the drainage angle and obstruction of the aqueous outflow.[1] In a study of 121 patients with MPS VI (estimated to be about 10% of MPS VI patients globally) 10% were on anti-glaucoma treatment.[12] In our study, the only child diagnosed with glaucoma also had MPS VI. However, the prevalence of glaucoma in our study could have been underestimated due to the complex nature of examining for glaucoma in a cohort of MPS children who often had intellectual impairment and ocular complications such as corneal clouding which prevented a clear view of the relevant ocular structures.

Retinopathy was noted in two children with MPS I and two children with MPS II. Previous studies have documented moderate to severe pigmentary retinal degeneration associated with ERG abnormalities as a prominent feature of MPS III.[1,13] In our study, no MPS III children were found to have any ocular complications. However, the onset of pigmentary retinal degeneration may be delayed until adolescence and our subjects were too young for this to be detected. Furthermore ERG had not been performed to detect the presence of retinal changes. Retinopathy was also not found in any of the children with MPS IV or MPS VI. This was confirmed in one individual with MPS V1 who had a normal ERG. Retinopathy has not been described among MPS VI children in the literature apart from one child who had reduced dark-adapted amplitude on ERG.[1,9]

Four children (two with MPS II and two with MPS VI) were found to have epiretinal membranes. This layer of tissue overlying the macula has been previously reported in MPS II[14] and Type III and IV mucolipidoses.[15,16] To our knowledge, epiretinal membranes have not been previously reported in MPS VI and this finding is suggestive of a new ocular association in this MPS subgroup. Whether or not these membranes represent deposition of GAG within the retinal layers is unclear.

In our series six children had optic nerve involvement including papilloedema, elevation of the optic nerves due to GAG deposition, and optic atrophy. Three of these children had MPS II, and optic nerve involvement in MPS II has been well documented.[17,18] This occurs as a consequence of raised intracranial pressure or direct GAG accumulation within the optic nerve and surrounding

meninges compressing the optic nerve. Increased scleral thickness, especially posteriorly, appears to be a common association in MPS II and no doubt contributes to the compression of the optic nerve at its exit from the eye.[18,19]

Bone marrow transplantation (BMT) has been reported to reduce corneal clouding,[20,21] to contribute to resolution of optic nerve swelling[8,20] and improvement in the retinal function as measured by ERG in MPS I.[20] In a study of 23 patients (19 with MPS I)[8] it was shown that a reduction of corneal clouding was seen in approximately one-third of patients, while a similar number showed worsening of corneal clouding (mean follow-up period of 6.1 years). Also in this study, approximately 80% of patients showed initial ERG improvement within one year of BMT followed by a decline after this time.[8] Interestingly, 30% of patients had papilloedema and raised intracranial pressure prior to BMT, which resolved following BMT.[8] No ocular improvement occurred in our two MPS I children following BMT although their visual acuity, refractive status and ocular findings remained stable. In one child however, significant corneal clouding precluded any view of the optic discs.

ERT has now become available for the treatment of MPS I, MPS II and MPS VI. Kakkis and colleagues found no improvement in corneal clouding over the course of a year despite the normalisation of liver size and near normalisation of urinary GAG and improvement in other systemic symptoms in eight MPS I children who received ERT.[4] Similar findings were also found among MPS I patients receiving ERT in another study with vision stable in five out of eight patients over a four-year follow-up period and vision deteriorating in three patients, two due to progressive corneal clouding.[10] In a more recent study of seven patients with MPS VI, ocular findings remained stable in five patients with no substantial change in corneal clouding or any improvement in the optic nerve pathology (mean follow-up period of 44 months).[11]

The MPS I child in our study who received ERT had progressive corneal clouding. Ocular findings remained stable throughout the course of follow-up in all our four MPS VI patients who received ERT (mean follow-up of 6.5 years). There was no evidence of improvement in visual acuity or reduction of the corneal clouding.

This study was a retrospective analysis, and shortcomings are acknowledged. At times medical record documentation was incomplete and variability of visual assessment techniques made analysis difficult. Ophthalmic investigation of MPS children was challenging and limited by the nature of their capabilities. Tests such as ocular ultrasound and electroretinogram were often not conducted which hindered the detection of compressive optic neuropathy and pigmentary retinopathy respectively.

CONCLUSION

Ocular involvement is common in MPS and in some individuals it may be severe enough to lead to significant vision impairment. This study has revealed that MPS children may not necessarily access regular ophthalmic care. To ensure MPS sufferers enjoy the best possible vision, formal ophthalmic review for the early detection of treatable ocular conditions is vital. Health professionals need to be aware of the likelihood of ocular involvement in MPS.

In view of the findings of this study, we propose that MPS children undergo comprehensive ophthalmic review on a yearly basis, to detect potentially treatable causes of vision impairment. Children with more severe ocular manifestations and progression should be seen more frequently. A prospective study at our centre has recently commenced and will gather detailed data on the ocular manifestations, progression and visual outcome of children diagnosed with MPS. The findings of this study will be used to establish guidelines regarding frequency of ophthalmic review and efficiencies in assessment of children with MPS.

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