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► **To cite this version:**

Stefano Ferrari, Diego Ponzin, Jane L Ashworth, Kristina Teär Fahnehjelm, C Gail Summers, et al..
Diagnosis and management of ophthalmologic features in patients with mucopolysaccharidosis. *British
Journal of Ophthalmology*, 2010, 95 (5), pp.613. 10.1136/bjo.2010.179937 . hal-00588352

HAL Id: hal-00588352

<https://hal.science/hal-00588352>

Submitted on 23 Apr 2011

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Diagnosis and management of ophthalmologic features in patients with mucopolysaccharidosis

Stefano Ferrari¹, Diego Ponzin¹, Jane L. Ashworth², Kristina Teär Fahnehjelm³, C. Gail Summers⁴, Paul R. Harmatz⁵, Maurizio Scarpa⁶

1. The Veneto Eye Bank Foundation, Venice, Italy

2. Manchester Royal Eye Hospital, Manchester, UK

3. Department of Clinical Neuroscience, Karolinska Institutet and Department of Paediatric Ophthalmology and Strabismus, St. Erik Eye Hospital, Karolinska University Hospital, Huddinge, Sweden

4. Departments of Ophthalmology and Pediatrics, University of Minnesota, Minneapolis, MN, USA

5: Children's Hospital & Research Center Oakland, Oakland, CA, USA

6. Department of Paediatrics, University of Padua, Padua, Italy

Corresponding author:

Maurizio Scarpa

Department of Paediatrics, University of Padua

Via Giustiniani 3

35128 Padua

Italy

Tel.: +39 049 8213505

Fax: +39 049 8213502

e-mail: scarpa@pediatria.unipd.it

Keywords: Diagnosis, Eye Diseases, Glycosaminoglycans, Mucopolysaccharidoses, Treatment

Keyword selection in submission from fixed list: pathology, imaging, diagnostic tests/investigation, treatment medical, child health (paediatrics)

Word count: 3254

Word count abstract: 228.

SUMMARY

Ocular pathology is common in patients with mucopolysaccharidosis (MPS), an hereditary lysosomal storage disorder, where the eye as well as other tissues accumulate excessive amounts of glycosaminoglycans. Despite genetic and phenotypic heterogeneity within and between different types of MPS, the disease symptoms and clinical signs often manifest during the first six months of life with increasing head size, recurrent infections, umbilical hernia, growth retardation and skeletal problems. Typical ocular features include corneal clouding, ocular hypertension/glaucoma, retinal degeneration and optic nerve atrophy. Visual deterioration and sensitivity to light may substantially reduce the quality of life in MPS patients, particularly when left untreated.

As an early intervention, haematopoietic stem cell transplantation and/or enzyme replacement therapy are likely to improve patients' symptoms and survival, as well as visual outcome. Thus, it is of utmost importance to ensure proper detection and accurate diagnosis of MPS at an early age. Fundamental herein is to increase awareness and knowledge among ophthalmologists of the ocular problems affecting MPS patients and to highlight potential diagnostic pitfalls and difficulties in patient care.

This review provides insight into the prevalence and severity of ocular features in patients with MPS and gives guidance for early diagnosis and follow-up of MPS patients. MPS poses therapeutic challenges in ocular management, which places ophthalmologists next to paediatricians at the forefront of interventions to prevent long-term sequelae of this rare but serious disease.

The clinical features of mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are a heterogeneous group of lysosomal storage disorders that are genetically inherited in an autosomal recessive manner (except for MPS II which is X-linked).[1] These inborn metabolic diseases are characterised by functional defects in particular lysosomal enzymes, involved in the breakdown of glycosaminoglycans (GAGs, acid mucopolysaccharides) (Table 1).[1] Depending on the type of MPS, the resulting catabolic error causes progressive accumulation of particular GAGs in lysosomes and their abnormally high excretion in urine (Table 1).[1] Histochemical examinations have demonstrated cytoplasmic membrane-bound vacuoles containing GAGs in almost all ocular tissues of MPS patients.[2,3] These deposits alter the cellular shape and tissue ultrastructure, resulting in progressive physiological dysfunction that presents clinically at a young age and ultimately can cause visual impairment or blindness.[3,4] Accumulation of GAGs in other organs are the cause of typical coarse facial features, skeletal deformities (e.g., dysostosis multiplex), growth retardation (often accelerated in the first 12-18 months), cardiac valvular abnormalities, respiratory difficulties and gastrointestinal problems (e.g., hepatosplenomegaly, bowel dysfunction) as well as intellectual and behavioural impairment (in the severe forms of MPS I, II and III) (fig 1).[3] About 70% of patients have central nervous system involvement, albeit to different extents. Ocular manifestations vary and include corneal clouding, ocular hypertension/glaucoma, retinal degeneration and optic nerve swelling with subsequent atrophy. The severity and relative predominance of the ocular features, depend on the MPS (sub)type (Table 1).[3] Nevertheless, phenotypic variation is often observed,[3] which is likely due to the mutational heterogeneity of the enzyme involved,[5,6] that may lead to absent or attenuated enzyme activity.[5,7] **Further mutational analysis studies may reveal potential genotype-phenotype correlations.**

Table 1. Classification of different MPS types according to enzyme deficiency and with indication of the severity of ocular pathologies (slightly adapted from Ashworth et al.[3]*) Note that there are inter-patient variations

MPS type (eponym)	Enzyme deficiency	Involved GAG	Eye diseases			
			Corneal clouding	Glaucoma	Retinopathy	Optic nerve abnormalities
MPS I H (Hurler)	α -L-iduronidase	DS, HS	+++	++	++	++
MPS I H/S (Hurler-Scheie)	α -L-iduronidase	DS, HS	++	++	++	++
MPS I S (Scheie)	α -L-iduronidase	DS, HS	+	+	++	+
MPS II (Hunter)	iduronate-2-sulfatase	DS, HS	+	+	++	++
MPS III (Sanfilippo) A-B-C-D	heparan sulfamidase (A) N-acetyl- α -D-glucosaminidase (B) acetyl-CoA- α -glucosaminidase N-acetyltransferase (C) N-acetylglucosamine-6-sulfatase (D)	HS	+	+	+++	+
MPS IV A (Morquio A)	N-acetylgalactosamine-6-sulfatase	KS	+	+	++	+
MPS VI (Maroteaux-Lamy)	N-acetylgalactosamine-4-sulfatase	DS	+++	++	unknown	++
MPS VII (Sly)	β -D-glucuronidase	DS, HS, CS	++	unknown	unknown	++
MPS IX (Natowicz)	hyaluronidase	CS	unknown	unknown	unknown	unknown

+: mild; ++: moderate; +++: severe; CS: chondroitin sulfate; DS: dermatan sulfate; GAG: glycosaminoglycan; HS: heparan sulfate; KS: keratan sulfate

Call for early detection and diagnosis of MPS

Early detection allows prompt intervention of this devastating disorder in a primary stage with haematopoietic stem cell transplantation (HSCT) and/or enzyme replacement therapy (ERT) and thus, better prognosis and outcomes for the patient. While a rapid colorimetric screening of the urinary GAG expression level is quite predictive,[7,8] the definitive diagnosis is mostly based upon a combination of clinical, radiological and laboratory (e.g., specific lysosomal enzyme activity assay) methods from collaborative medical specialties.[3,7]

Given its phenotypic heterogeneity and its rarity, with an overall cumulative incidence rate of 2 to 5 patients with MPS out of 100,000 live births,[9,10] medical awareness of MPS is essential in order to allow proper and timely diagnosis. Despite great variations in severity and associated progression rate of MPS (fig 1), the disease can manifest within the first 6 months of age, leading to limited life span, particularly for rapidly-progressing disease forms. Although paediatricians often encounter and recognise patients with MPS, patients with the attenuated form (e.g., MPS I S that present at later ages - older than 5 years) may be first seen and diagnosed by ophthalmologists because of the eye involvement.[3] Patients less than 5 years old with a severe form (MPS I H) have been described, who were not diagnosed until glaucoma developed.[11] These findings highlight the crucial role of ophthalmologists in contributing to early detection of MPS in children.

Ocular problems in MPS

Anterior segment

Corneal clouding can involve all layers of the cornea including the epithelium, stroma and endothelium. Structural alterations caused by GAG deposition, including an abnormal cell

shape and irregular collagen fibril diameter, spacing and arrangement in the stroma, result in reduced transparency and increased light scattering.[3,12] Corneal clouding varies from being subtle to severe and is often described as being of ground glass appearance. It typically has a diffuse pattern,[2] although primarily peripheral corneal clouding has been described in MPS I S.[13] A moderately positive correlation between corneal clouding and central corneal thickness has been reported,[14] although this has not been corroborated by others.[15] Progressive corneal clouding is a prominent feature of patients with MPS I, VI and VII (Table 1, fig 2).[3,4] It may first be asymptomatic and then present as photophobia associated with slowly progressive loss of visual acuity.[16] Signs and symptoms reported from the MPS I Registry revealed that corneal clouding is common, being present in over 80% of the patients, regardless of age at onset.[17] All 19 patients with MPS VI in a Brazilian study showed corneal clouding that ranged from mild to severe.[18] This high prevalence of corneal clouding in MPS was further confirmed by a retrospective case series, which found that MPS VI patients were more severely affected than MPS I patients (Table 2).[4] In addition to corneal clouding, peripheral vascularisation of the cornea may also be present in MPS patients.[3,19] This can occur following chronic corneal oedema due to raised intraocular pressure (IOP), or secondary to corneal exposure associated with pseudo-exophthalmos (fig 2) and/or post-treatment graft-versus-host disease.[3] Both superficial and deep vessels were observed in all four cases with glaucoma in association of MPS VI.[19]

Open-angle[11,19,20] and acute/chronic angle-closure glaucoma[19,21,22] have both been observed in MPS patients (Table 1). GAG accumulation and the consequent thickening of the cornea can lead to narrowing of the anterior chamber angle, and deposition within trabecular cells may cause obstruction of outflow.[11,19] Another potential cause of angle closure and subsequent increased IOP is the development of multiple iridociliary cysts.[23] The prevalence of glaucoma is estimated at 10% for the MPS I population.[17] While ocular

hypertension and glaucoma are fairly rare in other types of MPS, elevated IOP was observed in approximately half of the patients with MPS VI (Table 2) and could be due to their corneal changes because a statistically significant relationship between IOP and corneal clouding has been found.[4] **This illustrates the difficulty in distinguishing increased corneal rigidity and thickness from true raised IOP and potential glaucoma.** Only one patient with MPS VI, however, had an enlarged cup-to-disc ratio.[4]

Posterior segment

Ultrasound examinations in 65 patients with MPS have demonstrated significantly thicker sclera at the posterior pole and a widened optic nerve and its sheath.[24] These morphological changes probably develop very early in the course of the disease.[24] Thickened sclera may subsequently lead to vortex vein obstruction and development of the uveal effusion syndrome as described in one patient with MPS II.[25]

Optic disc and optic nerve pathologies are present in MPS (Table 1). Optic disc swelling of mild-to-moderate severity was noted in 50% of the patients with MPS VI, while optic nerve atrophy in 2 of 14 cases.[4] Similar rates for MPS VI were observed in a study by Collins et al, while optic nerve atrophy was slightly more common in MPS IH and IH/S patients (Table 2).[26] Optic disc swelling (i.e., papilloedema) and subsequent optic nerve atrophy can occur secondary to high intracranial pressure (ICP)[4], or follow nerve compression due to GAG-thickened dura and sclera.[27] Alternative causes of optic nerve atrophy may be the degeneration of optic nerve ganglion cells due to intracellular GAG deposition or optic disc cupping and atrophy due to increased IOP.[27]

Retinopathy occurs as a result of GAG deposition within retinal pigment epithelial (RPE) cells and in the inter-photoreceptor matrix, leading to progressive photoreceptor loss, retinal

degeneration and dysfunction (fig 2).[4] This may clinically appear as sensitivity to light, central or peripheral vision loss, clumsiness, night blindness, etc.,[3] and display an identical histopathology to retinitis pigmentosa.[2] Variable degrees of retinopathy, with associated changes in the electroretinogram (ERG), have predominantly been seen in MPS I, II and III (Table 1, Table 2).[4,28] ERG evidence of retinal dysfunction ranged from none to severe for MPS I and II patients, while all MPS III patients demonstrated moderately-to-severely affected ERGs.[28] The ERG findings were similar to those seen in primary and secondary rod-cone retinal degeneration, where the depression of rod-mediated responses exceeds that of the cone system,[15,28,29] causing a reduction in b-waves on dark adaptation.[30] In several cases, ophthalmological signs and symptoms did not correlate with the electrophysiological findings; funduscopic findings were restricted to only mild changes of the RPE or vascular attenuation.[28] Thus, as in any other disease, ophthalmological examination is not sufficient to rule out retinal involvement in MPS.[28] Lastly, macular oedema and maculopathy has been reported in MPS I S and MPS II.[31,32]

Best-corrected visual acuity (BCVA) differs in patients with MPS. Whereas a BCVA of at least 0.5 in more than half (58%) of the Swedish MPS I patients was found (Fahnehjelm KT et al, [accepted by Acta Ophthalmol 2010](#)), other reports demonstrated a high rate of visual impairment in patients with MPS I (Table 2).[4,14] This distinction could be caused by phenotypic variations, variable age at [examination or](#) diagnosis, and consequent compliance with correction of the high hypermetropia or treatment of amblyopia. Also patients with MPS VI can suffer from visual impairment (Table 2).[4] In addition, patients with both MPS VI and MPS I have been reported with amblyopia, ranging between 32 and 44% of the patients, and strabismus, ranging between 25 and 44%.[4] Refractive errors are also common in patients with MPS. The majority (> 90%) of patients with MPS I (of either sub-type) and MPS VI for whom refraction data were available had hypermetropia.[4,33-35] It has been

speculated that hypermetropia is caused by GAG-mediated increased rigidity of the cornea, thereby straightening its curvature and reducing its refractive power.[33] Hypermetropia could also result from scleral thickening and shortened axial length (Fahnehjelm KT et al, [accepted by Acta Ophthalmol 2010](#)).

Table 2. Prevalence of ocular features in patients with MPS I and VI (expressed as % of affected patients unless indicated otherwise)

MPS type	Corneal clouding [4] +; ++; +++	Ocular hypertension (> 21 mm Hg)[4]	Optic disc swelling [26] [#]	Optic atrophy [26] [#]	Retinopathy [4]	Visual impairment (<20/40*) [4]
MPS I H	N = 19 47%; 37%; 16%	N = 19 5%	N = 14 57%	N = 14 14%	N = 13; 69% (ERG) N = 19; 11% (atrophy)	N = 19 79%
MPS I H/S	N = 8 38%; 38%; 25%	N = 9 11%	N = 21 43%	N = 21 19%	N = 1; 1 patient (ERG) N = 9; 56% (atrophy)	N = 9 44%
MPS I S	N = 3 2 patients; 1 patient; none	N = 3 none	N = 4 none	N = 4 none	NA (ERG) N = 3; 2 patients (atrophy)	N = 3 none
MPS VI	N = 16 31%; 25%; 38%	N = 13 54%	N = 12 42%	N = 12 8%	N = 8; 12% (ERG) N = 16; 0% (atrophy)	N = 16 25%

*vision worse than 6/12 Snellen equivalent in the better eye

[#]values relate to eyes, not patients

ERG: electroretinogram; NA: not available; +: mild; ++: moderate; +++: severe

Assessment and diagnosis of eye disorders in MPS

An accurate diagnosis of the ocular manifestations in MPS patients may be a challenge because of poor cooperation of the patient and due to the different underlying ocular and other pathologies.[4] Severe photophobia may hamper clinical examination in general,[33] while the corneal involvement in MPS may make diagnosis of glaucoma difficult.

Firstly, thickening and increased corneal rigidity can falsely elevate the IOP values.[14,36] This effect on IOP validity is more observed in non-contact tonometry than in Goldman applanation tonometry.[36] In that sense, dynamic contour tonometry that uses the principle of corneal contour matching instead of applanation may be more reliable and suitable for patients with MPS.[37] Given its possible impact on IOP, it is certainly worthwhile to assess the corneal thickness by pachymetry.[38]

Secondly, another frequently encountered difficulty when assessing glaucoma is related to corneal clouding, which hampers a clear view by ophthalmoscopy and gonioscopy, limiting the assessment of optic disc cupping (i.e., cup-to-disc ratio) and visualisation of the drainage angle.[19,21] Similarly, corneal clouding can also lead to difficulties in diagnosing and monitoring papilloedema, optic nerve atrophy and retinal or macular degeneration by funduscopic examination after dilatation or by optical coherence tomography that can distinguish the different retinal layers.[39] Therefore, ultrasound examination may be a valuable and suitable alternative to obtain better image quality in patients with MPS. **In addition, an electroretinography (ERG) examination aids diagnosis of retinopathy.** To recognise corneal clouding as a clinical feature of MPS and discriminate it from other diseases (e.g., congenital glaucoma, staphylococcal hypersensitivity, cystinosis, corneal dystrophy), visualisation of the *in vivo* microstructure of the cornea with real-time, slit-scanning confocal microscopy is preferable to histological techniques.[40] Brighter

intercellular spaces in all corneal layers and microdeposits of 1.0 to 3.8 μm outside and inside stromal keratocytes that appear rounded with clearly demarcated hyporeflexive regions are characteristic features found in MPS I and MPS VI patients.[40-42]

In addition, the diagnostic assessment of ocular pathologies is frequently complicated by the patients' physical inabilities, young age and developmental delay (behavioural or intellectual disabilities), particularly when cooperation is needed for visual field measurements.[3]

Sometimes, an **ERG** examination under sedation or anaesthesia to determine severity of retinopathy can be helpful. General anaesthesia, however, can be dangerous in patients with MPS due to co-existent cardiovascular or respiratory problems (severe oro-pharyngeal and upper airway narrowing) [43]. This leads to problems with intubation and pre-/post-operative complications,[43-45], requiring an experienced anaesthesiologist (for children with MPS).[46]. Retinoscopy is also hampered in the anaesthetised child as the correct axis can only be approximated, which can be a major source of error. Therefore, simple clinical tests (e.g., colour vision Hardy Rand Rittler and Cone Adaptation Test) can be used in the office for initial screening of retinal pathology. Upon suspicion of retinal pathology, ERG under general anaesthesia may be considered.

Recording of visual evoked potentials (VEPs) is more easily performed. In patients with severe corneal clouding, flash VEPs show a decreased signal, while optic nerve pathologies due to increased ICP may reflect in attenuated amplitudes or delayed latencies of the VEPs. However, it is worth noting that normal VEPs may be found in patients with swollen optic discs in early (not chronic) stages.

International expert panels have recommended that MPS patients are evaluated on a regular basis for their ophthalmic problems, i.e., at least every 12 months for MPS I and MPS VI, and according to the individual patient's needs as determined by the treating physician.[17,27].

Apart from more specific investigations such as pachymetry, ultrasound examination and electrophysiology when needed, basic clinical follow-ups in children with MPS should include evaluation by an orthoptist to detect strabismus, evaluation of IOP, retinoscopy after cycloplegia to detect high refractive errors, and evaluation of the fundi, including photography in the cooperative patient.

Therapeutic approaches in MPS and its ocular features

Integrated medical care necessitates a multi-disciplinary expert approach in the treatment of patients with MPS.[1,3] Input from different paediatric sub-specialties, including ophthalmology, is important and needs to consider the risk-benefit balance of treatment.[1] Because many patients with MPS are at increased anaesthetic risk,[44,45] local anaesthesia is often preferable, though age and mental status are relative deterrents,[45] and any procedure with sedation must be performed in a specific referral centre.

Ocular therapies in MPS

The predominance of corneal clouding, glaucoma and concomitant visual deterioration in MPS necessitates thorough clinical examinations, prescription of optimal correction and if needed, corneal transplantation and glaucoma treatment. To correct corneal clouding, penetrating keratoplasty (PK) (fig 3) or, more advanced techniques such as lamellar keratoplasty, are valuable treatment options **in the absence of retinal degeneration (Pinello L et al, submitted to Clin Exp Ophthalmol)**. Deep anterior lamellar keratoplasty is currently favoured over conventional PK in MPS patients because of similar effectiveness and lower risks.[47] Although no systematic studies on the outcome of keratoplasty in patients with

MPS have been performed, good results with the maintenance of clear donor cornea for a period of 3 months up to 5 years (without systemic therapies) were obtained in various cases.[48-52] However, while clearing of the host cornea has been noted,[53] GAGs may re-accumulate in the grafted tissue.[49,54] Re-opacification, as early as one year post-surgery[49,54], likely correlates with disease severity[49] and could be attributable to anterior-posterior spread of host keratocytes and gradual replacement of epithelial cells by host epithelium.[54] In addition, concomitant **retinal degeneration**, optic nerve atrophy, glaucoma or other dysfunctions may limit the success of PK in terms of visual improvement (fig 3).[3,49] Therefore, the potential benefits to vision and quality of life, even if temporary, must be weighed against co-existent eye pathologies, anaesthetic risks, intensive post-operative care and risk of complications in patients with MPS.[3]

When glaucoma is suspected – bearing influencing factors in mind and taking diagnostic difficulties into account – balancing the pros and cons of anti-glaucoma therapy[55] is similarly important. Clinical reports of anti-glaucoma therapy in patients with MPS are scarce and relatively dated.[11,19-22,29] This finding highlights the rarity of the MPS disorder and the difficulty in identifying glaucoma in MPS patients, because co-existent corneal clouding frequently hampers gonioscopy and ophthalmoscopy and because visual fields are usually not obtained.[19,21]

Systemic therapies in MPS

Disease-specific systemic therapies, i.e., HSCT and ERT, re-establish the regular GAG catabolism in the body. With the aim to reverse, arrest or at least slow down disease progression and considerably improve the patients' outcome and quality of life,[3] it is

advantageous to start treatment early in life (i.e., HSCT before 24 months of age and ERT shortly after birth).[29,34,35,56-59] Such necessitates early diagnosis.

HSCT encompasses the transplantation of matched healthy donor cells (from bone marrow or umbilical cord blood) and has achieved beneficial effects on ocular problems, although not uniformly or in the long term.[15,29,33] Indeed, HSCT has been reported to reduce but not fully eliminate corneal clouding,[15,29,33] to resolve optic nerve oedema[15,29], and to improve ERG results.[29] (Summers CG et al, submitted to Clin Exp Ophthalmol) However, retinal degeneration can progress despite engraftment[29] and visual function may remain compromised.[33] (Summers CG et al, submitted to Clin Exp Ophthalmol) HSCT requires a suitable donor and there is significant risk of post-transplantation systemic morbidity and mortality (e.g., infection, graft-versus-host-disease, rejection and complications from adjuvant radiation or chemotherapy).[3,27] In addition, ocular complications may arise following HSCT, e.g., cataracts secondary to corticosteroid therapy and irradiation, keratoconjunctivitis sicca and post-intervention retinopathy.[3,29,60,61]

As an alternative to HSCT, ERT has been developed and recommended in patients because of its favourable safety profile.[27] ERT is also used before HSCT to improve the patient's respiratory function and somatic status.[62,63] The administration of purified recombinant enzyme via regular intravenous infusion is now approved for the Hurler/Hurler-Scheie MPS I syndrome (laronidase),[64] MPS II (idursulfase)[65] and MPS VI (galsulfase).[66] Clinically meaningful and sustained improvements in functional capacity and other systemic signs have been observed with ERT in phase III studies.[67-72] With respect to ocular manifestations, stability or improvement of corneal clouding and visual acuity was apparently found in some patients, but controversy about other ocular pathologies such as optic disc changes

remains.[34,35,69,71,73-75] (Summers CG et al, submitted to Clin Exp Ophthalmol) More assessments are necessary to provide a clear-cut picture of the effects of ERT, and its combination with HSCT, on the course of ocular changes.[4] Limitations of ERT include the risk of allergic or immune reactions related to the administration route (successfully managed by antihistamines and a slower infusion rate), infections associated with regular administration, as well as penetration problems at particular 'privileged sites'.[27]

The enzyme, at the doses currently administered, does not cross the blood-brain barrier and presumably, likewise, not the blood-retina barrier to an appreciable extent.[35] Consequently, the ocular involvement in MPS may require novel therapeutic strategies or tailored drug delivery routes, in order to ensure substantial concentrations and sufficient pharmacological effects. Promising attempts in MPS animal models include, amongst others, systemic gene therapy and local injections in the eye.[76,77] (Ponder KP et al, submitted to Clin Exp Ophthalmol) Results of recent phase I clinical trials in patients with Leber congenital amaurosis[78-80] bode well for local gene therapy in (posterior) eye complications associated with other well-defined, single-gene disorders such as MPS. Future interventions with gene therapy will likely change the outcomes of individuals affected with MPS, but early diagnosis will be required for maximum benefit.

CONCLUDING REMARKS

The multi-organ involvement and rarity of MPS hamper early recognition of this disease. The diagnosis is often delayed while precious time is spent on expert-to-expert referral.

Ophthalmologists can play a crucial role in diagnosing MPS because they encounter patients with corneal clouding and other ocular problems at a relatively early age, and must be informed regarding the various manifestations in MPS. (Ashworth JL et al, accepted by Clin Exp Ophthalmol)

Diagnosing ocular pathologies can be a challenging task due to concomitant influencing factors (e.g., corneal clouding hampering viewing techniques and corneal thickening with a risk of elevating IOP values) or because the patients' physical or mental incapacities reduce cooperation. (Ashworth JL et al, accepted by Clin Exp Ophthalmol) Similarly, ocular therapies need to take into account the compromised health condition of MPS patients when balancing the benefits and risks of procedures such as corneal transplantation or glaucoma treatment. Systemic therapies that re-establish GAG breakdown (such as HSCT or ERT) could bring relief as part of integrated care, although more investigations are warranted, particularly with regard to their effectiveness on ocular abnormalities in MPS.

FIGURE LEGENDS

Figure 1. Patients with MPS VI of varying severity [copyright BioMarin Inc]



Figure 2. Ocular features in MPS patients

A) Marked corneal clouding in the right eye of a 12.5-year-old male patient with MPS VI [copyright Fahnehjelm KT]

B) Areas of retinal pigment epithelial atrophy in the right eye of a 15-year-old patient with MPS I H/S[3]*

C) Bilateral pseudoproptosis exophthalmos due to shallow orbits in a 12.5-year-old male patient with MPS VI [copyright Fahnehjelm KT]

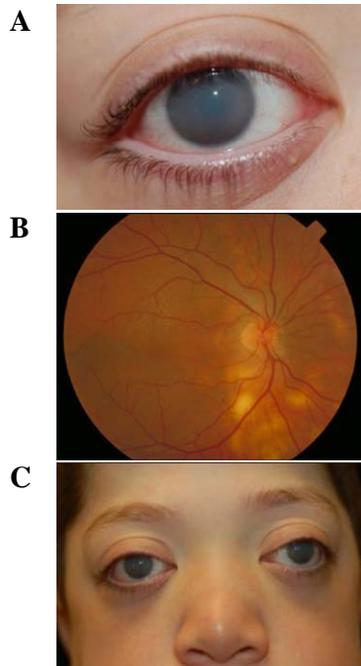
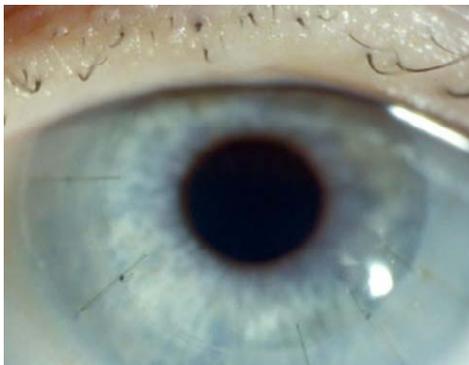


Figure 3. Penetrating keratoplasty with clear donor cornea in a 22-year-old patient with MPS VI (Note that co-existent severe optic atrophy limited visual acuity) [copyright Ashworth JL]



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ACKNOWLEDGEMENTS

The authors are grateful to Ismar Healthcare NV for their writing assistance, which was funded by BioMarin Europe Ltd, London, UK.

The content of the manuscript is based on presentations and discussions during a scientific meeting entitled 'MPS and The Eye', which took place from 7-9 October 2009 in Venice, Italy. The authors would like to thank the other faculty members for their contribution during this meeting, including Prof. A. Auricchio, Dr. B. Bachmann, Prof. M. Busin, Prof. H.S. Dua, Dr. L. Fontana, Prof. R. Giugliani, Prof. J.V. Jester, Dr. G.K. Klintworth, Prof. K. Landau, Mr. A.M. Lobo, Prof. Y. Omidi, Prof. G. Palù, Dr. S. Pitz, Prof. K.P. Ponder, Dr. A. Suppiej, Prof. A.P. Tormene and Dr. C.E. Willoughby. This meeting was supported by an educational grant from BioMarin Europe Ltd, London, UK. BioMarin had no role in the content presented and discussed at the meeting. All authors participated in the development and writing of the manuscript and are fully responsible for its content. BioMarin reviewed the manuscript with respect to the accuracy of statements concerning ERT for MPS VI.

COMPETING INTERESTS

S Ferrari, D Ponzin, JL Ashworth, KT Fahnehjelm, CG Summers: None

PR Harmatz has provided consulting support to BioMarin Pharmaceutical Inc., Novato, CA and received research grants, speaker's honorarium and travel support from BioMarin.

M Scarpa received unrestricted research and travel grants from BioMarin, Actelion, Genzyme and Shire.

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Severe phenotype

Attenuated phenotype

A



B



C



