

Retinal changes in mucopolysaccharidosis I- A case report

Vishaka D. Naik^{1,*}, Ugam P.S. Usgaonkar², Vedvati. H. Albal³

^{1,3}Junior Resident, ²Professor and HOD, Dept. of Ophthalmology, Goa Medical College, Bambolim, Goa, India

***Corresponding Author:**

Email: vishu1847@gmail.com

Abstract

Introduction: Mucopolysaccharidosis 1- Hurler's disease (MPS) is a rare, life threatening, autosomal recessive, inborn error of lysosomal metabolism which is known to have ocular manifestations.

Aim: To identify and document retinal findings in a case of mucopolysaccharidosis type 1.

Subjects and Methods: A male child, 12 years old, born out of consanguinity, was referred to Ophthalmology OPD, Goa Medical College with decreased vision for evaluation. He underwent a detailed ophthalmological examination.

Results: Fundus- showed pseudopapillitis with retinal pigment epithelium changes, and hypopigmented lesions in the parafoveal region. OCT- revealed increased retinal thickness, with accumulation of GAGs in outer retinal layers; ILM-RPE central subfield thickness: 281µm

Conclusions: Patients with MPS require regular ophthalmological assessment to diagnose, monitor and treat ocular complications. Ophthalmological assessment becomes important because signs of raised intracranial pressure such as papilledema may be picked up. Regular ophthalmological assessments may help to provide a better quality of life in these children.

Keywords: Fundus, Mucopolysaccharidosis, Retina.

Introduction

Mucopolysaccharidosis 1- Hurler's disease is a rare life threatening autosomal recessive inborn error of lysosomal metabolism.

Worldwide incidence of MPS1-H is 1 in 1,00,000 newborns.¹

90 mutations in the gene coding for lysosomal enzyme α -L-iduronidase are known to cause its deficiency or absence.

This leads to Intra and extracellular accumulation of glycosaminoglycans, such as dermatan and heparan sulfate, causing cell death, abnormal tissue growth and excretion of these substances in the urine.

Ocular complications commonly associated include protruding wide set eyes,² atypical eyebrows, corneal clouding,³ refractive errors, retinal dystrophies,³ glaucoma,⁴ chronic papilledema,³ optic atrophy,³ and posterior visual pathway or cortical problems due to accumulation of GAGs in white matter of the central nervous system.²

Aim

To identify and document retinal findings in a case of mucopolysaccharidosis type 1.

Subjects and Methods

A male child, 12 years old, born out of consanguinity, was referred to Ophthalmology OPD, Goa Medical College with decreased vision for evaluation.

The child complained of painless decrease in vision since many years, for which he was prescribed spectacles and had been using it since the age of 5 years.

Since last one year, he also complained of seeing objects distorted; however, he did not report any floaters and flashes.

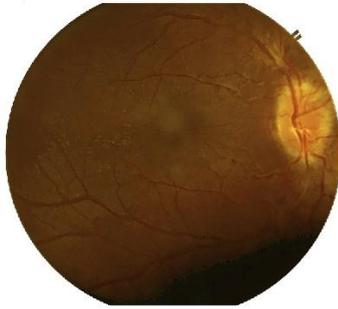
He was already diagnosed with MPS I-H on the basis of clinical findings, together with biochemical assessments of glycosaminoglycans in urine and enzyme α -L-iduronidase in the blood.

He underwent detailed ophthalmological examination - visual acuity assessment, slit lamp examination, tonometry, refraction under cycloplegia, keratometry, funduscopy, and posterior segment OCT.

Results

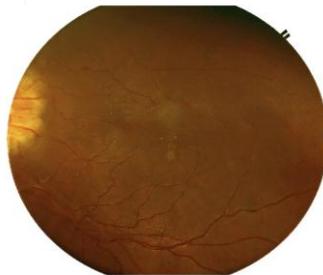
1. The child had a best corrected visual acuity of 6/12 by Snellens chart with +6.00 D in right eye and +5.50 D in left eye.
2. Colour vision was found to be normal, with the child identifying all plates in the Ishihara Chart.
3. Slit lamp examination showed clear corneas and normal anterior chamber angles.
4. Intraocular pressures were measured using non-contact tonometry (NCT) and which showed readings of 8 millimetres and 10 millimetres of mercury for the right and the left eyes respectively.
5. Owing to the child's spinal deformity, a visual field assessment using perimetry could not be carried out.
6. Fundus examination showed pseudopapillitis with retinal pigment epithelium changes (Fig. 1), and hypopigmented lesions in the parafoveal region (Fig. 2).
Since a clear view of the fundus was available, a B scan ultrasound was not performed.

7. Posterior segment OCT revealed a mild thickening of the external limiting membrane (Fig. 3) and, on scanning at an angle of 90 degrees, increased thickness was seen at the level of inner and outer nuclear layers and ganglion cell layer (Fig. 4). The retinal nerve fibre layer appeared normal.
8. The Internal Limiting Membrane to Retinal Pigment Epithelium central subfield thickness was found to be 281µm.



Right Posterior

Fig. 1: Right eye Fundus photography image of a 12 years old male with MPS type 1, showing pseudopapillitis with retinal pigment degeneration



Left Posterior

Fig. 2: Left eye Fundus photography image of a 12 years old male with MPS type 1, showing hypopigmented spots in parafoveal region

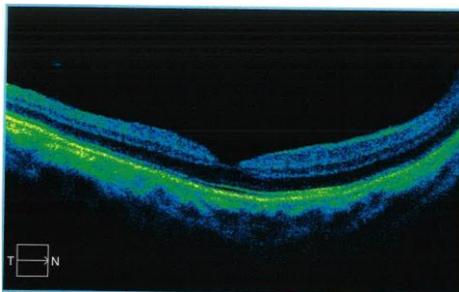


Fig. 3: Optical Coherence Tomography (OCT) image of right macula, showing mild thickening of the external limiting membrane

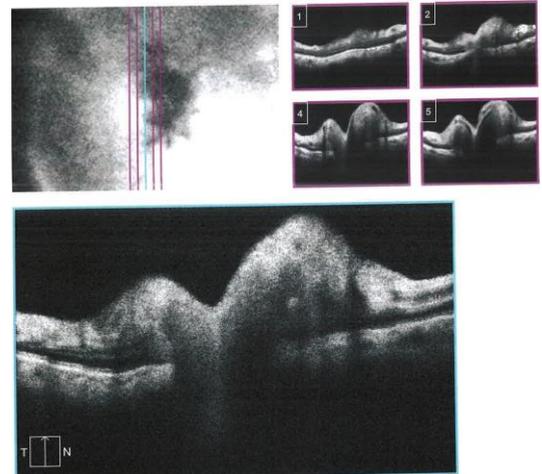


Fig. 4: Optical Coherence Tomography (OCT) of Right eye (Scan at 90 degrees) showing increased thickness at the level of inner and outer nuclear layers and ganglion cell layer

Discussion

Mucopolysaccharidoses (MPS) are a group of systemic diseases, where the eye as well as other tissues accumulate excessive amounts of glycosaminoglycans. They occur due to the deficiency or absence of enzymes involved in the catabolism of GAG, also called mucopolysaccharides. The diseases have broadly been classified into seven types- I, II, III, IV, VI, VII and IX.

MPS I, broadly called Hurler's Disease, has been further sub-classified into three forms: MPS I-S, Scheie's Disease, has milder systemic and ophthalmic manifestations; MPS I-H/S, the Hurler/Scheie phenotype, is an intermediate form, and MPS I-H Hurler's Disease is considered as the most severe form.

Ophthalmic complications are quite frequent in patients with MPS. Typical ocular features include corneal clouding, ocular hypertension or glaucoma, retinal degeneration and optic nerve atrophy. Shallow orbits give the eyes a prominent appearance.⁹

The clinical evaluation of children with MPS I-H in their early years offers a challenge to the paediatric ophthalmologist. Retinoscopy may be difficult to perform due to dull fundus reflexes. Clinical examination may be hampered by severe photophobia and lack of co-operation, cognitive delay or hyperactivity disorders. However, visual deterioration and sensitivity to light may substantially reduce the quality of life in MPS patients, particularly when left untreated,¹³ thus making an ophthalmologic evaluation vital.

Refractive errors, prominently high hyperopia may affect the visual acuity of the children substantially, particularly if present during ocular developmental years. Children may present with esotropia, exotropia and amblyopia.¹¹

Glaucoma is also known to occur as a complication in MPS I, considered to be due to GAG accumulation in cells located in the region near aqueous drainage channels.⁷ While vision loss in most patients with MPS is gradual, acute glaucoma can lead to a rapid fall in vision.¹²

Retinopathy is known to occur to a variable degree in MPS I, that is, Hurler's Disease, with severe retinopathy noted to be a feature of MPS III, that is, Sanfilippo Syndrome.

Retinopathy is common in older children with MPS I, but may be difficult to detect because of a co-existing corneal opacity.¹¹ It occurs due to accumulation of GAG within retinal pigment epithelial cells and in the interphotoreceptor matrix, followed by phagocytosis by Muller Cells or the retinal pigment epithelial cells, leading to progressive loss of photoreceptors.^{11,13}

Optical coherence tomography of the posterior segment enables the visualization of the different retinal layers, and thus allows the detection of thinning of the photoreceptor or nerve fibre layer, or cystoid macular oedema in patients with MPS.¹⁴

In MPS I, retinal findings commonly include retinal pigmentary degeneration and optic nerve head swelling.⁵ Collins et al also described optic disc abnormalities in MPS I.⁶

The optic nerve head swelling seen is often thought to be precedent to the optic atrophy seen in high frequency in these patients, causing irreversible loss of vision.⁶ Early optic atrophy is seen as temporal disc pallor, with decreased sensitivity to central visual field testing^[11]. Other factors such as raised intracranial tension seen in these children are also considered to be contributory, and increased retino-choroidal complex thickness and functional changes in the retina due to GAG accumulation may also be related to this finding.¹⁵ Optic disc changes have also been thought to occur as a result of compression of the nerve by accumulation of GAG in the dura and the sclera.¹¹ GAG accumulation within the ganglion cells may cause optic nerve atrophy directly by means of neuronal degeneration. Increase in intraocular pressure and subsequent optic disc cupping can be another cause of optic nerve atrophy in these children.¹²

Optic disc OCT can be used to assess and document the cup: disc ratio in patients with MPS without severe corneal clouding, and allow documentation of progression in those who have genuine glaucoma, in whom fundoscopy may be of limited value due to corneal clouding.¹⁶

Initially, retinal dysfunction may clinically be seen as sensitivity to light and night blindness. Later, patients may develop peripheral vision constriction, which presents clinically as gradual tunnel vision and often can be associated as clumsiness. Ultimately, the patient develops central visual field loss. The fundus picture may initially show only arteriolar attenuation

with no pigmentary changes.¹¹ In later stages, retinal pigment shows degeneration, particularly in mid periphery. Progressive retinal compromise with vascular narrowing, hyperpigmentation, and bony spicules are observed in an advanced stage.¹⁶

On histopathological examination, there is typical degeneration of the outer retinal layers. Patients without clinically apparent retinal degenerative changes have also been shown to have fine fibrillary inclusions in the retinal pigment epithelium and ganglion cells, along with multi-membranous inclusions in retinal ganglion cells.¹³

In a study conducted by the Brazilian Institute of Ophthalmology and Prevention of Blindness (IBOPC), Salvador, on 29 MPS patients, of which, 10 per cent were cases of MPS I, the most frequent alterations observed on fundus examination were radial folds of the retina in the perimacular region, occurring in 24 per cent of the patients. The occurrence of choroidal folds was reported, probably due to high hyperopia. However, with respect to the eyes examined in the stated study, this appearance of the retina folds was more compatible with that of striations in the internal retinal limiting membrane.¹⁵

Rare findings such as a macular epiretinal membrane¹⁷ and macular edema like changes¹⁸ have also been reported.

In a study carried out on two patients of MPS I being treated with Enzyme Replacement Therapy, retinal examination demonstrated Bull's eye maculopathy in both eyes. OCT scanning confirmed parafoveal atrophy, particularly in the region of ellipsoid line, and demonstrated similar appearing subfoveal hyperreflectant material in both cases. Further studies are required to determine the nature of this accumulated material, the incidence of this type of maculopathy and the effect of enzyme replacement therapy on these findings.¹³

In some studies, B Scan Ultrasonography of the globe was performed, and showed that the optic nerve sheath and sclera were clearly thickened in patients with MPS in comparison to normal values. Four major findings were reported: thickening of the sclera, abnormal optic head morphology, papilloedema and optic nerve sheath widening.⁸

Posterior segment ultrasound is also used to visualize deep cupping of the disc in patients with MPS I and advanced glaucoma, particularly when the severity of corneal clouding precludes an ophthalmoscopic view of the optic disc.¹⁶

Although the ultrasound is readily available to measure the optic nerve and scleral thickness, the patient needs to be still for a long time as compared to other techniques, and this may be exceedingly challenging in the paediatric population.¹⁶

Electroretinography (ERG) usually reveals a reduction in dark-adapted b-wave in the early stages, and in rare cases, reduced b-waves when light

adapted also.¹⁴ In one electrophysiologic study, a MPS I- H/S Hurler-Scheie patient showed negative scotopic but normal photopic ERG, which remained unchanged over a follow up period of 2 years. The MPS I-H Hurler patient in the aforementioned study showed negative scotopic and photopic ERG, which showed no improvement on therapy with bone marrow transplantation. The electronegative configuration of the ERG in the above study suggested that, in these cases, the primary retinal abnormality in MPS I may be faulty synaptic transmission from photoreceptors to more proximal elements, deficient bipolar responsivity, or Muller cell disease. Further deterioration with time was suggestive of the defect to be progressive with BMT causing little or no improvement. In the Hurler-Scheie syndrome case, the defect appeared to spare the cone system and to show little or no progression over time, when compared to the Hurler phenotype.¹⁹

In another study, evidence of retinal dysfunction ranged from none to severe in MPS I, and showed the pattern seen in rod-cone degenerations, where the rod mediated responses were more severely affected than the cone-mediated responses. The ophthalmoscopic signs were less striking than the electrophysiologic findings, and were usually restricted to mild changes of the retinal pigment epithelium.²⁰ One study reported that the ERG may even be abolished by 5 or 6 years of age.⁹

Spectral Domain Optical Coherence Tomography (SD-OCT) is proving to be a useful tool for detecting retinal pathology, particularly changes in external limiting membrane (ELM) and inner segment (IS) and outer segment (OS) of photoreceptors, with detailed measurements possible. One study employing SD-OCT showed thinning of the parafoveal photoreceptor IS/OS, and also of the perifoveal photoreceptor IS/OS. All MPS I patients under study exhibited a thickening of the central foveal ELM.²¹ Some of the type I patients also showed cyst formation and fluid in the outer nuclear layers.¹⁶

However, OCT can be difficult to use in a paediatric patient and requires the expertise of an imaging technician for optimal image quality. It also requires steady fixation, with an ability to follow directions, posing yet another challenge for its use in the paediatric population.¹⁶

It is important to differentiate MPS from other syndromic forms of Retinitis Pigmentosa, such as Usher Syndrome, Alport Syndrome, Cohen Syndrome, and from other inherited retinal pigment dystrophies. Systemic features of these diseases provide crucial aid in this distinction.²²

Treatment of the MPS disorders depends on the severity of clinical manifestations and usually needs a multidisciplinary approach with paediatricians, orthopedic surgeons, cardiologists, radiologists, neurologists, anesthesiologists, and ophthalmologists

working together to achieve the best outcome for the patient.²³

Ophthalmological treatment includes detecting and correcting refractive errors at an early age, and avoid sequelae like strabismus and amblyopia.²³

Glaucoma, if present, is managed medically and if needed, surgically. However, anagemnet in these cases is challenging, owing to eventual disease progression.²³

Management of corneal clouding depends on its severity. Corneal transplantation is helpful, but at a risk of re-opacification, due to GAG deposition in the graft. Deep anterior lamellar keratoplasty is recommended over penetrating keratoplasty, with lesser chances of rejection.²³

Treatment of optic disc pathology depends on the cause. Where increased intracranial pressure is implicated, systemic therapies specially HSCT have proven to be beneficial. In one study, 30 per cent of patients demonstrated optic disc edema associated with elevated intracranial pressure, all of which resolved after bone marrow transplantation and with no sign of optic disc atrophy afterward. Another study showed that 70 per cent of MPS I patients had normal optic nerves after receiving HSCT. Results with ERT are still inconclusive and warrant further study.²³

Data regarding the effects of these therapies on retinal degeneration is sparse and not very promising. One study showed little or no improvement with bone marrow transplantation treatment. Another study showed initial improvement in ERG in 81 per cent of MPS patients post bone marrow transplantation, with a progressive worsening after one year.²³ Documentation of progression of degeneration is to be carried out at every follow up.

Systemic therapies include Hematopoetic Stem Cell Transplantation (HSCT), seen to increase life expectancy and provide some improvement in symptoms. It is most effective when initiated early, before 2 years of age. This process helps by introducing enzymatically normal bone marrow cells from a matched donor, which then travel through the body and secrete the deficient enzyme. HSCT appears to stabilize or improve visual acuity, corneal clouding, and optic nerve swelling in MPS patients with no apparent effect on retinal degeneration. HSCT poses risks, including the development of cataract, epithelial punctate keratopathy, and dry eye syndrome, as well as graft versus host disease causing conjunctivitis, keratoconjunctivitis sicca, corneal epithelial defects, and pseudomembrane formation.²³

Another systemic therapy available currently is Enzyme Replacement Therapy (ERT). ERT uses recombinant DNA in mammalian cell lines to replace the enzyme deficiency via intravenous administration. Currently, ERT available for MPS I-H is Laronidase. ERT is recommended for use in patients with mild manifestations of MPS, with severely affected patients being given the option of HSCT. In general, ERT is

associated with stabilization of corneal opacification. Beginning ERT at an earlier age may have a greater effect on ocular findings. The effects of ERT on optic nerve edema and atrophy are yet inconclusive, with both stabilization and worsening of disease reported. Further studies are needed to determine the effects of ERT on ocular pathology related to MPS, especially if ERT is started early in life.²³

Conclusion

Patients with MPS require regular ophthalmological assessment to diagnose, monitor and treat ocular complications. These diseases pose therapeutic challenges in ocular management, thus placing ophthalmologists next to paediatricians at the forefront of interventions in order to prevent long-term sequelae of this rare but serious disease. In fact, ophthalmologists may be the first to recognize the disorder by meticulous examination of the eyes.²¹

1. Apart from poor vision, the child may be suffering from multiple physical and intellectual problems and hence, a multi-disciplinary approach is warranted in the care of these children.
2. Ophthalmological assessment also becomes important because signs of raised intracranial pressure such as papilledema may be picked up.
3. Documentation of retinal changes at every follow up is important to see for progression.
4. It is controversial whether the treatment of the systemic disease alters the course of ocular changes in patients with MPS. The therapeutic modalities currently advocated for MPS, such as Bone Marrow Transplantation and Enzyme Replacement Therapy have been shown to temporarily stabilize the ocular manifestations of the disease. However, considering the degenerative nature of MPS, halting or even slowing down the progression of ocular manifestations can be worthwhile in improving the patient's quality of life^[21]. And further studies are required to assess the long term impact of these modalities on the disease burden and the quality of life.
5. The need 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 is, therefore, absolutely fundamental.

Clarification of Abbreviations:

1. MPS: Mucopolysaccharidosis
2. MPS I- H: Hurler's Disease
3. MPS I- S: Schei's Disease
4. MPS I- H/S: Hurler/ Schei Disease
5. GAG: Glycosaminoglycans
6. NCT: Non Contact Tonometry
7. RPE: Retinal Pigment Epithelium
8. OCT: Optical Coherence Tomography

9. SD-OCT: Spectral Domain Optical Coherence Tomography
10. ELM: External Limiting Membrane
11. IS: Inner segment
12. OS: Outer segment
13. ERG: Electroretinogram
14. HSCT: Hematopoietic Stem Cell Transplantation
15. ERT: Enzyme Replacement Therapy

References

1. Malm G, Bondeson ML, von Do" beln U & Ma" nsson JE (2002): [Mucopolysaccharidoses. New therapeutic possibilities increase the need for early diagnosis.] *La" kartidningen* 99:1804-1809.
2. Wraith JE (2005): The first 5 years of clinical experience with laronidase enzyme replacement therapy for mucopolysaccharidosis I. *Expert Opin Pharmacother* 6:489-506.
3. Gullingsrud EO, Krivit W & Summers CG (1998): Ocular abnormalities in the mucopolysaccharidoses after bone marrow transplantation. Longer follow-up. *Ophthalmology* 105:1099-1105.
4. Guffon N, Souillet G, Maire I, Straczek J & Guibaud P (1998): Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. *J Pediatr* 133:119-25.
5. Caruso RC, Kaiser-Kupfer MI, Muenzer J, Ludwig IH, Zasloff MA, Mercer PA. Electroretinographic findings in the mucopolysaccharidoses. *Ophthalmology* 1986; 93(12):1612-1616.
6. Collins MLZ, Traboulsi EI, Maumenee IH. Optic nerve head swelling and optic atrophy in the systemic mucopolysaccharidoses. *Ophthalmology* 1990;97:1445-1449.
7. Spellacy E, Bankes JL, Crow J, Dourmashkin R, Shah D et al. Glaucoma in a case of Hurler disease. *Br J Ophthalmol* 1980; 64: 773-778.
8. Schumacher RG¹, Brzezinska R, Schulze-Frenking G, Pitz S. Sonographic ocular findings in patients with mucopolysaccharidoses I, II and VI. *Pediatric Radiology*. 2008 May;38(5):543-50. doi: 10.1007/s00247-008-0788-y. Epub 2008 Feb 26.
9. MPS I-HS : Hereditary Ocular Diseases- A Database of Hereditary Ocular Diseases, The University of Arizona Health Sciences.
10. Stefano Ferrari , Diego Ponzin, Jane L Ashworth, Kristina Teär Fahnehjelm, C Gail Summers, Paul R Harmatz, Maurizio Scarpa . Diagnosis and management of ophthalmological features in patients with mucopolysaccharidosis. *British Journal of Ophthalmology*, Vol. 95, Issue 5.
11. J L Ashworth, S Biswas, E Wraith, I C Lloyd. The ocular features of the mucopolysaccharidoses. *Eye* 20, 553-563 (2006).
12. C. Gail Summers Jane L. Ashworth. Ocular manifestations as key features for diagnosing mucopolysaccharidoses : *Rheumatology*, Volume 50, Issue suppl_5, 1 December 2011, Pages v34-v40
13. Heather G.Mack^{abc}R.C. Andrew Symons^{ab} Gerardde Jong^{bd}. Bull's eye maculopathy and subfoveal deposition in two mucopolysaccharidosis type I patients on long-term enzyme replacement therapy. *American Journal of Ophthalmology Case Reports*, Volume 9, March 2018, Pages 1-6.
14. Kristina T. Fahnehjelm, Jane L. Ashworth, Susanne Pitz, Monica Olsson, Alba Lucia Törnquist, Päivi Lindahl, C.

- Gail Summers. Clinical guidelines for diagnosing and managing ocular manifestations in children with mucopolysaccharidosis. *Acta Ophthalmologica*, Vol. 90, Issue 7, November 2012.
15. Flávia Silva Villas-Bôas , Dilson José Fernandes Filho, Angelina Xavier Acosta . Ocular findings in patients with mucopolysaccharidoses. *Arq. Bras. Oftalmol.* vol.74 no.6 São Paulo Nov./Dec. 2011.
 16. Ahmed Javed, Tariq Aslam, Jane Ashworth . Use of new imaging in detecting and monitoring ocular manifestations of the mucopolysaccharidoses: *Acta Ophthalmologica*, Vol. 94, Issue 8, December 2016.
 17. Susanne Pitz, MD, PhD; Olufunmilola Ogun, FWACS; Manal Bajbouj, MD; et al. Ocular Changes in Patients With Mucopolysaccharidosis I Receiving Enzyme Replacement TherapyA 4-Year Experience. October 2007, *JAMA Ophthalmology*, *Arch Ophthalmol.* 2007;125(10):1353-1356. doi:10.1001/archophth.125.10.1353.
 18. Usui T, Shirakashi M, Takagi M, Abe H, Iwata K. Macular edema-like change and pseudopapilledema in a case of Scheie syndrome. *J Clin Neuroophthalmol.* 1991 Sep;11(3):183-5.
 19. Tzetzis D, Hamilton R, Robinson PH, Dutton GN. Negative ERGs in mucopolysaccharidoses (MPS) Hurler-Scheie (I-H/S) and Hurler (I-H)-syndromes. *Doc Ophthalmol.* 2007 May;114(3):153-8. Epub 2007 Feb 16.
 20. Mucopolysaccharidoses: American Academy of Ophthalmologists, www.aao.org.
 21. Susie Seok, in Jeong Lyu, Kyung Ah Park, Sei Yeul Oh. Spectral domain optical coherence tomography imaging of mucopolysaccharidoses I, II, and VI A: *Graefes Archive for Clinical and Experimental Ophthalmology*, December 2015, Volume 253, Issue 12, pp 2111–2119.
 22. Christian Hamel. Retinitis pigmentosa. *Orphanet Journal of Rare Diseases*20061:40.
 23. Carlton R Fenzl, Kyla Teramoto, Majid Moshirfar. Ocular manifestations and management recommendations of lysosomal storage disorders I: mucopolysaccharidoses. *Clinical Ophthalmology* 2015; 9: 1633–1644.