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Mucopolysaccharidosis

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Abstract:

Mucopolysaccharidosis are group of inherited metabolic diseases caused by the absence or malfunctioning of lysosomal enzymes resulting in accumulation of glycosaminoglycans. Over time this accumulation damages cells, tissues, and organs. There are seven types of MPS and 13 subtypes that are associated with multiple organ systems, such as the respiratory, liver, spleen, central nervous systems, arteries, skeletons, eyes, joints, ears, skin, and/or teeth. The various types share some common ocular features that differ in terms of the severity of the affection. Visual loss in MPS patients is varied and can be due to corneal clouding, glaucoma, retinopathy, and optic neuropathy. The primary focus of this review is on changes in the cornea and anterior segment in MPS patients, including clinical and novel investigative modalities, current surgical management, effects of systemic therapy like hematopoietic stem cell transplants (HSCT)and enzyme replacement therapy (ERT), as well as significant research developments.

Keywords:

Anterior segment optical coherence tomography, corneal opacification measurement score, enzyme replacement therapy, glycosaminoglycans, hematopoietic stem cell transplant, *in vivo* confocal microscopy, mucopolysaccharidoses, ultrasound biomicroscopy

Introduction

Mucopolysaccharidoses (MPS) are the group of lysosomal storage disorders which are characterized by an inherent deficiency of lysosomal enzymes responsible for the degradation of glycosaminoglycans (GAGs) at cellular level, thus resulting in widespread accumulation of intra-and extracellular GAGs in multi-organ system including eye. Till date, seven types of MPS and 13 subtypes have been described, wherein majority of these are inherited in an autosomal recessive trait, except type II which is X-linked inheritance. It includes MPS IH (Hurler), MPS IS (Scheie), MPS IH/S (Hurler/Sheie), MPS II (Hunter), MPS III (Sanfilippo), MPS IV (Morquio), MPS VI (Maroteaux-Lamy), MPS VII (Sly), and MPS IX (Natowicz)[1] [Table 1].

The clinical symptoms of MPS are attributable to build-up of GAG in different body parts. Patients with MPS typically have dysmorphic facial traits, such as a flattened face, a sunken nasal bridge, thick lips, and an enlarged mouth [Figure 1]. Patients may also have serious neurological and intellectual issues, hearing impairment, bone disease, cardiorespiratory disease, and other comorbidities. The various types share some common ocular features and differ in terms of the severity of affection[1,2] [Table 2].

Ocular manifestations in MPS patients are varied and can include corneal clouding, glaucoma, retinopathy, and optic neuropathy. Evaluating these conditions can be challenging when combined with other medical and anesthetic problems. Moreover, few studies have been conducted on the nonfatal manifestations of MPS, such as ocular involvement, owing to its low incidence and high mortality rates.[1,3]

In recent decades, hematopoietic stem cell transplants (HSCTs) and enzyme

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Table 1: Subtypes of mucopolysaccharidoses, inheritance pattern, age of onset, enzymes affected, and type of glycosaminoglycan accumulated

MPS subtype[1,2]	Enzyme deficient	Accumulating substance	Gene involved	Inheritance pattern	Age of onset	Incidence
IS-Scheie syndrome	a-L-iduronidase	Dermatan sulfate, heparan sulfate	IDUA (4p16.3)	AR	5–13 years	1/100,000
I-HS Hurler-Scheie syndrome	a-L-iduronidase	Dermatan sulfate, heparan sulfate	IDUA (4p16.3)	AR	3–7 years	1/500,000–1/150,000
IH-Hurler syndrome	a-L-iduronidase	Dermatan sulfate, heparan sulfate	IDUA (4p16.3)	AR	1–2 years	1/500,000–1/150,000
II - Hunter	Iduronate-2-sulfatase	Dermatan sulfate, heparan sulfate	IDS (Xq28)	XR	1st decade	1/150,000–1/100,000 male births
IIIA - Sanfilippo A	Heparan-N-sulfatase (sulfamidase)	Heparan sulfate	SGSH (17q25.3)	AR	2–6 years	1/70,000 live births
IIIB - Sanfilippo B	α-N-acetyl glucosaminidase	Heparan sulfate	NAGLU (17q21)	AR	2–6 years	
IIIC - Sanfilippo C	Acetyl-Co-A-α-glucosaminide	Heparan sulfate	HGSNAT (8p11.1)	AR	2–6 years	
IIID - Sanfilippo D	N acetylglucosamine-6-sulfatase	Heparan sulfate	GNS (12p14)	AR	2–6 years	
IVA - Morquio A	N acetylgalactosamine-6-sulfatase	Keratan sulfate Chondroitin-6- sulfate	GALNS (16q24.3)	AR	After 1 year	1/200,000 in live births
IVB - Morquio B	β-galactosidase	Keratan sulfate	GLBI (3p21.33)	AR	After 1 year	
VI - Maroteaux Lamy	N-acetylgalactosamine-4-sulfatase	Dermatan sulfate Chondroitin-4-sulfate	ARSB (5q11-q13)	AR	2 years	1/600,000–1/250,000 live births
VII - Sly	β-glucuronidase	Heparan sulfate, dermatan sulfate	GUSB (7q21.11)	AR	Variable	1/250,000 live births
IX - Natowicz	Hyaluronidase	Hyaluronan	HYALI (3p21.3- p21.2)	AR	Unknown/ rare	Unknown

Ashworth *et al.*,[1] Ganesh *et al.*[2] AR=Autosomal recessive, XL=X-linked recessive, MPS=Mucopolysaccharidoses

Table 2: Subtypes of mucopolysaccharidoses and their ocular manifestations

MPS subtypes[1,2]	Ocular features
MPS I	Corneal clouding*
	Glaucoma, optic atrophy and disc swelling
	Hyperopia
MPS II (Hunters)	Hypertelorism and Exophthalmos*
	Corneal abrasions keratoconjunctivitis sicca optic nerve abnormalities retinopathy corneal cloudingrare
MPS III (Sanfilippo)	Retinopathy*, corneal opacification, glaucoma, optic nerve abnormalities rare
MPS IV (Morquio)	Corneal clouding and refractive errors*
	Exposure keratopathy and pseudoexophthalmos
MPS VI (Maroteaux-Lamy)	Corneal clouding*
	Optic atrophy, strabismus
MPS VII (Sly)	Corneal opacity*
	Optic nerve abnormalities rare
MPS IX (Natowicz)	None

*Most commonly seen feature. Ashworth *et al.*,[1] Ganesh *et al.*[2] MPS=Mucopolysaccharidosis

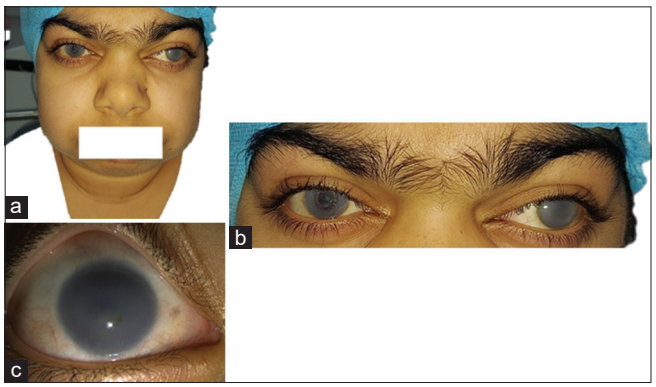

Figure 1: Coarse facial features (a) with operated penetrating keratoplasty in the right eye (b) and left eye - corneal clouding seen in a case of Hurler's syndrome (c)

replacement therapy (ERT) have greatly increased the life expectancy of these patients, causing researchers to focus on improving the quality of life. Hence, ophthalmologists play a critical role in multidisciplinary approach in evaluating and managing these patients, as visual disability contributes to their physical and mental impairments.[4] A primary objective of the review is to provide an overview of current knowledge regarding MPS-related ocular involvement with a particular focus on corneal and anterior segment manifestations, as well as to provide information regarding the diagnostic procedures and management of MPS with new instrumentation available.

Cornea Changes in the Mucopolysaccharidoses

Corneal clouding

It is the most common ocular manifestation of MPS, which affects all subgroups. However, it is a prominent

feature of MPS types I and VI. MPS types I-H, I-HS, VI, and VII are associated with severe corneal involvement. On the other hand, corneal involvement is not significant in MPS types I-S, II, III, IV, or IX.[1,5] GAGs can accumulate in all corneal layers, both intracellularly and extracellularly. Excessive storage of GAG in the cornea alters the keratocyte size and affects the regular arrangement of collagen fibrils, resulting in disruption of the regular shape of the corneal ultrastructure leads to increased corneal thickness, reduced transparency, increased light scattering, and visual disturbance.[6] Corneal clouding may be initially asymptomatic, but subsequently, the patient may suffer from photophobia and a slowly progressive loss of visual acuity.

Subjective assessment of corneal clouding

Based on slit-lamp observation, Couprie *et al*. clinically staged the corneal clouding which is detailed in Table 3.[3,7] Although subjective assessment by clinician and photographs is useful to evaluate the progression of corneal clouding, there could be examination difficulties in assessing young children and visual acuity could be affected by other ocular comorbidities such as glaucoma, optic nerve edema, optic atrophy, and retinal degeneration, refractive error (hyperopia).

Objective assessment of corneal clouding

There have recently been studies that demonstrate objective assessment of corneal opacification that helps in identifying the disease at a much early stage and document its progression, considering the fact that corneal clouding in patients with MPS is a slowly progressing phenomenon. The use of iris recognition cameras in combination with specific image analysis algorithms can be used to assess the corneal opacification measurement score by processing the captured image. The main advantage of this device is the ability to capture a standardized photo in a few seconds that does not require positioning a patient's chin and forehead onto a slit-lamp like device. It also has good repeatability and reliability. However, image quality with no artifacts is paramount to measure the corneal opacity score.[8,9]

The Scheimpflug imaging-based corneal imaging (Pentacam) with the densitometry software can be used to objectively measure the amount of corneal clouding. Elflein *et al*. demonstrated higher corneal density values in patients suffering from MPS I, IV and VI than in those with MPS II. They also observed higher corneal density values in patients affected with MPS II than healthy individuals indicating that there is corneal clouding even in MPS II, although it is clinically undetectable. Examinations at short intervals were infeasible due to physical impairment and limited compliance of most of our patients.[10,11]

Table 3: Clinically staged the corneal clouding

Stages	Clinical features[3,7]
Stage 1	Absence of any corneal clouding
Stage 2	Mild corneal clouding not impeding the visibility of details of iris and retina
Stage 3	Corneal clouding obscuring details of iris and retina
Stage 4	Severe corneal clouding wherein anterior chamber and fundus cannot be evaluated

Fahnehjelm *et al*.,[3] Couprie *et al*.[7]

Changes in corneal thickness, corneal topography, aberrometry, and biomechanical parameters

In most studies, MPS and healthy controls had similar minimal central corneal thickness (CCT) and corneal volume. Corneal density was increased when compared to healthy controls and strongly correlated with the degree of corneal clouding. Anterior segment optical coherence tomography (ASOCT) is a useful technique for measuring corneal thickness and measuring epithelium-endothelium affection. It also provides a detailed morphological information about structures in the anterior segment, especially in cases of severe corneal clouding.[12]

Scheimpflug imaging in MPS patients reveals significant asymmetry of the corneal surfaces and associated higher-order aberrations. Topographic indices such as index of vertical asymmetry, height asymmetry, and height decentration all increased and there was a significant correlation with density and grade of corneal opacity. Therefore, these parameters could be considered as new objective diagnostic and/or follow-up parameters for the evaluation of MPS-related corneal changes.[13]

Increase in corneal higher order aberrations, including spherical aberrations and asphericity coefficients from the front and back surfaces of the cornea, as a result of MPS. The symptoms such as monocular diplopia, halos, starbursts, glare as well as a visual disturbance and decreased levels of contrast sensitivity were observed in patients with altered ocular aberrations.[13]

GAG deposition in cornea can lead to increased corneal rigidity, thickness and reduced corneal elasticity, thus resulting in changes in biomechanical properties such as corneal hysteresis (CH) and corneal resistance factor (CRF). Both CH and CRF values are directly correlated with degree of corneal clouding.[14]

Microstructural changes in cornea

GAG deposition can occur in all the layers of the cornea and *in vivo* confocal microscopy (IVCM) [Table 4] a noninvasive method to detect the pathologic changes at an early stage of the disease, besides identifying the different patterns of corneal involvement in various types of MPS. Corneal epithelium is usually unaffected except in cases of MPS I-S, where bright cells have been observed in the

Table 4: *In vivo* confocal microscopy changes in mucopolysaccharidosis

MPS types	IVCM changes		
	Epithelium	Stroma	Endothelium
MPS IV	Normal	Anterior and midstroma show diffuse, irregular hyperreflectivity At posterior stroma - Keratocyte cytoplasm has a granular appearance and rounded nuclei with vacuoles	Normal
MPS IS	Bright cells at basal epithelium	Mid and posterior stroma - Altered keratocytes (round or elliptical and with well-defined hyporeflective centers)	Mild polymegatism
MPS VI	Normal	Posterior stroma contains altered keratocytes structures	Normal

MPS=Mucopolysaccharidosis, IVCM: *In vivo* confocal microscopy

basal layer. The corneal stroma is almost always affected, predominantly involving the middle and posterior layers. The accumulation of GAG alters the morphology as well as the internal structure of keratocytes. Endothelia cell count was normal with normal morphology or mild polymegathism.[15-17] In advanced cases, deposits and fibrosis lead to increased hyperreflectivity and obscures the detailed examination of the cellular structures in the stroma and endothelium by IVCM.[18]

On IVCM imaging, multiple small, larger hyperreflective deposits are seen in the epithelium, Bowman layer, and anterior stroma. Keratocytes in the anterior-mid stroma have been described to appear abnormally shaped and elongated with hyporeflective round structures, suggestive of vacuoles. ASOCT images show increased hypereflective appearance throughout the thickened cornea due to the accumulation of GAGs deposits.[19]

Histopathological findings in cornea

GAG deposition in the corneal stroma demonstrates irregular arrangement of collagen fibrils and increased mean fibril diameter; however, MPS type III eyes has lesser fibril diameter, correlating clinically in the form of relatively clear cornea. Mid-stromal keratocyte shows extensive inclusions of fibrillo-granular material. Endothelial cells demonstrate large vacuolated inclusion bodies with granular matrix or remain unaffected as in MPS VI eyes. All these can be visualized using various stains such as hematoxylin and eosin stain, periodic acid-Schiff stain, and the colloidal iron stain.[20,21]

Some reports suggest exposure keratopathy and keratoconjunctivitis sicca in certain types of MPS patients presenting with hypertelorism and exophthalmos.[22]

Management of corneal features in mucopolysaccharidoses patients

The management of corneal concerns in MPS patients comprises of the following:

- Correction of refractive errors (with photochromatic glasses to circumvent problems of glare and photosensitivity
- Corneal transplantation:

Keratoplasty is the effective treatment option for diffuse corneal clouding in MPS patients. Significant corneal clouding and visual impairment in early childhood can cause amblyopia and irreversible vision loss. Hence, proper patient selection and prompt corneal opacity intervention are the key for effective visual rehabilitation.

Following factors matters in the decision-making for corneal transplant surgery.

- General health and systemic status of the child
- Extend of corneal opacity that causing visual impairment
- Exclusion of other underlying ocular comorbidities
- Receptibility of ocular surface.

The benefit of a better visual outcome and quality of life must be outweighed against the possibility of anesthesia related intraoperative complications and graft-related postoperative complications. A detailed preoperative evaluation to be done in all cases to rule out any other ocular comorbidities such as retinopathy, optic nerve involvement, and glaucoma which are not uncommon with MPS ocular surface assessment and optimization comes next which determines the corneal graft survival in an otherwise normal recipient eye.[23] Dry eye disease, blepharitis, limbal stem cell deficiency, and corneal vascularization should be assessed and managed to avoid postoperative graft infection and rejection.[24]

Corneal transplantation in MPS can be either full-thickness optical penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK).

Penetrating keratoplasty and outcome in mucopolysaccharidoses

PK is considered as the definitive treatment for visual rehabilitation in MPS patients with corneal clouding. Full-thickness keratoplasty is easier to perform in pediatric eyes than DALK; however, it has its own limitations. Being an open sky procedure, it requires general anesthesia. Significant concerns in general anesthetic procedural steps can be anticipated in cases of MPS. Difficult intubation, increased positive pressure of vitreous and shallow anterior chamber make the surgery difficult in MPS eyes. Intraoperatively, graft suturing

and graft apposition will be difficult due to differences in thickness between host and donor corneas, since most MPS corneas are relatively thicker. Suture-related complications, post-PK secondary glaucoma, and suture-induced astigmatism are also expected, and hence, frequent follow-up is necessary in these patients. Graft rejection episodes and graft infections are not uncommon and require emergency intervention to avoid keratoplasty failure. Proper patient/parent counseling regarding all these risks and benefits of a corneal transplant procedure is the utmost important step before planning the surgery.[25]

Ohden *et al*. reported a 96% graft success rate in a series of 32 full thickness keratoplasties performed on matrix metalloproteinases patients.[26] According to various studies, MPS patients have a higher graft survival rate than non-MPS patients, which ranges from 62% to 86%. Several case studies have shown that graft clarity can be maintained for upto 5 years with significant visual gain.[26]

Deep anterior lamellar keratoplasty and their outcome in mucopolysaccharidoses patient

Patients with MPS have GAG deposits in the corneal stroma, and removing the affected stroma is sufficient for visual rehabilitation. The presence of excessive GAG in MPS may preclude a successive viscodissection and the "big bubble" technique while performing DALK in MPS.[27]

Therefore, DALK is currently preferred over conventional PK in MPS patients due to its similar effectiveness and lower risks of graft rejection, preserved endothelial cell density, nonopen sky procedure, and lesser suture-related complications. Studies have also shown that DALK may have a lower overall incidence of complications than PK.[28,29] However, performing DALK in a pediatric eye with significant corneal clouding is more challenging for a surgeon than PK. It can also have its own complications like intraoperative inadvertent DM perforation, double chamber formation, interface haze and delayed visual recovery.

da Silva Ricardo *et al*. performed DALK in MPS patients with significant corneal clouding and observed visual acuity improved in all eyes and there was no recurrence of in any of the corneal grafts.[30]

Systemic therapy and their effect on corneal clouding

HSCT and ERT are systemic therapies currently available to increase the life expectancy of the patient as they limit the GAG deposition in multiple organs in the body. However, their efficacy in improving the functions of the brain and avascular organ such as cornea remains unclear.

In 2015 a multi-center, multinational study in 217 MPS I Hurler, about 98% of the patients exhibited corneal clouding before HSCT. Following treatment, 74% of patients either showed a stabilization of their corneal clouding or a reduction in its severity.[31] Guffon *et al*. assessed the long-term residual disease burden in 25 MPSI-H patients after successful HSCT and observed that corneal clouding worsened in all patients and approximately half of the patients underwent corneal graft surgery at a median age of 17.8 years.[32] Gullingsrud *et al*. showed that 30% of a study group showed improvements in their corneal clouding, whereas 25% had worse corneal clouding following hematopoetic cell transplant and none of them showed complete resolution of clouding. These studies highlight the need for other novel treatment options to prevent and reverse corneal clouding.[33]

ERTs effect on corneal clouding is also limited and variable. There is a paucity of literature about the effect of ERT on corneal clouding specifically. However, few studies reported that photophobia and conjunctival irritation diminished following ERT, but corneal clouding and other ocular complications showed no improvement.[34-36] A recent prospective longitudinal study did not show any difference in progression of corneal clouding between patients not on treatment and those on ERT, HSCT, or no treatment.[25]

Anterior segment changes in mucopolysaccharidoses patients

Abnormal GAG deposition in the anterior segment results in thickened cornea, trabecular meshwork (TM), iris and ciliary body obstructing aqueous outflow leading to increased intraocular pressure (IOP) and glaucoma.

Glaucoma

A prevalence of glaucoma in MPS ranges between 2.5% and 12.5%, and it is most common in MPS types I, IV, and VI. Approximately 10% of MPS I type patients have glaucoma. As of yet, no cases of glaucoma have been reported in patients with MPS VII or IX. There is the possibility of open-angle glaucoma as well as closed-angle glaucoma in patients with MPS.[37]

Pathogenesis of glaucoma

The various causes for glaucoma in MPS has been elaborated due to the following reasons [Figure 2]:

1. It has been suggested that open-angle glaucoma may result from abnormal GAG deposition within the TM. An increase in chondroitin sulfate or a decrease in hyaluronic acid, in the TM narrows and slows the outflow of aqueous humor. It has been shown that proliferation and expression of fibronectin by TM cells leads to changes in GAG composition, pore

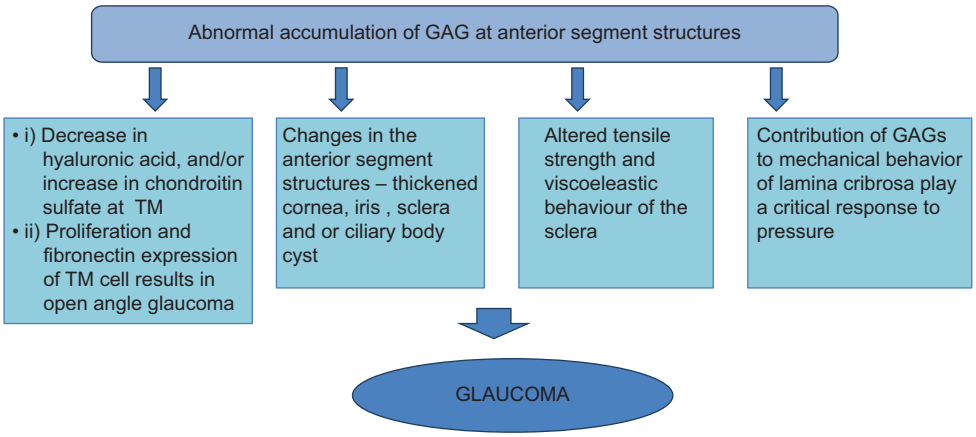

Figure 2: Causes for glaucoma in mucopolysaccharidoses. GAG: Glycosaminoglycan, TM: Trabecular meshwork

size and alignment, which contribute to open-angle glaucoma[38,39]
2. Angle closure glaucoma can develop as a result of a shallow anterior chamber and thickened cornea, as well as very thick retinal-choroidal and scleral involvement
3. The tensile and viscoelastic properties of the sclera are impacted by abnormal GAG deposition, which results in glaucoma[40]
4. Optic nerve head (ONH) stress and strain states are strongly influenced by IOP and mechanical properties of the cribriform plate. When glaucoma causes chronically elevated IOP, the cribriform plate, the weakest part of the sclera, bulges outward. The contribution of GAGs to the mechanical behaviour of the cribriform plate was important for its response to pressure.[41]

Investigations for evaluation of glaucoma in mucopolysaccharidoses patients

1. IOP: There are several factors that can influence the reliability of IOP measurements in patients with MPS. Many patients with corneal clouding in MPS have thickened corneas, and it is well established that increased CCT can lead to falsely raised IOP readings. A positive correlation has been demonstrated between IOP and CCT in patients with MPS I.[42,43] Corneal rigidity (hysteresis) has also been shown to influence IOP readings in patients with MPS which may lead to difficulty in interpreting IOP.[14] Therefore, while evaluating the glaucoma, optic cup size and visual field defects must also be considered
2. Gonioscopy to visualize the angle structures, which may not possible to perform due to corneal clouding
3. Imaging: ASOCT [Figure 3] and ultrasound biomicroscopy (UBM) are the alternate diagnostic tools which helps to evaluate the morphology of the anterior chamber in cases with severe corneal clouding. UBM also helps in preoperative planning of patients scheduled for glaucoma surgery by prior selection of the site of trabeculectomy and the position of tube placement
4. Optic disc evaluation, retinal nerve fiber layer OCT, ultrasound B scan, and visual field assessment used to assess optic nerve functioning.[37]

Management of glaucoma in mucopolysaccharidoses patients

Glaucoma in MPS patients could be treated according to the following clinical guidelines: (i) Topical antiglaucoma medications, primarily beta-blockers (ii) laser trabeculoplasty, (iii) surgical management, such as trabeculectomy, nonpenetrating deep sclerectomy, and/or other glaucoma surgeries, if they fail to achieve the target IOP at follow-up.

The presence of corneal opacity complicates the diagnosis of glaucoma in most MPS patients, which hinders the observation of chamber angles and the cupping of the optic disc in addition to visual field testing. Due to these diagnostic problems, we know very little about the benefits and risks of anti-glaucoma therapy in these children. There are also few reports of glaucoma surgery in patients with MPS.[44]

Systemic therapies and their effect on glaucoma

HSCT could be effective in treating glaucoma in MPS-IH patients, but more research is needed. The ERT procedure was also attempted to treat glaucoma in MPS VI patients; however, no improvement was observed.[45] As the retina–brain barrier and the cornea are avascular, ERT may not be as effective in treating eye diseases. More studies are needed to determine the effects of HSCT and ERT on ocular manifestations.

Novel Treatment Options in Mucopolysaccharidoses

Gene therapy

It is still under development with as shown promising results in animal models to prevent and reverse

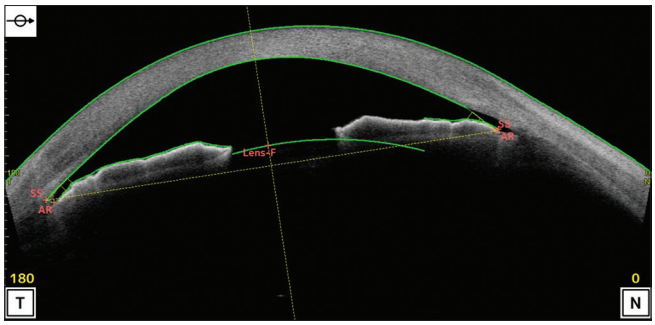

Figure 3: Anterior segment optical coherence tomography imaging of the cornea in a case of mucopolysaccharidoses showing dense corneal opacification

severe corneal clouding after intrastromal injection of adeno-associated virus gene therapy.[46,47]

Substrate deprivation therapy

It aims to reduce the production of GAG chains, which are the natural substrates for the deficient enzyme. It is thought that reduction in the levels of substrate balance the reduced levels of implicated enzyme and there by balance the reduced turnover of GAG. These chemical inhibitors are able to cross the blood-brain barrier as well as the blood-cornea barrier. Rhodamine B, a nonspecific inhibitor of GAG synthesis, acts on normal as well as MPS-affected cells. Studies reported reduced levels of lysosomal GAG as well as urinary GAG excretion in MPS III-A animal models. Genistein is another chemical inhibitor of GAG synthesis in MPS types I, II, III, VI, and VII fibroblast cells.[29,48]

These novel treatments are still limited to animal experiments, and human trials are yet to be done for better understand their effects and complications.

Summary

MPS is a multi-systemic disease and ocular manifestations are common in MPS. Corneal clouding and associated anterior segment changes are one of the common ocular features in MPS patients. Hence, a detailed and a careful ocular examination and use of novel investigative modalities like ASOCT, iris camera Pentacam, Corvis, and UBM help in early diagnosis of corneal clouding and glaucoma. Systemic treatment options such as HSCT, ERT increases the life expectancy of the patient but do not halt and reverse the ocular pathology. Corneal transplantation is the one definitive treatment option for severe corneal opacification. Targeted gene therapy and substrate deprivation therapy which are specifically targeting the element of corneal clouding are still under animal trial and human trials are needed to better understand their effects and complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author contribution

Conceptualization, data acquisition, interpretation and writing- Kusumitha, Manumuraleekrishna, Shifa Ahmed review and editing-Vanathi.M, Noopur Gupta, Radhika Tandon.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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