Review Article

Mucopolysaccharidosis: A broad review

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Mucopolysaccharidosis (MPS) is a group of genetic disorders with seven types and 13 subgroups which are characterized by an inherent deficiency of the enzymes responsible for the degradation of glycosaminoglycans (GAGs). Defective breakdown of GAG products leads to their widespread accumulation within the lysosomes of various organs involving the eye, central nervous system, skeletal, ocular, nervous, respiratory, cardiac, and the gastrointestinal systems. Clinical spectrum varies from mild systemic and ocular abnormalities with a normal life span to severe phenotype, fatal in the first few months of life. Visual disability due to corneal clouding, retinopathy, and optic nerve involvement causes additional impairment of physical and cognitive functions. Treatment modalities such as bone marrow transplantation and enzyme replacement therapies help in increasing the life span as well as the quality of life of the affected patients. For patients with significant corneal clouding, keratoplasty is the answer. The decision to proceed with keratoplasty is governed by various factors such as the motivation of the patient and his family, other systemic affections and anesthesia concerns. A detailed preoperative counseling should be done regarding the expected visual outcomes in the presence of other ocular comorbidities and the postoperative complication such as graft re-opacification, rejection and glaucoma. Future treatment options such as targeted gene therapy and substrate reduction therapy hold promise to reverse corneal clouding, thereby obviating the need for corneal transplantation. These treatment therapies are still in the experimental stages and human trials are needed to validate their outcomes.

Key words: Bilateral corneal clouding, diffuse corneal opacification, Hurler's syndrome, MPS, mucopolysaccharidosis

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Abnormal metabolism of glycosaminoglycans (GAGs) due to defects in lysosomal degradation enzymes leads to their intracellular and extracellular accumulation in various tissues of the body. This presents clinically as a heterogeneous group of disorders termed as mucopolysaccharidosis (MPS). These disorders may either be fatal in the first few months of life or present with symptoms and signs compatible with a normal lifespan.[1] The intra-lysosomal accumulation of GAG degradation products causes multiorgan dysfunction involving tissues of the skeletal, ocular, nervous, respiratory, cardiac, and the gastrointestinal systems. Seven types of MPS syndromes with 13 subgroups have been identified till date. The various types share some common ocular as well as systemic features and differ in terms of the severity of affection. Treatment modalities such as bone marrow transplantation and enzyme replacement therapy have contributed towards increasing the life span as well as the quality of life of these patients. Multiple ocular comorbidities such as corneal clouding, glaucoma, retinopathy and ocular nerve involvement are often difficult to evaluate and manage in the presence of other multiple medical and anesthetic issues. Ophthalmologists, therefore, have a key role to play as part of the multidisciplinary approach to manage these patients, since visual disability adds up to their physical and cognitive impairments. This review article includes an overview of the various types of MPS, their systemic and ocular features, investigative workup to evaluate the extent of ocular involvement and the therapeutic options available till date to target the systemic and ocular components of disease.

Subtypes of MPS

MPS is inherited as an autosomal recessive trait except type II, the Hunter's syndrome, which has an X-linked inheritance.

Type I MPS is caused by the deficiency of an enzyme, α-l-iduronidase, involving gene *IDUA* located on chromosome 4p16. This is further subdivided into three heterogenic phenotypes, termed as Hurler, Hurler-Scheie, and Scheie syndromes, with Hurler being the most severe form and Scheie being the milder one.[2] The deficiency of enzyme α-l-iduronidase results in accumulation of GAGs such as

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dermatan and heparan sulfates (DS and HS) in various tissues of the body, causing widespread organ dysfunction.

Type II MPS (Hunter syndrome) occurs due to the deficiency of enzyme iduronate-2-sulfatase (involving gene *IDS* in chromosome Xq28), which leads to the accumulation of DS and HS.[3]

Type III (Sanfilippo syndrome) involves multiple enzyme deficiencies involving heparan-N-sulfatase (IIIA), α-N-acetylglucosaminidase (IIIB), α-glucosaminide acetyltransferase (IIIC), and N-acetylglucosamine-6-sulfatase (IIID), causing accumulation of HS. MPS IIIA and IIIB are associated with mutations in the genes *SGSH* (chromosome 17q25.3) and *NAGLU* (chromosome 17q. 21.1: missense mutations being most common), respectively, and are associated with severe clinical phenotypes.[2,4,5]

Type IV MPS (Morquio syndrome) is of two types: type IVA which occurs due to the deficiency of N-acetylgalactosamine-6-sulfatase (accumulation of keratan sulfate and chondroitin-6-sulfate) and Type IVB which occurs due to the deficiency of β-galactosidase enzyme (accumulation of keratan sulfate) involving mutations in the genes GALNS (chromosome 16q24) and GLB1(chromosome 3p21).[2]

Type VI MPS (Maroteaux Lamy) occurs due to the accumulation of DS and chondroitin-4-sulfate (C4S) as a result of deficiency of the enzyme N-acetylgalactosamine-4-sulfatase involving gene *ARSB* located on chromosome 5q11.[2]

Partial degradation and accumulation of C4S, chondroitin-6-sulfate (C6S), DS, and HS as a result of β-galactosidase deficiency due mutation in the gene *GUSB* (chromosome 7q11) leads to Type VII MPS (Sly syndrome).[2] Type IX MPS (Natowicz syndrome) is the rarest of all types and occurs due to the deficiency of hyaluronidase enzyme resulting in accumulation of hyaluronan (gene *HYAL1*; chromosome 3p21).[2]

The overall incidence of MPS is approximately 1 in 25,000 live births.[6] Incidence rates vary according to the type of MPS syndrome. (MPS IH: 1 in 115,000 to 500,000 live births; MPS IS: 1 in 100,000 live births, MPS II: 1 in 100,000–170,000 live male births, MPS III: 1 in 70,000 live births, MPS IV: 1 in 76,000–640,000 live births, MPS VI: 1 in 250,000–600,000 live births, MPS VII: 1 in 250,000 live births)[6] Variations in geographic location have also been associated with different types of MPS with MPS II being the most commonly reported from Israel and MPS IV from Northern Ireland.[7] MPS II and MPS III are the most commonly reported types from British Columbia and United Kingdom respectively.[3]

The age of onset varies as per the phenotype and the severity of disease. Various systemic manifestations include growth restriction, cognitive impairment, skeletal abnormalities, cardiac valvular dysfunction, coronary artery disease, gastrointestinal problems, hepatosplenomegaly, umbilical hernias, dental abscess, sensorineural hearing loss, upper airway obstruction, and visual impairment.[6] Ocular abnormalities include corneal clouding, raised intraocular pressure (glaucoma and ocular hypertension), retinopathy and optic nerve involvement. Fig. 1 demonstrates various musculoskeletal manifestations in a patient with mucopolysaccharidosis.

Symptoms in Hurler's disease (Type 1H) begin in in the first two years of life, although IHS and IS syndromes have a later onset.[8] Ocular symptoms such as corneal clouding and glaucoma can manifest as early as one year of age. The child, may, however present in the first decade of life with corneal clouding, glaucoma, retinopathy, and eventually develop optic neuropathy by the end of second decade.[6,9] Systemic manifestations in type II MPS, start at the age of 2–4 years, and children usually present with glaucoma in the first decade of life.[2] In MPS III, IV, VI and VII, corneal manifestations and glaucoma appear around the first to second decade of life.[6]

Various types of MPS, their associated enzyme deficiencies, age of onset and systemic manifestations have been summarized in Tables 1 and 2.

Ocular Features

Clinical presentation

The most common ocular presentation in patients with MPS is progressive corneal stromal clouding. GAG deposition is known to affect all layers of the cornea. Diffuse accumulation of GAG throughout the corneal stroma disrupts the alignment of collagen fibers and results in increased corneal thickness with ground glass opacification [Fig. 2].[3,10] Accumulation of GAG also occurs in trabecular meshwork, predisposing to both open as well as closed-angle glaucoma. Hypertelorism and exophthalmos have been reported in certain types of MPS, leading to exposure keratopathy manifesting as keratoconjunctivitis sicca and corneal abrasions. Other reported symptoms include photosensitivity and visual disturbances, commonly in the form of hypermetropic refractive error and astigmatism. The higher prevalence of hyperopia in these patients is attributed to flat keratometric values due to GAG accumulation in the cornea and measured shorter axial length values owing to the deposition of GAGs in the sclera.[11] Patients with obstructive hydrocephalus can present with papilledema and associated optic disc changes. Pigmentary retinopathy manifesting as b-wave changes on electroretinogram, have also been reported in certain types of MPS. Extraocular accumulation of GAG can cause restriction in ocular motility, presenting as strabismus and consequent amblyopia.

The ocular manifestations of the various types of MPS have been tabulated in Table 3.

Changes in corneal topographic, aberrometric and biomechanical parameters

Scheimpflug imaging shows significant asymmetry of the corneal surfaces and associated higher-order aberrations in patients with MPS. Various topographic indices such as index of vertical asymmetry, index of height asymmetry, and index of height decentration have been found to increase in patients with MPS.[12] The density and grade of corneal opacity is said to correlate well with the topometric indices of corneal asymmetry.[12]

An increase in corneal higher-order aberrations (HOAs) including spherical aberrations and asphericity coefficient from both the front as well as the back surfaces of the cornea has been reported in MPS eyes. Alterations in HOAs to corneal opacification causes degradation of visual functions in terms of reduced levels of contrast sensitivity and occurrence of symptoms such as monocular diplopia, halos, starburst, and glare experienced by patients with MPS.[12] Corneal hysteresis (CH)

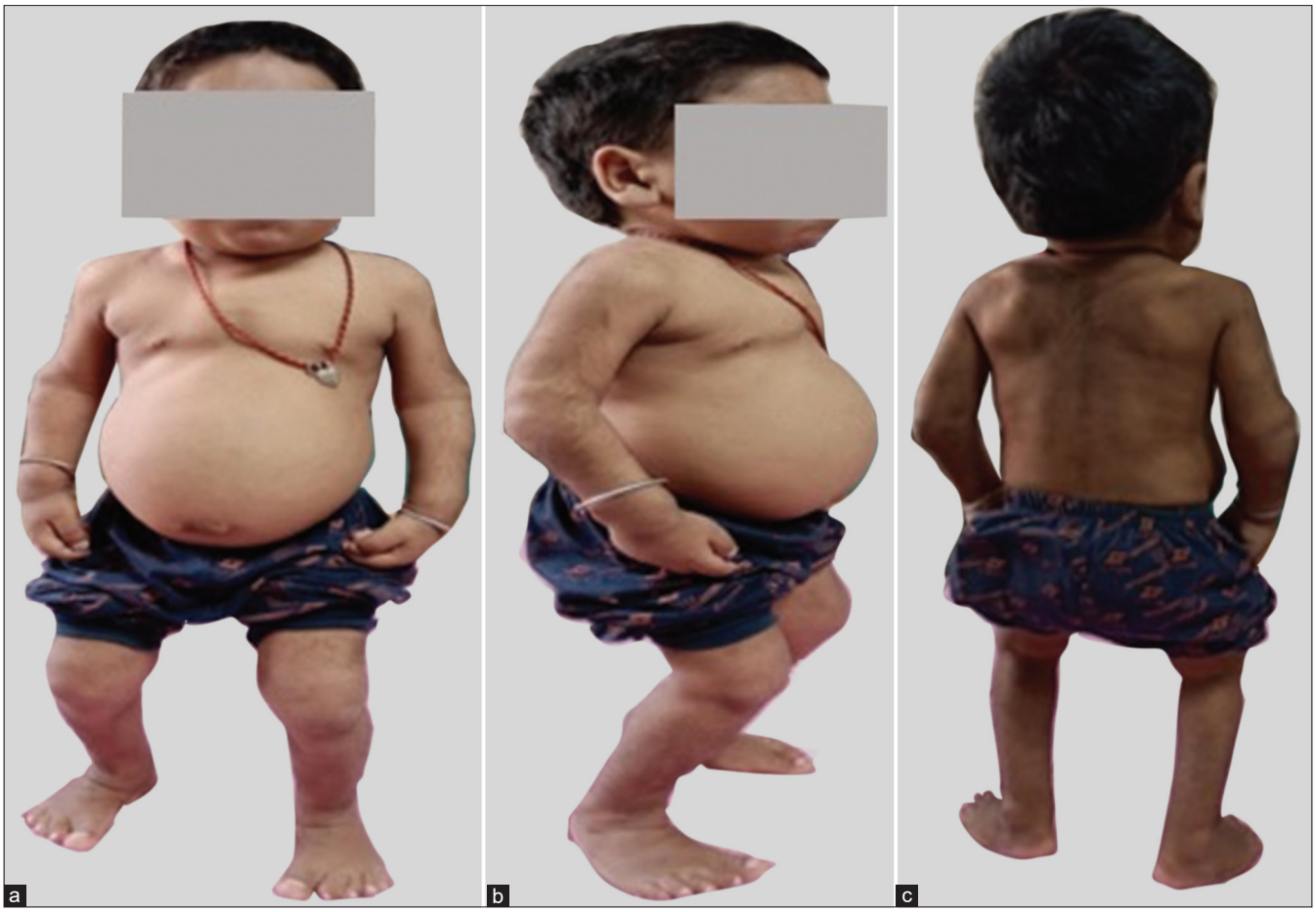


Figure 1: A collage showing various musculoskeletal manifestations associated with mucopolysaccharidosis, as visualized from the front, side, and rear views of the patient. The findings include short stature (a-c), macrocephaly (b and c), coarse facial features (a and b), micrognathia (a and b), short neck (a-c), pectus carinatum (a and b), prominent scapular margins (c) along with abdominal enlargement (a and b)

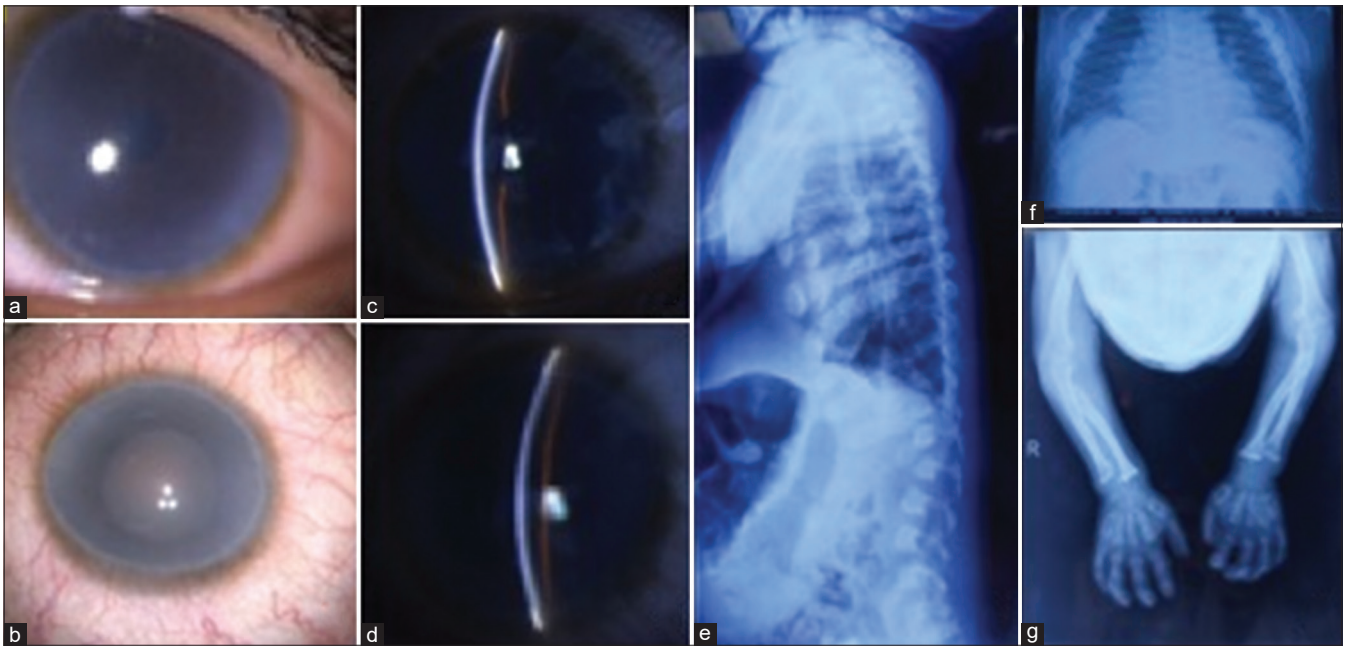


Figure 2: A collage showing ocular and skeletal system abnormalities in a patient with mucopolysaccharidosis. 2a-d represent diffuse and slit view of the right and left eye, respectively, showing diffuse corneal clouding in both eyes, the right eye being more severely affected as suggested by relatively better visibility of anterior segment details in the left eye. Skeletal abnormalities in this patient included presence of middle breaking of the lumbar vertebra (e), oar-shaped ribs (f) and pointed metacarpals (g)

Table 1: Classification of Mucopolysaccharidosis (MPS)

Type of MPS	Deficient Enzyme	Accumulated GAG	Age of onset of systemic features	Progression	Prognosis
IH - Hurler IHS - Hurler-Scheie IS - Scheie	α-l-iduronidase	HS, DS	IH: 1-2 years IHS: 3-7 years IS: 5-13 years	IH dies in 1st decade without treatment; HIS & IS have a longer lifespan	Mortality depends on the age of onset of symptoms and progression. Ocular symptoms are seen in all 3 phenotypes.
II - Hunter	Iduronate-2-sulfatase	HS, DS	Onset at birth but presents at 2-4 years	Progresses through the 1st decade	Mortality by 2nd decade except for mild cases which survive up to 6th-7th decade. Posterior segment ocular manifestations more prominent.
IIIA - Sanfilippo A IIIB - Sanfilippo B IIIC -Sanfilippo C IIID - Sanfilippo D	Heparan-N-sulfatase α-N-Acetylglucosaminidase α-glucosaminide acetyltransferase N-acetylglucosamine-6-sulfatase	HS HS HS HS	2-6 years	Initially presents with neurocognitive symptoms such as language delay, behavioral issues, and hyperactivity with progressive gait disorders and pyramidal signs.	Vegetative state and death by early 30s
IVA - Morquio A IVB - Morquio B	N-acetylgalactosamine-6-sulfatase β-galactosidase	KS, C6S KS	After 1st year of life	Progressive skeletal abnormalities; wheelchair-bound by teenage years	Mortality occurs due to respiratory obstruction and cervical spinal anomalies by 3rd decade of life.
VI - Maroteaux Lamy	N-acetylgalactosamine-4-sulfatase	DS, C4S	2 years	Progressive growth retardation	Mortality in late teens up to 5th decade due to cardiopulmonary complications
VII - Sly	β-glucuronidase	DS, C6S, C4S, KS	Variable	Not well understood due to rarity of disease	Can vary from prenatal death to survival up to 5th decade
IX - Natowicz	Hyaluronidase	Hyaluronan	Rare reports; earliest at 14 years old	Progressive craniofacial and skeletal abnormalities	Not well understood

HS, Heparan sulfate; DS, Dermatan sulfate; KS, Keratan sulphate; C6S, Chondroitin-6-sulfate; C4S, Chondroitin-4-sulfate

and corneal resistance factor (CRF) values also correlate with increased corneal thickness values due to GAG deposition. Ocular response analyzer values have been reported to better predict intraocular pressure (IOP) readings in these patients.[13]

Changes in different corneal layers and in various properties, as demonstrated clinically, have been summarized in Table 4.

Glaucoma in MPS

The overall prevalence of glaucoma in MPS ranges between 2.5% and 12.5%.[14] Glaucoma has been most commonly reported to be associated with MPS types I, IV, and VI. There are so far no reported cases of glaucoma in patients with MPS VII and IX. The reported prevalence of glaucoma in MPS I type is around 10%.[15] Abnormal thickening of limbus and trabecular meshwork has been hypothesized as the probable etiology for open-angle glaucoma.[16] Obstruction of trabecular meshwork occurs as a result of swelling of cells within Schlemm's canal along with the formation of abnormal vesicles. Additionally, formation of intracellular cysts has been noted to occur in various parts of the ciliary body and iris, contributing to angle-closure glaucoma in these patients.[17]

Histological and ultrastructural changes in the cornea

Ultrastructural evaluation of eyes with MPS has shown that GAG deposition involves various tissues such as the sclera,

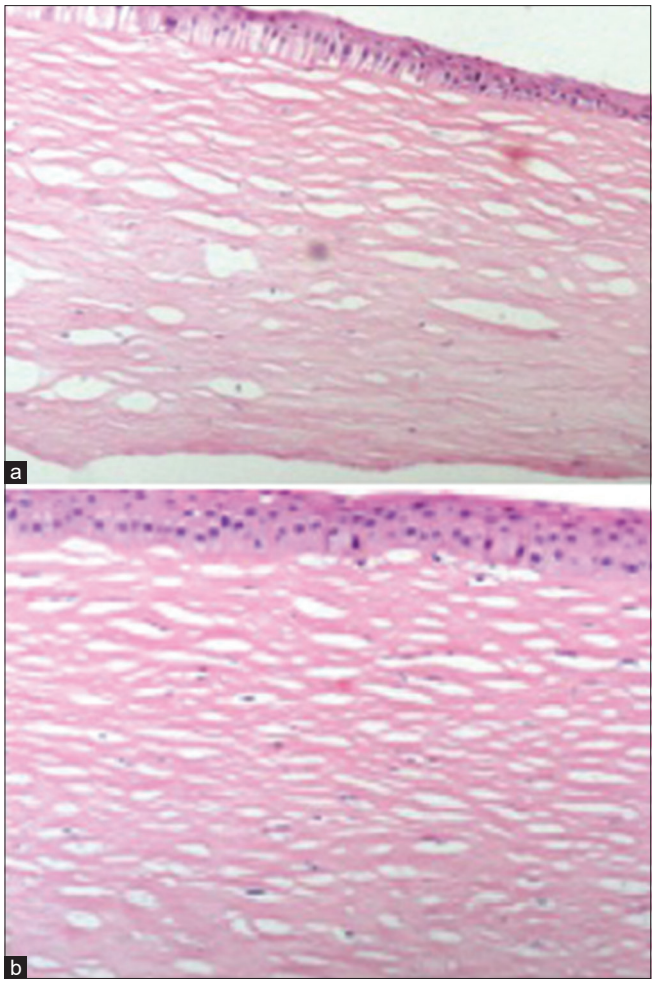


Figure 3: (a) Microphotograph showing basal epithelial edema along with granular deposition of stromal mucopolysaccharides, extending into the deeper layers as visualized by the H and E stain at 100× magnification. (b) Microphotograph taken from the same site as shown in 3a, showing stromal deposition of mucopolysaccharides at 200× magnification using the H and E stain

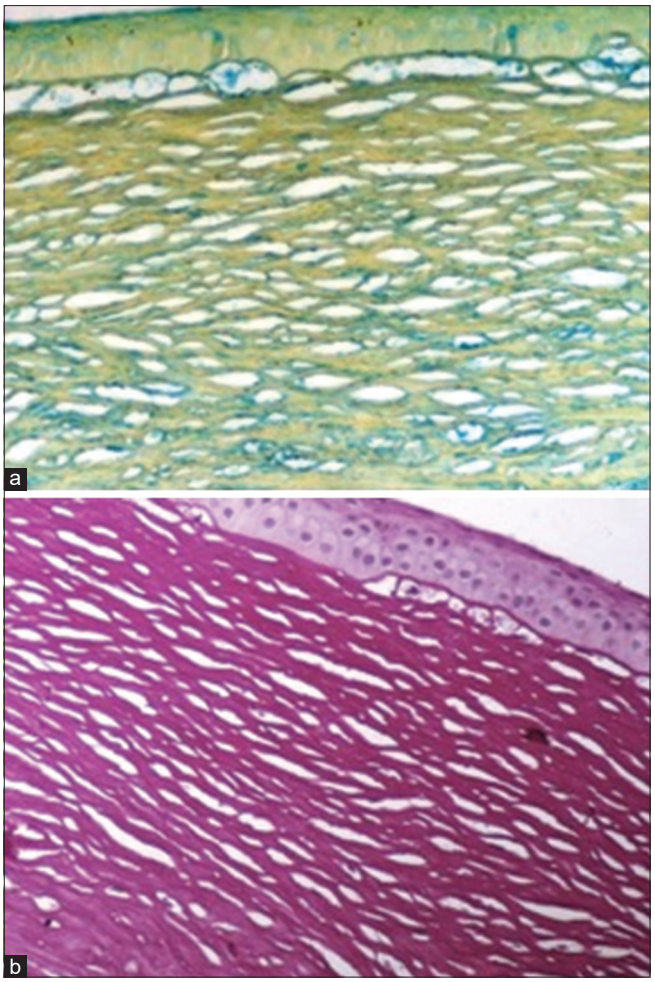


Figure 4: (a) Microphotograph (200×) showing prominent mucopolysaccharide deposition throughout the full-thickness stroma, as demonstrated by colloidal iron staining. (b) Microphotograph (200×) showing stromal mucopolysaccharide deposition as evident by periodic acid–Schiff (PAS) staining

cornea, conjunctiva, and trabecular meshwork. The extent of GAG deposition in the corneal stroma can be appreciated using various stains such as hematoxylin and eosin (H&E) stain, periodic acid–Schiff (PAS) stain and the colloidal iron stain [Figs. 3 and 4].

Corneas of patients with MPS I demonstrate altered spacing of collagen fibrils with irregular packing. The mean fibril diameter is also increased in these corneas compared to normal controls. MPS type III eyes, however, exhibit a lesser mean fibril diameter, correlating clinically in the form of relatively clear corneas seen in these patients, compared to MPS type I. The lysosomes and keratocytes of MPS III are also smaller in size compared to MPS I and VI.[18] These alterations in corneal stroma are a result of abnormal accumulation of GAGs within the lysosomes.

The endothelial cells in MPS I contain a large number of vacuolated inclusion bodies and have a granular matrix. Eyes with MPS VII have hypertrophied endothelial cells with vacuolated lysosomal inclusions. This is in contrast to MPS VI eyes, which do not demonstrate any ultrastructural changes in the endothelial cells.[19]

Investigative Modalities for Evaluation of Patients with MPS

Clinical examination in patients with MPS is challenging. A thorough examination may not be possible in all cases. The reasons include poor patient cooperation due to photophobia, their physical and mental disabilities, and the presence of dense corneal clouding, interfering with adequate visualization of anterior as well as posterior segment structures.[20] The presence of multiple ocular pathologies such as corneal clouding, glaucoma, optic neuropathy and retinal degeneration makes it difficult to attribute reduced visual acuity to one particular abnormality. Investigations help to determine the extent as well as the severity of ocular involvement. Use of investigative modalities such as corneal densitometry and iris recognition cameras allow for an objective assessment of the degree of corneal involvement, which is otherwise subject to variable

Table 2: Systemic Features of Mucopolysaccharidosis

Organ System	Features	Types of MPS
Craniofacial	Hydrocephalus	MPS I, VI, VII
	Facial changes	MPS I, VI
Skeletal	Dysostosis multiplex	MPS I, VII
	Odontoid dysplasia	MPS I
	Spondylolisthesis	MPS I
	Thoracolumbar gibbus	MPS I
	Joint contractures	MPS I, II, III, VI
	Carpal tunnel syndrome	MPS I, II MPS II, III, VI
	Cervical myelopathy	MPS IV
	Genu valgum	MPS VI
	Claw hand	MPS IX
	Periarticular soft tissue masses	
Respiratory system	Recurrent URTI	MPS I
	Upper airway obstruction	MPS I, II, VI, VII
	Obstructive sleep apnea	MPS I, II, VI, VII MPS IV
	Restrictive respiratory disease	
Cardiovascular system	Cardiomyopathy	MPS I, VI, VII
	Valvular heart disease	MPS I, II, IV, VI, VII
	Coronary artery disease	MPS I, II
Gastrointestinal system	Hernia	MPS I, II, III, IV, VII
	Hepatosplenomegaly	MPS I, II, VI, VII
	Diarrhea	MPS II
Central nervous system	Intellectual impairment	MPS I, II, III, VII
	Behavioral changes	MPS II, III
	Seizures	MPS II, III
	Sleep disturbance	MPS III
	Growth retardation	MPS IV
	Short stature	MPS VI, IX
Auditory	Middle ear disease	MPS I, II, III, IV, VI, VII
	Sensorineural deafness	MPS I, II, III, IV, VI, VII
Dental	Caries	MPS I, II, III, VI, VII
	Abscess	MPS I, II, III, VI, VII

clinical assessment.[21–23] In very young children, an examination under anesthesia is required for a detailed clinical as well as investigational workup.

Various clinical investigations which help in determining the overall extent of ocular involvement have been described below.

1.) Tonometry

The assessment of IOP may not be reliable in patients with MPS. This is due to the accumulation of GAG within the lysosomes of keratocytes, causing reduction in the elasticity of the cornea. The applanation tonometry readings, which are based on the assumption of normal corneal rigidity values for their accuracy, therefore become unreliable.[14] The IOP is thus interpreted as falsely raised, blurring the differentiation from a true onset glaucoma. A statistically significant association has been reported between IOP and the extent of corneal clouding in patients affected with MPS types I and VI.[14]

2.) Anterior segment optical coherence tomography

Anterior segment optical coherence tomography (ASOCT) is a useful tool to measure the corneal thickness and to delineate the level of affection from the epithelium to the endothelium. It provides detailed morphological information of the anterior segment structures, especially in patients with severe corneal clouding.[24,25] Another important clinical utility of ASOCT lies in the assessment of anterior chamber angles. Zhang *et al*.[26] found narrow angles in 80% of their study patients affected with MPS I, as documented using a swept source ASOCT.

3.) *In vivo* confocal microscopy cornea

Accumulation of GAG can involve all layers of the cornea. Histochemical studies report the presence of cytoplasmic membrane–bound vacuoles containing organized GAG material.[15,27] Stewart *et al*.[28] observed and reported the presence of cytoplasmic vacuoles in corneas of patients with MPS using *in vivo* confocal microscopy (IVCM). Use of IVCM allows for the detection of pathologic changes at an early stage of the disease, besides identifying 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 basal layer.[29] The corneal stroma is almost always affected, predominantly involving the middle and posterior layers. Accumulation of GAG alters the morphology as well as the internal structure of keratocytes.

Table 5[28–30] enumerates various changes observed and described using IVCM in different types of MPS.

4.) Objective assessment of corneal clouding

Almost all forms of MPS have some degree of corneal involvement, even though it may not be clinically evident. This is attributed to the biochemical nature of the disease. Various clinical parameters such as the extent of visibility of anterior segment structures and the amount of corneal clouding have been used to subjectively stage the disease.[31,32] Objective assessment of corneal opacification 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. Use of iris recognition cameras in combination with specific image analysis algorithms allow for more reliable imaging of patients with corneal clouding.[22]

The Scheimpflug imaging–based Pentacam is another diagnostic tool, the densitometry software of which can be used to objectively measure the amount of corneal involvement. Elflein *et al*.,[21] in their study, demonstrated higher corneal density values on Pentacam scans in patients affected with MPS II with clinically uninvolved cornea.

5.) Ultrasound biomicroscopy

Clinical assessment and monitoring of raised IOP in patients with MPS is challenging due to difficult evaluation of anterior segment structures. Ultrasound biomicroscopy (UBM) is an alternate diagnostic tool in such cases, which helps to evaluate the morphology of the anterior chamber. It 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.[33]

6.) Posterior segment optical coherence tomography

A posterior segment optical coherence tomography (OCT) is helpful to document the presence

Table 3: Systemic and Ocular Manifestations of MPS Syndromes

Type	Systemic Manifestations	Ocular Manifestations
MPS I	*Craniofacial*: Hydrocephalus, Coarse facies *Skeletal*: Dysostosis multiplex, Odontoid dysplasia, Spondylolisthesis, Thoracolumbar gibbus, Joint contractures, Carpal tunnel syndrome *Respiratory*: Recurrent URTI, Upper airway obstruction, Obstructive sleep apnea *Cardiac*: Cardiomyopathy, Valvular heart disease, Coronary artery disease *Gastrointestinal: Hernia,* Hepatosplenomegaly Learning abnormalities, Sensorineural hearing loss, Dental caries/abscess	Corneal clouding* Open- and Closed-angle glaucoma Optic atrophy and disc swelling Hyperopia
MPS II	*Neurocognitive*: Intellectual impairment, Behavioral changes, Seizures *Skeletal*: Joint contractures, Carpal tunnel syndrome, Cervical myelopathy *Respiratory*: Upper airway obstruction, Obstructive sleep apnea *Cardiac*: Valvular heart disease, Coronary artery disease *Gastrointestinal*: Diarrhea, Hernia, Hepatosplenomegaly Sensorineural hearing loss, Dental caries/abscess	Hypertelorism and Exophthalmos* Corneal abrasions keratoconjunctivitis sicca Optic nerve abnormalities Retinopathy Corneal clouding-rare
MPS III	*Neurocognitive*: Intellectual impairment, Behavioral changes, Seizures, Sleep disturbance *Skeletal*: Joint contractures, Cervical myelopathy *Gastrointestinal*: Hernia Sensorineural hearing loss, Dental caries/abscess	Retinopathy* Corneal opacification, glaucoma, optic nerve abnormalities rare
MPS IV	*Skeletal*: Genu valgum *Respiratory*: Restrictive respiratory disease *Cardiac*: Valvular heart disease *Gastrointestinal*: Hernia Growth retardation, Sensorineural hearing loss, Dental caries/abscess	Corneal clouding and refractive errors* Exposure keratopathy Pseudoexophthalmos
MPS VI	*Craniofacial*: Hydrocephalus, Coarse facies *Skeletal*: Joint contractures, Cervical myelopathy, claw hand *Respiratory*: Upper airway obstruction, Obstructive sleep apnea *Cardiac*: Cardiomyopathy, Valvular heart disease *Gastrointestinal*: Hepatosplenomegaly Short stature, Sensorineural hearing loss, Dental caries/abscess	Corneal clouding* Optic atrophy Strabismus and amblyopia Restriction of ocular motility
MPS VII	*Craniofacial*: Hydrocephalus *Skeletal*: Dysostosis multiplex *Cardiac*: Cardiomyopathy, Valvular heart disease *Gastrointestinal*: Hernia, Hepatosplenomegaly Learning abnormalities, Sensorineural hearing loss, Dental caries/abscess	Corneal opacity* Optic nerve abnormalities rare
MPS IX	Periarticular soft tissue masses, Short stature	None reported so far

*Most common ocular abnormality observed

of changes in the macula such as cystoid macular edema, atrophy of the nerve fiber layer or any changes occurring in the photoreceptor layer.[20]

7.) B scan ultrasonography
Ultrasound examination helps to assess the posterior segment changes such as scleral thickening and widening of optic nerve and its sheath.[34] Scleral thickening with subsequent vortex vein obstruction and development of uveal effusion syndrome has been described in patients with MPS II.[35]

8.) Pattern visual evoked potentials
Changes in pattern visual evoked potentials (VEPs), help to identify patients with underlying optic nerve involvement in the form of compression or atrophy.

9.) Electroretinography
An electroretinography (ERG) is recommended in patients with an underlying clinical suspicion of retinopathy. Reduction of b-waves on dark adaptation on an ERG is indicative of a rod–cone degeneration.[36] Retinal dysfunction has been reported in patients with MPS subtypes I, II, and III.[37]

The ocular evaluation of patients presenting with mucopolysaccharidosis has been summarized in Table 6.

Treatment Options for MPS

Managing patients affected with MPS is a joint effort that involves the patient's family members and a dedicated team of specialists including pediatricians, endocrinologists, cardiologists and ophthalmologists. The decision to choose a treatment modality, directed at either systemic or ocular abnormality should be made based on patient's best interests. Various treatment options for managing patients with MPS have been listed in Table 7.

Enzyme replacement therapy

Enzyme replacement therapy (ERT) affects most visceral organs and acts by lowering the amount of stored GAG

Table 4: Corneal Changes in Patients with Mucopolysaccharidosis

Investigations	Features
Slit Lamp Evaluation	Progressive corneal clouding (ground glass opacity) Exposure keratopathy or keratoconjunctivitis (due to GAG accumulation in extraocular areas leading to hypertelorism and exophthalmos)
Keratometry	Flat keratometry resulting in hyperopia
Scheimpflug Imaging	Increase in the index of vertical asymmetry Increase in the index of height asymmetry Increase in the index of height decentration Grading of corneal opacification with Pentacam densitometry
Aberrometry	Increased higher-order aberrations (including spherical aberration and asphericity coefficient) Reduced contrast sensitivity Symptoms - Monocular diplopia, halos, starburst, glare
Biomechanical Properties	Increased corneal hysteresis and corneal resistance factor
Histopathology and Ultrastructural Changes	Altered spacing of collagen fibrils Mean fibril diameter increased except in MPS III which presents with relatively clear corneas Smaller size of lysosomes and keratocytes in MPS III in comparison to types I and VI Alterations in corneal stroma as a result of GAG deposition in the lysosomes Endothelium: MPS I - Large vacuolated inclusion bodies with granular matrix; MPS VII - Hypertrophied cells with vacuolated lysosomal inclusions
ASCOT	Thickness of the cornea Depth of accumulation of GAG deposits
IVCM	Epithelium: Presence of bright cells in MPS I-S Stroma: MPS I-S - Keratocytes with hyporeflective centers in the mid stroma; MPS IV - Hyperreflectivity in the anterior and mid-stroma; MPS VI - Keratocytes with different shapes and hypo-reflective areas in the posterior stroma Endothelium and Descemet: Hyperreflective round bodies in anterior Descemet in MPS I-S; endothelium usually not affected

Table 5: *In Vivo* Confocal Microscopy Cornea Findings as Described in Various Types of Mucopolysaccharidosis

Type	Corneal features on *in vivo* confocal microscopy
MPS IV (Stewart S *et al*.[28])	Normal corneal epithelium and sub-basal nerves. Anterior and mid-stroma show diffuse, irregular hyperreflectivity. Keratocyte cytoplasm has a granular appearance and rounded nuclei with vacuoles, concentrated in the posterior stroma. Endothelium is unaffected.
MPS I-S (Grupcheva CN *et al*.[29])	Basal epithelium contains brightly appearing cells. Keratocytes in mid stroma appear round or elliptical and with well-defined hyporeflective centers. Anterior Descemet layer contains hyperreflective, round bodies.
MPS VI (Patel DV *et al*.[30])	Epithelium and Bowman's layer is unaffected. Keratocytes with different shapes and hyporeflective regions occupy posterior stromal layers. Endothelium is unaffected.

within the lysosomes to normal levels.[38] The effect on ocular structures as well as the central nervous system is, however, negligible due to the presence of blood–brain and blood–cornea barriers. ERT does not contribute toward halting the progression of either corneal or optic disc changes, and, therefore, has no role in preventing the deterioration of visual functions.[39] The effect of ERT on corneal clouding has been variably reported in the literature with some studies reporting a stabilizing effect[40] and others describing worsening of the corneal clouding.[41]

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is ideally indicated before two years of age. Initiation of treatment at an early age, preferably at the asymptomatic stage, has been shown to effectively reduce urinary GAG levels and the development of organomegaly.[42–46] However, it does not prevent or halt the progression of corneal involvement. The study, conducted by Guffon *et al*.,[47] involving 25 patients with MPS I which were treated with HSCT, found that 50% of the patients would eventually require corneal transplantation due to the progression of corneal clouding. Fahnehjelm *et al*.[48] studied eight patients with MPS I, all having corneal opacities before the onset of HSCT. Corneal clouding was found to increase during the follow up period, in five out of eight patients.

Corneal transplantation

Corneal transplantation is the only definitive treatment modality currently available for the treatment of diffuse corneal clouding seen in patients with MPS. The decision to proceed with a corneal grafting procedure should be taken after assessing various factors, such as the impact of visual impairment on the daily activities of the patient, ruling out other causes of reduced visual acuity, overall health of the patient and their suitability to anesthesia. Ocular surface issues such as blepharitis, dry eye, and corneal vascularization should be addressed beforehand. The possibility of re-opacification of graft and graft rejection should be clearly explained to the patient and his relatives. General anesthesia is required for very young patients and those with mental disabilities and behavioral problems. Table 8 highlights important preoperative checkpoints to be ensured before planning keratoplasty in patients with MPS.

Outcomes of penetrating keratoplasty in patients with MPS

Studies analyzing the outcomes of a full-thickness graft, performed in patients with MPS report maintenance of corneal clarity, ranging from a period of three months to up to five years postoperatively.[49–51] Ucakhan *et al*.[52] reported maintenance of corneal clarity after 13 years following a bilateral penetrating keratoplasty (PK), performed in a patient with type VI MPS, who had prior received a bone marrow transplant. This is the longest follow-up period reported in the literature till date.

A graft survival rate as high as 94% has been reported following PK.[53] In a multicentric study by Ohden *et al*.,[53]

Table 6: Ocular Evaluation of Patients with Mucopolysaccharidosis

Examination	Clinical Presentation	Types of MPS Involved	Special Investigations
Evaluation of ocular movements and deviation with visual acuity assessment	Strabismus due to accumulation of GAG in extraocular muscles (esotropia can also occur as a consequence of raised IOP) Acquired Brown's syndrome (vertical strabismus due to mechanical limitation of movement of superior rectus tendon)	Seen in all types of MPS except type IX; Brown's syndrome reported in MPS I-HS	Orthoptic evaluation: Cover-uncover test or Prism cover test and stereopsis evaluation, visual acuity assessment, refraction
Anterior segment evaluation	Corneal clouding: Diffuse and slowly progressive involving limbus to limbus with degenerative changes in the conjunctiva and sclera Anterior chamber depth, pupillary reaction, and lens transparency should also be evaluated in cases of mild corneal clouding	Most common in MPS IH; Seen in all types of MPS except MPS IX	Optical coherence tomography, ultrasound biomicroscopy, Pentacam densitometry, *in vivo* confocal microscopy
Anterior chamber angle assessment	Open-angle glaucoma: Deposition of GAG in trabeculocytes Angle-closure glaucoma: Deposition of GAG in the peripheral cornea, iris, and ciliary body Signs include enlargement of the optic cup, elevated intraocular pressure, and visual field defects	Most commonly detected in MPS I and VI; Seen in all types of MPS except MPS IX	Intraocular pressure measurement, gonioscopy, visual fields assessment, anterior segment optical coherence tomography, ultrasound biomicroscopy, RNFL OCT study
Posterior segment evaluation	Sensitivity to light or night blindness: Progressive photoreceptor loss due to deposition of GAG within retinal pigment epithelial cells; Marked pigment abnormalities and chorioretinal atrophy	Predominant in MPS III; also present in MPS I, II, IV	Indirect ophthalmoscope evaluation, optical coherence tomography to assess the thickness of the retina, electroretinography, ultrasound B scan in cases with corneal clouding
Optic nerve assessment	Optic disc swelling and subsequent nerve atrophy: Deposition of GAG in the sclera and dura resulting in compression of the optic nerve; Can also occur due to GAG deposition in the ganglion layer	Seen in all types of MPS except type IX	Optic disc evaluation, visual fields assessment, OCT-RNFL study, visual evoked potential (VEP)

Table 7: Current and future therapeutic treatment options for managing systemic and ocular mucopolysaccharidosis

Treatment options for systemic manifestations
Enzyme replacement therapy
Hematopoietic stem cell transplantation
Treatment options for ocular abnormalities
Symptomatic management: Photochromatic glasses
Definitive treatment for corneal clouding: Corneal transplantation
Penetrating keratoplasty
Deep anterior lamellar keratoplasty
Future treatment options for corneal clouding
Targeted gene therapy
Substrate deprivation therapy

improvement in visual acuity was seen in 63% of operated eyes, after a mean follow up of 70 months. Naumann *et al*.[50] observed clearing of the para transplant host cornea in three patients with MPS VI-A, receiving a full thickness graft. This was attributed to the diffusion of normal enzyme from the donor to the recipient's cornea, thereby correcting the enzyme defect and restoring the transparency of the cornea.

The abnormally thickened host cornea is a source of mismatch between the donor and the host corneal tissue and can be a potential source of surface irregularity. This is usually taken care of by ensuring good apposition of the anterior surfaces of the graft and host. This is usually difficult to achieve following a lamellar keratoplasty due to the intactness of Descemet membrane, creating a fixed posterior surface.[54] The donor cornea has been reported to re-opacify as a result of accumulation of GAG in the donor keratocytes.[53,55]

Outcomes of deep anterior lamellar keratoplasty in patients with MPS

In patients with MPS, deep anterior lamellar keratoplasty (DALK) is the preferred surgical treatment modality since GAG accumulation predominantly involves the corneal stroma. Endothelial involvement occurs only in the late stages of MPS. An intact Descemet membrane is also known to act as a barrier, and helps to prevent stromal recurrences in the graft.[2] The surgical technique, however, offers challenges in terms of difficult stromal dissection. Standard techniques of stromal separation such as the big bubble technique or the viscoelastic-assisted dissection might not be feasible in patients of MPS. Stromal rigidity due to GAG accumulation limits the passage of air and viscoelastic in between the corneal lamellae, making their separation difficult. Corneal opacification also hinders in assessing the exact depth of needle placement, while attempting a big bubble technique.[56]

Ricardo JR *et al*.[56] described the outcomes of DALK in MPS I patients having visually significant corneal clouding. A complete Descemet membrane baring could be achieved in three out of four eyes. The mean logMAR visual acuity

improved from a preoperative value of 0.59 ± 0.12 to 0.41 ± 0.17 in all eyes. None of the graft showed any evidence of recurrence of disease. In another study, Harding SA *et al*.[57] performed DALK in five eyes of patients with MPS I and VI, ages ranging from 7 months to 5 years. In four out of five children with MPS, manual technique of stromal dissection was employed to bare the Descemet membrane, and UBM was used to guide the depth of trephination. Table 9[49–53,56–58] summarizes the salient features of various studies reporting the outcomes of keratoplasty performed in patients with MPS.

Future Treatment Approaches

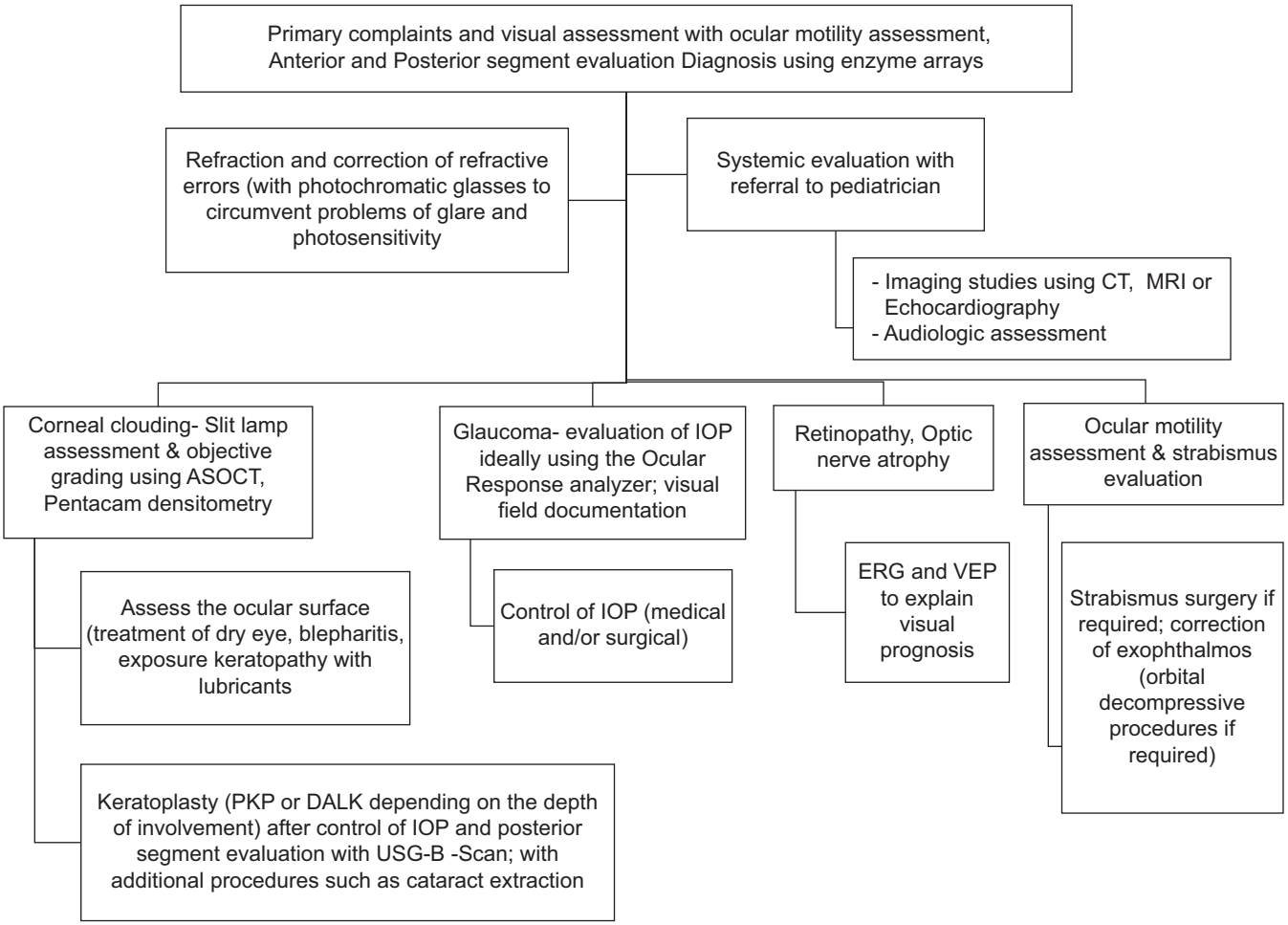
Targeted gene therapy

Treatment modalities specifically directed toward reversing or at least halting the progression of corneal clouding is the need of the hour. There is no currently available treatment which can address corneal clouding other than corneal transplantation, which has its own limitations and drawbacks. Targeted gene therapy is one such treatment approach which has shown favorable results in this direction.

To address the deficiency of enzyme alpha-L-iduronidase (IDUA) in MPS I, Miyadera *et al*.[59] investigated the role of adeno-associated virus (AAV) IDUA gene addition strategy, targeting the corneal stroma. After a single intrastromal injection of AAV8G9-IDUA in MPS I canine eyes having advanced form of corneal disease, resolution of corneal clouding was noted as early as one week, which persisted till 25 weeks. Kamata *et al*.,[60] in another study, successfully treated corneal clouding in mice affected with MPS VII by administering an adenovirus expressing human beta-glucuronidase (AxCAhGUS) into the anterior chamber and in the corneal stroma. Vance *et al*.[61] observed a more than 10-fold supraphysiological increase

Table 8: Preoperative check list for patients with mucopolysaccharidosis before planning for keratoplasty

Look for patient's desire and motivation for visual improvement.
Assess the level of family support for postoperative care after keratoplasty.
Ensure suitability of anesthesia (check for concomitant cardiovascular diseases, cervical spine instability, short neck, difficult intubation)
Rule out other ocular pathologies such as retinopathy, optic nerve pathology and glaucoma.
Optimize the ocular surface (treat dry eye, blepharitis, corneal vascularization).
Achieve adequate control of intraocular pressure.
Formulate a proper surgical plan in terms of additional surgical procedures required such as cataract extraction.
Explain the risk of graft re-opacification, rejection and glaucoma which may cause decline in postoperative visual acuity.



Flowchart 1: Evaluation and Workup of a Patient with Mucopolysaccharidosis

Table 9: Summary of various studies reporting the outcomes of keratoplasty performed in patients with mucopolysaccharidosis (MPS)

Author, Year	Type of MPS	*n*	Surgical intervention	Mean follow-up	Outcome	Complications
Ohden KL *et al.*,[53] 2017	I, IV, VI	48	PK (45) DALK (3)	70 months	94% had a clear graft at last follow-up.	Rejection episodes occurred in 23% grafts.
Bothun *et al.*,[49] 2011	I, IV, VI	8	PK	4.9 years (1-11 years)	Visual acuity improved in 7 out of 8 eyes. (*P*=0.002)	1 eye experienced early graft rejection. No recurrence noted in any of the corneal graft.
Naumann *et al.*,[50] 1993	VI-A (severe type)	3	PK	2.5-5 years	All transplants remained clear till the last follow-up.	None
Bergwerk *et al.*,[51] 2000	VII	2	PK	2 years	Both grafts retained clarity till the last follow-up.	None
Ucakhan OO *et al.*,[52] 2001	VI	2	PK	13 years	Both grafts retained clarity till the last follow-up.	None
Ricardo JR *et al.*,[56] 2013	I	4	Big-bubble DALK	16.7 months	Mean postoperative visual acuity in all eyes at last follow up was 20/50.	No recurrence noted in any of the corneal graft.
Eah KS *et al.*,[58] 2019	IHS	2	DALK	3-5 years	Both grafts retained clarity till the last follow-up. CDVA in right eye: 20/30 CDVA in left eye: 20/25	None
Harding SA *et al.*,[57] 2010	I, VI	5	Manual DALK (4) Viscoelastic assisted DALK (1)	10-80 months	All grafts retained clarity by last follow-up	Epithelial rejection developed in 1 eye requiring repeat graft.

n, Number of eyes; PK, Penetrating keratoplasty; DALK, Deep anterior lamellar keratoplasty

in IDUA activity, following intrastromal administration of AAV8G9-opt-IDUA in human corneas.

Substrate deprivation therapy

Substrate deprivation therapy is another potential therapeutic option which is being evaluated for various subtypes of MPS. The therapy aims to reduce the synthesis of GAG chains, which are the natural substrates for the deficient enzyme. Reduction in the levels of substrate is thought to balance the reduced levels of implicated enzyme, thereby balancing the reduced turnover of GAG.

These chemical inhibitors are able to cross the blood–brain barrier as well as the blood–cornea barrier, reaching the otherwise inaccessible tissues. Rhodamine B, a non-specific inhibitor of GAG synthesis, acts on normal as well as MPS-affected cells.[62] Animal studies show reduced levels of lysosomal GAG as well as urinary GAG excretion in MPS III-A.[62] Genistein is another compound which has been identified as a chemical inhibitor of GAG synthesis in MPS types I, II, III, VI, and VII fibroblast cells. It acts via epidermal growth factor-dependent pathway to prevent further synthesis of GAG.[63,64]

Research in these areas is still in its experimental stages and clinical trials are needed to evaluate their effect on corneal clouding in patients with MPS.

Summary

MPS is a multi-systemic disease requiring teamwork for its timely diagnosis, early initiation of appropriate systemic therapy and ocular assessment. Treatment options such as enzyme replacement therapy and hematopoietic stem cell transplantation have contributed toward increasing the life span of these patients. These therapies, however, do not prevent or reverse ocular sequelae. Keratoplasty is the only definitive treatment to address severe corneal clouding. Involvement of multiple organ systems, anesthesia concerns, ocular comorbidities and post keratoplasty complications limit an aggressive approach toward the decision of going ahead with corneal transplantation. Diagnostic evaluation and workup of patients with mucopolysaccharidosis have been summarized in Flowchart 1.

Treatment therapies aimed to prevent severe corneal clouding will be a game changer in managing these patients. Targeted gene therapy and substrate reduction therapies hold promise by specifically targeting the element of corneal clouding. Research in this area is, however, limited to animal experiments, 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(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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