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Objectively measuring anterior segment alterations in the eyes of mucopolysaccharidoses: Its utility in early diagnosis of glaucoma

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Purpose: Our study aimed to evaluate the utility of the anterior segment morphometry for objectively assessing anterior segment architectural changes of corneal clouding in the mucopolysaccharidoses (MPS) cohort and to investigate whether these measurements correlate with the slit-lamp findings on the cornea and early diagnosis of glaucoma. **Methods:** This retrospective study involved 70 eyes of 35 children with cloudy cornea due to MPS variants. Anterior segment architectural alterations were measured using anterior segment imaging and biometry in MPS children and compared with controls. **Results:** Mean age of the cohort at the time of assessment was 7.9 ± 4.5 years. Males constituted two-thirds of the cohort. Variants of MPS with cloudy cornea were as follows: Type I (62%), Type IV (11%), and Type VI (22%). Morphometric measurements were available in 22 eyes of 11 MPS children and an age-matched healthy control group. There were significant differences between MPS cohort and controls in refraction in Diopters (5.03 ± 0.39 and 0.01 ± 0.04; $P < 0.0001$), axial length (AXL) in mm (21.39 ± 0.28 and 23.04 ± 0.28; $P = 0.0002$), average keratometry in Diopters (40.67 ± 0.44 and 42.83 ± 0.44; $P < 0.0001$), anterior chamber depth (ACD) in mm (2.92 ± 0.07 and 3.65 ± 0.07; $P < 0.0001$), and intraocular pressure (IOP) in mmHg (25.2 ± 2.0 and 14.1 ± 2.3; $P = 0.0003$). Secondary glaucoma was observed in 28% of the MPS cohort. **Conclusion:** The anterior segment morphometry in the cloudy cornea due to MPS provides an objective measurement of anterior segment architectural changes, thus diagnosing early-onset secondary glaucoma. These findings highlight that cloudy cornea due to MPS variants merits close monitoring throughout life.

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Mucopolysaccharidoses (MPS) are a rare group of life-limiting inherited metabolic storage disorders caused by a deficiency of specific lysosomal enzymes involved in degrading intra- and extracellular glycosaminoglycans (GAGs), with an estimated prevalence of 2–6 per 100,000 live births.[1-4] All variants of MPS are autosomal recessive in inheritance, except type ll, which follows an X-linked recessive pattern.[5] Due to a low prevalence and high childhood mortality, research on MPS has focused primarily on life-threatening systemic consequences rather than ophthalmic manifestations. While recent advances, therapies such as hemopoietic stem cell transplantation and enzyme replacement therapy[1,6] are promising modalities in reversing systemic consequences, thus improving quality and life expectancy, but they are ineffective in reversing ophthalmic effects.

Corneal clouding is the most conspicuous ophthalmic finding in all variants of MPS, except type II. Typically, progressive corneal clouding starts in the first year of life due to abnormal deposition of dermatan sulfate in types l and Vl and keratan sulfate in type IV MPS.[1,7] Patients with MPS can develop secondary glaucoma due to an abnormal accumulation of GAGs in the trabecular meshwork, with an estimated prevalence of 2.1%–12.5%.[8] The risk of glaucoma has been underreported in literature due to the limited life span of MPS patients, which is not long enough to show the clinical manifestations of glaucoma. The systemic consequences of MPS, including cognitive issues and musculoskeletal abnormalities, take precedence over glaucoma diagnosis, and corneal clouding obscures accurate optic nerve assessment and thick cornea affects intraocular pressure (IOP) measurement.

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The plausible biological mechanism for causation of secondary glaucoma in these subsets of cases is the accumulation of unbroken GAG in the eye that might block trabecular meshwork outflow dynamics (open-angle glaucoma),[9] anterior segment crowding (an angle-closure mechanism), besides scleral thickening and alteration in the biomechanical behavior of lamina cribrosa.

Our study aimed to evaluate the utility of the anterior segment morphometry for objectively assessing anterior segment architectural changes of corneal clouding in the MPS cohort and to investigate whether these measurements correlate with the slit-lamp findings of the cornea and early diagnosis of glaucoma.

Methods

The institutional ethics committee approved this retrospective study, and all procedures adhered to the tenets of the Declaration of Helsinki. Clinical records of all subjects diagnosed with cloudy cornea due to an MPS variant between 1992 and 2021 were included. Patients with previous intraocular surgery (because this might influence corneal biometric parameters) or incomplete data were excluded from the analysis.

Patients underwent a comprehensive eye evaluation. Best-corrected visual acuity (BCVA) was measured using Teller acuity cards, Kay pictures, or Snellen visual acuity chart, based on the individual's age and intellectual ability. Cycloplegic refraction was obtained in all children, except those with dense corneal opacity. IOP was measured using a Goldman applanation tonometer or hand-held Perkins tonometer, followed by anterior segment and fundus evaluation. When possible, the diagnosis of MPS was based on systemic features, clinical characteristics, and enzymatic or genetic analysis.

Glaucoma was defined by elevated IOP (>21 mmHg), enlarged cup-to-disk ratio (CDR) (≥0.7), or CDR asymmetry (≥0.2) between two eyes, with the corresponding glaucomatous visual field defects when available. Ocular hypertension was defined as IOP >21 mmHg. We described early-onset glaucoma as glaucoma developing before the age of 3 years and late-onset glaucoma as glaucoma developing after 3 years of age.

Anterior segment imaging was performed as part of a comprehensive eye examination. Lenstar-LS 900 Biometry (Haag-Streit Global, Dallas, TX) was used to assess axial length (AXL) and corneal curvature, RTVue-100 FD-OCT (Optovue, Fremont, CA, USA) to assess central corneal thickness (CCT), Wavelight Pentacam Oculyzer (Alcon, Fort Worth, TX, USA) to evaluate corneal densitometry (CD), and specular microscopy (SM) EM3000 (Tomey Corporation, Nagoya, Japan) to assess endothelial cell density (ECD). We also included age-matched controls who had presented to our institute for refractive error evaluation, underwent biometry as part of a comprehensive eye examination, and were diagnosed as emmetropes in both eyes. Their clinical data were also retrospectively reviewed.

Statistical analysis was performed using STATA v14.2 (Stata Corp, College Station, TX, USA). Continuous data were expressed as mean and standard deviation, and categorical data as proportions. A mixed-effects model with a random intercept at the subject level was used to account for the correlation between the same patients' eyes during the analysis of BCVA, mean spherical equivalent (MSE) refraction, AXL, keratometry, CCT, densitometry, and ECD. The mixed-effects model was used to compare the MPS and control groups. A P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the MPS cohort

A total of 70 eyes of 35 subjects were included in the study. Most subjects were male (n = 25, 71%). Thirty-four patients had bilateral corneal clouding including Type I (n = 22, 62.9%) Type IV (n = 4, 11.4%), and Type VI (n = 8, 22.9%) variants, while cornea was uninvolved in Type II (n = 1, 2.9%). In 11% of families, more than one child had MPS. BCVA could be assessed in 66 eyes of 33 children, and a log of minimum angle of resolution (logMAR) equivalent was obtained in 47 eyes of 24 children. Visual acuity ranged from light perception to 20/25 in Snellen notation. Objective refraction was recorded in 37 eyes. The baseline characteristics and BCVA of the MPS cohort are shown in Table 1.

Anterior segment features in MPS and the effect of age, gender, and Type I variant

Corneal clouding was seen in the majority of the eyes. Corneal clouding was severe in 33 eyes of 17 children, where the posterior segment could not be assessed. Table 2 summarizes the anterior segment features and the effect of age, gender, and Type I MPS variant. In both bivariate and multivariate analysis, age at investigation and MPS Type 1 showed a statistically significant relationship with CCT. A significant positive correlation was noted between CD and CCT (P = 0.0006, slope: 0.32/μm) [Fig. 1].

Table 1: Baseline characteristics of children with mucopolysaccharidosis

Particulars	Parameters (%)
Number of eyes	70 eyes of 35 children
Gender, male: female	25:10
Age at presentation (years), mean±SD	8.2±4.5
Positive family history	4 (11.4%)
Types of mucopolysaccharidosis	
Type I (Hurler, Hurler–Scheie, and Scheie syndromes)	22 (62.9%)
Type II (Hunter syndrome)	1 (2.9%)
Type IV (Morquio syndrome)	4 (11.4%)
Type VI (Maroteaux–Lamy syndrome)	8 (22.9%)
Visual acuity at presentation	
Nonambulatory (hand movements and light perception)	14 (21.2%)
Ambulatory (20/200-20/800, counting fingers or fixes and follows)	21 (31.8%)
20/190-20/50	18 (27.3%)
Better than 20/50	13 (19.7%)
Not available	4 (5.7%)
Best-corrected visual acuity (logMAR), mean±SD	0.91±0.69
Spherical equivalent refraction (D), mean±SD	3.24±2.80

logMAR=log of minimum angle of resolution, SD=standard deviation

Ocular biometry was performed in 22 eyes of 11 children with MPS. The mean age at investigation was 11.3 ± 5.1 years. In bivariate analysis, the hyperopic refractive error showed a significant negative correlation with AXL ($P < 0.0001$) and anterior chamber depth (ACD; $P = 0.01$) [Figs. 2 and 3]. In multivariate analysis, hyperopic refractive error was significantly correlated only with AXL ($P = 0.005$, slope: −1.16 D/mm). Refractive error and keratometry were not correlated ($P = 0.72$). In both bivariate and multivariate analyses, CCT was significantly associated with age at investigation and MPS Type I. As age increased, CCT increased in MPS, and the Type I MPS variant had a higher CCT than the rest. AXL, keratometry, ACD, White To White (WTW) diameter, and refractive error did not correlate with age at investigation, gender, or MPS Type I.

Anterior segment features in controls and the effect of age and gender

Twenty-two eyes of 11 age-matched normal children who had undergone ocular biometry were retrospectively reviewed. The mean age of controls was 11.4 ± 1.0 years and was not significantly different from that of MPS cases ($P = 0.87$). These eyes had a BCVA of 20/20 in Snellen notation, with a mean refractive error of 0.01 ± 0.04 D and mean IOP of 14.1 ± 2.3 mmHg. Anterior segment and fundus evaluation were normal in both eyes. Table 3 summarizes the ocular biometry details of controls. Refractive error was not correlated with age, gender, AXL ($P = 0.76$), keratometry ($P = 0.58$), or ACD ($P = 0.17$). In bivariate analysis, age at investigation and male gender showed a statistically significant relationship with AXL. In multivariate analysis, only the male gender (male: 24.07 ± 0.72 mm and female: 22.66 ± 0.39 mm) showed a significant relationship with AXL. Average keratometry was significantly lower in males (male: 42.02 ± 0.29 D and female: 43.51 ± 0.95 D), whereas WTW (male: 12.79 ± 0.21 mm and female: 12.11 ± 0.46 mm) and ACD (male: 3.73 ± 0.15 mm and female: 3.53 ± 0.14 mm) were significantly higher in them.

Comparison between the MPS group and age-matched controls

Comparisons of ocular biometry characteristics between MPS and control groups are shown in Table 4. There were significant differences between the MPS cohort and controls in refraction in Diopters (5.03 ± 0.39 and 0.01 ± 0.04; $P < 0.0001$), AXL in mm (21.39 ± 0.28 and 23.04 ± 0.28; $P < 0.0001$), average keratometry in diopters (40.67 ± 0.44 and 42.83 ± 0.44; $P < 0.0001$), ACD in mm (2.92 ± 0.07 and 3.65 ± 0.07; $P < 0.0001$), and IOP in mmHg (25.2 ± 2.0 and 14.1 ± 2.3; $P = 0.0003$). Fig. 4a and b slit lamp images showing corneal clouding and Fig. 4c-f shows anterior segment imaging in MPS. The MPS cohort had shorter AXLs [Fig. 4c], lesser ACD [Fig. 4e and f], and flatter corneal curvature than the control group. Refractive error in MPS was higher than in controls. There was no significant difference in WTW diameter between the two cohorts.

Secondary glaucoma in MPS

The IOP was recorded in 43 eyes out of 70 eyes. As seen in Table 4, the IOP was significantly higher ($P < 0.001$) in the MPS

Table 2: Anterior segment features in mucopolysaccharidosis and the effect of age, gender, and Type I

Variables	Mean±standard deviation	*P*-value for age	*P*-value for male gender	*P*-value for MPS Type I
Refractive error (D), 22 eyes/11 children	5.03±0.94	0.17	0.58	0.27
Axial length (mm), 22 eyes/11 children	21.39±1.06	0.36	NA*	0.60
Keratometry (D), 22 eyes/11 children				
K1	39.0±2.0	0.24	NA	0.72
K2	41.8±1.4	0.92		0.48
Avg K	40.4±1.6	0.51		0.59
Central corneal thickness (μm), 36 eyes/19 children	609.3±80.5	**0.009 (coefficient=9.83)**	0.58	**0.0002 (coefficient=111.4)**
Anterior chamber depth (mm), 18 eyes/10 children	2.99±0.29	0.89	NA	0.56
White to white diameter (mm), 19 eyes/10 children	12.55±0.39	0.12	0.84	0.88

MPS=mucopolysaccharidoses. *Not available (NA) due to low sample size

Table 3: Anterior segment features in controls and the effect of age and gender

Variables (22 eyes of 11 children)	Mean±standard deviation	*P*-value for age	Male gender	
			P	Coefficient
Refractive error (D)	0.02±0.12	0.82	**0.69**	-
Axial length (mm)	23.04±0.80	**0.01 (coefficient=0.09)**	**<0.0001**	**1.41**
Keratometry (D)				
K1	42.75±0.98	0.86	**0.03**	**–1.24**
K2	43.46±0.59	0.61	**0.003**	**–1.76**
Avg K	43.11±1.06	0.72	**0.008**	**–1.50**
Anterior chamber depth (mm)	3.58±0.17	0.33	**0.03**	**0.20**
White to white diameter (mm)	12.30±0.52	0.27	**0.03**	**0.68**

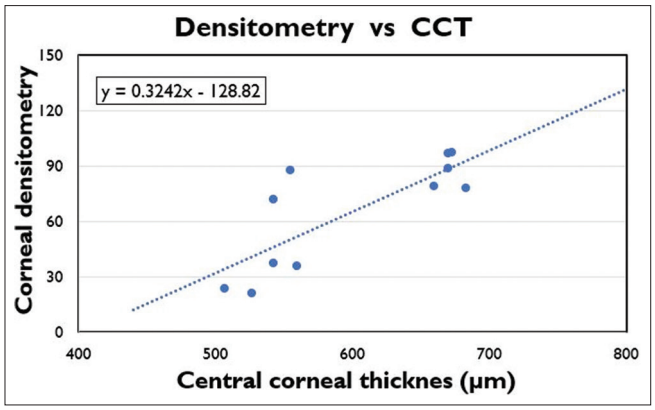

Figure 1: Correlation between corneal densitometry and central corneal thickness in the MPS group. This scatter plot shows the relation between corneal densitometry and central corneal thickness; the MPS group has a significant positive correlation between corneal densitometry and central corneal thickness. MPS = mucopolysaccharidoses

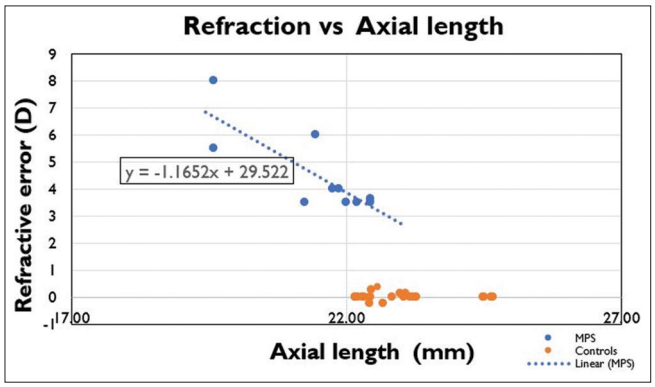

Figure 2: Correlation between refractive error and axial length in the MPS group and controls. This figure shows a scatter plot between refractive error and axial length in MPS and controls; a significant negative correlation is seen in the MPS group, whereas no correlation is seen in controls. MPS = mucopolysaccharidoses

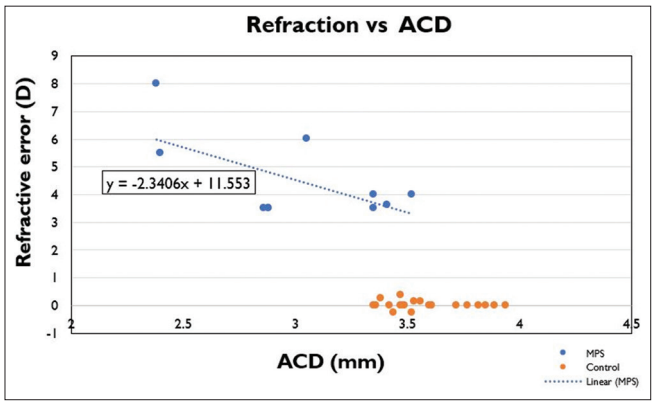

Figure 3: Correlation between refractive error and ACD in the MPS group and controls. This figure shows a scatter plot between refractive error and ACD in MPS and controls; a significant negative correlation is seen in the MPS group, whereas no correlation is seen in controls. ACD = anterior chamber depth, MPS = mucopolysaccharidoses

cohort than in controls [Table 4]. The short AXL with crowded ACD and thicker corneas could contribute to the elevated IOP. Secondary glaucoma was noted in 12 eyes (28%) (four eyes in Type I, two eyes in Type IV, and six eyes in Type VI). Elevated IOP was controlled using topical antiglaucoma medications (83%), except for two eyes (17%) of one child with Type VI Maroteaux–Lamy syndrome requiring glaucoma filtering surgery (GFS). Corneal clarity and visual acuity improved after decreasing the IOP in the two eyes of one child. Advanced disk damage and compressive optic atrophy were noted in four (6%) and eight (11%) eyes, respectively. Optic nerve head gliosis was noted in two eyes (3%). Seventeen eyes underwent keratoplasty, which involved deep anterior lamellar keratoplasty in 16 eyes and penetrating k eratoplasty in one eye.

Table 4: Comparison of ocular biometry and refraction between mucopolysaccharidosis group and age-matched controls

Parameters	MPSMean±SE (22 eyes of 11 children)	ControlsMean±SE (22 eyes of 11 children)	*P*
Refractive error (D)	5.03±0.39	0.01±0.04	**<0.0001**
Axial length (mm)	21.39±0.28	23.04±0.28	**0.0002**
Keratometry (D)			
K1	39.25±0.52	42.50±0.52	**<0.0001**
K2	42.09±0.42	43.18±0.42	**0.002**
Avg K	40.67±0.44	42.83±0.44	**<0.0001**
Anterior chamber depth (mm)	2.92±0.07	3.65±0.07	**<0.0001**
White to white diameter (mm)	12.44±0.16	12.39±0.15	**0.17**
Intraocular pressure (mmHg)	25.2±2.0	14.1±2.3	**0.0003**

MPS=mucopolysaccharidoses, SE=standard error

Discussion

Our study highlights anterior segment imaging characteristics and refractive error within the MPS spectrum, that is, corneal clouding [Fig. 4a and b], corneal thickening, flatter corneal curvature, crowded ACD [Fig. 4e], shorter AXL [Fig. 4c], and thus the resultant high hyperopic refractive error, in children with MPS. In emmetropic eyes, AXL increases with age. The maximum increase in AXL happens between 2 and 3 years of age; later, the ocular growth slows down and reaches the adult length by the age of 8.[10] In children with MPS, we noticed abnormal eyeball growth with a mean AXL of 21.4 ± 1.06 mm, whereas in controls, the mean AXL was 23.04 ± 0.80. The stunted eyeball in MPS was due to accumulation of GAG in the sclera, increasing the scleral thickness[11,12]; this might affect the normal emmetropization process of the eye. Reduction in ocular growth could be a significant factor for the hyperopic refractive error (5.03 ± 0.94). Our results are similar to earlier reports; Fahnehjelm *et al*.[12] reported that hyperopic refractive error (+7.00 D in the right and left eyes) is due to reduced AXL (ranging from 20.57 to 21.57) in Hurler syndrome (MPS-1).

Corneal curvature also undergoes periodic change, and greater keratometry values are reported in newborn infants. The most significant change in corneal refraction happens in the first 2 years of age.[10] In contrast, in the MPS group, keratometry values are lower (40.40 ± 1.6) than the average

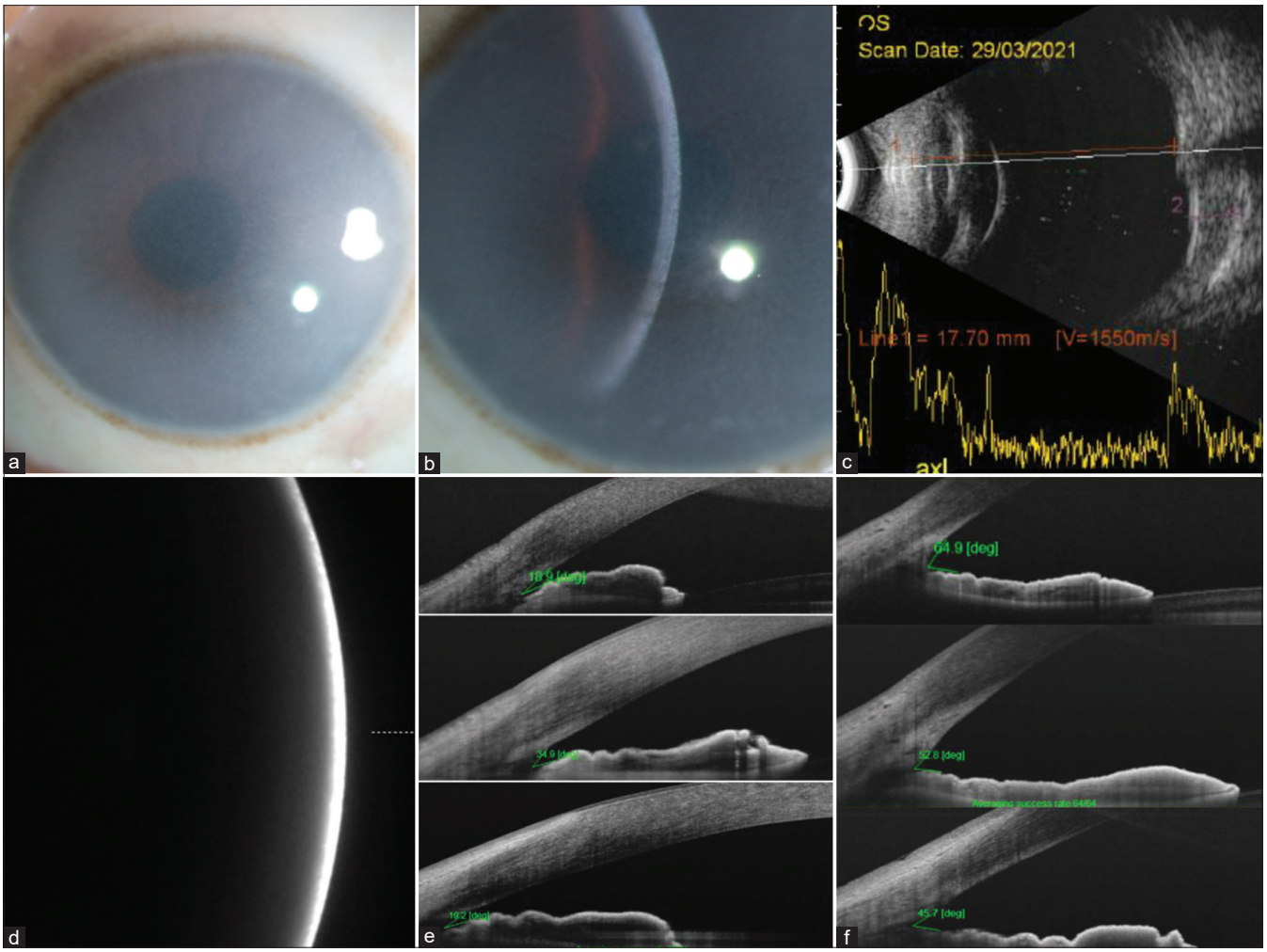

Figure 4: Slit-lamp and anterior segment imaging of the MPS. (a-b) Slit-lamp images showing corneal clouding. (c) Ultrasonography of the eye with MPS shows shorter axial length. (d) Corneal densitometry imaging. (e and f) Swept Source Optical Coherence Tomography (SS-OCT) showing anterior chamber angle in MPS and control. MPS = mucopolysaccharidoses

age-matched typical (43.11 ± 1.06) keratometry values. Flatter corneal contour in MPS could be due to rigidity of cornea because of GAG accumulation in the corneal layers.[11,12] However, our results did not show any significant relation between corneal curvature (40.40 ± 0.16) and hyperopic refractive error (5.03 ± 0.94).

In an emmetropic eye, AXL and keratometry are inverse; corneal curvature reduces as the globe length increases proportionally.[13] In MPS disorder, we noticed nonproportionality of the eyeball; we found shorter globe length and flatter corneal curvature. Due to dense corneal clouding, we could not observe crystalline lens parameters such as thickness.

CCT in the MPS group was markedly high (609.3 ± 80.5 µm). In an average population with an age range of 6 months to 18 years, CCT was expected to be between 533 and 555 µm.[14] An increase in corneal thickness could be due to GAG accumulation in the corneal stroma. We observed a relation between CD and CCT in children with MPS. CD [Fig. 4d] increased with an increase in CCT; loss of corneal transparency could be attributed to diffuse corneal opacification and increased corneal thickness.

MPS has a significant impact on vision due to corneal clouding, and can also be associated with secondary glaucoma, optic nerve involvement, and retinopathy. Our findings showed that corneal clouding was seen in all variants except Type II, and individuals with corneal abnormalities were more likely to require corneal transplantation. Moreover, MPS-related severe spectrum associated with glaucoma was diagnosed at a younger age and was more likely to require glaucoma procedures and corneal grafts. Therefore, individuals with a powerful spectrum of MPS require close follow-up and monitoring throughout infancy and adulthood. Raised IOP, glaucoma surgery, and corneal grafting are all associated with optic nerve head damage.

Hence, individuals with MPS should have a detailed anterior segment assessment. Pediatricians and ophthalmologists diagnose MPS, and the diagnosis is primarily clinical. Phenotypic and genotypic heterogeneity and overlap of clinical presentations can make diagnosing MPS challenging, especially in young children who require an examination under anesthesia to assess angle abnormalities. MPS can present with subtle corneal clouding and sometimes can be misdiagnosed as primary congenital glaucoma or Congenital Heriditary Endothelial Dystrophy (CHED) when the systemic features of

MPS are subtle. While some would argue that systemic features are essential in diagnosing MPS, our study showed that systemic features might not be evident early in the natural course. As a result, detailed metabolic work, including genotype–phenotype correlations and systemic features, can assist clinicians in making a correct diagnosis and disease classification. In this study, systemic features were present in more than three-fourths of patients on presentation, but in all individuals with MPS variants, and may have overlapping clinical features.

The estimated prevalence of secondary glaucoma in cases of MPS is 2.1%–12.5%.[8] In our cohort, 28% of subjects had secondary glaucoma (mean age: 6.74 ± 2.05 years; reported after 3 years of age). IOP spikes were reported in 30% of the eyes (mean age: 11.12 ± 4.13 years; reported after 3 years of age). The severe ocular spectrum is likely to have a higher propensity due to thickened uveal tissues, shallow anterior chamber structure, and accumulation of GAGs within the trabecular meshwork.[15,16] Earlier, Zhang *et al*.[9] reported glaucoma in MPS Type I, IV, and VI cases. In our study, ACD (2.99 ± 0.29) in MPS was smaller than ACD (3.58 ± 0.17) of age-matched normal. In our study, out of 12 eyes, two eyes showed improved corneal clarity and visual acuity after undergoing treatment for glaucoma; four eyes maintained the same visual acuity throughout the follow-up.

In comparison, six eyes presented with worsening visual acuity due to advanced disk damage, affecting their functional activities. In 17 eyes, suboptimal visual acuity was reported due to amblyopia related to dense corneal clouding. Fifteen eyes subsequently underwent anterior lamellar keratoplasty, and two eyes underwent penetrating keratoplasty.[17,18]

It has been previously reported that while the systemic features vary between types of MPS, so is the corneal cloudiness.[1,7] Patients with MPS have a higher risk of developing glaucoma, which can occur anytime during infancy, childhood, early adulthood, or middle age. Therefore, MPS patients should be examined annually for the changes in IOP and optic nerve head. MPS patients with corneal abnormalities and those who have undergone surgical interventions are at risk of developing glaucomatous optic atrophy. Therefore, these patients should be followed regularly with repeated IOP measurements after correcting for CCT and periodic angle assessment for picking up secondary glaucoma due to a different mechanism.

There were some limitations in the study. As it was a retrospective comparative study, data collection relied on information gathered from databases provided by medical notes when available. Some of the data, such as the age at diagnosis of MPS and age at diagnosis of glaucoma, were missing. However, variables with a significant component of missing data were not included in the final analysis. Considering the rarity of this clinical condition, our findings are valuable in managing these cases. However, all statistical tests were exploratory, and further studies with a larger sample size should be performed to support our findings.

Conclusion

In conclusion, anterior segment imaging allows objective assessment of anterior segment architectural changes in the cloudy cornea in MPS. It may provide the basis for the early onset of secondary glaucoma, independent of the optic nerve or visual field changes. It may also facilitate follow-up examinations and enable objective evaluation of disease progression in MPS. Furthermore, it could play a vital role in accurately monitoring anterior segment architectural changes following therapeutic interventions, thus aiding early diagnosis and improving the quality of life for patients with MPS. These findings have an important implication for managing patients with MPS, and future research should investigate these individuals' anterior segment architectural changes.

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Conflicts of interest

There are no conflicts of interest.

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