Outcome of Penetrating Keratoplasty for Mucopolysaccharidoses

Erick D. Bothun, MD; Alejandra Decanini, MD; C. Gail Summers, MD; Paul J. Orchard, MD; Jakub Tolar, MD, PhD

Objective: To describe the outcome of penetrating keratoplasty (PK) for corneal opacification in the setting of systemic mucopolysaccharidoses (MPS).

Methods: A consecutive case series and literature review.

Results: Eight eyes from 5 patients with MPS (MPS I, MPS IV, and MPS VI) and a history of PK met inclusion criteria for our case series at the University of Minnesota Medical Center. The mean age at the time of PK was 40.5 years (range, 11.7-65.3 years). Mean follow-up time after the PK was 4.9 years (range, 1-11 years). Mean (SD) visual acuity before PK was 0.90 (0.38) logMAR. The mean (SD) visual acuity at the last visit for all 8 eyes was 0.32 (0.16) logMAR. Visual acuity improved in 7 of 8 eyes ($P = .002$). Although early rejection led to repeat PK in 1 eye, no recurrent opacity consistent with MPS was noted in any of the corneal grafts. In a literature review, we found 23 reports documenting 40 initial and 3 repeat cases of PK in the setting of MPS. Of these, 31 initial and 2 repeat corneal grafts were reportedly clear during follow-up, ranging from 0.25 to 13 years.

Conclusions: Penetrating keratoplasty is often a beneficial intervention in appropriate patients with corneal clouding due to MPS. Improvement in vision can be obtained with stable, clear corneal grafts in this population.

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CORNEAL OPACIFICATION IS a common eye finding in many of the systemic mucopolysaccharidoses (MPS). Unfortunately, despite systemic enzyme replacement therapy (ERT) and/or bone marrow transplantation, clearing of the corneal opacity is unusual. In addition, patients with MPS may experience progressive corneal clouding and visual disability, despite systemic treatment. Penetrating keratoplasty (PK) has been reported to benefit certain patients with MPS when their visual loss is thought to be primarily related to opacity of the visual axis. We report a series of PKs for MPS performed at the University of Minnesota Medical Center and summarize the literature for this treatment in various forms of MPS.

Author Affiliations: Departments of Ophthalmology (Drs Bothun, Decanini, and Summers) and Pediatrics (Drs Bothun, Summers, Orchard, and Tolar), and Division of Hematology, Oncology, Blood and Marrow Transplantation (Drs Orchard and Tolar), University of Minnesota, Minneapolis.

BACKGROUND

Mucopolysaccharidoses are inherited systemic disorders caused by deficiencies in various lysosomal enzymes. These enzymopathies lead to inadequate degradation and secondary accumulation of glycosaminoglycans (GAGs), resulting in pathophysiologic changes. The MPS disorders vary in their clinical manifestations based on the specific enzyme deficiency, and characteristics include short stature, atypical facies, skeletal deformities, hepatosplenomegaly, cardiac and respiratory compromise, neurologic decline, and ophthalmologic abnormalities. Variations in symptoms, age of onset, and severity of disease are often present among the different types of MPS, and the phenotype may also be variable within each type of MPS.

The cornerstone for treating MPS disorders is currently the delivery of exogenous enzymes. Enzyme replacement therapy with intermittent infusions of recombinant enzyme is being used for many of these disorders. In addition, hematopoietic cell transplantation (HCT) holds promise for certain types of MPS disorders by providing a continuous source of enzyme produced by the blood cells of an unaffected individual.[1,2] Both interventions can successfully improve GAG degradation[3-6]; however, neither ERT nor HCT completely corrects MPS phenotypes. Enzyme replacement therapy does little for disease of the central nervous system be-

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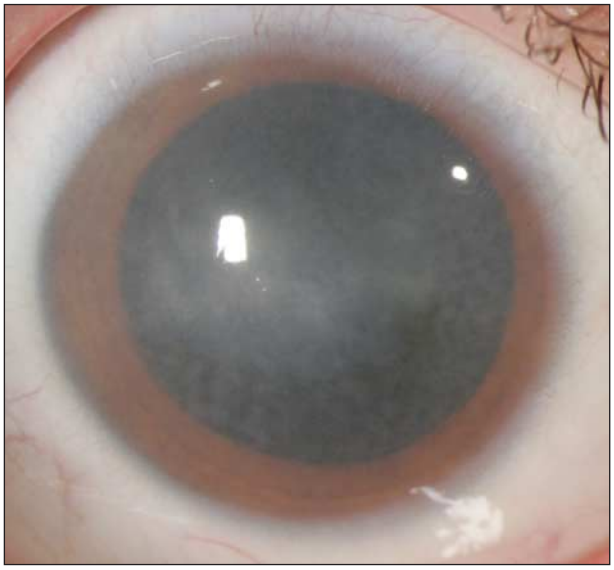

Figure 1. Corneal clouding seen in a patient with mucopolysaccharidosis type I (Hurler syndrome).

cause of the limited ability of the intravenously delivered enzyme to cross the blood-brain barrier.[7] Both ERT and HCT are ineffective in halting or reversing some aspects of MPS disease, such as heart valve disease and dysostosis multiplex in Hurler syndrome (MPS I-H). In addition, despite improvements in the morbidity and mortality of transplantation during the past few decades, HCT continues to be associated with significant risks[3,8,9] and is typically reserved for patients with severe neuronopathic MPS.

Ophthalmologic manifestations of MPS include pseudoexophthalmos with characteristic coarse facies and shallow orbits, ptosis, corneal opacity, glaucoma, papilledema from hydrocephalus or optic nerve compression or infiltration, optic atrophy, and retinopathy.[10] Histopathologic studies have documented progressive GAG accumulation in various ocular structures including the conjunctiva, cornea, iris, lens, and sclera.[11] Unfortunately, visual disability is common despite systemic and local management, including refractive correction and amblyopia treatment.[3]

Corneal clouding is a common cause of visual disability in MPS I, Morquio (MPS IV), and Maroteaux-Lamy (MPS VI) syndromes (**Figure 1**). Without treatment for these conditions, diffuse corneal clouding is typically progressive and is graded from mild (+1) to severe (+4), with corresponding visual disability and marked photosensitivity.[12] The histopathologic factors of corneal clouding in MPS I are related to the accumulation of GAGs in vacuolated stromal cells and abnormal arrangement, spacing, and size of collagen fibrils.[3,13-18] A normal cornea contains 4% mucopolysaccharides, of which 50% is keratan sulfate, 25% is chondroitin sulfate, and 25% is chondrointin-4-sulfate.[19] Intracorneal dermatan sulfate is found in healed corneal wounds, rejected grafts, and postviral opacification.[20] Using transmission electron microscopy, Quantock et al[16] and Rummelt et al[18] studied the architecture of corneas from an adult with Scheie syndrome (MPS I-S) and found an increased amount of sulfated GAG in all layers of the cornea. In addition to the increased GAG deposition of MPS in humans, abnormalities in collagen fibril size and packing were seen in the eyes of patients with MPS I and MPS VI, but not in those with MPS III.[15,17] Abnormal collagen fibrils of various length, size, and shape increase in the index of refraction and decreased corneal clarity. Increased corneal opacity, increased corneal thickness, and increased intraocular pressure tend to occur simultaneously.[21] Various studies have documented minimal improvement in corneal haze with systemic ERT and HCT treatment.[3,12,22-24]

Success of PK in this setting has been variable, and reports often have been limited to isolated cases. Corneal graft failure from recurrent GAG deposition has been described as early as 1 year after transplantation.[13,14,25] The series of PKs for MPS reported herein is, to our knowledge, the largest in the literature. We report that stability can be achieved for clear corneal grafts after PK for suitable patients with MPS.

METHODS

A consecutive chart review was done from January 1980 to November 2009 for patients with a diagnosis of MPS I, MPS IV, or MPS VI who underwent corneal transplantation in at least 1 eye at the University of Minnesota Medical Center and had follow-up of at least 1 year after PK.

The following data were collected: ophthalmic and medical history, Snellen best-corrected (spectacle) monocular visual acuity converted to the logMAR equivalent, slitlamp biomicroscopic examination of the anterior segment, and dilated funduscopic examination with indirect ophthalmoscopy. Baseline visual acuity measurements were obtained from the preoperative eye examination. Subsequent comparisons were made 1 year after PK. The end point of visual acuity was chosen to be the last recorded ophthalmologic evaluation at our institution.

We searched the PubMed database using combinations of the following search terms: *mucopolysaccharidosis*, *Hurler syndrome*, *Hunter syndrome*, *Sanfilippo syndrome*, *Morquio syndrome*, *Maroteaux-Lamy syndrome*, *Sly disease*, *MPS*, and *penetrating keratoplasty* or *corneal graft*. We also searched Google Scholar to find case reports in nonindexed journals. Finally, each article's references were reviewed for case reports not available through MEDLINE. Titles and abstracts of the identified English articles were reviewed and retrieved if they described cases of PK performed in patients with MPS. Articles published in languages other than English were accepted if an English abstract with sufficient information was available. Data collected included type of MPS, number of corneas transplanted, success of graft clarity, timing of graft failure, and follow-up duration. We excluded articles that contained insufficient clinical information to identify at least half of the aforementioned variables.

RESULTS

Eight eyes from 5 patients with MPS and a history of PK were identified. One man and 1 woman had MPS I (Hurler syndrome), 2 men had MPS IV (Morquio syndrome), and 1 woman had MPS VI (Maroteaux-Lamy syndrome). The mean age at the time of PK was 26.3 years. Mean follow-up time after PK was 59.9 months (range, 13-132 months) (**Table 1**). The 2 patients with MPS I (eyes 1

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Table 1. PK Patient Data

Patient No./Sex	MPS Type	Eye	Age at PK, y	FU, mo	VA per Snellen, Mean (SD)[a]		Complications	Other Surgical Procedures	Comorbidities
					Pre PK	Last Visit			
1/M	I-H	Right	11.7	13.0	20/80 (0.60)	20/70 (0.56)	. . .	Triple (PCIOL)	Elevated IOP
2/F	I-H	Left	19.2	24.0	20/160 (0.92)	20/50 (0.40)	. . .	. . .	. . .
3/M	IV	Right	52.0	132.0	20/300 (1.16)	20/25 (0.10)	. . .	PRK	Glaucoma
4/M	IV	Left	60.1	31.0	20/400 (1.30)	20/25 (0.10)	. . .	. . .	. . .
5/M	IV	Right	63.3	83.0	NA	20/40 (0.30)	. . .	Triple (PCIOL)	. . .
6/M	IV	Left	65.3	59.0	20/400 (1.30)	20/50 (0.40)	. . .	Triple (ACIOL)	. . .
7/F	VI	Right	24.4	91.0	20/40 (0.30)	20/50 (0.40)	Rejection	. . .	ON edema
8/F	VI	Left	28.2	46.0	20/100 (0.70)	20/40 (0.30)	Rejection	Repeat PK	. . .
Mean (SD)	. . .	. . .	26.3 (2.65)	59.9 (40.03)	20/150 (0.90) [0.38]	20/42 (0.32) [0.16]	. . .	. . .	. . .

Abbreviations: ACIOL, anterior chamber intraocular lens; FU, follow-up; I-H, Hurler syndrome; IOP, intraocular pressure; MPS, mucopolysaccharidosis; NA, not applicable; ON, optic nerve; PCIOL, posterior chamber intraocular lens; PK, penetrating keratoplasty; PRK, photorefractive keratectomy; SD, standard deviation; VA, visual acuity.

[a] Reported as logMAR.

and 2) had undergone successful HCT with bone marrow transplantation (engraftment 100%) 10 and 16 years before their PK, respectively, at the time of their corneal transplantation.

The mean (SD) visual acuity before PK was 0.90 (0.38) logMAR. Data from a 1-year follow-up visit were available in 4 of 8 eyes and, in these, the mean (SD) best corrected visual acuity at the 1-year examination was 0.56 (0.13) logMAR. The mean (SD) best corrected visual acuity at the last visit for all 8 eyes was 0.32 (0.16) logMAR. Visual acuity improved in 7 of 8 eyes ($P = .002$). All transplanted corneal grafts were clear at the last follow-up examination. No clearing of the surrounding host cornea was identified. Three of 8 eyes had cataract extraction and intraocular lens placement at the time of PK. One eye in a patient with MPS IV (eye 3) underwent photorefractive keratectomy 10 years after PK for severe anisometropia. There were no other ocular comorbidities.

Two of the 8 eyes (eyes 7 and 8) presented signs of graft rejection during the follow-up visits, both in the patient with MPS VI. The initial signs of endothelial rejection were noted 4 and 5 months after PK in the left and right eyes, respectively. The patient's therapy for both eyes was systemic and topical corticosteroids. The left eye (eye 8) developed recurrent episodes of rejection that were resistant to treatment, and a second PK was required 3 years after the original procedure. The second graft has remained clear in the follow-up period.

Our literature review found 23 reports documenting 40 initial and 3 repeat cases of PK in the setting of MPS (**Table 2**). Of these, 31 initial and 2 repeat corneal grafts were reportedly clear during follow-up, ranging from 0.25 to 12 years. Although patient details were occasionally incomplete, most PK procedures were done for patients with MPS I-HS, MPS I-S, or MPS VI.

COMMENT

To our knowledge, this study is the largest series of PKs for individuals with MPS. Stable, clear corneal grafts with improvement in vision were obtained for each of the represented MPS disorders (MPS I-H, MPS IV-Morquio, and MPS IV-Maroteaux-Lamy syndromes) (**Figure 2**). Limitations of this single-institution, retrospective study include the limited size and the varying periods of follow-up. In addition, 3 patients underwent cataract removal and intraocular lens implantation at the time of corneal grafting. Finally, it is possible that these patients with MPS were originally selected for corneal transplantation due to having rather few or mild systemic, neurologic, and even ocular comorbidities, including retinopathy. Although such factors might have affected the postoperative visual acuity, the primary measure of the study reported here and the literature review was corneal graft clarity.

To determine how our experience compares with that of others, the literature for all reported PKs for corneal clouding associated with MPS was reviewed. Since a literature summary for this rare condition had not been previously performed, we believed it was important to include all pertinent cases and references. We recognize that some of the references described transplantation performed in the era prior to modern microsurgical and preservation techniques. Further details regarding this review are summarized with respect to each of the MPS disorders characterized by significant corneal opacity.

MUCOPOLYSACCHARIDOSIS TYPE I

Mucopolysaccharidosis type I was first described by Gertrude Hurler[44] in 1919. Mucopolysaccharidosis type I is a recessive condition associated with α-L- iduronidase deficiency; this lysosomal enzyme cleaves the terminal α-L-iduronic acid residue in the GAGs heparan sulfate and dermatan sulfate.[24] Clinically, MPS I represents a phenotypic continuum of severity, but for historical reasons remains separated into 3 phenotypes: Hurler syndrome (severe form, MPS I-H), Hurler-Scheie syndrome (intermediate form, MPS I-HS), and Scheie syndrome (attenuated form, MPS I-S).[28] Systemic features of MPS I include skeletal, visceral, cardiac, respiratory, and central nervous system disease. Ophthalmic findings of MPS

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Table 2. Reports of PK for MPS

Source	MPS Type	No. of PK (No. of Patients)	Age, y	Outcome	Reported Follow-up, y
McKusick,[26] 1966	I-H or I-HS	2 (1)[a]	NA	1 Failed, 1 Clear-lamellar	. . .
Ashworth et al,[27] 2006	I-HS	2 (1)	NA	Clear	3, 6
Orgül et al,[28] 1991	I-HS	2 (1)	14	Partial clearing	. . .
Rosen et al,[29] 1968	I-HS or I-S	2	10, 13	Clear	2, 3
Vajpayee et al,[30] 2007	I-HS or I-S	2[a]	NA	Clear	0.5
Gollance and D'Amico,[31] 1967	I-HS or I-S	2	NA	Failed	0.5
		1 repeat PK	NA	Clear	5
Edmison et al,[32] 1972	I-S	2	22	Clear	2.5
Lahdensuu,[33] 1943	I-S	2 (1)	NA	Failed	. . .
Scheie et al,[34] 1962	I-S	1	NA	Failed	. . .
Pitz et al,[22] 2007	I-S[b]	5 (3)[a]	NA	Clear	2 – 12
Käsmann-Kellner et al,[35] 1999	IV	1	12	Failed	1
Maumenee,[36] 1978	IV	1	NA	Failed	"Early"
Iwamoto et al,[37] 1990	IV	1	NA	Failed	"Early"
Schwartz et al,[13] 1985-1986	VI	2	18, 21	Clear	1
	VI	1 repeat PK	NA	Failed	1
		1 repeat PK	NA	Clear	
Naumann and Rummelt,[38] 1993	VI	3 (2)	7, 11	Clear	2.5, 5
Uçakhan et al,[39] 2001	VI[c]	2	17	Clear	13
Varssano et al,[14] 1997	VI	1	7	Clear	0.25
Ashworth et al,[27] 2006	VI	1	NA	Clear	5
Rosen et al,[40] 1972	VI	1	10	Clear	5
Bergwerk et al,[41] 2000	VII	1	15	Clear	2
Gullingsrud et al,[3] 1998	Unknown[c]	2 (1)	NA	Clear	0.7, 1.5
Cowden,[42] 1990	Unknown	1	NA	Cleat	1
Higaki et al,[43] 2008	Unknown	1[a]	21	Clear	7.5

Abbreviations: I-H, Hurler syndrome; I-HS, Hurler-Scheie syndrome; I-S, Scheie syndrome; MPS, mucopolysaccharidosis; NA, not available; PK, penetrating keratoplasty.
[a] Lamellar keratoplasty.
[b] After enzyme replacement therapy.
[c] After bone marrow transplant.

I include corneal clouding, cataracts, glaucoma, retinal dystrophy, nystagmus, strabismus, optic atrophy, and optic disc swelling resulting from hydrocephalus and/or sclera or optic nerve thickening.[3,6,8,28]

Systemic ERT with recombinant α-L-iduronidase deficiency has been shown to reduce hepatosplenomegaly and improve sleep apnea, joint mobility, and cardiac function in mild and attenuated forms of MPS I.[45,46] After ERT, photophobia and conjunctival irritation diminish, but corneal clouding and other ocular complications usually do not improve.[22-24,45]

Hematopoietic cell transplantation improves many of the severe visceral sequelae of MPS I.[4,5,47-51] However, the effect of transplantation on the ocular complications, including clearing of corneal opacity, are variable.[3,12] Vellodi et al[52] described 2 patients with Hurler syndrome who showed complete resolution of corneal clouding after HCT when evaluated using unaided visual examination. Fahnehjelm et al[53] showed a reduction in corneal clouding without improvement in vision after HCT in 4 children with Hurler syndrome. Other investigators[3,12] described improvement in corneal clarity in 30% of patients with MPS I after HCT, whereas corneal clarity declined in 25% and was unchanged in the remaining patients. Of note, Aguirre et al[54] found no improvement in an opacified MPS corneal graft transplanted into a healthy feline. This suggests that once mechanical disruption to keratocyte structure occurs, opacification might not resolve, despite the local presence of α-L-iduronidase deficiency and reduction in corneal GAG deposition.

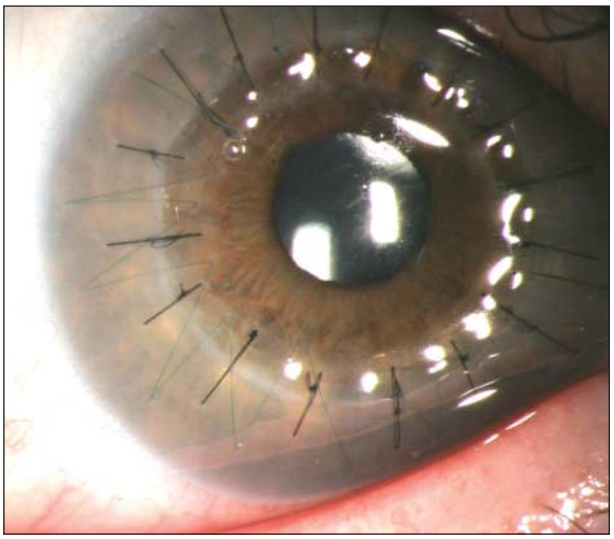

Figure 2. Clear corneal graft in a patient with mucopolysaccharidosis type I (Hurler syndrome).

There is a paucity of literature on the success of PK for MPS I. Most reported cases involved adults with MPS

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I-S; well-documented case reports on the success of corneal transplantation in MPS I-H are rare (Table 2).[26-28,55] Pitz et al[55] described 3 adults with MPS I-S and bilaterally clear corneal grafts (including 1 lamellar graft) while the patient was receiving ERT; follow-up ranged from 1 to 12 years. Rosen et al[29] described clear corneal grafts in 2 patients with MPS I: 1 with MPS I-H and 1 with MPS I-S. Lahdensuu[33] reported failed bilateral transplants in 1 patient with MPS I-S.

Our results in 2 eyes of patients with MPS I who had undergone bone marrow transplantation suggest that PK can be as successful in MPS I-H as has been described for MPS I-HS and MPS I-S. Pharmacologic therapy that accompanies recent bone marrow transplantation might lower the risk of corneal graft rejection; however, this was not a factor because these 2 patients underwent bone marrow transplantation several years before their PK. No evidence of opacification of the donor graft has been identified in the follow-up period.

MUCOPOLYSACCHARIDOSIS TYPE II

Mucopolysaccharidosis type II (Hunter syndrome), caused by genetic deficiency of iduronate-2-sulfatase, was the first MPS disorder described.[56] It is the only MPS with X-linked recessive inheritance. Although elevated GAGs (dermatan sulfate and heparan sulfate) are present, corneal clouding is not a typical finding in X-linked Hunter syndrome. Older patients with Hunter syndrome may have subtle stromal haze shown on examination with slitlamp biomicroscopy.[57]

MUCOPOLYSACCHARIDOSIS TYPE III

Patients with MPS III (Sanfilippo syndrome) have severe neurologic impairment due to accumulation of heparan sulfate but, remarkably, have only faint corneal haze shown on slitlamp examination.[57,58] To date, there are no reported cases documenting the necessity or success of PK for MPS III.

MUCOPOLYSACCHARIDOSIS TYPE IV

Mucopolysaccharidosis type IV-A (Morquio type A syndrome) is the more severe form of this disorder. It is caused by a deficiency of *N*-acetyl-galactosamine-6-sulfatase.[59,60] A milder form and later onset of disease is seen with MPS IV-B (Morquio type B syndrome), which is caused by a deficiency in β-galactosidase activity, leading to an accumulation of keratan sulfate. A patient's hearing is impaired and intelligence is near normal. Ophthalmic manifestations most notable in Morquio type A syndrome include corneal haze, glaucoma, retinal changes (dark-adapted electroretinography abnormalities), optic nerve atrophy, and, rarely, papilledema.[35]

There are 3 reports[35-37] on PK documenting recurrent opacification of the cornea. In contrast, our study of 4 eyes in 2 patients with Morquio type A syndrome suggests that corneal grafting can be successful in this condition. Our patients with Morquio type A syndrome have maintained excellent corneal clarity and vision, without recurrence or rejection, for up to 10 years.

MUCOPOLYSACCHARIDOSIS TYPE VI

Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) is caused by deficiency of *N*-acetyl-galactosamine-4-sulfatase.[61] Phenotypic characteristics include growth retardation, skeletal deformity, coarse facies, normal intelligence, and marked corneal opacity related to dermatan sulfate accumulation.

Corneal clouding is a prominent feature of MPS VI[62] and, importantly, does not seem to be influenced by ERT. Pitz et al[55] described little change in corneal clarity or vision during 3½ years of ERT in a 21-year-old patient. As mentioned earlier for MPS I, this is likely due to the abnormalities in keratocyte shape as well as collagen fibril size and packing.[17,63] Other ultrastructural findings described in MPS VI eyes include thickening of the corneal periphery, lamellated material in keratocytes and endothelial cells, and thinning of the Descemet membrane with excrescences.[64-67]

Mixed success has been reported in the use of PK for MPS VI. Schwartz et al[13] described prompt reopacification in 2 eyes of 2 patients and suggested a poorer graft prognosis in patients with this disorder. On retransplant, GAG deposits in the opacificied graft were concentrated anteriorly.[13] Other investigators, including Ashworth et al[27] and Uçakhan et al,[39] described a clear corneal graft in single cases at 5 years and 13 years post-corneal transplant, respectively. Furthermore, Naumann and Rummelt[38] and Naumann[68] reported on 3 successful PKs for MPS VI in children aged 7 to 11 years and obtained long-term graft stability 2½ to 5 years after the procedure. Remarkably, these reports describe partial clearing of the host cornea adjacent to the donor button.

Our report of achieving long-term bilaterally clear grafts in a patient with MPS VI supports the successful findings in these case reports. However, these 2 eyes were the only ones in our series with rejection, 1 of which resulted in graft failure and need for repeat PK. Considering this and the cases previously described, MPS VI corneal grafts may have a higher risk of rejection than grafts for other MPS conditions.

MUCOPOLYSACCHARIDOSIS TYPE VII

Mucopolysaccharidosis type VII (Sly disease), first described in 1973, is a rare MPS disorder caused by deficiency in β-glucuronidase and accumulation of dermatan sulfate and heparan sulfate.[41,64] The clinical phenotype is similar to that of MPS I, with small stature, dysmorphism, hepatosplenomegaly, inguinal hernias, and mental retardation. Enzyme replacement therapy in MPS VII mice has shown systemic benefit in GAG clearance but no favorable corneal changes.[69-71] We identified a single case report of PK in which a 2-year-old graft in a 15-year-old patient remained clear.[41]

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CONCLUSION

Corneal opacification remains a common cause of visual disability in MPS, despite advances in HCT and ERT. In this review, we have summarized both our experience and reports in the literature regarding the use of PK for MPS. We conclude that PK is often a beneficial intervention in the appropriate patient with corneal opacification resulting from MPS I, MPS IV, or MPS VI. Because endothelial function is not thought to be impaired, advances in keratoplasty techniques, such as anterior and deep anterior lamellar keratoplasty,[61] may further improve outcomes and reduce the frequency of rejection in these patients. For instance, Vajpayee et al[30] described excellent visual acuity outcome using anterior lamellar keratoplasty for a patient with MPS. Larger, collaborative studies for these rare, varied disorders will prove important in determining factors that affect the optimal outcomes in these complex patients.

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Correspondence: Erick D. Bothun, MD, Department of Ophthalmology, University of Minnesota, Mail Code MMC 493, 420 Delaware St SE, Minneapolis, MN 55455-5501 (bothu003@umn.edu).
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