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CASE REPORT PEER REVIEWED | OPEN ACCESS

Bilateral penetrating keratoplasty revealed advanced glaucoma in a case of mucopolysaccharidosis type VI

Christoph Spartalis, Simon Dulz, Yevgeniya Atiskova

ABSTRACT

Introduction: We report a case of a patient with mucopolysaccharidosis (MPS) type VI disease who underwent bilateral penetrating keratoplasty. The insight into deeper ocular structures after successful keratoplasty enabled the diagnosis of glaucoma.

Case Report: A 24-year-old male patient with genetically confirmed MPS VI disease was referred for ophthalmological co-assessment to our Department of Ophthalmology. The patient presented with low visual acuity of 6/200 in both eyes, and increased corneal thickness. The bilateral intraocular pressure was difficult to evaluate in association with the corneal thickness and rigidity. Due to total corneal opacification bilateral penetrating keratoplasty was performed. The successful keratoplasty allowed proper funduscopy and further diagnostic measurements leading to the diagnosis of advanced glaucoma.

Conclusion: Although MPS VI is an orphan disease, intravenously applied enzyme replacement therapy with galsulfase has been established as a successful treatment. However, systemically administered therapy with galsulfase does not reduce or affect ocular symptoms and manifestations. The case demonstrates the high impact of early and regularly ophthalmic co-assessment in MPS VI patients, especially keeping in mind that not only corneal involvement can be present in MPS patients. Furthermore, preservation of visual acuity is of high importance for participating in social and professional life.

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INTRODUCTION

Mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux-Lamy syndrome, is a rare, autosomal recessive inherited lysosomal storage disorder. Its prevalence at birth ranges from 1 in 43,261 to 1 in 1,505,160 live births [1]. A deficiency of N-acetylgalactosamine-4-sulfatase leads to a consecutive accumulation of dermatan sulfate and chondroitin-4-sulfate in several tissues, causing a multisystemic, complex disease [2].

In addition to characteristic manifestations, such as skeletal dysplasia, growth failure, facial dysmorphism, valvulopathies, reduced pulmonary function, hepatosplenomegaly, hearing loss, sleep apnea, or carpal tunnel disease, corneal clouding, glaucoma, and optic nerve atrophy are related to ocular symptoms [3, 4].

Although MPS VI is an orphan disease [5], intravenously applied enzyme replacement therapy (ERT) with galsulfase has been established for MPS VI patients [6, 7]. Systemically administered therapy with galsulfase, however, does not reduce or affect ocular symptoms and manifestations, which is believed to be due to the retina-brain barrier and the avascular corneal tissue [8].

Here, we report a case of a 24-year-old male patient with genetically confirmed MPS VI disease who underwent

bilateral penetrating keratoplasty due to total corneal opacity. The insight into deeper ocular structures after successful keratoplasty revealed advanced glaucoma. This case indicates the difficulties when glaucoma and anterior segment disease collide.

CASE REPORT

In 2016, the Department of Pediatrics referred a 24-year-old male patient with genetically confirmed MPS VI (ARSB gene mutation, p.R327X homozygote) diagnosed in 2004 for ophthalmological co-assessment to our Department of Ophthalmology. The patient had a long and complex past medical history. Importantly, he suffered from tracheal stenosis, associated with tracheal granulomas, which led to a tracheostomy in 2005. In the same year, the patient received a ventriculoperitoneal shunt due to hydrocephalus. Furthermore, he suffered from neurogenic bladder and bowel disorder along with chronic progressive myelopathy and spastic tetraparesis. Moreover, multiple orthopedic surgeries, e.g., decompression of C1 due to cervical spinal canal stenosis, were performed. Since 2006, the patient was treated with systemic ERT galsulfase.

From an ophthalmologic point of view, the patient presented in 2016 with low visual acuity of 6/200 in both eyes (OU), and the intraocular pressures (IOPs) were 20 mmHg in the right eye (OD) and 21 mmHg in the left eye (OS), without IOP-lowering medication. The IOP was evaluated by using a Goldmann applanation tonometer. However, the validity of the measured IOP values was limited due to highly elevated corneal thickness. Slit lamp examination showed an irritation-free conjunctiva and advanced corneal opacification of the stromal layer, classified as grade III according to Del Longo et al. (2018), and blurry visibility of the iris. Further details were not visible and thus gonioscopy was not performed to evaluate angle abnormalities (Figure 1A and B). A proper fundoscopy was not possible due to total corneal clouding. Anterior segment optical coherence tomography (AS-OCT) (Figure 1C and D) showed an elevated central corneal thickness of 1189 µm (OD) and 1193 µm (OS) as well as a narrow angle configuration. To exclude pathological findings, e.g., retinal detachment, sonography was performed. An attached retina and optical free vitreous were observed (Figure 2A and B). Further diagnostics such as an electroretinogram or visually evoked potential measurements were not performed. After a fully informed discussion with the patient and his parents, we decided to perform bilateral (OS > OD) penetrating keratoplasty in order to achieve visual improvement.

We performed OS penetrating keratoplasty in 2018. Postoperative visual acuity improved to 20/400, and the transplant was clear with only some folds in the Descemet layer (Figure 3B). Postoperative medications included topical prednisolone 1% and systemic corticosteroids, topical antibiotics, and artificial tears. Prednisolone 1% eye drops were used for 12 months. Seven months after corneal transplantation visual acuity increased to 20/125 and IOP was not elevated at this time point, but measurements were difficult due to modified corneal surface and rigidity. Fundoscopy showed an attached retina and a cup-disc ratio of 0.4 of the optic nerve.

After an improved vision on OS, penetrating keratoplasty of the contralateral eye (OD) was performed, combined with suture removal of the left eye in 2019 (Figure 3A and B). Postoperative aftercare revealed an elevated IOP of OD 31 mmHg and low visual acuity of 20/4000, despite regular postoperative findings and a clear transplant four weeks after surgery. Meanwhile, OS visual acuity increased to 20/50.

Inpatient IOP analysis over 48 hours showed an IOP between OD 34–45 mmHg and OS 17–21 mmHg, two (OD) and 12 (OS) months after keratoplasty (Figure 4). Also, the IOP of the left eye was elevated to 25 mmHg 11 months after keratoplasty. Hence, not only postoperative IOP increased due to keratoplasty, but also glaucoma was suspected. At this time, feasible fundoscopy through the clear transplant showed advanced excavation of the optic disc with a cup-disc ratio of 1.0 in OD and 0.4 in OS (Figure 5A and B). Optical coherence tomography revealed a decreased retinal nerve fiber layer (RNFL) thickness, which supports the suspected glaucoma diagnosis, but due to decreased insight, measurements were not fully reliable. The decrease was more pronounced in OD, detailed numbers in microns are given in the figure for 12 sections in each eye (Figure 5C and D). Also, the observed narrow angle configuration in AS-OCT (Figure 1C and D) underpinned our suspicion. Perimetry was not performed due to the patient's poor cooperation. Ultimately, it should be considered whether glaucoma is a primary feature of MPS VI disease or secondary to the corneal surgery. Acknowledging that both eyes were affected and OD was in an advanced stage of disease only weeks after keratoplasty was performed, we assumed a long genesis related to MPS VI disease. Independently of the cause, we started IOP-lowering therapy with topical medication (OU bimatoprost and timolol), but IOP could not be controlled. Of note, the patient reacted with massive arterial hypotonia to orally applied acetazolamide, which was given once, when IOP reached 45 mmHg.

As a result of uncontrolled IOP under topical IOP-lowering medication, we decided to perform transscleral cyclophotocoagulation (CPC) OU to reduce IOP. Three sessions of CPC on OD were necessary to reach tolerable IOP levels under 20 mmHg; however, OD IOP continued to fluctuate (Figure 4). The latest IOP measurements in June 2020 in our department showed satisfying IOP values for both eyes (OD, 15 mmHg; OS, 7 mmHg) under topical IOP-lowering therapy with OD dorzolamide, brimonidine, and bimatoprost and OS bimatoprost (Figure 5). Topical therapy OS was discontinued. Visual acuity was 20/10,000 on OD and 20/50 on OS at last visit. Of note prednisolone 1% eye drops were used for 10 months postoperative in the right eye.

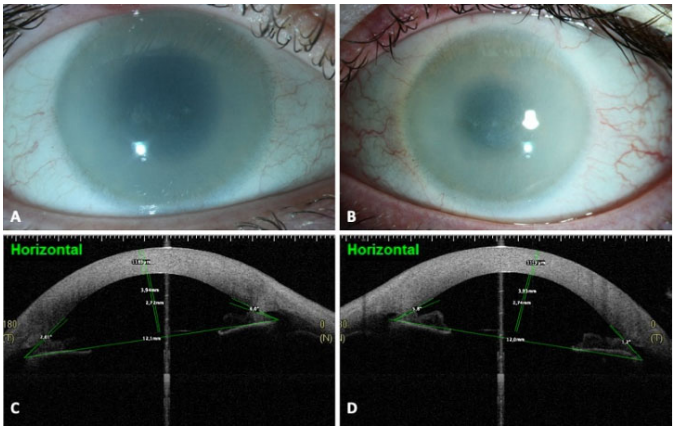

Figure 1: Anterior segment photographs of (A) OD and (B) OS showing corneal opacification before keratoplasty was performed. Horizontal anterior segment optical coherence tomography of (C) OD and (D) OS showing high density cornel stroma, corneal thickening and a narrow angle configuration. Measurements indicating central corneal thickness (CCT) (1189 µm OD, 1193 µm OS), angle to angle distance (ATA) (12.1 mm OD, 12.0 mm OS), anterior chamber depth (ACD) (2.72 mm OD, 2.74 mm OS) and the angle in degrees (2.01° and 6.0° OD, 5.8° and 1.2° OS).

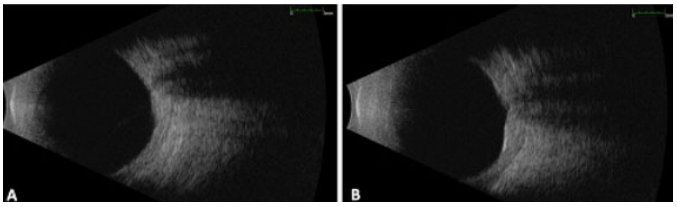

Figure 2: Sonography of the (A) OD and (B) OS showing attached retina and irritation free vitreous.

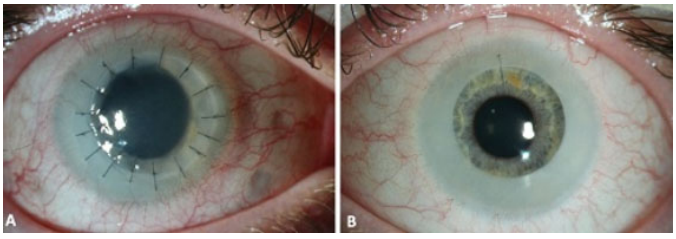

Figure 3: Anterior segment photographs of (A) OD and (B) OS after keratoplasty was performed. (A) Corneal graft with suture six months after keratoplasty. (B) OS with corneal graft 4.5 months after corneal transplantation with only one suture left for correction of astigmatism; host cornea continues to show opacification in both eyes.

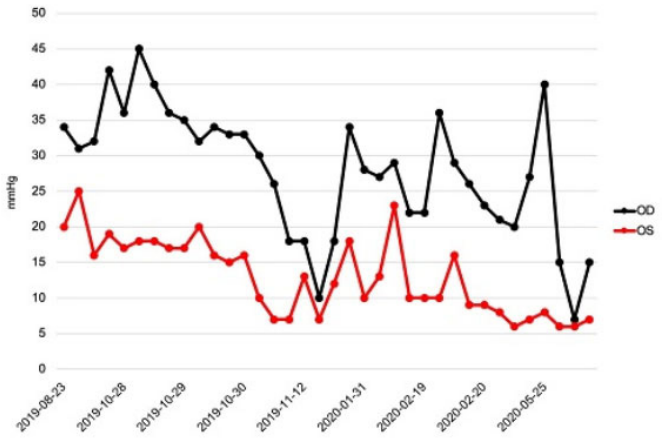

Figure 4: IOP diagram showing IOP in mmHg over a time period of 10 months. Both eyes showed IOP elevation at some time points. IOP in the right eye (OD) was higher increased than in the left eye (OS).

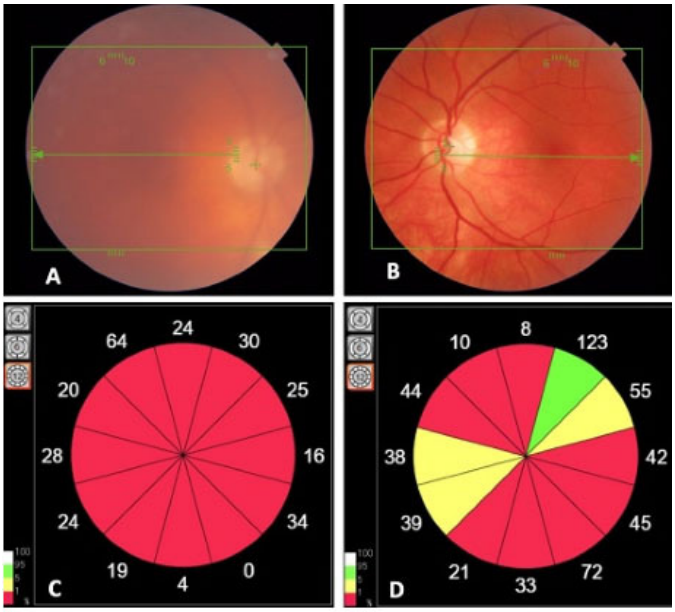

Figure 5: Fundus photography of (A) OD and (B) OS showing optic discs; (A) reduced quality due to reduced insight. Optical coherence tomography retinal nerve fiber layer of (C) OD and (D) OS showing bilateral decreased nerve fiber layer.

Unfortunately, the different operative procedures, including penetrating keratoplasty and multiple transscleral CPC, have led to severe ocular surface disease. The patient currently suffers from severe symptoms of dry eye, wears safety goggles to protect the eyes from wind and applies artificial tears (hyaluronic acid) every 2 hours and ointment (hyaluronic acid + vitamin A) at night to manage his symptoms. Despite this, the patient does not regret his choice for keratoplasty and is happy with the improved visual outcome. Moreover, the visual outcome allows the patient a regulated, monitor-related professional life and even more importantly, his social connection improved.

DISCUSSION

Mucopolysaccharidosis type VI is a severe multisystemic disorder and may affect different types of tissue due to the accumulation of dermatan sulfate and chondroitin-4-sulfate. Besides severe systemic symptoms, including skeletal dysplasia, cardiac valve disease, reduced

pulmonary function, hepatosplenomegaly, or restriction of joint movement [1], several structures of the eye can also be affected. Quite common is corneal opacification with corneal thickening, such as in the presented case (Figure 1) [8]. Moreover, chronic open-angle glaucoma and optic nerve atrophy have been associated with MPS VI [8–10]. Additionally angle configuration seems to be a relevant factor in evaluating glaucoma and IOP especially in MPS VI compared to other subtypes [11]. Some findings, such as scleral deposits of glycosaminoglycans, have only been described in individual cases, but might occur more often in the future due to increased life expectancy [12]. In contrast to other forms of MPS (MPS I, MPS III, MPS IV), retinopathy has not been described in MPS VI. It is also highly relevant that patients with MPS VI do not suffer from behavioral or intellectual impairment [10].

The detection and management of glaucoma is especially challenging for following reasons: increased corneal thickness and hysteresis impede the evaluation of IOP measurement [13, 14]; and corneal opacification inhibits proper fundoscopy, and therefore, evaluation of the optic disc, as well as supportive technical diagnostic facilities [e.g., OCT or Heidelberg Retina Tomography (HRT)] are difficult to perform. These features result in late diagnosis finding, advanced disease stages, therapy delay, and vision loss in patients.

The described case represents all these issues. Our patient was referred quite late for ophthalmologic co-assessment, and thus, keratoplasty, which ultimately revealed untreated glaucoma, was performed late. Likewise, corneal thickness and corneal clouding made supporting OCT or HRT measurements impossible to perform, and thus delayed the diagnosis. A retrospective study in 2017 by Ohden et al. showed that visual outcomes in patients with MPS VI who underwent keratoplasty can be improved in the majority [15]. Therefore, it is justifiable to recommend this procedure for those patients. Nevertheless, it is essential to explain to the patient that visual acuity may not increase due to other preoperative unknown ophthalmologic findings, e.g., glaucoma. However, keratoplasty can improve vision and contribute to the early detection and treatment of ophthalmologic diseases of the posterior segment. Despite the possibility of improved vision, keratoplasty is a single-case decision which precisely weighs its risks and benefits. It is important to keep in mind that the systemic conditions of our patients might become relevant or pose a risk for general anesthesia.

Our case illustrates several difficulties in patients with anterior and posterior ophthalmological issues and indicates that early ophthalmologic co-assessment is crucial in MPS. Early ophthalmological assessment may capture early disease stages with slight corneal clouding (classification of Del Longo et al. [9]) and allow a feasible examination of the posterior eye segment, including fundoscopy and technical diagnostics. This possibly allows the assignment of visual deterioration to glaucoma or risk for corneal opacity, and therefore, adequate initiation of therapy. Early and regular ophthalmological follow-up examinations could prevent patients from blindness due to glaucoma, which is already challenging to manage in MPS VI patients. Since ERT is currently recommended as the first-line therapy for MPS VI and life expectancy may increase, these considerations may become even more relevant.

Enzyme replacement therapy, however, does not address ophthalmologic issues [16]. To date, there has been no causative treatment option for the ocular involvement in MPS VI. Therefore, early diagnosis and efficient symptomatic therapy is determinative for vision and quality of life in MPS VI patients.

CONCLUSION

As patients diagnosed with MPS VI frequently suffer from severe life-threatening systemic symptoms, the eye may quickly fade into the background. However, our case clearly demonstrates the high impact of early and regularly ophthalmic co-assessment, especially keeping in mind that one's social and professional life is highly dependent on tolerable vision. Early ophthalmological investigation can enable proper investigation of the anterior and posterior segment of the eye, contribute to early treatment of glaucoma, dry eye disease, and detailed tracking of vision and corneal clouding. The presented case showed a benefit from bilateral perforating keratoplasty. It should be highlighted that the patient may have retained unilateral visual function because penetrating keratoplasty allowed the diagnosis of glaucoma of the OD and protected the OS, through appropriate IOP-lowering management, from further disease progress.

Not limited to ophthalmologists, the presented case underlines the difficulties when anterior segment disease and glaucoma collide.

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Author Contributions

Christoph Spartalis – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Simon Dulz – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yevgeniya Atiskova – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.