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Case Report

Implication of Corneal Refractive Surgery in Duchenne Muscular Dystrophy

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Keywords
Duchenne muscular dystrophy · Muscular dystrophy · Cataracts · Laser-assisted in situ keratomileuses · Photorefractive keratectomy · Small incision lenticule extraction

Abstract
Duchenne muscular dystrophy (DMD) is an X-linked disorder due to a dystrophin mutation and is the leading cause of muscular dystrophy. DMD presents with characteristic systemic effects, including severe muscular atrophy, cardiomyopathy, and ocular manifestations. Performing corneal refractive surgeries in patients with DMD raises concerns regarding patient positioning, risk of cataracts, and other comorbid conditions. Published reports of photorefractive keratectomy, laser-assisted in situ keratomileuses, and small incision lenticule extraction are lacking in this population. Here, we discuss a patient being evaluated for a corneal refractive surgery. This article also discusses the current understanding of DMD, known ocular manifestations, and factors to consider when evaluating a patient for potential corrective vision laser surgery.

Introduction

Duchenne muscular dystrophy (DMD) is the most common cause of muscular dystrophy [1]. A patient with this condition may seek an evaluation for corrective refractive surgery. Although there is a plethora of literature on DMD, only one article mentions a corneal

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procedure (collagen-crosslinking) on a patient with DMD [2]. No published literature discusses photorefractive keratectomy (PRK), laser-assisted in situ keratomileuses (LASIK), and small incision lenticule extraction (SMILE) in these patients. We report a patient with DMD who presented for vision-correcting surgery. This article also examines our current understanding of DMD, particularly assessing known ocular manifestations and considerations when evaluating affected individuals for vision corrective surgery. The data and results of this paper are based on previously conducted studies and do not contain any formal studies with any animal or human participants performed by the authors. However, a patient with DMD was previously evaluated for LASIK by one of the authors.

DMD is an X-linked recessive disorder caused by mutations of the *Xp21* gene (MIM 300377, Xp21.2-p21.1), one of the largest genes in the human genome [1]. Mutations of this gene lead to either deficient or defective synthesis of the dystrophin protein [1]. In unaffected individuals, the dystrophin protein is located in the muscle fiber plasma membrane [1, 3]. This protein forms a dystrophin-associated complex that stabilizes the sarcolemma plasma membrane. When this complex is absent or reduced, the membrane is prone to tears, allowing for a massive calcium influx, leading to eventual muscle fiber necrosis [1, 4]. Depending on the severity of the phenotype and the genetic differences, patients are classified as DMD or the milder-variant Becker muscular dystrophy (Fig. 1).

Since DMD is X-linked, it has an extensive predilection toward male patients. The worldwide prevalence is approximately 19.8 out of 100,000 male births [5]. Although carrier mutations are the most common cause, approximately one-third of mutations are due to spontaneous mutations [6]. Patients with DMD first show signs of muscular dystrophy around the mean age of three but are diagnosed at the mean age of five (+/− 0.5) years [6]. Females are also affected by DMD, where 8% of carriers manifest symptoms consistent with DMD (e.g., muscle weakness with pathologic confirmation) [7]. Interestingly, females who have been diagnosed with DMD have been found to have skewed X-inactivation, gene translocation, monosomy of the X-chromosome, mutations of both X-chromosomes, or unilateral inheritance of the X-chromosome causing the condition [8]. There are limited studies examining DMD prevalence at a global level, as such prevalence in a specific population has not been identified [9].

Patients typically show a characteristic pattern and progression through the disease. Patients can first show signs of DMD before the age of two, with a delay in reaching motor milestones. At 2 to 6 years of age, the patient has more specific signs for DMD. Patients typically have enlarged calves, and parents report frequent falls. Other notable features reported are difficulty standing, running, jumping, and squatting. At 6 years, patients have a progressive decline in muscle strength, with a necessity to use wheelchairs by the age of nine to 11 years in resource-limited countries and thirteen to 14 years in developed countries. As these patients age, they have characteristic limb weakness, extremity contractures, respiratory weakness, progressive cardiomyopathy, and kyphoscoliosis. Patients with this condition also have a wide variation of intellectual performance, with an average IQ of 85 [10]. Life expectancy has increased with improvements in technology, with an average life expectancy of 25–30 years of age [1, 10, 11].

Case Summary

We present a 21-year-old male with DMD referred for corrective visual evaluation. This patient used a wheelchair due to mobility issues and had concomitant cardiomyopathy, restrictive lung disease, extremity contractures, diabetes, hypertension, and significant kyphoscoliosis. The patient was on prednisone 70 mg 3 times per week. He was also on carvedilol, spironolactone, and lisinopril.

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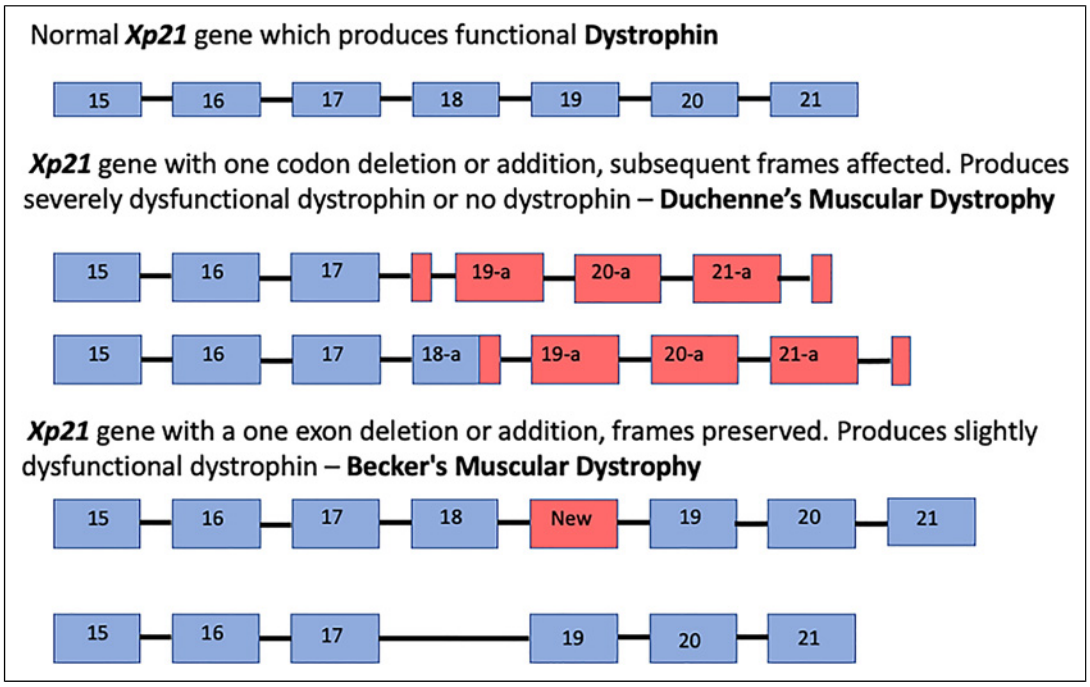

Fig. 1. Removal or addition of an exon caused a mildly affected dystrophin protein. Frameshift mutations lead to severe dystrophin, causing DMD. The blue box represents the unaffected (wild-type) allele, and the red represented the mutated allele.

The patient's right eye was –2.50 D × –1.00 @005, and the cornea was 44.2/43.8 @176. Uncorrected visual acuity was 20/300 (LogMAR 1.176), and best-corrected visual acuity (BCVA) was 20/20–3 (LogMAR 0.06). The patient's left eye was –2.25 D × –1.75 @155 with an uncorrected visual acuity of 20/500 (LogMAR 1.4) and a BCVA of 20/20 –1 (LogMAR 0.02). The cornea was 44.6/42.9 @135. Both pupils were equal, round, and reactive to light and accommodation. In addition, visual fields were found to be full to confrontation bilaterally. These findings are consistent with previous reports of patients with DMD [12].

On slit lamp examination, the patient showed a posterior subcapsular cataract (PSC) of 3 mm × 2 mm on the right eye and 2 mm × 2 mm on the left eye (Fig. 2). These cataracts were attributed to DMD with chronic corticosteroid use. However, the PSC was not dense enough in the central vision to significantly reduce the BCVA but would have likely led to a further decrease in BCVA as time progressed. The patient was also unable to lie supine with his neck in the neutral position, and severe upper extremity contractures limited the ability to position the patient for corrective vision surgery. Given these findings, the patient was not found to be a candidate for visual corrective surgery. Cataract surgery was not advised at the time of consultation. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533579).

Discussion

Studies examining this population's visual acuity, refractive error, and binocular vision allow us to assess an expected ocular phenotype for patients with DMD. In one study examining 21 patients with DMD, Sigesmund et al. [12] found a BCVA ranging from 20/20 to 20/25.

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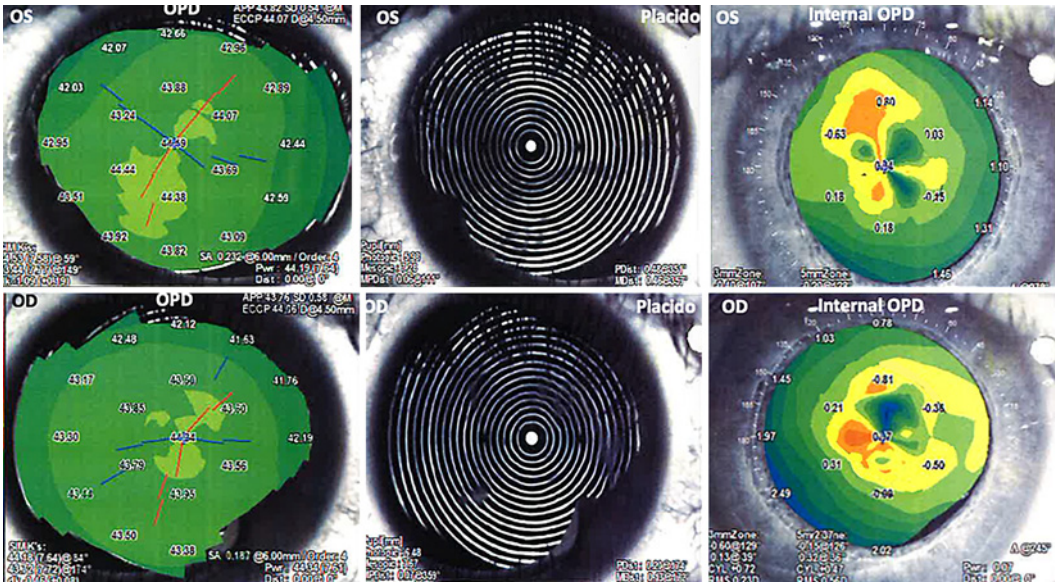

Fig. 2. Examination of OPD, Placido, and internal OPD of the left and right eyes. OPD and Placido show normal uniform corneal topography. Internal OPD shows cloverleaf pattern consistent with PSC (courtesy of Hoopes Vision). OPD is defined as the difference of phase shift between two light waves that are from the same source which are emitted, but one goes through a change in medium, altering the refraction. Ophthalmologists assess OPD to assess corneal topography and internal ocular refraction. OPD, optical path difference.

It should be noted that visual acuity was found to be central and maintained in patients with DMD who could not comply with visual acuity testing due to decreased cognitive ability. Patients' refractive error ranged from −7.75 to 5.00 diopters (D), with astigmatism generally with-the-rule. Astigmatism ranged from +0.25 to +3.00 D. Extraocular muscle testing showed deviations from 0 to 8 D of heterophoria, with some having congenital strabismus. Except for those with congenital strabismus, patients had gross stereopsis.

Patients with DMD are often found with elevated intraocular pressure and PSC [13]. They are placed on long-term glucocorticoid therapy (e.g., deflazacort), as studies have shown a decreased risk of undergoing spinal surgery (p = 0.001) [13]. It was believed that cataracts were due to the long-term glucocorticoid use, as there was a strong association (p = 0.005) [13, 14]. However, animal models have shown that Dp71, one product of the DMD gene, is involved in stopping the progressive opacification of the lens. On further analysis, Fort et al. [15, 16] noted a structural difference in the lens of the affected mice. They were found to have a decreased lens size, disorganization in the fiber cells, and vacuole formation in the lens. These were found in mice at 7 months of age, which correlates to human adulthood. This suggests a genetic component to the development of cataracts. However, as patients who are not on long-term glucocorticoid therapy have a shorter life expectancy, it is difficult to separate whether glucocorticoid use is a contributing factor to the presentation or if genetics alone plays a part in the presentation [15].

The abnormal dystrophin is likely what plays a role in these patient's retinal dysfunction as well. Several isoforms of dystrophin are expressed throughout the retina. These include isoforms such as Dp71, Dp1400, Dp427, and Dp260. Mutations in different dystrophin isoforms result in different pathologies [17]. One such manifestation is the progressive retinal damage seen from dystrophin mutations. The retina may experience increasing hypoxic stressors with age and is much more prone to developing retinal neovascular changes. While there are retinal changes that occur, some patients with DMD may be asymptomatic [17, 18].

Thus, patients with DMD should be evaluated with electroretinography to monitor visual change. Several different dysfunctions have been noted in the photoreceptors of the retina, such as significantly impaired color vision discrimination, particularly with the red-green color [19]. These results indicate that one of the dystrophin isoforms is responsible for a stage in perceiving or interpreting the red-green color spectrum [19]. One such explanation is a mechanical change in the L-cone or M-cone [19, 20]. Examining stimuli in dark-adapted rods also shows a deficit rod system function [21]. Both deficits in the rod-cone system have been linked to a specific dystrophin isoform, Dp260, but more research is required to understand how the isoform affects vision [19–21]. Specific manifestations of these have been evaluated on electroretinography, where patients with DMD have a asymmetry in response to "ON" and "OFF" stimuli. As a result, they have significant alterations in contrast sensitivity [22]. Given the increased risk of neovascularization, patients with DMD also have reports of extensive artery nonperfusion and retinal detachment due to hypoxic triggers [23]. A case of progressive bilateral proliferative retinopathy has also been reported in a patient with DMD who had normal cardiac function [24].

Other ocular findings in patients with DMD are impaired saccadic eye movement. Extraocular muscles were initially considered to be spared in DMD as animal models, histology, and clinical examination did not show any degradation of the extraocular muscles [25, 26]. However, electrooculographic testing has shown that patients with DMD have slower velocity and longer duration in saccadic eye movements, which were significantly pronounced in large eye movements [27].

Iris neovascularization, vitreoretinopathy, and vitreous hemorrhages have also been reported in patients with DMD. These findings are due to the same hypoxic stressors which cause retinal neovascularization [23]. An increase in corneal neovascularization has also been noted in Dp71 mutated mice, suggesting its role as a negative regulator for angiogenesis [28]. The manifestations of the ocular pathologies can be found in Figure 3 and Table 1.

It is important to take specific considerations when evaluating patients with DMD for corrective vision surgeries. As of this time, there is no definitive treatment for DMD. Patients will have progressive deterioration of their muscles and other progressive systemic effects. In this setting, it is important to assess medication history as glucocorticoid use, particularly deflazacort, is associated with reducing the need for major surgeries, and it is expected that patients will present with long-term use [15]. Given a genetic predisposition for developing PSCs, concurrent glucocorticoid use can cause an earlier presentation of these cataracts [13, 15, 16].

These patients must have a thorough retinal examination given the concurrent retinal pathology. Evaluation should include dilated fundal exam, assessment of color vision, electroretinography, and retinal optical coherence tomography. If available, the assessment of extraocular muscle dysfunction can also be performed through either a referral for an electrooculography or a specifically designed virtual reality headset device [29]. However, it should be noted that findings from electroretinography should not be considered a prognostic factor for the development of cataracts in this population [15].

Surgery for these patients also carries other inherent risks. Patients with DMD have cardiac manifestations starting at the age of 10 years. By 18 years of age, all patients with DMD will have a cardiac abnormality, including features of dilated cardiomyopathy, arrhythmias, and steroid-induced hypertension [10]. As such, patients with DMD are expected to have a yearly cardiac evaluation after 10 years of age. Patients also require a respiratory evaluation as effective airway clearance requires manual and mechanical interventions [10]. The combination of cardiac and respiratory dysfunction might affect their ability to stay supine during the procedure. Only one case of a corneal procedure was available on review of published literature. Farooq et al. [2] previously performed a modified collagen-crosslinking while sitting at the slit lamp for a patient with DMD, given the patient's high risk of remaining supine. Although this procedure was able to be modified, as it does not have the same

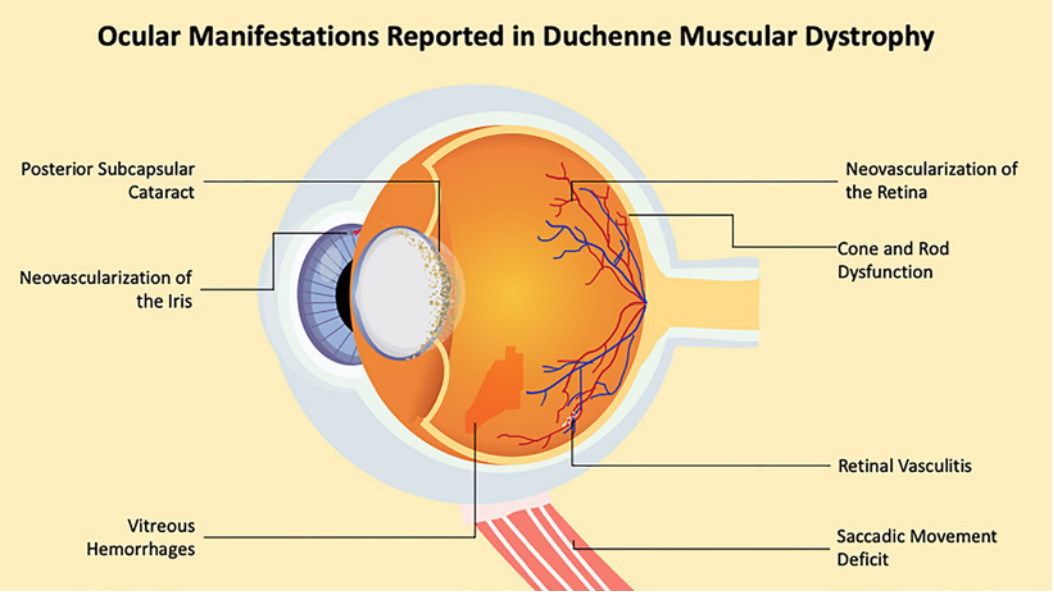

Fig. 3. Ocular manifestations reported by studies for patients with DMD.

Table 1. Examinations and tests to perform in patients with DMD for a thorough ocular examination and the associated findings in documented literature

Examination or test	Possible finding
Visual acuity	
BCVA	Ranges 20/20 to vision loss [12]
Refraction	The cylinder and axis are variable [12]
	Patients generally present with with-the-rule astigmatism [12]
Slit lamp examination	
Cornea	Corneal neovascularization [28]
Iris	Neovascularization [23]
Lens	PSC [15]
Fundoscopy	
Vitreous humor	Hemorrhages [23]
Retinal vessels	Vasculitis [23]
	Neovascularization [23]
Retinal testing	
Electroretinography	Significant amplitude response decrease [27]
Color and contrast sensitivity	Decreased red-green color sensitivity [19]
	Decreased contrast sensitivity [22]

technological barriers, such alterations are not possible for corrective vision procedures. As such, it is recommended that baseline cardiac and respiratory function be assessed prior to the procedure.

Patients in the later stages of this disease often have contractures and scoliosis, making proper positioning for a procedure difficult [10]. Depending on the degree of scoliosis or kyphoscoliosis, various interventions have been utilized in unaffected individuals in cataract surgery. One approach for a patient who could only recline to 40° from the vertical axis utilized a 6 o'clock suture to adjust the eye as needed [30]. However, this technique might lead to undesirable

outcomes in corrective vision procedures. Other adaptations could include pillows or adjusting the table to reverse Trendelenburg upward of 80° to position the patient appropriately. However, this requires more significant consideration of cardiac ability as greater strain is placed on the heart in the setting of increased venous return [31]. Although the beds for cataract surgeries can tilt to various angles, the beds used for corrective vision surgery cannot exhibit the same tilt. Thus, it is crucial to consider these physical limitations of the procedure during evaluation.

Although not the standard for corneal procedures, patients with DMD have adverse effects to anesthetics given their comorbid conditions. Depolarizing and volatile agents are not used in most cases, as they trigger rhabdomyolysis in an already compromised population [32]. If an ophthalmologist considers anesthesia for a procedure, the patient should be evaluated by an anesthesiologist prior to surgery to assess surgical candidacy.

Conclusion

The ocular manifestations of DMD include PSCs, retinitis, and iris neovascularization. There are also associated risks of cardiomyopathy, kyphoscoliosis, and chronic glucocorticoid use that ophthalmologist must consider. To the authors' knowledge, no case reports of PRK, LASIK, or SMILE for patients with DMD have been published. Here, we present on case of a patient being evaluated for corneal refractive surgery. A lack of defined guidelines for DMD makes it challenging to determine if LASIK, PRK, or SMILE can be safely performed in this patient population. Patients should be counseled on the risks and suboptimal surgical outcomes of refractive surgery, especially given their history [33]. In persistent patients with DMD seeking corrective vision surgery, the ophthalmologist and patient should be made aware of the lack of documented outcomes and must have a detailed discussion about the relative risks of refractive surgery in this patient population.

Statement of Ethics

This publication was approved by the Hoopes Vision Privacy and Ethics Board on August 04, 2023. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Majid Moshirfar, MD contributed to the perspective conception. Neil Kelkar, BS wrote the first draft of the manuscript. Yasmyne Ronquillo, MD and Phillip C. Hoopes, MD contributed to revisions. Medical writing/editorial assistance: special thanks to Yasmyne Ronquillo, MD for her assistance in editing.

Data Availability Statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study. Further inquiries can be directed to the corresponding author.

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