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COMMENTARY

Charcot–Marie–Tooth Disease and Implications on Corneal Refractive Surgery

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ABSTRACT

Charcot–Marie–Tooth (CMT) disease is the most common inherited polyneuropathy, with a characteristic phenotype of distal muscle weakness, atrophy, and sensory loss. Variable ocular involvement has been documented in patients with CMT, with optic atrophy as the most frequently reported symptom. Although the Charcot–Marie–Tooth Association has generally deemed laser-assisted in situ keratomileuses (LASIK) a safe option for patients with CMT, reports of corneal refractive surgery are lacking in this patient population. This commentary discusses the current understanding of CMT, including its ocular manifestations, and additional specific testing to consider when evaluating these patients for corneal refractive surgery.

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Key Summary Points

Charcot–Marie–Tooth (CMT) disease is the most common inherited polyneuropathy, with systemic symptoms of distal weakness, muscle atrophy, and sensory loss.

Ocular involvement is less common, though documented symptoms have included optic atrophy, Argyll Robertson-like pupils, fixed miosis, color vision abnormalities, and retinitis pigmentosa, among others.

The Charcot–Marie–Tooth Association states that "patients with CMT are at no additional risk in having laser-assisted in situ keratomileuses (LASIK) or other corrective procedures," though data is lacking on outcomes of corneal refractive surgery in this patient population.

A LASIK evaluation for a patient with CMT should include corneal confocal microscopy, formal visual field testing, retinal and optic nerve optical coherence tomography (OCT), visual evoked potentials, electroretinograms, and genetic testing.

Because ocular involvement is variable in CMT and the literature is lacking in reports of LASIK in patients with CMT, surgeons should consider a patient's disease presentation in the context of thorough preoperative testing when counseling patients on the appropriateness of corneal refractive surgery.

INTRODUCTION

As an ophthalmologist, you may encounter a patient with Charcot–Marie–Tooth (CMT) disease seeking corneal refractive surgery. The Charcot–Marie–Tooth Association states that "to our knowledge, people with CMT are at no additional risk in having LASIK or other corrective procedures" [1]. While this statement is encouraging for patients interested in pursuing corneal refractive surgery, it falls short in elucidating specific considerations regarding laser vision correction in CMT. We would like to share our perspective on corneal refractive surgery in patients with CMT given the disease pathophysiology and ophthalmic manifestations. We also explore additional specific testing to consider in the preoperative evaluation for potential laser-assisted in situ keratomileusis (LASIK) or other corneal refractive surgery in patients with CMT.

Interestingly, CMT is named after the three neurologists who described the disease in 1886 [2]. Jean-Martin Charcot, an anatomy professor and the "father of neurology" [3], alongside his student Pierre Marie [4], published reports in Paris while Howard Henry Tooth documented similar cases for his doctoral thesis at the University of Cambridge [5]. Also known as hereditary motor and sensory neuropathy (HMSN), CMT is the most common inherited polyneuropathy with an estimated prevalence of 1 in 2500 [6]. CMT is caused by multiple mutations in structural protein genes responsible for myelin sheath and Schwann cell formation, mitochondrial metabolism, and axonal transport, resulting in length-dependent neuropathy. The distal nerves are affected first, followed by progressive proximal involvement [7]; thus, the classic presentation of CMT includes distal muscle weakness and atrophy. Other less common findings can include scoliosis, hip dysplasia, restless leg syndrome, tremor, and hearing loss [6]. Disease onset is usually in the first [6] or second [8] decade of life, though presentation and severity of symptoms can differ depending on the underlying gene mutation.

According to conduction velocity abnormalities, CMT is classified as axonal, demyelinating, or intermediate (Table 1) [6]. As a result of genetic heterogeneity, disease presentation can be highly variable and difficult to diagnose. The diagnosis involves clinical assessment, review of family history, nerve conduction velocity studies, electromyogram, and genetic testing [7]. Currently, there are no pharmacological treatments for CMT. Management instead revolves around supportive therapies, such as physical therapy and orthopedic devices [7]. Some investigational therapies, such as progesterone antagonists, neurotrophic growth factor, ascorbic acid, and curcumin, have not yet revealed definitive results [8].

Although less common than symptoms of peripheral neuropathy, ocular involvement has been documented. There are reports of Argyll Robertson-like pupils [9] and fixed miosis secondary to involvement of sympathetic postganglionic fibers [10]. Oculomotor abnormalities due to cranial nerve involvement have also been documented [10]. Optic atrophy has been observed in the CMT2A variant, secondary to mitofusin-2 *MFN2* gene abnormalities [11, 12]. Other ocular manifestations of CMT include red/green color vision abnormalities, premature presbyopia, nystagmus, retinitis pigmentosa, peripapillary vessel attenuation, retinal nerve fiber layer thinning, and central/paracentral scotoma [13]. Table 2 outlines the abnormalities described above.

Dry eye disease is not a well-documented ocular manifestation of CMT, though it is a possible symptom given that CMT affects nerves throughout the body and the cornea is one of the most densely innervated tissues [14]. This relationship becomes significant when

Table 1 Overview of CMT subtypes and associated characteristics

Subtype	Inheritance pattern*	Pathophysiology	Phenotype
CMT1	AD	Demyelinating disease → slowed nerve conduction velocity [7]	Muscle weakness, peripheral atrophy [2]. Severity of symptoms does not correlate with degree of reduction in nerve conduction velocity [23]
CMT1A**	AD	Duplication of peripheral myelin protein 22 kD (*PMP22*) gene [6, 7]	Symptom onset in infancy; distal weakness, atrophy, high stepping gait, decreased sensation, pes cavus, reduced/absent reflexes [6, 8]
CMT2	AD	Axonal abnormalities → reduced amplitude but normal velocity of nerve conduction [7]	Onset age 5–25 years, distal weakness, atrophy, sensory loss, decreased reflexes, foot deformities [2]; optic atrophy [6]; tremors, migraines [23]
CMT3***	AD or AR	Abnormalities in genes *PMP22, MPZ, GJB,* among others → slowed nerve conduction [2]	Onset in infancy, hypotonia, delayed motor development, sensory loss, distal to proximal weakness, absent reflexes, ataxia [2]
CMT4	AR	Demyelinating disease → slowed conduction velocity [7]	Distal weakness, atrophy, sensory loss, foot deformities, cataracts, deafness [2]; severe early onset sensory motor neuropathy, vocal cord paresis [23]
CMTX	X-linked	Most commonly due to mutation in gene *GJB1* (codes for gap junction connexin-32) [7, 23]	Distal weakness, atrophy, sensory loss [2]; Primarily affects males, females with later onset (age 20–30 years) and less severe disease [7, 23]
Intermediate	AD or AR	Unclear if primarily axonal/ demyelinating → intermediate conduction velocity [7]	Similar symptoms of distal weakness, atrophy, and sensory loss; grouped with traditional subtypes when possible [2]

CMT5 and CMT6 are now attributed to *MFN2* gene abnormalities and grouped with CMT2A [7]
CMT Charcot–Marie–Tooth disease, *AD* autosomal dominant, *AR* autosomal recessive
*CMT can also be acquired through de novo mutations [7]
**Most common subtype of CMT
***CMT3 is more commonly known as severe, early-onset CMT, Dejerine–Sottas disease, and congenital hypomyelinating neuropathy [2]

considering corneal refractive surgery, especially LASIK, in patients with CMT. Post-LASIK dry eye disease is postulated to occur as a result of corneal nerve damage in the process of LASIK flap creation, with subsequent tear film dysfunction causing chronic dryness [15]. A prospective study found an inverse relationship between post-LASIK reinnervation and dry eye symptoms, thus supporting that LASIK-associated dry eye disease is a neuropathic process [15]. We are concerned that the underlying pathophysiology of LASIK-associated dry eye disease could be exacerbated in patients with CMT, and surgeons should be cautious about proceeding with corneal refractive surgery in this population.

To further explore the option of LASIK in a patient with CMT, additional testing beyond the standard LASIK evaluation is warranted to better understand the extent of ocular

Table 2 Ocular abnormalities identifiable as part of the eight-point eye exam for patients with CMT

Eight-point eye exam	Abnormalities associated with CMT
Visual acuity	Premature presbyopia [13]
	Severe astigmatism [11]
	Decreased VA secondary to retinal or optic nerve pathology
Pupils	Fixed miosis [10]
	Argyll Robertson pupils [9]
Extraocular motility	Impaired motility [24]
Intraocular pressure	No reports of glaucoma
Confrontation visual fields	Central/paracentral scotoma [13]
External examination	Nystagmus [13]
Slit lamp examination	Cataracts [11]
Fundoscopic examination	Macular pigment changes [13]
	Pigmentary retinopathy [13]
	Retinal nerve fiber layer thinning [13]
	Optic nerve atrophy [11–13]
	Peripapillary vessel attenuation [13]

CMT Charcot–Marie–Tooth disease, *VA* visual acuity

Table 3 Additional tests to perform and associated findings in evaluating patients with CMT

Additional testing	Potential findings
CCM	Decreased corneal nerve fiber density and nerve branch density [16]
NCCA	Decreased corneal sensation [16]
Formal visual field	Central or paracentral scotoma [13]
Retinal OCT	RNFL thinning [10, 13]
	GCC thinning [10]
Optic nerve OCT	Optic nerve atrophy [10, 13]
FA	Central tapetoretinal degeneration [13]
	Macular pigmentary changes [13]
VEP	Normal or prolonged latency, decreased amplitude [10, 13, 18, 19]
ERG	Usually normal [13]
Genetic testing	Multiple genetic abnormalities have been identified [6, 7]

CMT Charcot–Marie–Tooth disease, *CCM* corneal confocal microscopy, *NCCA* non-contact corneal aesthesiometer, *OCT* optical coherence tomography, *RNFL* retinal nerve fiber layer, *GCC* ganglion cell complex, *FA* fluorescein angiography, *VEP* visual evoked potential, *ERG* electroretinogram

involvement and potential for a successful corneal refractive surgical outcome (Table 3). One of the most important evaluations is corneal confocal microscopy (CCM), a non-invasive tool that allows direct visualization of the corneal nerves. Specifically, CCM allows for characterization of the sub-basal nerve bundles, which are typically unmyelinated C fibers that sense thermal and chemical stimuli [16]. A patient with CMT may demonstrate decreased nerve fiber density on CCM [16, 17]. Additionally, corneal sensation is reduced with testing such as the non-contact corneal aesthesiometer (NCCA). Taken together, the CCM and NCCA findings demonstrate the corneal nerve integrity of a patient with CMT. Those with severely diminished nerve density and sensation are at risk for more postoperative complications such as dryness and poor postsurgical healing.

In addition to confocal microscopy, other testing can help characterize the extent of ocular CMT. Formal visual field testing can identify any pre-existing deficits secondary to optic atrophy. Central/paracentral scotomas are the most common visual field abnormality in CMT [13]. Furthermore, retinal and optic nerve optical coherence tomography (OCT) are critical to evaluate the integrity of these structures. If a

patient has significant retinal nerve fiber layer or optic nerve thinning causing impaired vision, their visual potential is compromised and they are unlikely to experience significant improvement in best corrected visual acuity from corneal refractive surgery. These patients should be counseled that their structural limitations prevent optimal surgical outcomes and thus are not good candidates for corneal refractive surgery. Visual evoked potentials (VEP) and electroretinograms (ERG) can be performed as part of a thorough evaluation. Although they may be normal in some patients, increased latency or decreased amplitude has been observed on VEP [18, 19]. Lastly, the patient should be referred for genetic testing if they have not yet undergone molecular analysis. Identifying the gene abnormality and inheritance pattern of CMT can help characterize the expected disease progression and severity.

Since the literature lacks reports of corneal refractive surgery in patients with CMT, it is difficult to assess outcomes such as postsurgical healing. Therefore, it is helpful to investigate LASIK outcomes in other diseases with corneal neuropathy, such as diabetes. Both CMT and diabetes demonstrate decreased corneal subbasal nerve density [20]. In diabetes, chronic hyperglycemia results in axonal degeneration of unmyelinated corneal nerves, producing symptoms of corneal desensitization, decreased cellular regeneration, and slow wound healing [21]. Although diabetes is generally considered a relative contraindication to LASIK, a literature review revealed that patients with good glycemic control generally had favorable postsurgical outcomes [21]. Patients with poorer glycemic control were more likely to experience delayed wound healing, punctate epithelial erosions, and persistent epithelial defects [22]. By extension, we infer that patients with severe corneal neuropathy secondary to CMT can have similar complications associated with poor corneal healing, whereas patients with minimal corneal manifestations of CMT might be candidates for corneal refractive surgery.

In summary, CMT presents a broad spectrum of disease severities and variable ocular involvement. Although the Charcot–Marie–Tooth Association has generally deemed LASIK a safe option for patients with CMT, our understanding of the current literature has identified numerous ophthalmic manifestations that can impact whether a patient is a good candidate for corneal refractive surgery. A surgeon should consider a patient's disease presentation in the context of thorough preoperative testing when counseling patients on the appropriateness of corneal refractive surgery.

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