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Assessment of response to multimodal management of neurotrophic corneal disease

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ABSTRACT

Purpose: To characterize patients with neurotrophic keratopathy (NK) and describe treatment outcomes.
Methods: **Setting**: Two institutional tertiary cornea clinics. **Patients**: Medical record review of 37 consecutive patients (37 eyes) with NK. **Intervention:** Management of NK. **Main Outcome Measures:** Best-corrected visual acuity (BCVA), epithelial defects (ED), re-epithelialization time, number of perforations, need for penetrating keratoplasty and tarsorrhaphy.
Results: Average age was 64.4 ± 15.0 years, with 59.5% male patients. Average follow up time was 20.8 ± 32.6 months. Moderate to severe NK (Mackie Stage) was present in 62.1% of patients. Herpetic, neurosurgical and pars plana vitrectomy were the top three causes in each Mackie Stage. 72.9% used topical steroids to treat inflammatory ocular disease. Mean number of EDs was 1.6 per patient averaging 85 days to heal. Persistent EDs affected 56.7%. Corneal perforation (18.9%) was more likely with advanced age, herpetic cause and Stage 3 presentation. Tarsorrhaphy was performed in 35% of patients and were more likely with Stage 3 presentation. Referral for neurotization occurred in 10.8%. Evisceration was required in 2 eyes. BCVA of 20/40 or better was achieved in 21.6% of eyes at last follow up.
Conclusions: NK is chronic, frequently visually disabling with multiple contributing factors requiring different treatment modalities. Herpetic, pars plana vitrectomy and neurosurgical causes constitute a significant proportion of NK. Persistent epithelial defects should be rapidly managed as corneal perforation is a serious complication. Advanced age, herpetic cause and Mackie Stage 3 at diagnosis are significant risk factors for corneal perforation.

1. Introduction

Neurotrophic keratopathy (NK) has been defined as "a disease related to alterations of corneal nerves leading to impairment in sensory and trophic function with consequent breakdown of the corneal epithelium, affecting the health and integrity of the tear film, epithelium and stroma" [1]. Pathogenesis of neurotrophic keratopathy ultimately involves a deficit at any level of the fifth cranial nerve. Ocular surface discomfort is usually not expressed but rather, symptoms of blurry vision are present, caused by disturbed tear film integrity, diffuse asymmetric punctate epithelial erosions, frank epithelial defect or scarring. It is a chronic condition with varied ocular and systemic causative factors [2] and has the potential to profoundly affect visual function and quality of life.

NK has been classified as a rare orphan disease and its prevalence was estimated to be less than 5 per 10,000 individuals. Other than herpetic keratitis and neurosurgical causes, little epidemiological data exists [3]. Saad et al. recently reported in a large epidemiological study that the frequency of neurotrophic keratopathy is approximately 0.11% [4].

Treatment of neurotrophic keratopathy is multimodal, ranging from intensive topical therapy such as preservative-free lubricants and autologous serum tears to invasive surgical intervention such as tarsorrhaphy, amniotic membrane placement and corneal transplantation. Although there is much literature on treatment modalities for specific forms of neurotrophic keratopathies, only a small number of studies

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provide quantitative data on the spectrum of neurotrophic keratopathies presenting to subspecialty corneal clinics and their outcomes in the real-life setting.

In this study, we report the clinical characteristics and outcomes of patients diagnosed with neurotrophic keratopathy and treated at two tertiary cornea practices in Toronto, Canada.

2. Materials and methods

A retrospective chart review was conducted on consecutive patients diagnosed with neurotrophic keratopathy from January 2013 to December 2018 at two tertiary cornea offices at the Toronto Western Hospital. This study received Research Ethics Board approval from the University of Toronto and was conducted in compliance with the tenets of the Declaration of Helsinki.

Data collected included patient demographics, Mackie Staging and etiology for neurotrophic keratopathy, best corrected visual acuity (BCVA) at baseline and end of follow up, treatment modalities utilized, and presence of epithelial defects, healing times and complications. Outcome measures included changes in BCVA, final BCVA, epithelial defect healing times, complications including perforation, and need for surgical intervention. Complications were analyzed according to development of epithelial defect, presence of persistent epithelial defect (lasting more than 2 weeks), and progression to perforation.

Neurotrophic status was determined by complete slit lamp ocular surface examination and quantitative assessment of corneal sensitivity via a cotton wisp against the central cornea graded as fully sensate, hypoaesthetic or anaesthetic prior to the use of any topical anaesthetics or mydriatics. Patients suspected of herpes simplex virus (HSV) involvement were given polymerase chain reaction (PCR) testing to confirm but were treated as herpetic despite negative PCR if determined clinically appropriate by the treating clinician.

Data were recorded and analyzed using Minitab Software, version 19 (Minitab Inc, State College, PA). For comparison of continuous and categorical data the Student T test and chi-square test were used respectively. Snellen values were converted to logMAR for analysis of BCVA. All presented means were recorded with standard deviations.

3. Results

Thirty-seven eyes of 37 patients aged 64.4 ± 15.0 years (range 21–90 years) were included. Males accounted for 59.5% of the study population (22/37) and left eyes were involved in 56.7% of cases (21/37). There were no cases of bilateral involvement. Average follow up time was 20.8 ± 32.6 months (range 4–165 months). Mean BCVA at diagnosis and at final follow up was 1.3 logMAR (Snellen equivalent 20/400, range 20/20 to perception of light). A BCVA of 0.3 logMAR or better (Snellen equivalent 20/40) was present in 16.2% (6/37) of cases at diagnosis and 21.6% (8/37 eyes) at final follow up. Overall, BCVA was maintained in 29%, improved from baseline in 32% and decreased from baseline in 37% of cases. Of those that had visual acuity improvement (10/37 eyes), 83% improved by 2 lines or more.

Causes and staging of neurotrophic keratopathy are summarized in Table 1 and Table 2. In 35.1% of patients, there were two or more contributing factors to the development of neurotrophic cornea and over half (54.1%) of eyes had herpetic involvement (simplex or zoster). Neurosurgical causes (either direct compression or iatrogenic) accounted for 24.3% of cases (9/37) and 21.6% of cases had previous pars plana vitrectomy (PPV) and laser retinopexy (8/37). Ocular surface diseases with reduced sensitivity such as graft versus host disease (2/37), previous laser-assisted in situ keratomileusis (LASIK) (1/37), radiation keratopathy(1/37), and limbal stem cell disease secondary to chemical burns, Sjögren syndrome and chronic contact lens wear accounted for 18.9% (7/37) of cases with several cases having multiple aetiologies.

Mackie staging of all cases found 37.8% to be classified as Stage 1, 27% to be Stage 2 and the remaining 35.1% to be Stage 3. Moderate to severe neurotrophic keratopathy (Stage 2 and 3) disease was present in 62.1% of the study population. With respect to Stage 1 patients, 42.9% had HSV/VZV, 28.6% were caused by neurosurgical causes and 7.1% were due to past PPV. Stage 3 patients showed a similar trajectory with 53.8% having HSV/VZV involvement, 30.8% due to neurosurgical causes and 15.4% having a past history of PPV. Of the Stage 2 patients, 70% had HSV/VZV, 10% had neurosurgical causes and 50% had prior PPV (Table 2).

Table 1
Causes of neurotrophic keratopathy.

Cause	N = 37	% of Cases
Herpetic Involvement (HSV/VZV[a])	20	54.1
Neurosurgical Cause	9	24.3
Previous Vitrectomy and Laser Retinopexy	8	21.6
Ocular Surface Disease	7	18.9
Graft versus Host Disease	2	5.4
Prior LASIK[b]	1	2.7
Radiation	1	2.7
LSCD[c] (chemical, Sjogren, Contact lens)	3	8.1
Multiple Sclerosis	1	2.7
Genetic/Congenital	0	0.00
>1 Contributing Factor	13	35.1

[a] HSV: herpes simplex virus, VZV: varicella zoster virus.
[b] LASIK: laser-assisted in situ keratomileusis.
[c] LSCD: limbal stem cell disease.

Table 2
Staging of neurotrophic keratopathy.

Mackie Staging	N = 37	% of all cases	HSV/VZV	Neurosurgical	Pars Plana Vitrectomy
1	14	37.8%	42.9%	28.6%	7.1%
2	10	27%	70%	10%	50%
3	13	35.1%	53.8%	30.8%	15.4%

NB Some cases will have more than one contributing cause to neurotrophic keratopathy.

Mean number of epithelial defects was 1.6 per patient (range 1–16) and average time to healing was 85 days (range 7–151 days). Persistent epithelial defects (PEDs) were observed in over half of the study population (56.0%). Epithelial defects complicated by corneal perforation were observed in 18.9% of cases with 5.4% having two perforations or more. Stage 1 patients had a 28.6% rate of developing a later persistent epithelial defect. Stage 2 patients developed an average rate of 1.8 PEDs per patient whereas Stage 3 patients averaged 2.7 PEDs per patient. Of all cases that progressed to perforation of an ulcer, the average number of PEDs per patient was 3.6. There were 2 cases that proceeded to evisceration; in both cases the patients were over 80 years of age, had a history of HSV/VZV and had experienced 1 prior perforation prior to requiring evisceration.

Perforation was a complication in 7.14% of Stage 1, 11.11% of Stage 2 and 38.46% of Stage 3 eyes (Table 4). Patients with a history of HSV/VZV were more likely to develop a perforation compared to those without (31.58% v 5.88%, $p = 0.04$). Stage 3 patients were more likely to develop a perforation (33.46%, $p = 0.03$) and more likely to require a tarsorrhaphy comparative to Stage 1 or 2 patients (61.52% vs 25%, $p = 0.03$). Patients with more advanced age were more likely to develop a perforation compared to those of a younger age (76.6 years vs 61.4 years, $p = 0.004$).

Treatment modalities employed are summarized in Table 3. Topical lubricants were used in all cases. Preservative free lubricants were offered to all patients however only 75.7% of eyes were able to access this due to cost. Topical steroids to treat ocular surface disease or associated immune related disease were employed in 72.9% of eyes and 10.8% of eyes were treated with either lifitegrast 5% or cyclosporin

Table 3
Treatment modalities for neurotrophic cornea.

Treatment Modality	*N = 37*	*% of Cases*
Medical Intervention		
Lubricant Use	37	100.00
Preservative Free Lubricants	28	75.7
Vitamin A Ointment	2	5.4
Serum Tears	23	62.2
Topical Steroid Use	27	72.9
Lifitegrast 5%	2	5.4
Cyclosporin 0.05%	2	5.4
Amnion Drops	1	2.7
Bandage Contact Lens	13	35.2
Scleral Contact Lens or PROSE*	4	10.8
Surgical Intervention		
Surgical Intervention of any kind	25	67.6
Tarsorrhaphy	13	35.1
Gunderson Flap	1	2.7
Amniotic Membrane Transplantation	3	8.10
Keratoplasty (total)	8	21.6
Keratoplasty for tectonic stability	6	16.2
Keratoplasty for visual rehabilitation	2	5.4
Referral for corneal neurotization	4	10.8

*PROSE: Prosthetic Replacement of the Ocular Surface Ecosystem Lens.

Table 4
Risk factors for perforation in neurotrophic keratopathy.

Risk Factor	With Risk Factor	Without Risk Factor	P Value
HSV/VZV*	31.58%	5.88%	0.04
Stage 3 disease at presentation	33.46%	8.7%	0.03
Advanced Age	Mean age 76.57 yrs	Mean age 61.4 yrs	0.004

*HSV: herpes simplex virus, VZV: varicella zoster virus.

0.05% drops. Fifty percent of Stage 1 eyes required steroid treatment compared to 100% in Stage 2 and 72.92% in Stage 3 ($p = 0.008$). Autologous serum (30%) tears were utilized in 62.2% of cases overall. Stage 1 and Stage 2 required serum tears at 71.4% and 70% respectively, whereas Stage 3 patients used serum tears 46.15% of the time. Bandage contact lenses were used in 35.2% of cases to aid healing of epithelial defects and these tended to be in Stage 2 and 3 disease but did not attain statistical significance (50% and 46.2% respectively vs 14.3% Stage 1, $p = 0.09$). Two cases utilized scleral lenses. The self-retained cryopreserved amniotic membrane (PROKERA®, Bio-Tissue, Miami, FL) was used in one case.

Surgical intervention was required in 32.4% (12/37) of cases (excluding tarsorrhaphy) and consisted mostly of penetrating keratoplasty for tectonic stability following perforation in 6 cases and for visual rehabilitation in 2 cases. Stage 1 disease required PKP 14.29% of the time, Stage 2 disease 20% of the time and Stage 3 disease 46.15% of the time but did not reach statistical significance ($p = 0.15$). Surgical amniotic membrane grafts prepared by the Eye Bank of Canada (Ontario division) were used in 8.1% (3/37) whereas 35.1% (13/37) of cases underwent a tarsorrhaphy. Stage three patients were more likely to require a tarsorrhaphy treatment than Stage 1 and 2 patients (61.54% vs 25%, $p = 0.03$). Four patients were referred for consideration of neurotization surgery with one patient declining surgery and another patient considered unsuitable for neurotization. The two remaining patients were awaiting assessment at the time of manuscript preparation.

4. Discussion

This study provides an overview of the typical real-life stratified treatment approach employed in the treatment of neurotrophic cornea and its complications. Neurotrophic keratopathy remains a chronic and challenging disease entity to treat, requiring the simultaneous use of multiple modes of medical and sometimes surgical treatment.

Causes of neurotrophic keratopathy may exist in isolation or in conjunction. In our sample, over thirty percent of cases identified two or more contributing causes. Mackie staging was fairly evenly distributed despite the tertiary nature of the clinic. Consistent with the literature, the most common cause in this study was herpetic keratitis (54.1%) [4] followed by neurosurgical causes (24.3%). A previous history of pars plana vitrectomy and laser retinopexy accounted for a significant proportion of cases at 21.6%. In addition, HSV/VZV, neurosurgical causes and PPV were consistently the top three main causes in each Mackie Staging group. Confluent laser treatment over the long ciliary nerves is a well-documented cause of neurotrophic corneal ulceration and should be avoided if possible during detachment repair [5]. Ocular surface disease was also present in 18.9% of the sample. No congenital causes were identified in our study population. Current studies on diabetic peripheral neuropathy have demonstrated correlations with reduction in corneal nerve fibre density and subsequent corneal neuropathy and impaired ocular surface integrity [6]. Two patients were recorded to have had vitrectomy procedures for diabetic retinopathy and their corneal healing may have been influenced by their diabetes. Similarly, patients with multiple sclerosis have been found to have reduced corneal nerve fibre density, nerve branch density and nerve fibre length [7,8] but little is known about the clinical effect on the cornea. Only one patient in our sample had a diagnosis of multiple sclerosis but concurrently had neurosurgery to treat trigeminal neuralgia and a pituitary adenoma.

The persistence and recurrence of epithelial defects in neurotrophic corneas remains a challenging problem. Very limited literature exists on the prevalence of persistent epithelial defects in a neuropathic corneal population as a whole [4]. In our series, the average patient was likely to have at least 1–2 epithelial defects from the time of diagnosis. Mean healing time per epithelial defect was just under three months (85.6 days). Over half of the study population experienced persistent corneal epithelial defects (epithelial defects lasting longer than 14 days). Furthermore, of the Stage 1 at diagnosis cohort, 28.6% still progressed to eventually develop a persistent epithelial defect; reflecting that careful maintenance of a healthy ocular surface preventing epithelial breakdown is paramount. In addition, of all ulcers progressing to a perforation, the average number of PEDs was 3.6, consistent with the pathophysiology that inability to prevent recurrent ulceration is a risk factor for more serious complications. There is significant morbidity associated with this in terms of disabling vision, ocular discomfort, and potential for chronic visual impairment due to scarring, melt or perforation.

With respect to the more serious consequences of corneal stromal melt leading to perforation, a total of 9 (18.9%) corneal perforations were recorded with 2 patients afflicted by more than one perforation. In our series, 7.14% of Stage 1 eyes still proceeded to a perforation, reinforcing the importance of aggressively maintaining a healthy ocular surface in the absence of an epithelial defect. There was a trend towards an increasing rate of perforations with staging of disease (11.11% of Stage 2 eyes and 38.46% of Stage 3 eyes) but this was not found to be statistically significant. Additionally, we found that a history of HZV/VZV was associated with a higher likelihood of perforation (31.58% v 5.88%, $p = 0.04$), with Stage 3 disease at diagnosis (33.46%, $p = 0.03$) and also with advanced age (76.6 years vs 61.4 years, $p = 0.004$). In support of this, of the two cases that required eventual evisceration, both patients were over 80 years old with a history of HSV/VZV and had at least 1 prior perforation managed prior to requiring evisceration. A heavily insensate cornea due to viral disease combined with advanced age and advanced stage at diagnosis would impact heavily on the ability of the ocular surface to regenerate itself, and we would suggest that more aggressive surgical procedures used at an earlier stage may be required ie tarsorrhaphy. Recognition of this pathophysiology was

reflected in our surgical practice where 61.52% of our stage 3 patients proceeded to a tarsorrhaphy.

The initial treatment of any neurotrophic cornea involves removal or control of any offending agent. For example, topical medications should be ideally ceased, reduced or switched to preservative free options where available as preservatives can exacerbate dry eye and induce chronic inflammatory changes [9]. Contact lens wear should be minimized or ceased where possible. At our centre, the treatment of neurotrophic keratopathy was approached in a similar stepwise manner offered to the patient. Briefly, for stage 1 disease, topical medications were discontinued where possible and any concurrent ocular surface disease was aggressively managed. The use of non-preserved tears, vitamin A ointment, tetracycline 100 mg BID and serum tears were utilized. Stage 2 disease necessitated margin debridement (when clinical appearance appeared to be rolled up), the use of bandage contact lenses and amnion derivatives, tarsorrhaphy and corneal or scleral lenses. Finally, Stage 3 disease utilized corneal glue applied to impending or actual perforation, tarsorrhaphy augmented with amnionic membrane derivatives, lamella or penetrating keratoplasties and conjunctival flaps. Given that neurotrophic keratopathy is a chronic disease, whether or not the patient ended up using all therapy types was highly dependent on individual compliance, finances and tolerance of therapies. A more detailed discussion of therapies is discussed below.

Dry ocular surfaces should be firstly be aggressively managed with topical lubricants. This practice was consistent in our sample where 100% of patients were placed on frequent lubricant therapy (range four times per day to every half hour) and over 75% of patients were able to comply with treatment with preservative free tears specifically. Punctal occlusion could be considered to retain tears, however, the pooling of inflammatory mediators and debris can at times paradoxically lead to further injury. In our series punctal occlusion was accepted in one patient.

Inflammatory causes of dry eye may be ameliorated by pulsed steroid courses or with lifitegrast or topical cyclosporine. The high rates of concurrent steroid use in our sample overall (72.9%) was due to the need to treat underlying inflammatory causes of dry eye. In our series we found that Stage 2 and Stage 3 eyes (100% and 72.9% respectively) were more likely to require steroid use compared to Stage 1 eyes (50%, $p = 0.008$). Steroid therapy should be monitored closely as it may contribute to impaired stromal healing and increase infection risk. Topical non-steroidal anti-inflammatories can exacerbate stromal melt and should not be employed in neurotrophic corneas [10]. The anti-collagenase activity of oral tetracyclines may assist in controlling cases of melt. Prophylactic topical antibiotics are also important in prevention of infectious keratitis. All of our patients with a history of herpetic neurotrophic keratopathy were placed on at least prophylactic dosing of acyclovir or valaciclovir long term to control herpetic recurrence.

Autologous serum tears (30–50% concentration) were used in 62.2% of eyes in our study. They contain some of the same vitamins, nutrients, growth factors, and cytokines as healthy human tears. More importantly, for a neurotrophic cornea, they contain epidermal growth factor (EGF) and transforming growth factor-β, which support epithelial cell homeostasis, growth, and migration [11–13]. Autologous serum tears should be prescribed soon after failure of conservative treatment measures, especially if a persistent epithelial defect develops. Azari et al. demonstrated an average healing time of 22 days with 92% (23 of 25 eyes) achieving complete clearance of the epithelial defect [14]. Combination with silicone hydrogel lenses was also found to be an efficacious treatment method achieving 100% recovery [15]. It should be noted however that use of autologous serum tears was lower in Stage 3 eyes in our study, and this is due to the fact that the presence of stromal ulceration and significant thinning as defined by Stage 3, are where procedures providing more tectonic support such as penetrating or lamellar keratoplasty are required or other procedures that can provide accelerated epithelial coverage such as amnion membrane use or glue patches. Whilst they do promote epithelial healing, the use of serum tears in this context would take too long to work and would be unlikely to prevent progression to perforation on their own.

Ocular surface protection in the form of therapeutic bandage or scleral contact lenses can also be employed to aid healing by providing protection against abrasive forces of the eyelid on a desiccated ocular surface. Thirty-five percent (13/37) of patients overall in our study used bandage contact lenses during their treatment course, with a tendency towards Stage 2 and 3 eyes. This is likely to be due to the presence of epithelial defect by definition and the use of a BCL to promote epithelial healing once a defect has been detected. The prosthetic replacement of the ocular surface ecosystem (PROSE) lens is one such FDA approved device. It was found to be a good alternative to lid surgery in eyes that had failed conventional therapy [16], and the additional use of a non-preserved topical fourth-generation fluoroquinolone placed within the reservoir reduced microbial keratitis rates for overnight PROSE wearers treated for persistent epithelial defect [17]. Eight percent (3/37) of patients in our study successfully used scleral lenses without breakdown of the ocular surface during their use.

Despite the aforementioned medical interventions, 32.4% of the patients in the current study required surgical intervention overall. As such, it is clear that there is room in improving medical therapy for neurotrophic keratopathy. Recombinant human nerve growth factors (rhNGF) with the intent of restoring corneal nerve integrity has been of intense interest as most other treatment modalities are supportive and do not target the underlying pathology. Safety and efficacy of the Cenegermin (rhNGF) has been demonstrated in patients with moderate to severe neurotrophic keratitis [18,19], however significant financial barriers preclude widespread clinical use and experience to date. As for its mechanism of action, NGF is typically found in the aqueous humour and tear film and binds to NGF receptors expressed on anterior segment structures of the eye (iris, lens, cornea) [20]. It has been found to stimulate corneal epithelial growth and survival as well as stimulate limbal stem cell potential. It has also been shown to support corneal re-innervation, its most important feature, though the exact mechanism is yet to be elucidated [21].

Surgical management for neurotrophic corneas is employed when conservative methods have failed to heal the ocular surface or when perforation is present or imminent and not amenable to corneal cyanoacrylate application. Causes of exposure or eyelid dysfunction or malposition should be identified on careful history and examination and treated, which may involve the use of suture or botulinum A tarsorrhaphy or lid repositioning or weighting surgery. There is significant evidence supporting tarsorrhaphy as a useful adjunct to prevent or aid epithelial healing. In our study, suture tarsorrhaphy was employed in over 35.1% of cases overall, and expedited, where necessary, to permanent tarsorrhaphy in select cases. Stage three patients were also more likely to require a tarsorrhaphy treatment than Stage 1 and 2 patients (61.54% vs 25%, $p = 0.03$) reflecting the aggressive management required to manage the increase in disease severity. All epithelial defects healed after tarsorrhaphy. This is consistent with the literature reporting fairly high epithelial healing rates after tarsorrhaphy to the order of 83–90% [22,23] with one study having neurotrophic ulcers and persistent epithelial defects post keratoplasty accounting for 50% of their sample. Although tarsorrhaphy is very good at resolving persistent epithelial defects, there can be unacceptable visual impairment or cosmetic appeal in which scleral contact lenses should be considered as a more acceptable option if able to be retained with comfort in the eye [24,25].

Amniotic membrane application for treatment of corneal ulcers, first described in 1997 by Lee and Tseng [26], can be used to treat persistent epithelial defects by promoting healing and preventing perforation [27]. Our study population utilized amniotic membrane application in 8.1% of cases and purified amniotic fluid drops for one case. Rate of amnion use is low in our study due to two factors: PROKERA® (Bio-Tissue, Miami, FL) had only recently been Health Canada approved, and the Eye Bank of Ontario had just recently expanded its services to include

amniotic membrane sourcing on request by surgeons so that patients no longer have to pay out of pocket. Expectations are that rates of amnion usage will increase in Toronto as access to tissue is easier. Cryo-preserved amnion was not available at our institution during this study period.

Of the total number of penetrating keratoplasties performed in our study (8/37, 21.6% of total cases), only two were for visual rehabilitation, indicating that the need for tectonic stability (6/37) due to stromal thinning or perforation was more frequent than the need for visual rehabilitation for keratoplasty. There was a trend toward stage three eyes requiring PKP but this was not found to be statistically significant, most likely due to small numbers, as this would be a naturally expected consequence of severity of disease. However, it must be emphasized that tectonic or optical penetrating keratoplasty has a poor prognosis since post-operative epithelial healing is a significant challenge. A recent study of penetrating keratoplasty for herpes zoster corneal complications demonstrated a 22.6% rate of persistent epithelial defects after surgery with up to 30% requiring additional surgery in the form of tarsorrhaphy or amniotic membrane placement to aid healing [28]. Thus, it is common practice in our centre that where poor healing is expected, penetrating keratoplasty is performed using amniotic membrane grafting as an adjunct along with lateral tarsorrhaphy.

Corneal neurotization is an evolving technique for the re-innervation of the cornea involving the use of sural nerve graft and donor facial sensory nerves [29]. Epithelialization and the regaining of sensation has been demonstrated using this technique in the paediatric and adult population, and has permitted successful optical keratoplasty for visually limiting corneal opacities [29–32]. Four of our patients were referred for corneal neurotization; one was waitlisted for surgery, one declined and the other two were awaiting consultation at the time of manuscript submission.

There is minimal literature on visual outcomes for patients with neurotrophic corneas. In our series, just over 60% of eyes had maintained or improved or maintained visual acuity from their baseline. Two patients ended up requiring evisceration for painful blind eyes. BCVA of 20/40 or better was retained by 21.6% of eyes at the study's conclusion. Mean average BCVA at diagnosis and at final follow up was unchanged at 1.3 logMAR (Snellen equivalent 20/400). This most likely signifies that recurrent pathology tends to recur and eyes that have difficulties regenerating their ocular surface. The fact that our centre is a tertiary cornea referral centre means that baseline vision tended to be poor from the start, as they were referred from other centres, having exhausted treatment elsewhere. Of our study patient, 62.1% presented with at least moderate to severe disease, a by-product of the tertiary referral centre. Pre-existing corneal opacity formation or distorted cornea from scarring processes are therefore highly likely to pre-exist. Scarred corneas face a significant battle to maintain vision, therefore a lack of deterioration in the main BCVA at final follow up signifies benefit to the instigated treatments and prevention of progression to perforation or loss of the eye. This suggests that visual gain if any is modest, that vision is more likely to remain unchanged and that the focus should remain on preventing further deterioration.

Limitations of our study include its retrospective nature; the tertiary nature of the cornea clinic (with a potential for selection bias towards more severe disease presentation), and the multimodal nature of treatment which precludes direct comparisons with published literature. However, the treatments provided by our facility do reflect the "real life" actions of most ophthalmologists in the treatment of neurotrophic corneas.

In conclusion, it is important for the comprehensive ophthalmologist to consider neurotrophic keratopathy in the assessment of the asymptomatic dry eye patient as delayed diagnosis may cause significant visual morbidity. Management of neurotrophic keratopathy is challenging and requires addressing of its multifactorial nature. Herpetic etiology, pars plana vitrectomy and neurosurgical causes make up a significant proportion of neurotrophic keratopathy. Associated HSV/VSV, advanced age and Stage 3 disease at diagnosis are significant risk factors for perforation. Persistent epithelial defects should be expectantly managed as corneal perforation is a serious complication. Current treatment approaches aim to utilize conservative medical treatments to promote healing and ocular surface maintenance before utilizing surgical methods, which are more invasive and often require concurrent medical management to be successful. Novel approaches using surgical sensory neurotization have shown potential to improve clinical outcomes.

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