Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

Minimally invasive corneal neurotization for neurotrophic keratopathy: The potential effect of age, denervation chronicity and lesion location

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ARTICLE INFO

ABSTRACT

Purpose: Neurotrophic keratopathy (NK) is an uncommon but challenging clinical condition characterized by altered corneal nerves and sensation leading to corneal damage. Corneal neurotization, a surgical technique that aims to "re-innervate" the cornea, has gained increasing popularity in view of the potential to permanently improve or even restore the normal corneal sensation. In this study, we aimed to report the outcomes of two cases of NK that underwent indirect minimally invasive corneal neurotization (MICN) with a sural nerve autograft, and to provide plausible explanations for the observed clinical outcomes.

Observations: This was an interventional case series of two patients who underwent MICN for severe unilateral NK. The MICN technique was adapted from the technique originally described by Elbaz et al., in 2014. Clinical severity of NK was graded according to Mackie's grading system. Corneal sensation was measured using the Cochet-Bonnet esthesiometer (0–60mm) and corneal nerves were examined using *in vivo* confocal microscopy (IVCM) with Heidelberg HRT3 Rostock Corneal Module. Patient 1 was a 70-year-old man with a right grade III NK following trigeminal nerve decompression for trigeminal neuralgia. Patient 2 was a 62-year-old man with a left grade II NK following a left-sided acoustic neuroma resection. The denervation time was 23 years for both patients. Following the MICN surgery, none of the patients achieved sustained improvement in the corneal sensation (though patient 1 achieved a transient improvement in central corneal sensation to 20mm at 4 months' postoperative before returning to 0mm at 6 months' postoperative). IVCM did not reveal any changes in the corneal nerve density and morphology post-MICN.

Conclusions and Importance: Based on our observations and the literature, we postulate that long denervation time, proximal injury to the trigeminal nerve and older patient age may serve as poor prognostic factors for MICN. As CN is being increasingly adopted in clinical practice for treating NK, understanding of these potential factors will facilitate better risk-benefit stratification and patient counselling. Future larger studies are required to elucidate these findings.

1. Introduction

Neurotrophic keratopathy (NK) is an uncommon but challenging clinical condition characterized by altered corneal nerves leading to impairment in sensory and trophic functions with consequent corneal epithelium breakdown.[1] Significant insult to any part of the corneal sensory pathway between the cornea and the trigeminal ganglion may lead to the manifestation of NK. A wide range of etiologies have been reported, including infectious keratitis, inflammation, chemical/thermal eye injury, iatrogenic causes (e.g., corneal and neurosurgery), metabolic disease (e.g., diabetes), radiation keratopathy, and neurological conditions affecting the trigeminal nerve (e.g., cerebellopontine angle tumor).[1–6] The loss of corneal sensation can be partial (hypoesthesia) or complete (anesthesia). Depending on the cause, severity and

laterality of the disease, NK can be managed by a range of treatments, including conservative measures such as topical lubricants, antibiotics, steroids (used with caution), contact lens, and surgeries such as tarsorrhaphy, amniotic membrane transplant.[1] However, the majority of the treatments aim at supporting the ocular surface homeostasis instead of addressing the underlying pathophysiology of NK. More recently, topical cenegermin, a recombinant nerve growth factor (NGF), has shown promise in improving the corneal healing and/or corneal sensation in NK, though evidence of corneal nerve regeneration and long-term efficacy (beyond 1-year post-treatment) is lacking.[7–9]

In the recent years, corneal neurotization (CN) – a surgical technique that aims to "re-innervate" the cornea – has gained increasing popularity in view of the potential to permanently improve or even restore the normal corneal sensation.[10–12] The novel concept and technique was first proposed by Terzis et al. in 2009.[13] Since then, various modifications of the technique have been proposed and performed, with variably good success.[10–12,14–18] In this study, we aimed to report the outcome of two patients with severe unilateral NK who underwent corneal neurotization using the technique described by Elbaz et al.[18] We also aimed to provide plausible explanations about the reasons associated with the observed outcomes in these two cases.

2. Findings

This was an interventional case series of two cases that underwent CN surgery for severe unilateral NK. Ethics approval was not required for this retrospective case series, but the study was conducted in accordance with the tenets of the Declaration of Helsinki.

2.1. Surgical technique

The surgery was performed using the CN technique described by Elbaz et al.,[18] or also known as the indirect, minimally invasive corneal neurotization (MICN). Briefly, a segment of sural nerve was harvested as a nerve graft from the posterior aspect of the leg of the same patient. The contralateral supratrochlear nerve was isolated using a short transverse medial upper eyelid incision just below the eyebrow and dissected cranially for a short distance. The harvested sural nerve autograft was then passed via the eyelid incision underneath the skin of the bridge of the nose and through a subcutaneous tunnel emerging in the upper fornix of the NK eye and then subconjunctivally towards the limbus at 12 o'clock. The end of the sural nerve was then separated into the smallest possible individual fasciculus, passed 360° around the neurotrophic cornea individually underneath the Tenon's and the conjunctiva, and fixated in position by interrupted sutures at 4–5 points just alongside the limbus using 10/0 Ethilon nylon sutures (Ethicon, J&J Medical Devices, UK). This was followed by a lateral tarsorrhaphy. In both patients the contralateral supratrochlear nerve was of small caliber, hence the sural nerve graft was coapted end-to-end (rather than end-to-side) to the supratrochlear nerve with 10/0 Ethilon sutures.

2.2. Clinical measurement of the structure and function of corneal nerves

The presence and severity of NK was determined by clinical evaluation of corneal sensations (centrally and at 4 quadrants) using the Luneau Cochet–Bonnet esthesiometer (CBE) (Western Ophthalmics, WA), which provided a quantitative measurement of corneal sensation in millimetres, ranging from 0 mm (absent sensation) to 60 mm (full sensation). Clinical grading of NK was done using the Mackie's classification: (a) Stage I (punctate corneal staining with decreased tear breakup time), (b) Stage II (epithelial defect with rolled edge, stromal swelling with Descemet's fold, and/or anterior chamber inflammation), and (c) Stage III (stromal melt and/or perforation).[19] The presence (or absence), morphology, density and distribution of the sub-basal corneal nerve plexus was visualized using *in vivo* confocal microscopy (IVCM) with Heidelberg HRT3 laser scanning technology and Rostock Corneal

Module (Heidelberg Engineering Inc, Franklin, MA). All tests were performed pre and postoperatively at regular intervals to monitor the clinical progress.

2.3. Case 1

A 65-year-old man was referred to the ophthalmology department in 2012 for management of his right NK, which developed following a right microvascular decompression for trigeminal neuralgia in 1994. The patient was asymptomatic for 8 years after the initial procedure, until the neuralgia recurred in 2002. Since the recurrence, he had been taking regular analgesia (including paracetamol, amitriptyline, and pregabalin) and had undergone several surgical procedures, including multiple nerve blocks, but none provided long-term relief from the neuralgic pain. The patient was an ex-smoker (stopped >30 years ago) and was otherwise healthy with no other past medical history such as diabetes, cardiovascular, pulmonary, or renal diseases.

On presentation in Mar 2012, he complained of ongoing right periocular pain. The corrected-distance-visual-acuity (CDVA) was 20/40 in the right eye and 20/20 in the left eye. Slit-lamp microscopic examination of the right eye revealed inferior paracentral corneal scarring and thinning, inferior superficial punctate epithelial erosions (stage I NK), and absent corneal sensation (Fig. 1A–C). No lagophthalmos was noted. The left cornea was healthy with normal corneal sensation, centrally and in all 4 quadrants. The patient was started on intensive topical lubricants and remained under the care of the pain management team for his periocular neuralgic pain. During the subsequent 5-year follow-up period (Nov 2012–Jun 2017), the patient suffered from multiple episodes of corneal epithelial breakdown with recurrent corneal ulcers, leading to progressive central corneal scarring, melting and peripheral neovascularization (stage III NK). The patient was treated with intensive topical lubricants, insertion of punctal plugs, and intermittent topical antibiotics combined with bandage contact lens.

In July 2017 (at the age of 70 years old), a right MICN surgery was performed. Preoperatively, the right CDVA was 20/30 and the corneal sensation was completely absent in the entire cornea (0 mm on CBE). Schirmer's test over 5 mins with topical anesthesia was normal in both eyes (>10 mm). IVCM demonstrated attenuated sub-basal corneal nerve plexus in the right eye and normal nerve appearance and distribution in the left eye. The denervation time was approximately 23 years.

At 1 month postoperative, some improvement in the right forehead sensation was noted. At 2 months postoperative, the right eye corneal sensation improved to 5 mm in the superotemporal and inferonasal quadrants and to 5 mm in superonasal quadrant. The sensation remained absent (0 mm) in the inferotemporal quadrant and centrally. At 4 months postoperative, the corneal sensation improved to 20 mm centrally and 10 mm in superonasal quadrant. Unfortunately, the corneal sensation reduced to 0 mm in all areas, including centrally and peripherally in all four quadrants, at 6 months postoperative. The CDVA and ocular surface remained stable with intensive topical lubricating drops and intermittent short courses of topical steroids. IVCM of the right cornea at 2-year postoperative demonstrated the presence of attenuated sub-basal nerve plexus, which was similar to the preoperative findings. Schirmer's test over 5 mins with topical anesthesia remained normal in both eyes postoperatively. During the last follow-up visit in Aug 2019 (2 years post-CN), the patient's eye remained stable with a CDVA of 20/30, though he complained of some extent of numbness affecting the area from where the right sural nerve was harvested and a degree of mild instability in his right foot (with preserved walking ability).

2.4. Case 2

A 58-year-old man was referred to the ophthalmology department by the neurosurgical team for further management of exposure keratopathy and NK in the left eye in 2014. He was previously diagnosed with left-
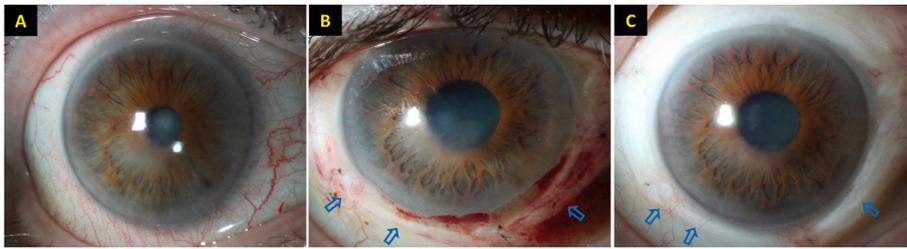
Fig. 1. Slit-lamp photography of the right eye of Patient 1. **(A)** Preoperative slit-lamp photography demonstrating conjunctival inflammation and central corneal scarring before the minimally invasive corneal neurotization (MICN) surgery. The corneal sensation was completely absent throughout the cornea [0 mm on Cochet-Bonnet esthesiometer (CBE) centrally and in all 4 quadrants]. **(B)** Slit-lamp photography at 3-week post-MICN demonstrating the presence of grafted sural nerve (*blue arrows*) at the perilimbal region, with some residual subconjunctival hemorrhage. **(C)** Slit-lamp photography at 4-month post-MICN demonstrating the presence of grafted sural nerve (*blue arrows*) at the perilimbal region with stable ocular surface with some improvement in the extent of corneal scarring. Central corneal sensation improved to 20 mm but reduced to 0 mm at 6-month postoperative. The ocular surface remained stable until the last follow-up at 2-year postoperative. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

sided acoustic neuroma in 1994, which was surgically excised. Following the surgery, he developed a complete left lower motor neuron facial palsy (House-Brackmann grade 6)[20] with progressive and recurrent corneal epithelial breakdown, leading to gradual reduction in visual acuity. In 1997 the patient suffered from a recurrent left acoustic neuroma for which he underwent a repeat surgical resection of tumor via a translabrynthine approach, followed by gamma knife radiosurgery in 1998. The surveillance MRI scanning showed evidence of residual tumor that has since remained stable. The patient was a non-smoker and his past medical history included mild asthma with no other significant systemic diseases such as diabetes, cardiovascular, pulmonary, or renal diseases.

On presentation to the ophthalmology department in June 2014, his CDVA was hand movement (HM) in the left eye and 20/30 in the right eye. Slit-lamp microscopic examination revealed left central corneal scarring, stromal edema, vascularization, inferior epithelial hypertrophy, lower lid entropion with trichiasis, partial lateral tarsorrhaphy, and lagophthalmos. No epithelial defect was noted at that visit. Corneal sensation was completely absent, centrally and in all 4 quadrants, in the left eye (0 mm on CBE). These findings were consistent with an exposure keratopathy with stage II NK (with healed epithelial defect). The right cornea was healthy with normal corneal sensation, centrally and in all 4 quadrants. The patient was started on intensive topical lubricants and intermittent short courses of topical steroids. He subsequently underwent a left lateral wedge resection with inferior retractor plication and lateral tarsorrhaphy to manage the entropion and exposure keratopathy in Oct 2014. A further left lower lid repositioning and tightening was performed 6 months later. Subsequently the ocular surface remained stable, and the patient was asymptomatic despite a 4 mm residual lagophthalmos.

In Feb 2018 (at the age of 62 years old), the patient underwent the above mentioned left MICN surgery with the aim of improving and stabilizing the ocular surface before proceeding to an optical keratoplasty. The denervation time was approximately 23 years. Postoperatively, the patient was followed up regularly but there was no evidence of improvement of the corneal sensation, centrally and peripherally in all four quadrants, noted at any time point (Fig. 2). At the last follow-up visit (18 months post-CN), his left vision remained at HM. Schirmer's test with topical anesthesia after 5 mins was 12 mm in the right eye and 10 mm in the left eye. A stable ocular surface with central corneal scarring, vascularization, epithelial hypertrophy, and perilimbal circumferential nerve graft was noted. The corneal sensation in the left eye remained completely absent (0 mm) and IVCM did not reveal any sub-basal nerve plexus.

3. Discussion

Since the first description of the CN technique by Terzis et al. in 2009,[13] the literature has seen a rapid proliferation of various CN techniques.[11,21,22] The surgical techniques can be broadly divided into direct and indirect CN. The original direct CN technique[13] involves
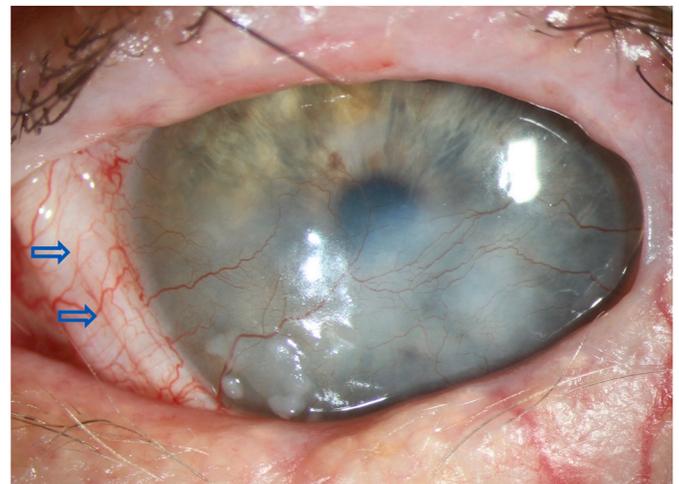

Fig. 2. Slit-lamp photography of the left eye of Patient 2 at 3-month post-minimally invasive corneal neurotization (MICN) surgery. There was significant corneal vascularization and scarring in the central and inferior cornea, with localized epithelial hypertrophy. The presence of grafted sural nerve (*blue arrows*) at the perilimbal region was noted. The corneal sensation remained absent throughout the entire follow-up period. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

transplantation of the contralateral supratrochlear and supraorbital nerves to the ipsilateral perilimbal area of the neurotrophic cornea. While good results have been reported in several studies, this technique requires a large bicoronal incision and extensive nerve dissection, which can negatively affect the cosmetic appearance and result in a longer recovery time.[22] In 2014, Elbaz et al.[18] described an innovative indirect MICN technique where sural nerve autograft was harvested, coapted to the supratrochlear nerve and transplanted to the perilimbal region of the affected cornea. This technique not only obviates the need for a bicoronal incision but can also be used to treat bilateral NK cases.

Previously, we reported two cases of NK that underwent direct CN, using Terzis et al. technique, with a 50% success rate.[12] That report also provided one of the earliest accounts of visualizing the regeneration of corneal nerves following CN using IVCM. We also demonstrated the lack of direct connection of the nerves from the perilimbal fascicles, suggesting that the regeneration of corneal nerves is likely attributed to the paracrine trophic support instead of direct sprouting from the perilimbal fascicles. In view of our previous relatively successful experience and the advantages offered by the newer indirect CN techniques, we shifted our technique from direct CN to MICN in mid 2017.

In this study, we reported the clinical outcomes of two patients who underwent MICN described by Elbaz et al. While the efficacy of MICN has been favorably demonstrated in many studies,[14,18,23] we did not

observe the same positive outcome. Patient 1 achieved a transient and mild improvement in the corneal sensation (from 0 mm to 20 mm on CBE) lasting for only 4 months and patient 2 did not achieve any improvement of corneal sensation throughout the entire follow-up period. This raised the question whether indirect CN was less effective than direct CN. Catapano et al.[14] reported promising results in 16 patients (n = 19 eyes), with an average age of 12.5 years, who underwent MICN for various causes of NK, with a mean improvement of corneal sensation from 0.8 mm preoperative to 49.7 mm at final follow-up (mean 24.0 ± 16.1 months). Fogagnolo et al.[15] recently conducted a multi-center study of 25 patients (n = 26 eyes), with an average age of 45.4 years, in Italy comparing the effectiveness and safety between direct and indirect CN techniques for NK. It was shown that all patients with NK achieved complete corneal healing, with a mean healing duration of 3.9 months and a mean improvement of corneal sensation of ~20 mm on CBE at 1-year follow-up, suggesting that both techniques were comparably effective and safe. Regeneration of corneal nerves in the affected corneas were also confirmed on IVCM.

Based on our findings and the knowledge gleaned from the literature, we aimed to provide plausible explanations about the potential factors for the unsuccessful outcome observed in our study. Firstly, the long denervation time may play an important role. It is established that the regenerative ability of affected peripheral nerves diminishes over time.[24,25] In our previous report,[12] we observed that the patient who achieved good restoration of the corneal sensation following CN had a denervation duration of 3.7 years as compared to the other unsuccessful case which had a denervation duration of 13.6 years. In this study, both our patients had a prolonged denervation time of 23 years, which might have negatively affected the prognosis of corneal sensation improvement following CN. Comparing with other studies that reported good outcomes following CN, the majority of the included patients had a considerably shorter denervation time (around 1–6 years).[14,17,26] On the other hand, Lin et al.[27] included 13 patients with herpes simplex keratitis (HSK) with a mean denervation time of 15.2 years and demonstrated that CN was able to improve the severity of NK in in 11 (84.6%) patients. However, the extent of improvement in corneal sensation following CN was not fully reported.

Secondly, the original pathology and/or severity of the underlying condition may play a contributory role. Both of our patients included in this study suffered from severe surgical injury affecting the proximal part of the fasciculus of trigeminal nerve. It is well known that axonal injury to the nerve fibers, including the cranial nerves, can result in antegrade degeneration of the distal axon, a phenomenon known as "Wallerian degeneration".[28] It is likely that patients with more proximal trigeminal nerve injury will have less "functional reserve" (e.g., trigeminal injury following acoustic neuroma surgery) compared to patients with more distal trigeminal nerve insult (e.g., HSK), therefore the former group may have a lesser chance of improvement in corneal sensation following CN. In a recent study of 11 eyes, Elalfy et al.[23] demonstrated 9 (81.8%) patients achieve some improvement in corneal sensation following MICN. However, a closer look at each individual case revealed that patients with more proximal trigeminal injury (i.e., 4 patients with vestibular or trigeminal schwannoma) only achieved minimal improvement in corneal sensation (from 0 mm to 0–10 mm on CBE) following MICN whereas patients with a more distal pathology/injury to the trigeminal nerve (e.g., ocular pathology such as HSK or injury from ethmoidal carcinoma resection) achieved a significant improvement in corneal sensation postoperatively (from 0 mm to 50 mm on CBE). This observation may also explain the good outcome of the 13 patients with HSK shown in Lin et al. study despite a long denervation duration of 15 years.[27]

Another potential factor that may have negatively contributed to the outcome of CN is the patients' old age. In our study, our patients underwent MICN at the age of 70 years and 62 years. This was significantly higher than the studies reported in Catapano et al.[14] and Fogagnolo et al.,[15] who included patients with a mean age of 12.5 years and 45.4

years, respectively, at the time of CN. Ageing has been shown to negatively affect neural plasticity[29] and peripheral nerve function and regeneration,[30,31] including the loss of myelinated and unmyelinated nerve fibers, slower axonal regeneration, and lower amount of trophic and tropic factors secreted by reactive Schwann cells during the regenerative process after nerve injury. In addition, the supratrochlear nerves of our two patients were found to have a much smaller caliber than the sural nerve graft. This could mean that there were fewer axons from the supratrochlear nerves available to support the regeneration and functioning of the harvested sural nerve graft.

Our current study is primarily limited by the small sample size, due to the rarity of the disease and the number of patients that are suitable for CN. However, as the field of CN is rapidly expanding and the technique is likely to be increasingly adopted by more ophthalmic and plastic surgeons globally, we believe that these unsuccessful cases will provide important insights into the potential contributing factors for the success (and failure) of CN, thereby guiding the patient selection criteria. Future larger studies of CN for NK, consisting of a case-mix with heterogeneous pathologies (including both central and peripheral causes), patient age group, clinical severity, and surgical outcomes (including both successful and unsuccessful cases) will help to further elucidate our observations and postulations.

4. Conclusions

This study highlights the unsuccessful outcomes of MICN and provides plausible explanations and insights into the potential prognostic factors, which can potentially help improve the patient selection for CN surgery in the future.

Patient consent

Written informed consent was obtained from both patients for all the performed procedures and for the use of clinical information for publication purpose.

Authors' contributions

All authors attest that they meet the current ICMJE criteria for authorship. Study design and conceptualization: FF; Conduct of study: EB, OAA, FF; Data collection: SPP; Data interpretation and analysis: DSJT, FF; Manuscript drafting: DSJT, SPP; Critical revision of manuscript: EB, OAA, FF; Approval of final manuscript: All authors.

Funding

No funding was received for this work.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Written consent to publish potentially identifying information, such

as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Authorship

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2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement 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.

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Declaration of competing interest

None.

Acknowledgement

None.

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