CORNEAL NEUROTISATION FOR NEUROTROPHIC KERATOPATHY: CLINICAL OUTCOME, IN VIVO CONFOCAL MICROSCOPIC AND HISTOPATHOLOGIC FINDINGS

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Conflict of interest: None

Funding / support: None

Key words: Corneal anaesthesia; corneal neurotisation; aesthesiometer; in vivo confocal microscopy; neurotrophic keratopathy; keratitis; meningioma
ABSTRACT (Word count: 288 words; max. 250 words)

Purpose: To describe the long-term outcome, in vivo confocal microscopic (IVCM) and histopathologic findings following corneal neurotisation surgery for unilateral neurotrophic keratopathy.

Methods: Two patients with severe unilateral neurotrophic keratopathy secondary to cerebellopontine angle meningioma were included. Corneal neurotisation surgery was performed at a tertiary referral centre. Corneal sensation was measured using Cochet-Bonnet aesthesiometer. IVCM was performed using Heidelberg HRT3 laser scanning technology combined with Rostock Corneal Module. Histopathologic examination was performed on the excised corneo-scleral disc of patient 2.

Results: Preoperatively the corneal sensations of the affected eyes of patients 1 and 2 were 0.5mm and 0mm, respectively. Following the corneal neurotisation surgery, patient 1 noticed subjective improvement of corneal sensation at two months and objective improvement by thirteen months (60mm in 3 quadrants). Sub-basal and stromal corneal nerves were identified with IVCM at 15-months and 4-years postoperative. In patient 2 the corneal sensation improved to 10mm in 3 quadrants at nine months postoperatively. However, the corneal sensation was absent at two years postoperatively despite the presence of sub-basal and stromal nerves identified on IVCM. At five years postoperative, evisceration was performed to ameliorate uncontrolled ocular pain and poor cosmesis. Histopathologic examination of the excised corneo-scleral disc confirmed the presence of normal sized, corneal stromal nerve fascicles (stained positive for neurofilament) but without direct continuity with the transplanted peri-limbal nerve bundles.

Conclusion: This is the first report to elucidate the mechanism of corneal neurotisation surgery at a cellular level. Although only one patient achieved short-term improvement of corneal sensation postoperatively, the findings on IVCM and histopathologic examination suggest that the partial regeneration / maintenance of corneal nerves following corneal neurotisation surgery is likely attributed to the paracrine neurotrophic support, instead of direct sprouting, from the peri-limbal transplanted nerve fascicles.

INTRODUCTION
Corneal sensory innervation plays pivotal roles in maintaining ocular surface homeostasis, including blink reflex, corneal wound healing, tear production, and limbal stem cell function (Heigle and Pflugfelder 1996; Ueno et al. 2012). Neurotrophic keratopathy (NK) is a type of degenerative corneal disease characterised by impairment of corneal sensation. It is an orphan disease with an estimated prevalence of 1-5 per 10000 people (http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=137596). Depending on the severity of NK, which can be graded by Mackie’s classification, the clinical features can range from punctate epitheliopathy (stage 1), persistent epithelial defect (stage 2), to corneal ulcer with stromal involvement that may be complicated by stromal melt and subsequent perforation (stage 3). Various aetiologies have been implicated in the manifestation of unilateral and bilateral NK. The common causes include herpetic keratitis, chemical eye injury, nerve transection due to anterior segment surgery and injury/damage to the trigeminal nerve (e.g. intracranial space occupying lesion such as acoustic neuroma and/or neurosurgical procedures that damage the trigeminal ophthalmic branch) (Pushker et al. 2001).

The management of NK is clinically challenging (Bonini et al. 2003). Various medical and surgical therapeutic strategies are available for unilateral or bilateral NK. However, the majority of the treatment to date aims at protecting the corneal surface and promoting corneal epithelial healing instead of addressing the underlying corneal anaesthesia (Pushker et al. 2001; Bonini et al. 2003). Terzis et al. (2009) reported a small series of 6 patients using an innovative and effective surgical technique in restoring the ipsilateral anaesthetic cornea with the use of contralateral supraorbital and supratrochlear nerves (named corneal neurotisation). They proposed that the mechanism of corneal neurotisation was related to direct sprouting from the healthy contralateral transplanted nerves into the anaesthetic cornea. However, no anatomical or histopathological evidence was provided to confirm the proposed mechanism.

We describe two cases of unilateral NK that were managed with corneal neurotisation surgery as described by Terzis et al. (2009). We report the long-term outcome of the treatment and aim to describe the potential underlying mechanism of corneal neurotisation surgical procedure at a cellular level using in vivo confocal microscopy (IVCM) and histopathologic examination.

MATERIALS AND METHODS
This study included two interventional cases of NK managed with corneal neurotisation surgery. The surgical technique was adopted with minor modifications from the method described by Terzis et al. (2009). The surgery involves identification of supratrochlear and supraorbital nerves of the contralateral / unaffected side via a bicoronal incision, dissection proximal to supraorbital margin and tunnelling the nerve branches over the nasal bridge to the ipsilateral upper lid crease. Followed by passing the nerves through superior conjunctival fornix and tunnelling the nerves within the sub-Tenon’s space circumferentially around the limbus of the affected cornea under general anaesthesia. Informed consent was obtained from both patients preoperatively and permission to perform this new surgical procedure was also obtained from the Clinical Governance Body.

Corneal sensation was measured using Cochet-Bonnet aesthesiometer (CBA). In vivo confocal microscopy (IVCM) was performed using Heidelberg HRT3 laser scanning technology using the Rostock Corneal Module. For histopathological assessment, the surgically removed corneo-scleral disc was fixed in standard 10% buffered formalin for 24 hours. After fixation, the specimen was bisected down the middle and embedded along the long cut surface, allowing the transplanted nerve to be seen in continuity with the corneal stroma. The tissue was exposed to conventional histopathology laboratory processing to paraffin blocks. Sections measuring 4µm were cut and stained with haematoxylin and eosin (H&E). Sections were also stained immunohistochemically for neurofilament (Dako Denmark clone 2F11, diluted 1:500 with antigen retrieval using Dako high pH buffer).

RESULTS

Case 1
A 25-year old male was referred to the ophthalmology department for management of left eye exposure keratopathy and NK following the removal of left cerebellopontine angle meningioma in May 2008. Examination revealed multiple cranial nerve palsies (V, VI, VII, VIII nerves), evidenced by left sided total corneal anaesthesia, abduction deficit, facial nerve palsy, and severe hearing loss.

From June 2008 to December 2009, patient’s left eye best corrected visual acuity (BCVA) had deteriorated from 6/9 (Snellen) to counting fingers (?at 1m) due to the progression of NK from Mackie’s stage 1 (presence of punctate epitheliopathy only) to stage 3 (recurrent breakdown of the corneal epithelium with stroma involvement). There was worsening corneal neovascularisation and central corneal involvement.
despite good eyelid closure and intensive treatment (Figure 1A). The treatment included frequent lubricating eye drops, bandage contact lens, punctal plug insertion, repeated tarsorrhaphy, Botox ® (onabotulinumtoxin A) injection of the upper lid, and gold weight implantation in the upper lid combined with lower lid tightening. Right eye BCVA was 6/9. Since February 2010, the left cornea remained quiescent with central scar and vascularisation without any epithelial defect (Figure 1B).

In 2011, the patient requested to explore the possibility of removal of the left upper eyelid gold weight with the view of improving their facial appearance (Figure 1C). However, he was advised of the risk of exposure keratopathy and worsening of neurotrophic keratopathy, unless the corneal sensation was improved / restored. In January 2012, the patient underwent left corneal neurotisation surgery following a lengthy discussion of the risks and benefits. His left BCVA was hand movements. The denervation time was 3.7 years. Preoperatively the patient’s corneal sensitivity was nearly absent in the left eye (0.5mm centrally) and completely normal in the right eye (60mm centrally). Schirmer’s test with topical anaesthesia was 19mm/5mins (left eye) and 38mm/5mins (right eye). By two months postoperatively, he had regained motor and sensory functions of the right forehead and was subjectively more aware of the sensation of the left eye. BCVA was 6/60 (left eye) and 6/6 (right eye). At thirteen months postoperative, his corneal sensation in the left eye had improved to 40mm centrally and he regained a completely normal level (60mm) in 3 quadrants except for the superior-nasal quadrant (0mm). Corneal nerves were successfully identified on IVCM at this stage (Figure 1D-F). Normal corneal sensation (60mm) was achieved in all 4 quadrants by two years postoperative and maintained until the last visit at four years postoperative. BCVA had improved to 6/18 (left eye) at two years postoperative and maintained at 6/36 four years postoperative (Figure 1G). Schirmer’s test was 13mm/5mins. Attenuated corneal nerves were identified at the sub-basal and stromal levels on IVCM at four years postoperative (Figure 1H-I).

Case 2
A 39-year-old male, who suffered from left V, VII and VIII cranial nerve palsies following the removal of left cerebellopontine angle meningioma in October 1997, was referred to the ophthalmology department 2 weeks later for the management of a large corneal ulcer affecting his left eye (Mackie’s stage 3 NK). BCVA was 6/60 (left eye) and 6/5 (right eye). The corneal sensation was absent in the left eye (0mm centrally and in all 4 quadrants) and completely normal sensation in the right eye (60mm). The corneal ulcer healed with resultant central corneal scar following a
central and lateral tarsorraphy. From February 1998 to January 2011, patient had suffered from multiple episodes of left corneal epithelial and stromal breakdown (stage 3 NK) with progressive peripheral and central corneal neovascularisation, scarring and inferior keratinisation, resulting in hand movements vision (Figure 2A). During this period patient had also undergone facial reanimation surgery to improve the left sided facial palsy.

In May 2011, left corneal neurotisation surgery was performed under general anaesthesia with the aim of improving the corneal sensation and potentially the vision. The denervation time was 13.6 years. Preoperatively the BCVA was hand movements and there was complete absence of corneal sensation centrally and in all 4 quadrants (0mm on CBA). Schirmer’s test with topical anaesthesia was 10mm/5mins (left eye) and 12mm/5mins (right eye). At 9-months postoperative, the left corneal sensation improved to 10mm centrally and at three quadrants on CBA except for inferior temporal quadrant (0mm) (Figure 2B). Corneal sensation was maintained at 7.5mm in the superior-nasal quadrant and 5mm in three other quadrants at 15-months postoperative. However, at 2-years postoperative left corneal sensation was completely absent despite the presence of sub-basal and stromal corneal nerves on IVCM (Figure 2C-D). Since then patient’s left eye had deteriorated to perception of light (PL) vision only in the subsequent years. Schirmer’s test with topical anaesthesia was 8mm/5mins (left eye). Patient had been offered the treatment option of Boston keratoprosthesis (KPro); however patient declined and chose to proceed with left eye evisceration and orbital implant in August 2016 to ameliorate his severe uncontrolled eye pain and poor cosmesis.

Histopathologic findings of the dissected left eye corneo-scleral disc
The H&E assessment confirmed the presence of a viable transplanted nerve within the conjunctival stromal tissue beyond the limbus, composed of numerous viable axon fascicles of varying diameter (Figure 3A-B). The transplanted nerve was associated with some adjacent stromal oedema but no inflammation was identified. Assessment of the paraxial superficial and mid corneal stroma showed the presence of neurofilament (NF) positive corneal stromal nerve fascicles (Figure 3C). This staining was compared with two controls. The first control was a ‘normal’ corneo-scleral disc from an enucleation performed for a posterior uveal melanoma and the second control was a penetrating keratoplasty host cornea that was anaesthetic due to herpes simplex keratitis. The first control showed occasional similar-sized NF positive nerve fascicles in the paraxial superficial and mid stroma but they were
fewer in number compared to the nerve transplanted case (Figure 3D). The second control showed very occasional NF positive nerve bundles that were thinner, smaller and distorted (Figure 3E) compared to the nerve transplanted case (i.e. corneal neurotisation) and the first control.

**IVCM findings**

Postoperative IVCM was obtained following corneal neurotisation surgery for patients 1 and 2. Unfortunately IVCM facility was not available preoperatively. To address the issue of absent preoperative IVCM findings, we examined 2 other patients who suffered from complete corneal anaesthesia; one was following the removal of right acoustic neuroma (patient 3) and another was following microvascular decompression of right trigeminal nerve (patient 4). IVCM obtained from the affected and unaffected ‘control’ eyes of patients 3 and 4 demonstrated attenuated, beaded sub-basal and stromal nerves in the affected eyes and normal corneal nerves in the unaffected eyes (Figure 4A-H).

The postoperative IVCM of our patients 1 and 2 showed healthier corneal nerves (with less attenuation and beading) when compared to patients 3 and 4 who did not have corneal neurotisation surgery. This finding supports the regenerative mechanism of the corneal neurotisation surgery – at least partially – on a microscopic anatomical ground.

**DISCUSSION**

Management of NK is often clinically challenging and the majority of the treatment serves as supportive rather than restorative measures for the underlying corneal anaesthesia. In this study we present the heterogenous long-term outcome of two patients who underwent corneal neurotisation surgery. More importantly we describe the previously unreported IVCM and histopathologic findings after corneal neurotisation surgery, providing an invaluable insight into the underlying mechanism.

The concept of neurotisation, which involves the transfer of a healthy nerve segment into the affected area to restore either the sensory or motor functions, has been applied across different specialties but not in ophthalmology until recently (Brunelli 2004; Flores et al. 2009). Terzis et al. (2009) was first to report the use of a revolutionary technique to restore ipsilateral corneal sensation with contralateral supratrochlear and supraorbital nerves in 6 patients who suffered from unilateral facial nerve palsy and neurotrophic keratopathy. Their patients achieved significant
objective improvement in corneal sensation (based on CBA) at 2.80 ± 2.17 years. In our cases, the corneal sensation objectively improved by nine months and fifteen months postoperatively for patient 1 and patient 2, respectively, which was quicker than previously described by Terzis et al. (2009). However a sustained improvement of corneal sensation was not observed in patient 2 by 2 years postoperatively. This might be attributed to the considerably longer denervation time in patient 2 (13.6 years) than in patient 1 (3.7 years). Studies have shown that the regenerative capacity of the denervated peripheral nerves diminishes over time (Gordon et al. 2011; Fu and Gordon 1995). However, this was not observed in Terzis et al. (2009) study where one of their patients who had a denervation time of 4 years due to acoustic neuroma achieved low corneal sensation (<20mm on CBA) whereas another patient who had an acoustic neuroma with a denervation time of 24 years achieved good corneal sensation (>50mm) following corneal neurotisation surgery. This suggests that denervation time is not the sole prognostic factor of corneal neurotisation surgery.

Elbaz et al. (2014) reported another novel and effective corneal neurotisation technique by harvesting the medial cutaneous branch of the sural nerve followed by coaptation with the supratrochlear nerve (donor nerve) either unilaterally or bilaterally in 3 young patients. In comparison to the technique described by Terzis et al., this approach allows restoration of bilateral corneal sensitivity and obviates the need for a large bicoronal incision, which can be potentially cosmetically unappealing.

The regenerative ability of the corneal nerves has been reported in various observational and experimental studies. It was shown that the dissected corneal nerves (e.g. following laser in situ keratomileusis, photorefractive keratectomy, and penetrating keratoplasty) could regenerate and re-innervate the cornea, emanating from the peripheral cornea and branching towards the central and superficial corneal layer (Erie et al. 2005). In addition, Aggarwal et al. (2015) demonstrated regeneration of corneal nerves in 16 patients with corneal neuropathy after being treated with autologous serum tears. Despite the success in restoring the corneal sensation observed clinically in the previous studies, Terzis et al. (2009) and Elbaz et al. (2014) did not confirm the corneal re-innervation on anatomical or histopathologic ground (i.e. direct visualisation of the corneal nerves on IVCM or histopathology postoperatively). Terzis et al. (2009) and Elbaz et al. (2014) postulated the improvement in corneal sensation was attributed to the axonal regeneration of the
nerve graft fascicles inserted around the corneal limbus with subsequent growth into the corneal stromal or subepithelial level.

The availability of IVCM and histopathological findings in our study allowed us to investigate the actual mechanism of corneal neurotisation at a cellular level and whether it was related to direct sprouting from the peri-limbal transplanted nerve fascicles. Due to the absence of preoperative IVCM findings (IVCM was not available at the time), we have utilised the IVCM photos of two other patients (Patient 3 & 4) with complete corneal anaesthesia (one was following the removal of right acoustic neuroma and another was following microvascular decompression of right trigeminal nerve) as references. When compared to their unaffected eyes, the corneal nerves in the affected eyes were more beaded and attenuated – indicators for neurotrophic cornea (Cruzat et al. 2017). In patients 1 and 2, we observed less attenuation and less beading of the corneal nerves on the postoperative IVCM; however the quantity and quality of these nerves were poorer than the normal ‘control’ eyes of patients 3 and 4. This suggests that corneal neurotisation surgery supports and potentially regenerates (to a certain extent) the affected corneal nerves. Interestingly there was a good amount of corneal nerves visible postoperatively in patient 2 (more than patient 1 who had complete recovery of corneal sensation) despite the absence of corneal sensation, suggestive of a poor anatomical-functional correlation in these patients.

Furthermore, we confirmed the presence of stromal corneal nerves on histopathologic examination in patient 2, with no evidence of any direct re-innervation from the peri-limbal transplanted nerve fascicles into the cornea. We also utilised the histopathologic findings of two controls (one ‘normal’ eye and one anaesthetic cornea secondary to herpes simplex keratitis) for comparison purpose. Intriguingly we observed more abundant corneal nerves in the neurotisation case than the normal eye and larger calibre nerves than the herpes simplex keratitis case. This again supported the regenerative mechanism of corneal nerves following corneal neurotisation surgery. Although the patient’s cornea was completely anaesthetic during evisceration, it would be very unlikely that all the previously established re-innervation had disappeared if the underlying mechanism was related to direct sprouting.

Based on these findings we hypothesise that, instead of direct sprouting, the peri-limbal nerves fascicles stimulate the release of neurotrophic factors, providing a
paracrine neurotrophic support to the original affected corneal nerves, ultimately culminating in its partial / complete regeneration. In addition, the regenerative ability of a denervated peripheral nerve was similarly demonstrated in a rat model when an intact donor nerve graft was laid parallel to the denervated nerve, even without any cross-bridges between the intact donor nerve and the affected nerve (Gordon et al. 2015). These suggest that the underlying mechanism of the regeneration was more likely attributed to the neurotrophic support instead of direct sprouting from the donor nerve. However, the regenerative effect was 67% less when compared to the group that had cross-bridges performed between the donor nerve and the affected nerve.

In recent years there is growing evidence in the literature demonstrating the efficacy of newer biological treatments, including the use of topical nerve growth factor (NGF), neurotransmitters, and matrix therapy agent. Bonini et al. (2000) reported that topical NGF achieved complete resolution of persistent corneal epithelial defect secondary to stage 2 and stage 3 NK by approximately 1 month with significant improvement in corneal sensitivity and visual acuity in 43 patients. Interestingly the improvement of corneal sensitivity was maintained for a long period (means of 9 months and 20 months for stage II and stage III NK, respectively) despite the discontinuation of topical NGF 2 weeks after the resolution of the corneal epithelial defect. It was hypothesised that NGF improves corneal sensation and corneal healing by replenishing the deficit of endogenous NGF release or by simulating corneal sensory innervation, and consequently proliferation and differentiation of epithelial cells. Intriguingly, 3 patients with trigeminal nerve resection had recurrence of persistent corneal epithelial defect that required further treatment of NGF, suggesting that this subgroup had a more severe type of neurotrophic keratopathy with potentially lower level of endogenous NGF with less regenerative property. Yanai et al. (2015) also demonstrated that neurotransmitters like substance P and insulin-like growth factor-1 promote corneal epithelial healing in patients with NK.

Furthermore, the clinical efficacy and safety of a new matrix therapy agent (RGTA, CALCICOL20), resembling heparin sulfates, has been reported in a non-controlled, prospective clinical study in 11 patients with severe NK (Aifa et al. 2012). All these innovative therapeutic avenues can potentially revolutionise the management of NK and provide permanent solution to this previously deemed incurable and severe debilitating disease.
Corneal neurotisation surgery, aiming to address and repair the underlying corneal anaesthesia, provides a potentially efficacious and safe expansion to the current therapeutic armamentarium of NK. Our study supports the concept of partial regeneration/maintenance of corneal nerves following corneal neurotisation surgery on IVCM and histopathologic assessment. We are currently recruiting more patients for corneal neurotisation surgery and are performing pre- and postoperative IVCM examination on all these patients. This will not only help shed light on the underlying regenerative mechanism of the corneal neurotisation surgery but also help quantify and qualify its beneficial effect. Further histopathologic studies and animal model work examining neurotised cornea with restored corneal sensation could also be helpful to further confirm the theory of paracrine neurotrophic support, instead of direct sprouting, from the transplanted nerve fascicles.
REFERENCES


**FIGURE LEGENDS**

**Figure 1.** (A) Slit-lamp photography of patient 1 showed left central corneal and stromal defect with scarring (*red arrow*) and inferior corneal neovascularisation (*black arrow*) secondary to progressive neurotrophic keratopathy. (B) Left cornea became quiescent with central corneal scarring (*red arrow*) and inferior corneal vascularisation (*black arrow*) following 2-year intensive treatment. (C) There was noticeable facial asymmetry due to the presence of gold weight implant in the left upper eyelid (*black arrow*) prior to the corneal neurotisation surgery. (D-F) At 13-month post corneal neurotisation surgery, a mixture of normal-sized and attenuated corneal nerves (*red arrows*) were visualised on in vivo confocal microscopy (IVCM) at sub-basal (40µm and 45µm) and stromal (180µm) levels. Corneal vessels were also visualised (*yellow arrow*). (G) At 4-year postoperative, left eye remained stable with a central corneal scarring without epithelial defect. Supraorbital and supratrochlear nerve grafts from the contralateral side were visible around the limbus (*yellow arrows*). (H-I) At 4-year postoperative, corneal nerves (*red arrows*) were visualised at the sub-basal (46µm; attenuated) and stromal levels (131µm; normal) using IVCM.

**Figure 2.** (A) Slit-lamp photograph of patient 2 demonstrated severe left corneal scarring (*red arrow*) with peripheral corneal vascularisation (*black arrows*) and inferior keratinisation (*yellow arrow*) despite intensive treatment provided. (B) Slit lamp photograph showed central scarring (*red arrow*), peripheral corneal vascularisation (*black arrows*) with inferior keratinisation (*yellow arrow*) of the left cornea and perilimbal transplanted nerve fascicles (*blue arrows*). (C) In vivo confocal microscopy demonstrated the presence of normal-sized corneal nerves (*red arrows*) at the sub-basal (35µm) and stromal levels (169µm) at 2-year post corneal neurotisation surgery despite the complete absence of corneal sensation.

**Figure 3.** (A) Immunohistochemical neurofilament (NF) stained section. Brown is positive staining. The small arrow is the cornea, the asterisk is the sclera and the largest arrow points to one of the axon fascicles of the transplanted nerve. (B) Immunohistochemical NF stained section. Brown is positive staining. This shows the variable size of the fascicles of the transplanted nerve. (C) Immunohistochemical NF stained section. Brown is positive staining. The arrows point to NF positive nerves in the superficial and mid depth paraxial corneal stroma of the nerve transplanted case. (D) Immunohistochemical NF stained section. This is a ‘normal’ cornea control showing fewer NF positive nerves in the superficial and mid depth paraxial corneal
stroma compared to Figure 3C. Note that the magnification of Figures 3C and 3D is identical. (E) Immunohistochemical NF stained section from the anaesthetic cornea caused by herpes simplex keratitis. Despite this image being at a higher magnification compared to Figures 3C and 3D, the arrow points to a smaller, distorted NF positive nerve in the superficial to mid depth paraxial corneal stroma.

**Figure 4.** These *in vivo* confocal microscopy (IVCM) images were obtained from 2 other patients with complete corneal anaesthesia; figures on the left column were obtained from the anaesthetic eyes and figures on the right column were obtained from the unaffected ‘control’ eyes of the same patients. (A-D) IVCM demonstrated attenuated sub-basal corneal nerves (*red arrows*) and borderline attenuated anterior stromal corneal nerves (*yellow arrows*) in the affected right eye, and normal-size corneal nerves (*blue arrows*) at sub-basal and stromal levels in the unaffected left eye of a patient with right corneal anaesthesia secondary to removal of right acoustic neuroma. (E-H) IVCM demonstrated attenuated corneal nerves (*red arrows*) at sub-basal (31μm; *red arrows*) and anterior stromal (66μm; *yellow arrows*) levels in the affected right eye, and normal-size corneal nerves (*blue arrows*) at sub-basal (54μm) and anterior stromal (94μm) levels in the unaffected left eye of a patient with right corneal anaesthesia following microvascular decompression of right trigeminal nerve.