Clinical and Morphologic Outcomes of Minimally Invasive Direct Corneal Neurotization

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Purpose: To describe clinical outcomes of a minimally invasive technique for direct corneal neurotization to treat neurotrophic keratopathy.

Methods: All cases of corneal neurotization for neurotrophic keratopathy performed by a single surgeon using minimally invasive direct corneal neurotization were reviewed. The supraorbital donor nerve was directly transferred to the cornea through an upper eyelid crease incision using either a combination of endoscopic and direct visualization or direct visualization alone. Detailed ocular and adnexal examinations as well as Cochet–Bonnet esthesiometry of the affected cornea were performed. Corneal histopathology and in vivo confocal microscopy after minimally invasive direct corneal neurotization were reviewed in one patient who underwent simultaneous penetrating keratoplasty.

Results: Five consecutive cases in 4 patients were included, with a mean follow up of 15.8 months (range: 11–23 months). Average denervation time was 17.8 months (range: 6–24 months). Baseline corneal conditions were Mackie stage 1 (20%), Mackie stage 2 (40%), and Mackie stage 3 (40%). All patients demonstrated improvements in corneal sensibility and appearance postoperatively. All patients demonstrated stable or improved visual acuity. No patients developed persistent epithelial defects postoperatively, and all achieved return of tactile skin sensation in the donor nerve sensory distribution. In vivo confocal microscopy after minimally invasive direct corneal neurotization and simultaneous penetrating keratoplasty demonstrated regeneration of corneal nerves. Complications included an asymptomatic small bony excrescence lateral to the supraorbital notch in one patient and cataract progression in the patient who underwent penetrating keratoplasty.

Conclusions: Minimally invasive direct corneal neurotization is a safe and effective treatment of neurotrophic keratopathy.

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Neurotrophic keratopathy (NK) is a potentially blinding disease resulting from damage to the ophthalmic division of the trigeminal nerve.[1] The absence of normal nerve function in the cornea can lead to severe visual loss via corneal scarring, ulceration, and perforation.[2–5] Severity of NK may be described using the Mackie staging criteria,[6] wherein stage 1 includes the presence of punctate epithelial erosions, corneal neovascularization, and stromal scarring, stage 2 includes the presence of a frank epithelial defect, and stage 3 includes corneal ulceration, melting, or perforation.

Historically, available treatments such as ocular lubrication, bandage contact lenses, tarsorrhaphy, and amniotic membrane grafting have often failed in preserving visual acuity (VA).[2] Recently, a new topical treatment using recombinant human nerve growth factor, cenegermin (Oxervate, Dompé, Milan), approved by the US Food and Drug Administration in August 2018, has demonstrated encouraging initial results for epithelial healing, but no improvement in corneal sensation.[7–9]

Several techniques for surgical management of NK via corneal neurotization have been described in recent years. Corneal neurotization for NK has demonstrated the ability to achieve improved epithelial integrity,[2,3,10–13] improved corneal sensation,[2,3,10–12] and improved VA.[10–12] In vivo confocal microscopy has also demonstrated increased density of corneal nerves following neurotization.[10,12,14,15] The original techniques for corneal neurotization involved coronal or hemicoronal incisions with reflection of the scalp for direct isolation of the supraorbital and supratrochlear nerves[16,17] with direct nerve transfer.[11,18,19] An alternative surgical approach involves interposition nerve grafting after isolation of the supraorbital or supratrochlear nerve, which can be accomplished with autografts from several locations including the sural nerve,[2,3,13,20] lateral antebrachial cutaneous nerve,[21] and great auricular nerve,[14] or with allografts.[10,22] Direct nerve isolation via coronal incision carries inherent shortcomings, including need for a large incision with subsequent scarring, need for extensive dissection, prolonged operative time, and risk of postoperative hematoma and alopecia.[23,24] Use of interposition nerve grafts creates reliance on an additional coaptation site, axonal regeneration through the graft, and, with the use of autografts, creates potential for additional donor site morbidity. The previously described minimally invasive technique using endoscopic guidance[22,25] for direct nerve transfer mitigates many of these risks. Herein, we report the clinical outcomes of our minimally invasive approach for direct nerve transfer with or without endoscopic guidance, termed minimally invasive direct corneal neurotization (MIDCN).

METHODS

A retrospective review was conducted on all consecutive patients who underwent MIDCN by a single surgeon (I.M.L.). Approval for this study was obtained from the Duke University Institutional Review Board. The study was conducted in accordance with Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

Average corneal sensibility was assessed on all patients using a Cochet–Bonnet (CB) esthesiometer in 4 peripheral quadrants and the

central portion of the cornea to diagnose NK and to assess corneal sensation postoperatively. All patients underwent serial measurements of VA and comprehensive ocular examination with slit-lamp biomicroscopy and fluorescein staining at each preoperative and postoperative visit. Mackie stage values based on slit-lamp examination were recorded for each preoperative patient. Nerve donor site viability was assessed preoperatively in the regions of the bilateral supraorbital, supratrochlear, and infraorbital nerve sensory distribution using a light touch with a cotton wisp. At each preoperative or postoperative visit, patients were asked for subjective symptomatic reports of ocular irritation, pain, and foreign body sensation. Patients were also asked for reports of synesthesia and return of sensibility within the donor nerve sensory distribution at each visit. One patient who underwent simultaneous penetrating keratoplasty (PK) and MIDCN obtained S-100 protein staining to identify corneal nerves in the denervated corneal button and subsequent in vivo confocal microscopy of the transplanted corneal graft postoperatively.

Corneal neurotization was recommended only for patients with visually significant NK due to dense corneal punctate epithelial erosions, persistent epithelial defects, ulceration, neovascularization, or scarring, with denervation time of at least 6 months. Viability of donor sensory nerves was also required preoperatively. Patients with active infectious or inflammatory ocular conditions, known corneal limbal stem cell deficiency, active neoplastic conditions, active local radiotherapy or chemotherapy, immunocompromise, and severe conjunctival scarring were not candidates for neurotization. Also, patients with fewer than 6 months of postoperative follow up or those whose corneal condition deteriorated preoperatively or post-operatively due to causes other than NK (e.g., traumatic corneal injury) were excluded from the study. Patients who underwent surgery with interposition nerve grafts were also excluded from this review. All patients underwent standard processes for informed, written consent and preoperative clearance for general anesthesia.

All patients included in this study underwent MIDCN with or without endoscopic visualization. An endoscopic technique for contralateral supraorbital nerve harvest has been previously described (see Videos A and B, Supplemental Digital Content 1, available at http://links.lww.com/IOP/A215, http://links.lww.com/IOP/A216).[22] Ipsilateral supraorbital nerve transfer was performed in a similar fashion as previously described for endoscopic contralateral supraorbital nerve transfer, but without scalp incisions and glabella tunneling.[25] The isolation of the ipsilateral donor nerve was performed solely through the upper eyelid crease incision under direct visualization (see Video, Supplemental Digital Content Video 2, available at http://links.lww.com/IOP/A217). In some cases, endoscopic guidance was used for dissection of the distal portion of the nerve (i.e., the last 1–2 cm of the donor nerve). Donor nerve length of 4 cm from the supraorbital foramen was harvested for ipsilateral transfer and 7–8 cm for contralateral transfer. All cases involved coaptation of the intact ipsilateral or contralateral supraorbital nerve to the affected eye. A temporary tarsorrhaphy with a 4-0 silk suture was placed at the completion of the procedure. If a patient had a permanent lateral tarsorrhaphy prior to MIDCN, the tarsorrhaphy was reformed in the same fashion at the completion of the surgery. No new permanent lateral tarsorrhaphies were performed during the surgery. The operative eye was patched for one day postoperatively.

Postoperatively, patients were asked to return for follow up within the first week of surgery, at which point their temporary tarsorrhaphy was released. Then, patients were scheduled for clinical examination at approximately 1, 3, 6, 12, and 24 months postoperatively. Follow-up times varied depending on patient-specific variables such as geographical proximity to the clinic and scheduling conflicts. Patients were prescribed ophthalmic antibiotic drops placed in the operative eye and ophthalmic antibiotic ointment placed on the eyelid incision twice daily after the eye patch removal for the first 2 weeks postoperatively. The rest of their preoperative ophthalmic medications were continued postoperatively and tapered based on the clinical improvement.

RESULTS

Five eyes representing consecutive cases in 4 patients met the inclusion criteria for the study, with a mean postoperative follow-up period of 15.8 months (range: 11–23 months). There were 2 males (50%) and 2 females with ages ranging from 5 to 86 years. The average denervation time was 17.8 months (range: 6–24 months), with Mackie stages 1 (20%), Mackie stage 2 (40%), and Mackie stage 3 (40%). All patients demonstrated improvement in CB esthesiometry measurements, subjective increases in corneal sensibility, and improved corneal appearance on slit-lamp biomicroscopy at their last postoperative visit. No patients demonstrated persistent epithelial defects postoperatively, and all patients achieved return of light touch and subjective skin sensation in the sensory distribution of the donor nerve. Three of 4 patients demonstrated significant improvements in VA postoperatively. One patient who was 5 years old was unable to reliably participate in VA testing; however, his postoperative corneal examination improved dramatically. In vivo confocal microscopy 13 months after MIDCN and simultaneous PK demonstrated regeneration of nerves in the anterior corneal stroma. The only postoperative complications included an asymptomatic small bony excrescence lateral to the supraorbital notch in one patient and progression of cataract in the patient who underwent simultaneous PK. The detailed summary of each patient is described below.

Patient 1. An 86-year-old Caucasian woman with a history of herpes zoster keratitis in the left eye (OS) and supraorbital postherpetic neuralgia was referred for the evaluation of NK OS. In the left eye, best corrected VA (BCVA) was counting fingers at face, CB esthesiometry demonstrated a complete absence of corneal sensation for 6 months (Table 1), and slit-lamp biomicroscopy of the cornea demonstrated a central neurotrophic ulcer with no infiltrates and with mild corneal thinning. Tactile testing of her skin sensation revealed decreased sensation to light touch with a wisp of cotton on the ipsilateral forehead compared with the contralateral forehead. Her preoperative ocular medication regimen included ophthalmic dexamethasone/neomycin/polymyxin B drops 4 times daily (QID) OS with dexamethasone/neoymcin/polymyxin B ointment at bedtime (QHS) OS, and 500 mg oral valacyclovir daily. Her valacyclovir was increased to 500 mg 3 times daily (TID) 1 week preoperatively and for 2 weeks postoperatively before decreasing the dose to her baseline regimen.

After MIDCN with the contralateral supraorbital nerve, the appearance of her cornea improved, with resolution of her corneal ulcer (Fig. 1A–D). After 23 months of follow up, she achieved BCVA of 20/80 OS, and her peripheral corneal sensation improved in all quadrants (Table 1). She complained of more corneal irritation in the left eye after her corneal sensibility started to improve at 2 months postoperatively (Table 2). Sensation in the distribution of the donor nerve as measured by cotton wisp testing had returned by 9 months postoperatively. She experienced no complications during the follow-up period. By the end of the follow-up period, her ophthalmic medications had been adjusted to artificial tears as needed OS with erythromycin ointment QHS OS, and 500 mg oral valacyclovir daily.

Patient 2. A 59-year-old Caucasian man with a history of right nasolacrimal duct obstruction status post dacryocystorhinostomy, ocular hypertension, and herpes zoster keratitis status post two amniotic membrane grafts in the right eye (OD), presented for evaluation of NK OD. In the right eye, BCVA was 200E at 4′, CB esthesiometry demonstrated complete loss of corneal sensation for 20 months (Table 1), and slit-lamp examination demonstrated no epithelial defect and a central corneal descemetocele. He had intact skin sensation of the ipsilateral forehead. Preoperative ocular medication regimen included a once daily difluprednate ophthalmic drop OD and oral acyclovir 500 mg TID.

The decision was made to conduct PK in combination with MIDCN due to impending corneal perforation and high likelihood of transplant failure without corneal neurotization, respectively. In the perioperative period, his acyclovir was continued at the same regimen.

TABLE 1. Patient characteristics and outcomes

Patient	Age (y)	Sex	Etiology	Other surg.	Preop Denervation time (mo)	Epi defect pre /postop	Mackie Stage	Donor nerve	Follow up (mo)	Preop K sensibility*	Postop K sensibility*	BCVA (preop)	BCVA (postop)	Complications	Ocular comorbidities
1	86	F	HZO	None	6	Yes/No	III	Contra SO	23	0 / 0,0,0 / 0	3 / 2,0,4 / 2	CF @ face	20/80	None	Low-risk glaucoma suspect
2	59	M	HSV	Combo: PKP Later: CEIOL	20	No/No	III	Ipsi SO	19	0† / 0,0,0 / 0	3† / 3,2,2.5 / 2.5	200E @ 4′	20/70	Cataract progression	NLDO s/p prior DCR, OHTN
3	82	F	Multiple ocular surg	Prior: PPV ×2 SB CEIOL	15	No/No	II	Ipsi SO	15	4 / 2,2,1 / 1	3.5 / 6,6,5 / 6	CF @ 3′	20/70	None	POAG, Hx of recurrent RD
4**	5	M	Suspect viral etiology	None	24	No/No	I	Ipsi SO	11	1 / 1,1,1 / 1	4.5 / 4.5,4.5,4.5 / 4.5	^F&F (fixation preference)	^F&F	None	None
4**	5	M	Suspect viral etiology	None	24	Yes/No	II	Ipsi SO	11	0 / 0,0,0 / 0	6 / 6,6,6 / 6	^F&F (inconsistent)	^F&F	Asymptomatic bony excrescence lateral to the SO foramen	None

All columns above apply only to the eye operated on for treatment of NK.

*Cochet–Bonnet measurements are reported in centimeters. Measurements were taken in 4 quadrants and centrally.

†Cochet–Bonnet measurements taken in native cornea apart from central value.

**Same patient, bilateral surgery performed on the same day due to bilateral disease, developmental delay, and international travel.

^Patient had difficulty cooperating with visual acuity testing.

BCVA, best-corrected visual acuity; CEIOL, cataract extraction with intraocular lens; CF, count fingers; DCR, dacryocystorhinostomy; Epi, epithelial; F, female; F&F, fix and follow; HSV, herpes simplex virus; Hx, history; HZO, herpes zoster ophthalmicus; K, cornea; M, male; NLDO, nasolacrimal duct obstruction; OHTN, ocular hypertension; POAG, primary open-angle glaucoma; PPV, pars plana vitrectomy; R, right; RD, retinal detachment; SB, scleral buckle; SO, supraorbital s/p, status post; y, year.
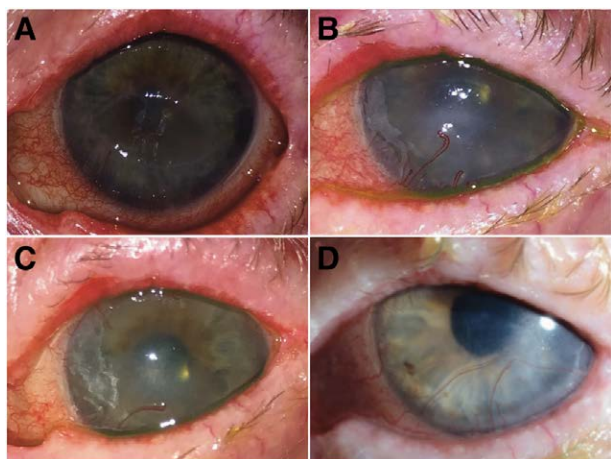
FIG. 1. An 83-year-old woman with herpetic keratitis who underwent MIDCN with contralateral supraorbital nerve. **A**, Preoperatively. **B**, Five weeks postoperatively. **C**, Three months postoperatively. **D**, Fifteen months postoperatively. MIDCN, minimally invasive direct corneal neurotization.

After removing the temporary tarsorrhaphy on postoperative day 1, he was started on the standard post-PK drop regimen, which included moxifloxacin TID and difluprednate QID with dexamethasone/neomycin/polymyxin B ointment QHS, in addition to aggressive ocular lubrication. His initial postoperative course was notable for prolonged corneal epithelial irregularities (6 months), but no prolongation of corneal edema or epithelial breakdown was noted. By 4 months postoperatively, he started experiencing ocular irritation and was noted to have objective improvement in corneal sensation at 4.5 months. By 10 months postoperatively, his central cornea became clear enough to undergo cataract extraction with posterior chamber intraocular lens using a temporal clear corneal incision, which avoided the location of the regenerating nerve fibers which were inset at 1 and 11 o´clock positions. Nineteen months after PK and MIDCN, he maintained improved corneal sensibility in all 4 quadrants of the native (Table 1) and donor cornea (donor CB esthesiometry values included 1 cm at 12 o'clock, 1 cm at 3 o'clock, 2.75 cm at 6 o'clock, 0.5 cm at 9 o'clock, and 2 cm centrally), and demonstrated corneal reinnervation as evidenced by in vivo confocal microscopy (Fig. 2A–D). His cornea remained clear with only superior epithelial haze and irregularities. His VA OD improved to 20/70, with the corneal surface remaining healthy after 19 months of follow up. The patient did experience transient ocular hypertension OD following cataract surgery that resolved in subsequent visits without the addition of intraocular pressure-lowering drops. He is currently being considered for a prose contact lens to correct irregular astigmatism. No recurrence of corneal thinning or other complications were noted in the follow-up period. At his last follow up, the postoperative ophthalmic medication regimen had been adjusted to a once daily difluprednate eye drop, 500 mg oral valacyclovir TID, and artificial tears as needed.

Patient 3. An 82-year-old Caucasian woman with a history of retinal detachment status post two retinal detachment repairs including pars plana vitrectomy with silicone oil and scleral buckling OD, cataract surgery OD, and primary open-angle glaucoma OD, presented for evaluation of NK OD after treatment failures with autologous serum tears and bandage contact lenses. In the right eye, BCVA was counting fingers at 3′, and corneal sensibility was diminished for 15 months, as represented in Table 1. The patient had a history of persistent epithelial defect OD. On the day of preoperative evaluation, slit-lamp examination demonstrated severe diffuse punctate epithelial erosions, neovascularization of the inferior cornea, and corneal thinning inferiorly. Her preoperative ophthalmic medication regimen for the OD included serum tears QID, artificial tears QID, ofloxacin TID, erythromycin ointment QHS, bimatoprost QHS, and oral doxycycline 100 mg daily.

After MIDCN of the right eye, corneal sensibility improved throughout the cornea, the diffuse corneal punctate epithelial erosions improved on slit-lamp examination, and serum tears and bandage contact lens wear were able to be discontinued without recurrence of her epithelial defect. Subjective corneal sensibility also improved (Table 2). After 15 months of follow up, her BCVA had improved to 20/70 and no postoperative complications were noted. Her postoperative ophthalmic medication regimen remained unchanged apart from the discontinuation of ofloxacin.

Patient 4. A 5-year-old boy from Dubai with a history of developmental delay, corneal scarring OU, and persistent central epithelial defects OS, presented for evaluation for corneal opacities OU with a 2-year history of corneal denervation. Prior to his presentation, he underwent multiple tarsorrhaphies, corneal stroma micropuncture, autologous serum tears, bandage contact lens placement, antibiotic drops, and aggressive ocular lubrication with artificial tears and ointment. At presentation, the right eye demonstrated severely diminished sensibility with CB esthesiometry, and the left eye demonstrated complete absence of corneal sensibility (Table 1). Slit-lamp examination demonstrated central corneal scars OU, a large central epithelial defect OS, and corneal neovascularization inferiorly OS. He struggled to participate with VA assessment, but demonstrated the ability to fix and follow with each eye individually, albeit inconsistent in the left eye. His preoperative medication regimen included a combination tobramycin/dexamethasone eye drop QID in both eyes (OU), artificial tears QID OU, and gel tears QHS OU.

The patient underwent bilateral MIDCN of both eyes. Bilateral surgery was performed on the same day due to international travel. Eleven months after surgery, (Fig. 3A,B), he presented with slit-lamp examination demonstrating significant improvement in the central corneal scarring and resolution of epithelial defect OS. Parents reported that the child has had an easier time performing visual tasks, such as playing video games and watching television. He had restoration of corneal sensibility by CB testing bilaterally (Table 1). However, he remained unable to cooperate with rigorous VA assessment, but was able to fix and follow with each eye individually. On adnexal examination, he was found to have a small (less than 1 × 1 cm) firm nonmobile, painless nodule at the supraorbital notch on the left side, which was not bothersome to him, but was palpable on examination. T1 weighted MRI

TABLE 2. Subjective postoperative changes

Patient	Corneal sensation	Corneal appearance	Donor nerve sensation
1	More irritation	Improved	Returned by 9 months
2	Notices some sensation	Improved	Returned by 4 months
3	Increased sensitivity	Improved	Returned by 2 months
4*	Increased sensitivity	Improved	Returned by 3 months
4*	Increased sensitivity	Improved	Returned by 3 months

*Same patent, bilateral surgery performed on the same day due to bilateral disease, developmental delay, and international travel.
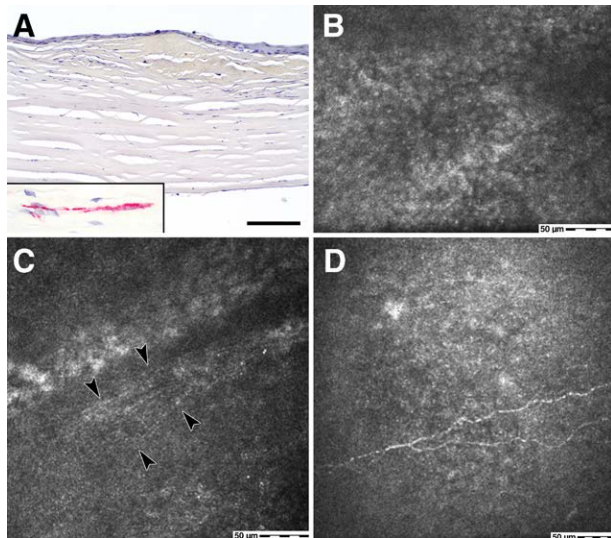N/A, not available.

FIG. 2. A 59-year-old man with herpetic keratitis who underwent MIDCN with ipsilateral supraorbital nerve and concurrent penetrating keratoplasty. **A**, S-100 staining of corneal tissue button demonstrating paucity of corneal nerves. The inset shows a control (keratoconus) cornea with a nerve stained red using antibodies to S100 protein. The scale bar for part A represents 100 μm. **B**, In vivo confocal microscopy at postoperative month 3 without evidence of corneal reinnvervation in the graft tissue. **C**, In vivo confocal microscopy at postoperative month 13 demonstrating corneal reinnervation in the corneal graft tissue. Black arrows indicate the margins of the nerve bundle. **D**, In vivo confocal microscopy at postoperative month 19 further demonstrating corneal reinnervation of the graft tissue with branching patterns. MIDCN, minimally invasive direct corneal neurotization.
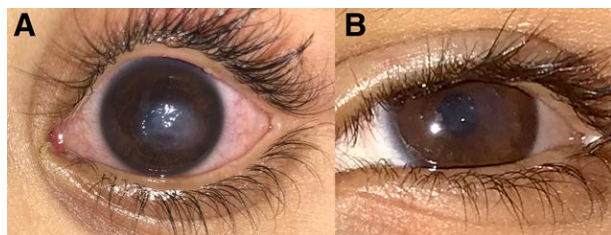

FIG. 3. A 5-year-old boy with bilateral NK underwent bilateral MIDCN with the ipsilateral supraorbital nerves. **A**, Photograph of the patient's left eye at presentation, demonstrating a large central epithelial defect with underlying corneal opacification. **B**, Photo of the left eye 11 months postoperatively demonstrating resolution of the epithelial defect and the corneal opacity. MIDCN, minimally invasive direct corneal neurotization; NK, neurotrophic keratopathy.

of the orbits showed a small bony excrescence just lateral to the supraorbital notch (Fig. 4). Given the asymptomatic and benign nature of the lesion, the parents elected for observation. His ophthalmic medication regimen postoperatively remained unchanged apart from the discontinuation of the tobramycin/dexamethasone eye drop and decrease in ocular lubrication.

DISCUSSION

Previously, several articles have described direct corneal neurotization using coronal, hemicoronal, and endoscopic approaches.[11,18,19,22] Herein, we present the clinical outcomes of the first case series using MIDCN.
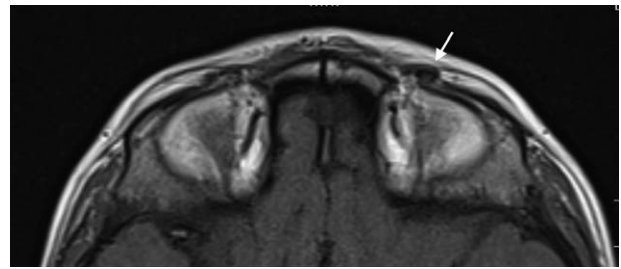

FIG. 4. T1 weighted MRI image in a 5-year-old boy 11 months status postbilateral MIDCN. On examination, he demonstrated a less than 1 × 1 cm firm nodule at the left supraorbital notch. The MRI demonstrates a small bony excrescence just lateral to the left supraorbital notch. MIDCN, minimally invasive direct corneal neurotization.

As shown in Table 1, all cases demonstrated improvement in CB esthesiometry measurements and improvement or stability in BCVA. No persistent epithelial defects were noted postoperatively, and all cases demonstrated improvement in the corneal integrity and appearance on postoperative slit-lamp examination at their last follow-up visit (Table 2). All patients achieved return of sensation in the donor nerve distribution postoperatively. Corneal sensation appeared to improve within 2–4 months postoperatively in most patients (80%). The return of corneal sensibility in this study is comparable to or slightly more rapid than the results reported with other techniques.[2,3,10,18–20,22] However, given the limited number of patients and variability of follow up, direct comparison is not possible. There were no significant intraoperative or postoperative complications in our 5 cases. Bony excrescence found lateral to the supraorbital foramen in patient 4 may have resulted from reactive bony overgrowth at the site of dissection. While palpable on clinical examination, this finding did not warrant any additional treatment. Cataract progression in patient 2 was likely due to a combination of prolonged topical steroid application and PK.

The advantage of MIDCN is avoidance of a large incision and extensive dissection compared with hemicoronal and coronal approaches. For contralateral nerve transfer, additional small radial incisions have to be made in the hair-baring scalp to reach more distal portions of the donor nerve, resulting in more extensive dissection compared with ipsilateral transfer. However, the area of dissection is significantly smaller in comparison with coronal incision. The procedure also avoids potential donor site morbidity and reliance on additional neurorrhaphy in contrast to previously described nerve grafting techniques.[2,10,26] MIDCN can be performed in an outpatient setting, under general or intravenous anesthesia, with an average operative time of 60–120 minutes, with ipsilateral transfers being significantly shorter. While the nerve harvesting techniques using infra- or supra-eyebrow incisions can be considered as alternative options, these approaches have several downsides in comparison to the described technique. First, given the thicker skin and more conspicuous area of the face involved in infra- and supra-eyebrow incisions, the resultant scar may be less acceptable, particularly in children, young adults, and those with sparse eyebrow hair. Second, the supra-eyebrow incision carries a greater risk of injury to the facial nerve given the wide lateral extent of the incision needed for optimal surgical exposure. Finally, given that at least 7–8 cm of the nerve segment is needed for contralateral transfers, visualization of the distal portion of the donor nerve can still be very difficult without endoscopic guidance despite a more direct incision.

In MIDCN, we prefer to harvest the supraorbital nerve instead of the supratrochlear nerve for several reasons. First,

the supraorbital nerve contains a larger number of axons than the supratrochlear nerve,[17] theoretically allowing more axons to reach the cornea. Second, the deep branch of the supraorbital nerve (i.e., the periosteal branch) has consistent anatomy after exiting the supraorbital foramen, running superiorly and slightly laterally in the loose areolar tissue above the periosteum.[22] Third, the effective length of the supratrochlear nerve available for corneal neurotization is limited as it penetrates the muscular layers and the dermis more quickly after emergence from its foramen than the deep branch of the supraorbital nerve.[27] Finally, we have found that both the subjective and objective sensibility of the affected scalp returns in almost all patients after supraorbital nerve harvesting for corneal neurotization.[10,22] Recovery of forehead sensation after the supraorbital nerve has been damaged or transected has been previously described for other surgical techniques.[28] The recovery of skin sensation in the supraorbital nerve's sensory distribution is likely due to collateral sprouting of the adjacent sensory nerves with associated cortical sensory remapping.[29,30]

To our knowledge, Patient 2's case represents the first report of successful corneal neurotization performed simultaneously with PK. Previous reports have described performing corneal transplantation a year or longer after corneal neurotization to allow for adequate reinnervation of the cornea.[12,15,19,20] However, we found that performing MIDCN in conjunction with corneal transplantation was effective in restoring corneal sensibility and maintaining corneal integrity. Figure 2B demonstrates objective evidence of reinnervation in the corneal graft to support subjective changes in sensibility. While neurotrophic support of existing nerve fibers has been proposed as the primary driver of reinnervation after corneal neurotization,[31] the more likely mechanism is direct axonal sprouting from the donor nerve terminals.[32] Given our patient's relatively rapid improvement after combined PK and MIDCN, we suggest this combined procedure may be a prudent approach in patients with impending corneal perforation and NK as was the case with patient 2.

One of the primary limitations of MIDCN is its steep learning curve, especially in contralateral nerve transfer cases where endoscopic guidance is essential. In addition, the length of the supraorbital nerve isolated may be inadequate to reach the contralateral eye in some patients and may necessitate an interposition nerve graft. In this particular scenario, however, this technique still offers a shorter gap length, ranging from 1 to 2 cm in the senior author's experience, in comparison to longer gap lengths (7–11 cm) reported in previously described techniques utilizing interposition nerve grafts.[2,22] Greater gap lengths have been correlated with decreased nerve regeneration.[33]

In summary, this study demonstrates that MIDCN is a safe and effective option for corneal reinnervation. It may be particularly appealing for ipsilateral nerve transfers given its efficiency, minimally invasive nature, direct coaptation to the affected cornea, and shorter nerve length needed for neurotization.

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