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SPECIAL TOPIC

Craniofacial/Pediatric

Corneal Neurotization: Preoperative Patient Workup and Surgical Decision-making

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Background: The use of sensory nerve transfers to the anesthetic cornea has transformed the treatment of neurotrophic keratopathy by restoring ocular surface sensation and activating dysfunctional epithelial repair mechanisms. However, despite numerous reports on surgical techniques, there is a scarcity of information on the interdisciplinary management, preoperative assessment, and surgical decision-making, which are equally critical to treatment success.
Methods: This Special Topic presents a standardized, interdisciplinary preoperative workup based on our 10-year experience with corneal neurotization in 32 eyes of patients with neurotrophic keratopathy.
Results: Our assessment includes a medical history review, ophthalmic evaluation, and systematic facial sensory donor nerve mapping for light touch and pain modalities. This approach enables evidence-based patient selection, optimal surgery timing, and suitable donor nerve identification, including backup options.
Conclusions: Based on a decade-long experience, this special topic highlights the importance of interdisciplinary collaboration and provides a practical roadmap for optimizing patient selection and surgical decision-making in patients undergoing corneal neurotization. *(Plast Reconstr Surg Glob Open 2023; 11:e5334; doi: 10.1097/GOX.0000000000005334; Published online 11 October 2023.)*

INTRODUCTION

Since its first report in the peer-reviewed literature in 2009,[1] corneal neurotization has complemented the therapeutic repertoire for corneal anesthesia and neurotrophic keratopathy in several academic centers around the world, with encouraging results.[2–8] Now, over a decade later, a growing number of technical reports have been published, providing surgeons with detailed step-by-step instructions on intraoperative procedures and technical refinements.[5,7–11] (**See Video 1 [online],** which shows our surgical technique). However, conclusive information on the preoperative, interdisciplinary patient workup and surgical decision-making is scarce. Yet, both aspects are essential for successful clinical implementation of a novel surgical technique.

Although randomized controlled trials provide the highest level of evidence, ethical and practical considerations often limit their applicability in rare conditions. Patients with a rare disease, such as neurotrophic keratopathy, are usually referred to specialized academic centers in an effort to centralize clinical management. This enables physicians to interact with these diseases on a regular basis, gain experience, and refine their diagnostic and therapeutic strategies based on the best available evidence.[12] Based on our 10-year experience in clinical management and research with prospectively collected data on 32 eyes of patients with neurotrophic keratopathy who underwent corneal neurotization, we present our strategy on preoperative patient workup and

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surgical decision-making. Further, we emphasize therapeutic goals and recognize current limitations of corneal neurotization to frame a realistic set of expectations for patients undergoing corneal neurotization.

THERAPEUTIC GOALS AND CURRENT LIMITATIONS OF CORNEAL NEUROTIZATION

Restoring Corneal Sensation

The fundamental principle of corneal neurotization is providing innervation to the anesthetic cornea. The absent (or insufficient) trigeminal nerve fiber population that physiologically serves the cornea is replaced or supplemented by healthy nerve fibers arising from a rerouted donor nerve. This concept is backed by conclusive retrograde neuronal tracing studies in animal models of corneal neurotization[13] and by clinical in vivo confocal microscopy[6,7,14,15] and magnetoencephalography experiments,[16] indicating that the cortical representation of corneal stimuli after corneal neurotization corresponds to the brain region usually representing the donor nerve dermatome. For either congenital or acquired cases, the new innervation ideally provides corneal sensation and, thereby, protection for the susceptible ocular surface. Nerve fibers that normally sense mechanical, thermal, and chemical stimuli in the skin are rerouted to the cornea, thereby (re)building a functional neuronal connection between the cornea and the somatosensory cortex. Thus, a healthy sensory cutaneous nerve, preferably with a periocular dermatome, provides a suitable axon source for corneal neurotization and may facilitate sensory relearning.

Stabilizing the Corneal Epithelium and Maintaining Ocular Surface Health

In neurotrophic keratopathy, the ocular surface progressively degenerates. Corneal neurotization aims at stabilizing the ocular surface to improve or maintain corneal transparency and rebuild a barrier against pathogens. It is well accepted that sufficient corneal innervation is essential for maintaining the epithelial integrity and allow for healing after epithelial injury,[17–21] even though some of the underlying cellular mechanisms remain elusive. In neurotized corneas, recent evidence suggests that the rerouted donor nerve fiber population takes on this task of promoting the epithelial renewal and repair mechanisms.[13,16] In addition, restored protective sensation decreases the risk for corneal injuries and thereby may unburden an overwhelmed epithelial repair system. This general concept is supported by experimental in vivo data showing improved epithelial recovery after corneal neurotization,[13] as well as clinical results demonstrating a substantially reduced recurrence rate for the pathognomonic nonhealing corneal epithelial defects in neurotized patients.[2,6,14,16]

Takeaways

Question: How to assess eligible patients and what to consider for surgical decision-making before corneal neurotization?

Findings: Standardized preoperative workup includes thorough history-taking, ophthalmic examination, and facial sensory mapping. Based on these, eligible donor nerves and fallback options are defined as well as the appropriate timing for corneal neurotization depending on the presented stage of neurotrophic keratopathy and the disease dynamics.

Meaning: Incorporating a standardized preoperative workup enables well-informed surgical decision-making by revealing contraindications and identifying suitable donor nerves. This facilitates favorable outcomes, minimizes complications, and enables high-quality data-sharing.

Current Limitations: Stromal Scars and Insufficient Lacrimation

Ulcers in advanced neurotrophic keratopathy may involve deeper corneal layers, including the corneal stroma. Even after successful corneal reinnervation, preexisting stromal scars often remain.[15] This is because stromal transparency relies on a uniform stromal architecture of specialized, thin collagen fibrils.[22] The stromal repair mechanisms, however, tend to fill defects with a less-organized pattern of larger collagen fibrils, leading to light scattering and opacity.[22,23] Consequently, depending on the severity and location of the stromal scar in relation to the optical axis, the visual acuity may remain impaired even after successful corneal neurotization. In severe cases of stromal scarring, secondary corneal transplantation may be an option for visual rehabilitation (Fig. 1).

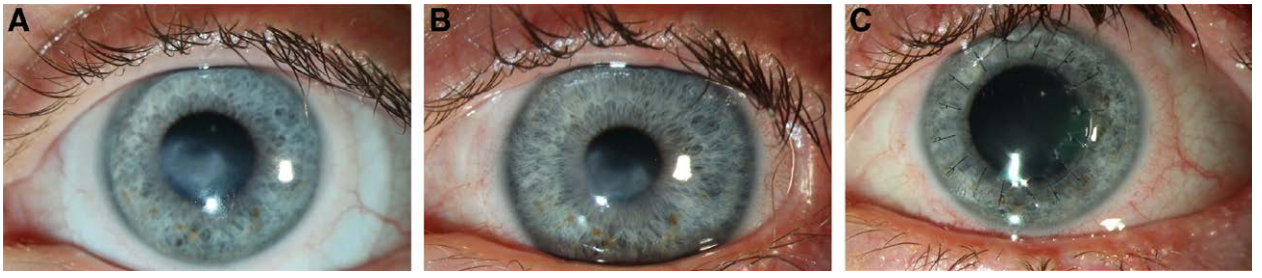

Fig. 1. Deep stromal scars may require secondary corneal transplantation after successful neurotization. A, Cornea with stromal scars in the optical axis presurgery. B, Cornea after successful corneal neurotization. Epitheliopathy improves but deep stromal scars may remain. C, Corneal transplantation secondary to corneal neurotization successfully restored corneal clarity.

Further, lacrimation often remains below normal levels after corneal neurotization, even when corneal sensation has been restored.[1] Physiologically, lacrimation is regulated by a constant input of cold-sensitive nerve terminals in the cornea that sense small temperature drops of the ocular surface caused by evaporation of the tear film and communicate with the lacrimal glands to achieve a demand-based tearing.[24] Although corneal neurotization may rebuild a neuronal connection to the somatosensory cortex, the physiological tearing reflex arc cannot be restored by presently available surgical techniques. Therefore, the application of topical lubricants might remain necessary even after successful corneal neurotization. Understandably, patients classify this information as important for their decision on whether they want to undergo surgery.[1] It should therefore be included in any preoperative patient discussion.

PREOPERATIVE ASSESSMENT AND SURGICAL DECISION-MAKING

Patient Selection

Presently, the main indication for corneal neurotization is neurotrophic keratopathy. Thus, patients who have absent corneal sensation, nonhealing epithelial defects, and decreased tear film stability are potential candidates for corneal neurotization. For patient selection, the criteria listed in Table 1 may be used.

Contraindications for corneal neurotization include active eye infections, particularly herpetic keratitis. Relative contraindications include abnormal sensation in the donor nerve dermatome, and active epithelial defects or corneal melt, as those should ideally be healed before surgery by conventional means. Further, patients with extensive scarring or surgical resection of the conjunctiva should be viewed cautiously, as it may be difficult to reliably obtain full-thickness vascularized coverage of the nerve grafts.

Preoperative Patient Workup

Medical History

Key points include previous ophthalmic conditions and systemic diseases, as well as neurological disorders, injuries, or operations that potentially affect cranial nerve function. This information is essential for defining the etiology and estimating the time period of corneal denervation. They also include a history of ophthalmic procedures (eg, vitreoretinal, glaucoma, or strabismus surgery), as these are common causes of neurotrophic keratopathy and may induce conjunctival scarring, which will make neurotization difficult. A thorough medical history may also reveal potential donor nerves that are involved in the disease process and, therefore, may not be ideal axon donors for corneal neurotization.

Table 1. Patient Selection Criteria for Corneal Neurotization

Patient Selection Criteria for Corneal Neurotization
1. Impaired or absent corneal innervation
2. History of neurotrophic keratopathy
3. Situations in which recovery of corneal innervation is unlikely based on:
a. the cause of corneal denervation (ie, congenital trigeminal hypoplasia) or ophthalmic nerve resection
b. a prolonged period of time has passed since the event that caused corneal denervation (at least 1 year)
4. Availability of an appropriate regional sensory donor nerve
5. Absence of active eye infection (viral, bacterial, or mycotic)

Ophthalmic Examination

The objectives of the eye examination are to confirm the diagnosis of neurotrophic keratopathy, determine the extent of epitheliopathy, and identify factors that affect the prognosis or may complicate ophthalmic surgery.

First, the external eye and the eyelids are evaluated. Eyelid deformities, incomplete lid closure (lagophthalmos), and reduced blinking due to impaired neuronal feedback loops in the anesthetic cornea worsen the prognosis for the eye. In these cases, a tarsorrhaphy may be used to protect the ocular surface before corneal neurotization.

Ocular examination may reveal conjunctival injection (red eye), which can indicate inflammation or dry eye. In advanced disease, subconjunctival scarring and fibrosis may be present. In these cases, such adhesions potentially complicate the subconjunctival nerve graft tunneling during surgery and, therefore, may require the surgeon to dissect larger conjunctival flaps to cover the nerve graft without tension.

Slit lamp examination of the cornea reveals the extent of epitheliopathy, and identifies corneal ulceration and stromal scarring. Fluorescein staining can be used to detect punctate epithelial lesions and determine tear breakup time (normal >10 sec.) as an indicator for impaired lacrimation and abnormal tear composition. Ideal candidates for corneal neurotization may show punctate epitheliopathy but no large, coalesced defects, as well as minimal stromal scarring and no signs of inflammation.

By definition, neurotrophic keratopathy is associated with corneal hypesthesia or complete anesthesia (Fig. 2). For a first qualitative check of corneal sensation, the wisp of a cotton tip may be used to touch the center of the cornea and elicit a patient response. However, we strongly recommend a standardized assessment of the center and all four peripheral quadrants of the cornea via Cochet Bonnet esthesiometry using a clinical monofilament testing device (Luneau, France). Patients with a normal level of sensation reliably detect 60 mm, whereas 0 mm defines complete corneal anesthesia. Additionally, in vivo confocal microscopy may be used in unclear cases or for research purposes to visualize the corneal nerve plexus.

Facial Sensory Mapping

Successful corneal (re)innervation and restoration of corneal sensation requires a healthy donor nerve with a functioning sensory axon population. To provide sufficient protection, these axons are ideally capable

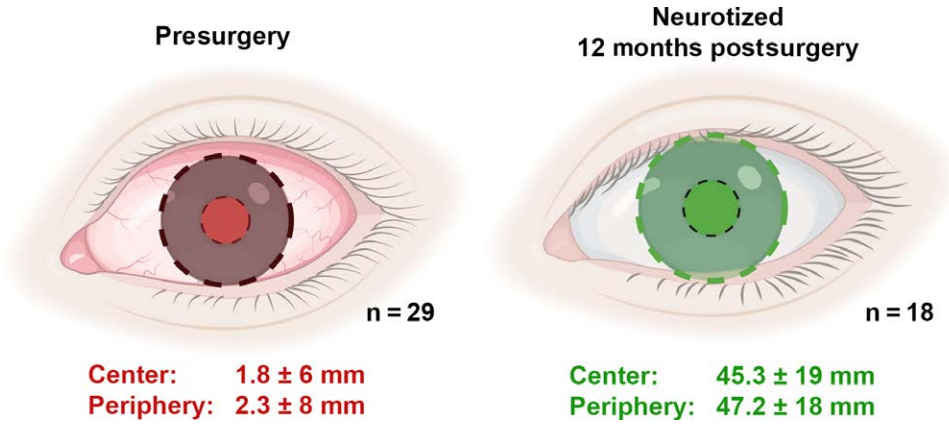

Fig. 2. Corneal sensation pre- and 12 months postsurgery. Presurgery, the mean Cochet Bonnet corneal esthesiometry in our patients revealed almost absent sensation of 1.8 mm in the center and 2.3 mm in the peripheral quadrants. Of note, 90% of our patients had complete preoperative anesthesia (Cochet Bonnet esthesiometry = 0 mm). Corneal neurotization restored corneal sensation in 94% of patients, with average Cochet Bonnet corneal esthesiometry results of 45.3 mm in the center and 47.2 mm in the periphery 12 months postsurgery.[2]

of detecting and processing mechanical, thermal, and chemical stimuli (including pain) that could cause harm to the cornea. A number of cutaneous nerves are located in reasonable distance to the eye and, therefore, represent possible donor nerves and intraoperative fallback options. Facial sensory mapping aims at extracting objective information on nerve function to reduce the risk of rerouting dysfunctional donor nerve fibers to the anesthetic cornea. In our experience, patient-reported, subjectively normal sensation is not a reliable metric. This is particularly true in congenital/developmental, or longstanding acquired nerve dysfunction when patients may have adapted to hypo- or paresthesia.

For systematic sensory mapping, we recommend testing light touch thresholds using a Semmes Weinstein monofilament facial set, in combination with comparative touch perception (ten test)[25] and pain perception (pinch test). Sensory mapping can be performed jointly with staff from occupational therapy and should include the dermatomes of each donor nerve candidate, bilaterally and including nontrigeminal donors (ie, lesser occipital nerve and supraclavicular nerves) to reveal locally or regionally diminished sensation (Fig. 3). This

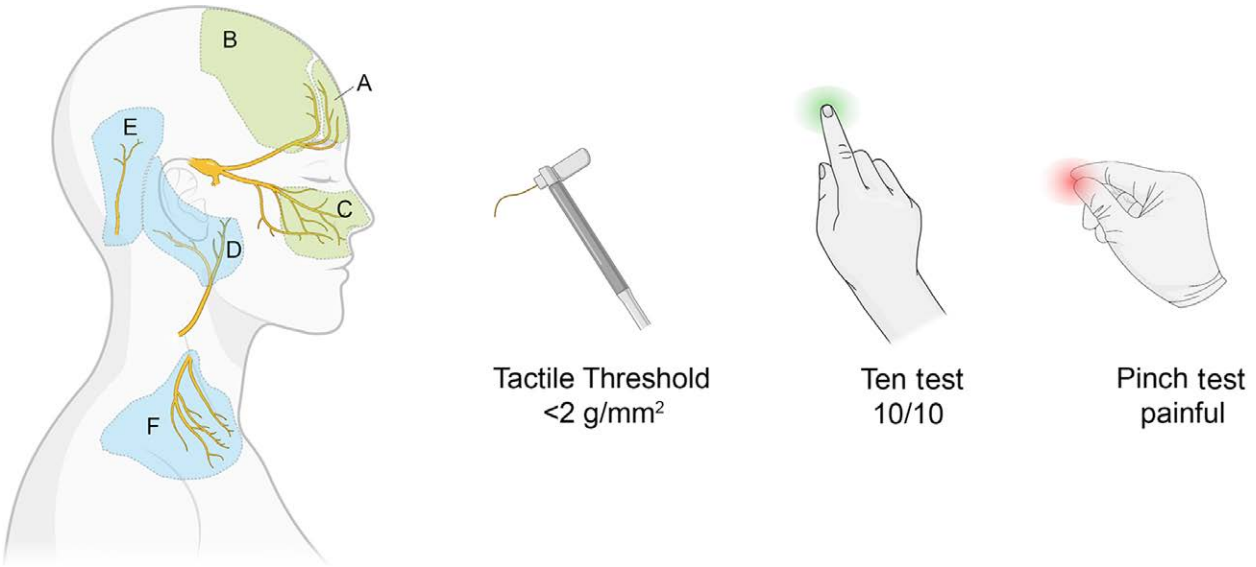

Fig. 3. Systematic sensory mapping. Green corresponds to trigeminal axon donors and blue, to nontrigeminal donors. A, supratrochlear nerve; B, supraorbital nerve; C, infraorbital nerve; D, great auricular nerve; E, lesser occipital nerve; and F, supraclavicular nerves. For tactile thresholds, Semmes Weinstein monofilaments are used, and values below 2 g/mm^2 represent a normal tactile sensation.[26] The ten test evaluates subjective touch perception, with 10 of 10 representing a normal sensation compared with the contralateral side. The ability to perceive pain can be tested by pinching the skin.

reliably identifies donor nerves with abnormal sensory function. A thorough sensory mapping is of particular importance when proximal trigeminal nerve pathologies cause corneal denervation, because frequently used donor nerves, such as the supraorbital and supratrochlear nerves, arise from the trigeminal nerve as well.

Usually, an autologous nerve graft (eg, the sural nerve) is required to bridge the distance between donor nerve and the affected cornea. Before nerve grafting, we recommend the inspection and a qualitative sensory evaluation of the intended graft harvesting site to identify potential issues with the nerve graft, such as intraneural scarring as a result of previous injuries.

Donor Nerve Selection

Selecting a suitable donor nerve for corneal neurotization is a two-stage process. First, before surgery, suitable candidate nerves are identified based on reasonable regeneration distance, surgical accessibility, expected donor site morbidity, and a normal function. Here, we recommend defining a first-choice donor and several fallback options in a joint decision with the patient. The second step is the intraoperative, macroscopic assessment of the predefined first-choice donor nerve for its caliber and branching pattern to evaluate its suitability for corneal neurotization. We prefer larger caliber nerves to achieve a good size match to the autologous nerve graft (usually a sural nerve graft) and to ensure a sufficient number of rerouted nerve fibers. If the donor nerve of first choice is small, nonexistent, or with considerable proximal branching, the predefined fallback options may be evaluated for better suitability.

Based on these considerations, the supratrochlear and/or supraorbital nerves are ideal candidates for corneal neurotization due to their short regeneration distance, superficial course, surgical accessibility, and favorable caliber match with a sural nerve graft. The supratrochlear nerve produces a noncritical donor side sensory deficit that usually resolves within months and may even reach preoperative levels of sensation. Beyond that, their close anatomic proximity to each other can be of value in case a fallback option is needed. Therefore, those nerves have been the most commonly used donors for corneal neurotization in our patients (Fig. 4). Further donor nerve candidates include the infraorbital nerve, the greater auricular nerve, the lesser occipital nerve, and even supraclavicular nerves as well as their contralateral counterparts (Fig. 3). Of note, in our 10-year experience with corneal neurotization in over 30 eyes, the loss of sensation in the donor nerve dermatome was usually transient with only one adult patient reporting impaired forehead sensation long-term. Further, scars to the donor and recipient sites are usually well hidden and, therefore, are not an aesthetic concern. The sural nerve has been proven to be a reliable source of adequately sized autologous nerve grafts, and a well-tolerated donor site functional loss that does usually not impair ambulation, even in patients with ataxia.

The number of fascicles used for corneal neurotization depends on the selected donor nerve, the nerve graft, and the extent of intraneural dissection. The authors usually connect three to four fascicles to the corneo-scleral junction. However, in 9% of our patients, more than six fascicles were used (Fig. 5). If the nerve graft contains many small-diameter fascicles, one may use bundles of two to three fascicles per insertion. Interestingly, in our cohort, the number of fascicle insertions was negatively correlated with achieved corneal sensation ($r_s = -0.458$, $P = 0.014$), and the proportion of eyes with four insertion sites or

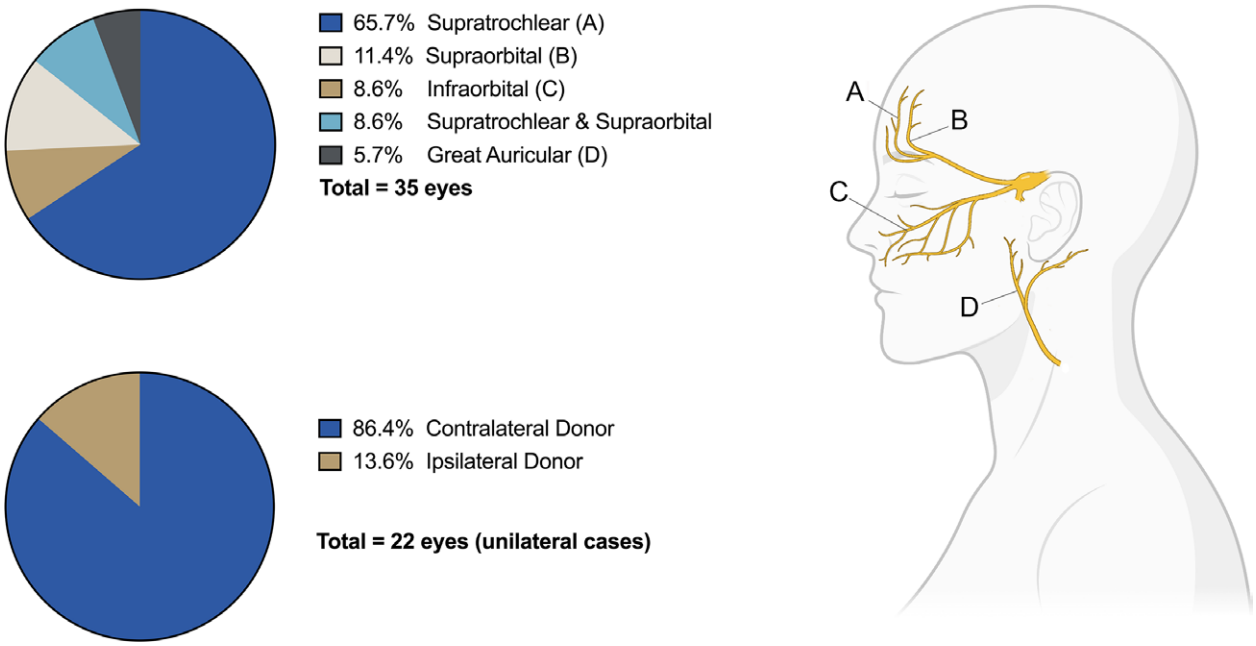

Fig. 4. Frequency distribution of donor nerves used for corneal neurotization. The supratrochlear nerve was the most common axon donor, used in two-thirds of the authors' cases.

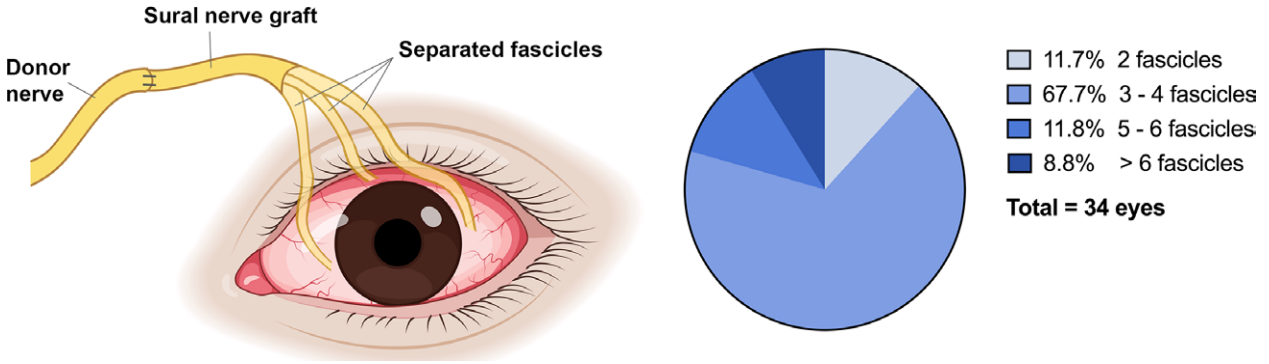

Fig. 5. Number of nerve fascicles used for corneal neurotization. In two-thirds of all eyes, three to four fascicles were used to reinnervate the cornea.

fewer was higher in eyes with a final normal or near-normal corneal sensation.[2]

Timing of Surgery

The conventional ophthalmic management of neurotrophic keratopathy aims at symptom control and preventing disease progression but does not address the underlying lack of innervation. By rerouting healthy nerve fibers, corneal neurotization offers a potentially definitive treatment option for neurotrophic keratopathy. The traditional therapeutic stepladder approach, from topical ointments to more invasive strategies escalated with increasing disease severity, may not be appropriate. In our current understanding, early (re)innervation of the anesthetic cornea reduces the risk for disease progression, corneal ulceration, and irreversible stromal scarring. Early intervention, therefore, may be more likely to salvage vision long-term compared with neurotization in advanced disease. Beyond that, active advanced disease stages with preoperative presence of large epithelial defects increase the risk for postsurgical corneal infection and thereby may put the eye at risk. To stage the disease and identify contraindications for surgery, a thorough preoperative assessment is mandatory.

The ideal timing for corneal neurotization depends on the presented stage of neurotrophic keratopathy and the disease dynamics. As a general principle, we aim for timely corneal reinnervation to prevent any irreversible structural damage to the eye, such as stromal scars, corneal perforation, severe infections and loss of the affected eye. In particular, patients with rapidly progressing disease and or advanced disease stages may benefit from early surgical intervention. This risk-reduction rationale applies to patients in early disease stages; however, two additional considerations may become particularly relevant in early-stage patients: (1) the chance of spontaneous corneal reinnervation and (2) risk of perioperative infection.

The Chance of Spontaneous Corneal Reinnervation

Patients with acute loss of corneal innervation due to skull trauma, surgery, or herpetic infection have a certain chance of trigeminal nerve regeneration and corneal reinnervation, depending on the type of nerve trauma and the time that has passed since the event. In these cases, corneal neurotization may not be necessary. Consequently, in those cases, we recommend reassessing corneal sensation and surface health in regular intervals up to 12 months after corneal denervation and then reevaluate the need for corneal neurotization. However, we recommend intervening early when recovery is unlikely, to allow neurotization to prevent progression of neurotrophic keratopathy.

Risk of Perioperative Eye Infection

An intact corneal epithelium and a healthy tear film serve as a barrier against pathogen penetration. In neurotrophic keratopathy, large, coalescing epithelial defects provide a portal of entry for pathogens and thereby pose a high risk for penetrating infections, particularly in the context of surgical manipulation. This puts the eye at risk. After surgery, rerouted donor nerve fibers need to grow through the nerve graft before reinnervating the cornea and potentially contributing to epithelial wound healing. Whenever possible, we therefore recommend healing epithelial defects using conventional ophthalmic strategies before surgery. Accordingly, any active eye infection represents an absolute contraindication and requires thorough infection control before corneal neurotization.

CONCLUSIONS

Corneal neurotization provides a surgical solution for neurotrophic keratopathy in children and adults by directly addressing the underlying neurological deficit. Although lacrimal dysfunction and stromal scarring cannot be improved by presently available techniques, epithelial integrity and corneal sensation can be restored up to normal levels. A thorough preoperative assessment enables well-informed surgical decision-making by revealing contraindications and identifying suitable donor nerves. We therefore encourage surgeons to incorporate a standardized preoperative workup to facilitate favorable outcomes, minimize complications, and enable high-quality data sharing for multicenter studies on this rare disease.

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DISCLOSURES

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