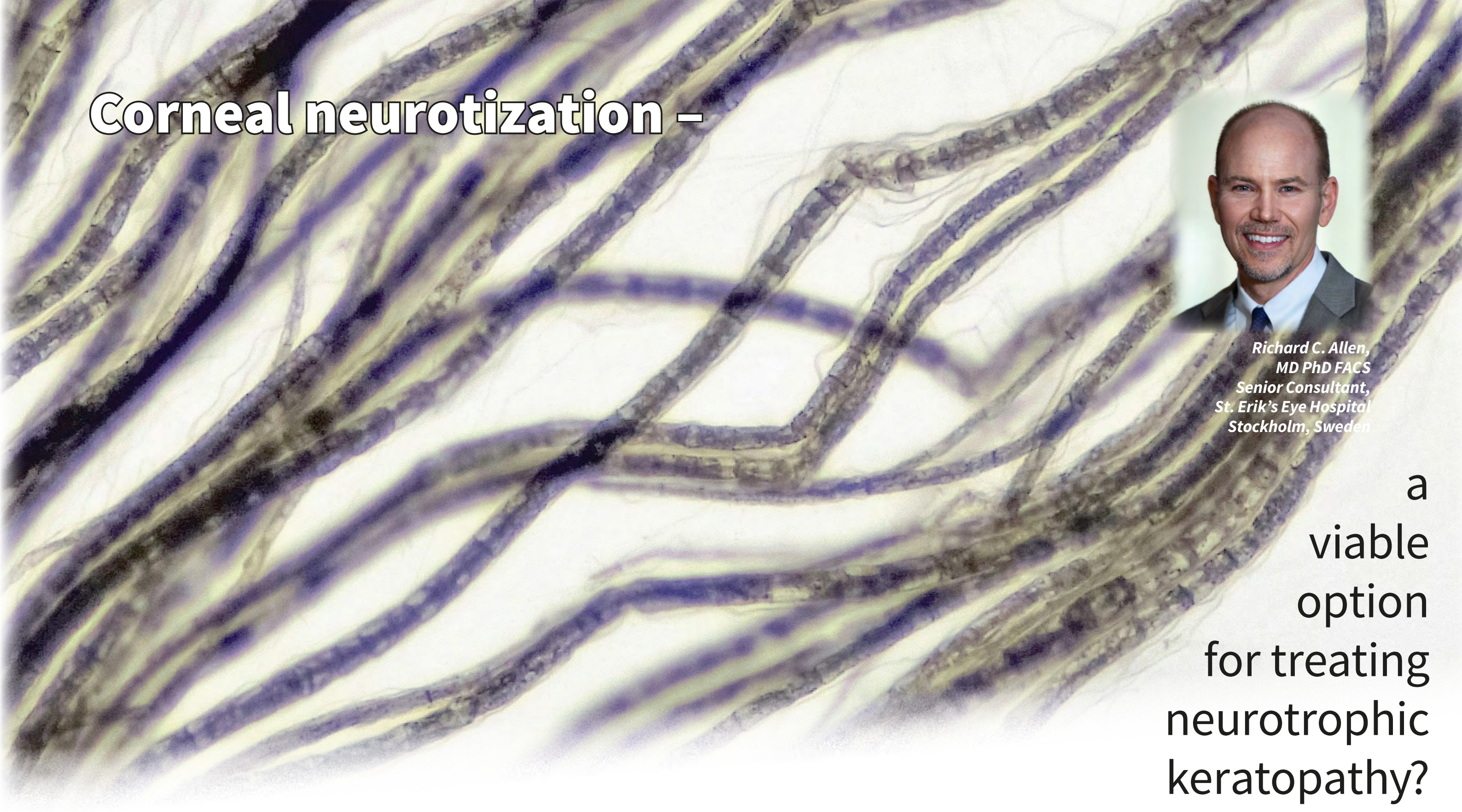

Corneal neurotization – a viable option for treating neurotrophic keratopathy?

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First submitted: September 30, 2024
Revision accepted: October 7, 2024
Revision submitted: October 7, 2024
Published: Winter 2024

Peer reviewed

Abstract

Corneal neurotization was introduced in 2009 as a surgical method to reestablish corneal sensation in patients with neurotrophic keratopathy. Initial procedures described direct neurotization from a branch of the trigeminal nerve; however, indirect neurotization using autologous and donor nerve grafts has shown equivalent results. The goal of the surgery is to connect a sensitive area of the patient's face with the affected eye. Promising results have been reported with this surgery. The purpose of this review is to describe relevant factors to consider in candidate selection and the performance of the procedure.

The cornea is the most sensitive and densely innervated tissue in the human body with 7,000 nociceptors per square millimeter.[1] Sensation originates in the ophthalmic branch of the trigeminal nerve, then travels in the nasociliary nerve and its long ciliary nerve branches to the cornea.[2] Corneal sensation provides the blinking reflex, wound healing through trophic neuropeptides, and tear production.[3] Neurotrophic keratopathy is caused by a loss of corneal sensation. The prevalence is approximately 5 in every 10,000 people. Loss of sensation results in the breakdown of the corneal epithelium, which can cause significant ocular morbidity.[4]

There are many causes of neurotrophic keratopathy.[4] Trigeminal denervation can be caused by viral infections (e.g., herpes zoster virus and herpes simplex virus), chemical burns, physical injuries, corneal surgery, retinal laser (pan-retinal photocoagulation), compression of the trigeminal nerve (tumors), neurosurgical procedures, and systemic disease (diabetes, multiple sclerosis, leprosy). There are also inherited and congenital causes including familial dysautonomia, familial corneal anesthesia, hereditary and sensory autonomic neuropathy, pontine tegmental cap dysplasia, Möbius syndrome, and Goldenhar syndrome. It is critical to determine the cause of neurotrophic keratopathy to adequately treat the patient.

Examination of the patient centers on evaluating the amount of corneal anesthesia and documenting the extent of corneal involvement. In addition, in preparing for possible neurotization, the fields of sensation on the face should be evaluated. The Mackie classification of neurotrophic keratopathy has been generally adopted by corneal specialists.[5] Grade 1 keratopathy consists of punctate keratitis, epithelial hyperplasia, and corneal neovascularization. Grade 2 demonstrates persistent epithelial defect with possible anterior chamber reaction or sterile hypopyon. Grade 3 shows stromal ulceration, with possible edema, infiltrates, thinning, or perforation. Evaluation of corneal sensation is performed with a Cochet-Bonnet aesthesiometer. This should be performed on the central cornea and each of the quadrants. Zero millimeters implies no sensation, while 60 mm implies full sensation.

Traditional treatment of neurotrophic keratopathy involves the use of preservative-free lubricants, which are escalated as needed.[4] Serum drops can be added if the lubricants are not sufficient. Surgical treatment involves tarsorrhaphies, amniotic membrane transplantation, and conjunctival flaps.[6] Scleral lenses are a recent advancement in which an aqueous reservoir is trapped under the lens to lubricate the cornea.[7] Cenegermin is a topical recombinant human nerve growth factor that has shown efficacy in wound healing.[8] Although cenegermin has not shown significant improvement in corneal sensation, it has been used in postherpetic and post-surgical causes of neurotrophic keratopathy.

The key concept of corneal neurotization is to restore corneal sensation and trophic influences by reconstituting the neural pathways between the cornea and a healthy

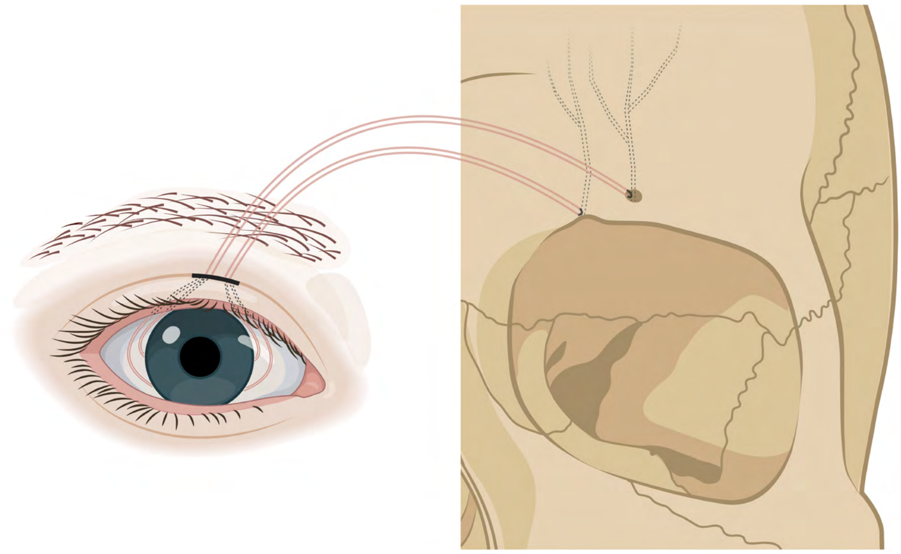

Figure 1. Direct transfer from the left supraorbital and supratrochlear nerves to the right side. Created by Tanya Cross using BioRender.com.

branch of the trigeminal nerve.[9] The procedure was first described by Terzis et al. in 2009 in six patients with facial nerve palsy and central nervous denervation, who underwent direct transfer of the supratrochlear and supraorbital nerves to the corneoscleral limbus (**Figure 1**).[10] This procedure was somewhat labor intensive, requiring a coronal flap and meticulous dissection of the branches of the transferred nerves. Others describe the use of endoscopic techniques for nerve dissection, avoiding a coronal incision.[11]

Nerve grafts are commonly used in plastic surgery, and case series were soon published describing the use of an indirect interpositional nerve graft between a branch of the trigeminal nerve and the corneoscleral limbus.[12] This graft could either be autologous or allogeneic. The most common autologous graft is the sural nerve. The use of allogeneic grafts allows the surgery to be much quicker due to the lack of nerve dissection or harvesting of a donor nerve.[13] However, allogeneic grafts add significant cost, and there is always the small chance of transmissible disease.

In order to determine which branch of the trigeminal nerve to graft the donor nerve to, sensory mapping of the face is performed.[14] In general, subjective touch perception works well, asking the patient if they can feel the touch in a particular field of the trigeminal nerve. The most common branches used are either the supratrochlear / supraorbital nerves (corresponding to forehead sensation) or the infraorbital nerve (corresponding to cheek sensation). The infraorbital nerve has the significant advantage of higher axonal counts, which increases the likelihood of success of the procedure; however, there is usually some loss of sensation in the field of the nerve that is being grafted to, and loss of sensation on the cheek/lip is much more bothersome to patients than loss of sensation on the forehead.[15] In choosing the branch of the trigeminal nerve, the first choice is usually ipsilateral infraorbital, followed by ipsilateral supraorbital, contralateral supraorbital, and contralateral infraorbital.

Connecting the graft to the branch of the trigeminal nerve can be performed in an "end-to-end" or "end-to-side" coaptation (**Figure 2**).[16] In the end-to-end technique, the branch of the trigeminal nerve is exposed and transected, and the end of the trigeminal nerve is anastomosed to the end of the donor graft. This is usually performed when using the supraorbital nerve (**Video 1**). In the end-to-side technique, the perineurium of the branch of the trigeminal nerve is incised and a portion of the nerve is disrupted. Then the end of the donor graft is sutured to the side of the branch of the trigeminal nerve. This is usually performed when using the infraorbital nerve, which results in less sensation loss in the field of its innervation (**Video 2**).

Many case series have been published using different techniques.[17-19] There appears to be no advantage of direct corneal neurotization over indirect corneal neurotization. Because of this, most oculoplastic surgeons prefer indirect corneal neurotization since it is a quicker surgery. In addition, there is no evidence that the use of an autologous graft over an allogeneic graft increases success. Although harvesting the sural nerve is usually straightforward and without complication, most oculoplastic surgeons prefer using an allogeneic graft.

With regards to the success of the procedure, patients demonstrate an improvement in the epithelium and Cochet-Bonnet aesthesiometry.[18-20] Improvement typically begins three months after the procedure. By six months, there should be

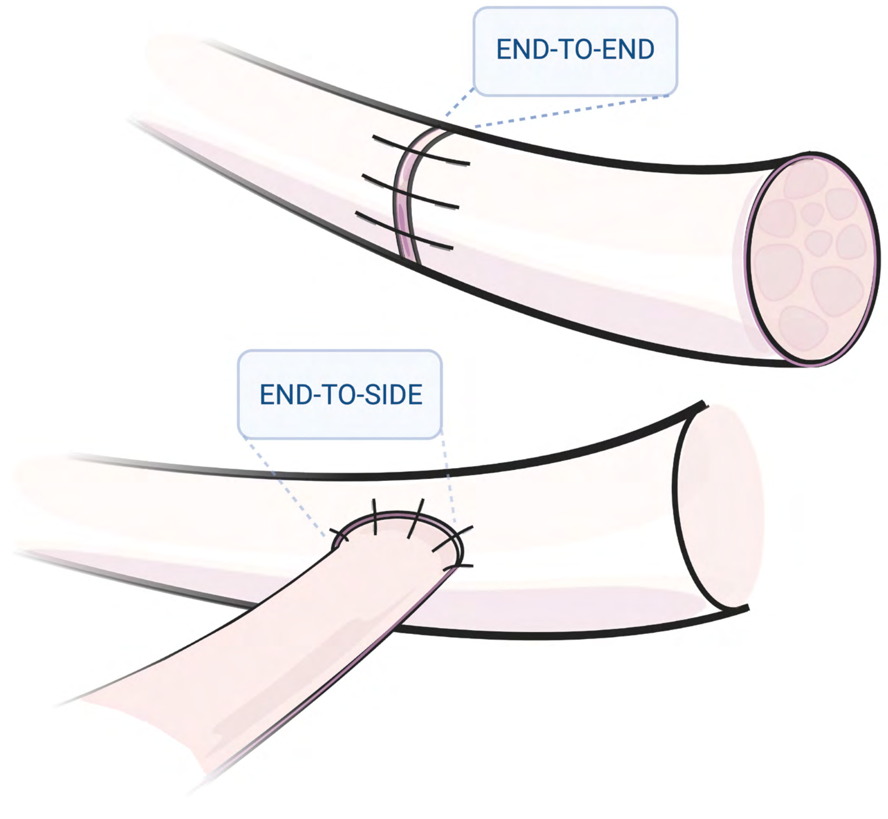

Figure 2. Illustration of end-to-end and end-to-side coaptation. Created by Tanya Cross using BioRender.com.

evidence of improved sensation which continues to improve over the 12–24 months after the procedure. The sensation described by patients is more of a dysesthesia, which is often localized to the area of sensation from the donor branch of the trigeminal nerve. Confocal microscopy shows evidence of reestablishment of corneal nerves after neurotization.[21,22] There is some evidence that poor prognostic indicators are longer periods of denervation prior to the surgery and older age. Patients who have sensation loss due to central or peripheral denervation (e.g., due to tumors, surgery, or herpes zoster virus) have a greater chance of success compared to those with neurotrophic keratopathy due to systemic disease (e.g., diabetes).[23]

Key points:

- There are multiple causes of neurotrophic keratopathy; the cause must be determined before treatment.
- Treatment of neurotrophic keratopathy begins with frequent lubrication.
- Corneal neurotization is a technique that connects a functioning branch of the trigeminal nerve to the corneoscleral limbus.
- Nerve grafts are commonly used to make the connection between the functioning branch of the trigeminal nerve and the eye.
- This is a promising treatment for patients who fail conservative treatment of neurotrophic keratopathy.

Conflict of interest
none

Videos

Take a peek into the OR and watch the procedures on YouTube:

Video 1. *Corneal neurotization using an end-to-end technique to the contralateral supraorbital nerve.*

Video 2. *Corneal neurotization using an end-to-side technique to the ipsilateral infraorbital nerve.*

References

1. Zander E, Weddell G. Observations on the innervation of the cornea. *J Anat.* 1951 Jan;85(1):68-99.
2. Marfurt CF, Kingsley RE, Echtenkamp SE. Sensory and sympathetic innervation of the mammalian cornea. A retrograde tracing study. *Invest Ophthalmol Vis Sci.* 1989 Mar;30(3):461-72.
3. Yang AY, Chow J, Liu J. Corneal Innervation and Sensation: The Eye and Beyond. *Yale J Biol Med.* 2018 Mar 28;91(1):13-21.
4. Vera-Duarte GR, Jimenez-Collado D, Kahuam-López N, Ramirez-Miranda A, Graue-Hernandez EO, Navas A, Rosenblatt MI. Neurotrophic keratopathy: General features and new therapies. *Surv Ophthalmol*. 2024 Sep-Oct;69(5):789-804.
5. NaPier E, Camacho M, McDevitt TF, Sweeney AR. Neurotrophic keratopathy: current chal-lenges and future prospects. *Ann Med.* 2022 Dec;54(1):666-673.
6. Trinh T, Mimouni M, Santaella G, Cohen E, Chan CC. Surgical Management of the Ocular Surface in Neurotrophic Keratopathy: Amniotic Membrane, Conjunctival Grafts, Lid Surgery, and Neurotization. *Eye Contact Lens*. 2021 Mar 1;47(3):149-153.
7. Witsberger E, Schornack M. Scleral Lens Use in Neurotrophic Keratopathy: A Review of Current Concepts and Practice. *Eye Contact Lens*. 2021 Mar 1;47(3):144-148.
8. Deeks ED, Lamb YN. Cenegermin: A Review in Neurotrophic Keratitis. *Drugs*. 2020 Apr;80(5):489-494.
9. Park JK, Charlson ES, Leyngold I, Kossler AL. Corneal Neurotization: A Review of Pathophysiology and Outcomes. *Ophthalmic Plast Reconstr Surg.* 2020 Sep/Oct;36(5):431-437.
10. Terzis JK, Dryer MM, Bodner BI. Corneal neurotization: a novel solution to neurotrophic keratopathy. *Plast Reconstr Surg.* 2009 Jan;123(1):112-120.
11. Leyngold I, Weller C, Leyngold M, Tabor M. Endoscopic Corneal Neurotization: Technique and Initial Experience. *Ophthalmic Plast Reconstr Surg.* 2018 Jan/Feb;34(1):82-85.
12. Bains RD, Elbaz U, Zuker RM, Ali A, Borschel GH. Corneal neurotization from the supratrochlear nerve with sural nerve grafts: a minimally invasive approach. *Plast Reconstr Surg*. 2015 Feb;135(2):397e-400e.
13. Leyngold IM, Yen MT, Tian J, Leyngold MM, Vora GK, Weller C. Minimally Invasive Corneal Neurotization With Acellular Nerve Allograft: Surgical Technique and Clinical Outcomes. *Ophthalmic Plast Reconstr Surg*. 2019 Mar/Apr;35(2):133-140.
14. Vinee F, Grobnicu O, Errera C, Gomart G, Tuzin N, Heitz A, Liverneaux P, Bourcier T. Assessment of Tactile Sensitivity Threshold Using Cochet-Bonnet Esthesiometer and Semmes-Weinstein Monofilaments and Their Use in Corneal Neurotization. *Ophthalmic Plast Reconstr Surg.* 2021 May-Jun 01;37(3S):S39-S43.
15. Domeshek LF, Hunter DA, Santosa K, Couch SM, Ali A, Borschel GH, Zuker RM, Snyder-Warwick AK. Anatomic characteristics of supraorbital and supratrochlear nerves relevant to their use in corneal neurotization. *Eye (Lond)*. 2019 Mar;33(3):398-403.
16. Liu CY, Arteaga AC, Fung SE, Cortina MS, Leyngold IM, Aakalu VK. Corneal neurotization for neurotrophic keratopathy: Review of surgical techniques and outcomes. *Ocul Surf.* 2021 Apr;20:163-172.
17. Wisely CE, Rafailov L, Cypen S, Proia AD, Boehlke CS, Leyngold IM. Clinical and Morphologic Outcomes of Minimally Invasive Direct Corneal Neurotization. *Ophthalmic Plast Reconstr Surg*. 2020 Sep/Oct;36(5):451-457.
18. Fogagnolo P, Giannaccare G, Bolognesi F, Digiuni M, Tranchina L, Rossetti L, Dipinto A, Al-levi F, Lozza A, Rabbiosi D, Mariani S, Pellegrini M, Cazzola FE, Bagaglia S, Mazzotta C, Ga-briele G, Gennaro P, Badiali G, Marchetti C, Campos EC, Biglioli F. Direct Versus Indirect Corneal Neurotization for the Treatment of Neurotrophic Keratopathy: A Multicenter Pro-spective Comparative Study. *Am J Ophthalmol.* 2020 Dec;220:203-214.
19. Sweeney AR, Wang M, Weller CL, Burkat C, Kossler AL, Lee BW, Yen MT. Outcomes of corneal neurotisation using processed nerve allografts: a multicentre case series. *Br J Ophthalmol*. 2022 Mar;106(3):326-330.
20. Wu Y, Zhang J, Ding W, Chen G, Shao C, Li J, Wang W, Wang W. Clinical Outcomes of Minimally Invasive Corneal Neurotization After Cerebellopontine Angle Neurosurgical Procedures. *Curr Eye Res*. 2022 May;47(5):670-676.
21. Ebner R, Fridrich G, Socolovsky M, Luna A, Croxatto JO. In Vivo Corneal Confocal Microscopy: Pre- and Post-operative Evaluation in a Case of Corneal Neurotization. *Neuroophthalmology*. 2019 Jan 25;44(3):193-196.
22. Ting DSJ, Figueiredo GS, Henein C, Barnes E, Ahmed O, Mudhar HS, Figueiredo FC. Corneal Neurotization for Neurotrophic Keratopathy: Clinical Outcomes and In Vivo Confocal Microscopic and Histopathological Findings. *Cornea*. 2018 May;37(5):641-646.
23. Ting DSJ, Pradhan SP, Barnes E, Ahmed OA, Figueiredo FC. Minimally invasive corneal neurotization for neurotrophic keratopathy: The potential effect of age, denervation chronicity and lesion location. *Am J Ophthalmol Case Rep.* 2023 Jan 21;29:101804.