

Neurotrophic Keratitis

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Key Words

Neurotrophic keratitis · Corneal sensitivity · Trigeminal nerve · Corneal vascularization · Stromal ulcers

Abstract

Neurotrophic keratitis (NK) is a rare degenerative corneal disease that occurs as a result of partial or total impairment of trigeminal innervations, leading to a reduction (hypoesthesia) in or loss (anaesthesia) of corneal sensitivity. The impairment of sensory innervation causes a reduction in the lacrimation reflex and the vitality, metabolism and mitosis of epithelial cells, with subsequent deficiency in epithelial repair, stromal and intracellular oedema, loss of microvilli, and abnormal development of the basal lamina. Several recent studies have proposed different therapies based on different aetiopathogenetic theories. The aim of the therapy is to treat aetiopathogenesis and, at the same time, promote corneal healing. In this paper, we report the aetiology, diagnosis, management, and medical and surgical treatment of NK, also indicating future treatments based on the most recent studies.

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Introduction

Neurotrophic keratitis (NK) is a degenerative corneal disease that follows a partial or total impairment of trigeminal innervation, leading to a reduction (hypoesthesia)

in or loss (anaesthesia) of corneal sensitivity [1]. In this article, we review the aetiology, diagnosis and management of NK.

Aetiopathogenesis

An animal study conducted in 1954 revealed the molecular basis of this disease for the first time, showing its development by sectioning of the trigeminal nerve [2]. The trigeminal ophthalmic branch has 2 reflex arcs: one motor arc, regulating the opening and closing of the eyelids, and one autonomic arc, regulating the lacrimal gland, Meibomian gland and goblet cell secretion. The integration of these 2 reflex arcs ensures the stability of the tear film and, together with related neurotrophic factors (neurotrophins), the vitality of the epithelium and stroma [3]. Cavanagh et al. [4, 5] described the bi-directional regulation of corneal epithelial proliferation through sensory and autonomic sympathetic innervation. The impairment of sensory innervation, as demonstrated by Sigelman [2], causes a reduction in the lacrimation reflex and the vitality, metabolism and mitosis of epithelial cells, with subsequent deficiency in epithelial repair, stromal and intracellular oedema, loss of microvilli, and abnormal development of the basal lamina [2, 6–8].

The study of NK has directed the attention of researchers to the role of neurotransmitters such as substance P (SP), calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal peptide, galanin, methionine-enkeph-

alin, catecholamine, and acetylcholine (Ach) [5, 9]. Studies have shown a decrease in SP and Ach resulting from injury to the corneal nerves [10, 11], the ability of SP alone to stimulate the synthesis and growth of corneal epithelial cells [12], and epithelial proliferation in vitro by SP, cholecystokinin gene-related peptide and Ach [5, 12, 13]. Although studies performed in humans could not show that the treatment with SP alone promotes corneal re-epithelialization [14], Chikama et al. [15] reported the complete recovery of a patient with NK after treatment with SP and insulin-like growth factor-1 (IGF-1) eye drops. These studies have suggested that treatment with a combination of SP and IGF-1 stimulates epithelial cell migration, integrin β and α_5 , essential for epithelial cell anchoring. Ach released from sensory neurons increases intranuclear cyclic guanosine monophosphate (cGMP) levels and promotes epithelial growth, and the severe depletion of Ach seen in corneal denervation causes decreased epithelial growth. Adrenergic stimulation partially reverses the effects of sympathetic denervation [11, 16, 17], and in animal studies, in which corneal anaesthesia is induced, corneal epithelial effects are mitigated by cervical sympathetic denervation [11].

The role of neurotrophins such as nerve growth factor (NGF) in NK has also generated increasing interest [18, 19]. These neurotrophins seem essential for the maintenance and regulatory functions of the nervous system. The discovery of the first neurotrophin, NGF, triggered the search for factors influencing the development and maintenance of the nervous system [20]. NGF is a neurotrophin essential to the development and survival of selected neurons, including sympathetic and sensory neurons, and for trophic support after neuronal injuries. It is normally present in the healthy cornea, where it regulates the proliferation and differentiation of epithelial cells. NGF also appears to be involved in epithelial and stromal interactions that induce stromal healing as well as in the remodeling mechanism that promotes the onset of stromal opacity.

NK can be the expression of systemic or ocular congenital or iatrogenic diseases resulting from damage to the fifth cranial nerve (table 1). The most common causes of loss of corneal sensitivity are herpes keratitis, chemical burns, long-term use of contact lenses, corneal surgery [21], ablative procedures for trigeminal neuralgia [22], and surgical procedures for reduction of jaw fractures [23]. Other less frequent causes are space-occupying intracranial masses (e.g., schwannoma, meningioma and aneurysms) that can lead to compression of the nerve and reduce corneal sensitivity. Systemic diseases that may compromise trigeminal function are diabetes, multiple

Table 1. Aetiopathogenesis of NK

Infections	Herpes simplex Herpes zoster Leprosy
Corneal pathologies	Chemical burns Contact lens wear Surgeries Laser-assisted in situ keratomileusis Corneal incision Lamellar and penetrating keratoplasty Dystrophies Lattice Granular
Topical medications	Anaesthetics Timolol Betaxolol Trifluridine Sulfacetamide
Cranial nerve V palsy	Trigeminal neuralgia surgery Neoplasm Aneurysm Facial trauma Congenital Riley-Day syndrome Möbius corneal hypoesthesia
Systemic diseases	Diabetes Vitamin A deficiency Multiple sclerosis
Miscellaneous	Increasing age Adie's syndrome

sclerosis and leprosy [24, 25]. NK may also be a complication of radiation therapy. Congenital causes, such as the Ridley-Day syndrome, anhidrotic ectodermal dysplasia, Moebius syndrome, Goldenhar syndrome, and congenital corneal anaesthesia, are very rare.

Diagnosis

Epidemiological data on NK have not been reported in the literature. Diagnosis can be achieved by obtaining a detailed medical history to investigate all possible risk factors, followed by a careful examination of the ocular and periocular area, including the globe and ocular adnexa.

Medical History

Previous episodes of redness and eye pain or the presence of cutaneous blistering or scarring suggest previous herpetic infections. A history of corneal surgery, trauma,

abuse of topical anaesthetics, long-term use of topical medications, chemical burns, or contact lens abuse may be contributory. Long-term use of eye drops such as timolol, betaxolol, sulfacetamide sodium, or diclofenac can cause a loss of corneal sensitivity, as can the abuse of topical anaesthetics [3, 26, 27]. Corneal hypoesthesia can sometimes occur in advanced stromal dystrophies such as latex or granular dystrophies [3]. Any neurological signs or symptoms or expression of fifth cranial nerve disease such as brain tumours, vascular accidents and thromboangiitis obliterans should be explored. A history of previous surgical resection of an acoustic neuroma may suggest a iatrogenic trigeminal nerve injury. The presence of hearing problems may indicate intracranial tumours such as neuromas of the eighth cranial nerve, especially when the fifth and seventh cranial nerves are involved [28]. A history of long-term therapy with neuroleptics, antipsychotics and antihistamines should be investigated, as should a history of diabetes mellitus, because reduction in corneal sensitivity in diabetes increases with the duration of the disease [24].

Physical Examination

The symptoms reported by the patient vary depending on the degree of corneal anaesthesia, but usually, the patient complains of a red eye and a slight reduction in visual acuity. The corneal sensitivity test is the basic examination and can be performed by touching the central and peripheral cornea with a Cochet-Bonnet aesthesiometer, which locates and quantifies the loss of corneal sensitivity by recording the patient's response to the touch of a nylon thread (less than 5 mm is regarded as clinically significant corneal hyposensitivity) [29]; a less sensitive test is the response to touch with the tip of a cotton swab [30]. In general, the severity of NK is related to the severity of corneal sensory impairment. The disease is usually unilateral, but if it is bilateral, there will also be a reduction in blinking as well as reduced tear production due to lack of the afferent arm of the lacrimation reflex [31, 32]. Fluorescein, rose bengal and lissamine green stains show a reduction in tear break-up time and formation of geographic dry spots and corneal and/or conjunctival epithelial defects. It is useful to perform a careful examination of the eyelid, including eyelid edges, positions and motility, to rule out exposure keratitis and diagnose blepharitis, which is often associated with NK. Microbiological examination of large, persistent epithelial defects must be performed to exclude bacterial, fungal or viral infection. The combination of an afferent pupillary defect and hypoesthesia must be studied to rule

Table 2. Classification of NK

Stage 1	Punctate epithelial staining Decreased tear breakup test Rose bengal staining of inferior palpebral conjunctiva Dellen Gaule spots Stromal scarring
Stage 2	Epithelial defect Stromal swelling Surrounding rim of loose epithelium Rare anterior chamber reaction
Stage 3	Corneal ulcer Stromal lysis Perforation

out intraocular orbital nerve injury. A reduction in accommodation can indicate damage to the motor ciliary nerve of the ciliary ganglion. Iris atrophy is often an expression of a previous herpetic keratouveitis or a lepromatous lesion. NK should be suspected in all patients who have a discrepancy between reported symptoms and ocular signs or in patients who have a decreased frequency of eyelid closure.

Classification of NK

NK can be classified into 3 stages according to the Mackie classification (table 2) [21, 22]. The first stage is characterized by punctate keratitis, epithelial hyperplasia, stromal scarring, and corneal neovascularization. The second stage is characterized by a persistent epithelial defect [21, 22], usually in the paracentral area, of oval shape with the horizontal axis surrounded by an irregular, oedematous, opaque epithelium capable of spontaneous detachment. A reaction in the anterior chamber or sterile hypopyon is rarely seen. At this stage, the mechanism of loss of the corneal epithelium is similar to that of recurrent erosions, promoted by reduced lubrication of the corneal surface and by the abnormal corneal epithelium. In the third stage, there is stromal involvement that appears as a stromal corneal ulcer and stromal oedema and infiltrates; this may result in perforation and/or corneal thinning due to stromal melting [21, 22].

Differential Diagnosis

Stage 1 NK may be confused with other eye diseases such as dry eye, exposure keratitis, topical drug toxicity, contact lens abuse, and corneal limbal deficiency. The presence of marked symptoms of burning, foreign body sensation, photophobia, and dry eye may direct the diag-

nosis towards other diseases of the ocular surface, but the hallmark of NK is anaesthesia. Sometimes, the epithelial defect can take on a dendritic form, but it can be distinguished from herpetic infection by the absence of benching. Limbal stem cell deficiency is distinguished by impression cytology, which enables the identification of cytokeratin (CK; the corneal epithelium is positive for CK3 and negative for CK19, while the conjunctival epithelium is positive for CK19 and negative for CK3) [33]. The clinical history, signs and symptoms, and results of microbiological tests for bacteria, fungi and viruses allow a definitive diagnosis. Any topical treatment should be discontinued to rule out iatrogenic corneal ulcers, and evaluation for systemic immune disorders should be considered.

Treatment

The aim of the therapy is to prevent the progression of corneal damage and promote healing of the corneal epithelium [34]. In stage 1 disease, all topical medications and systemic therapies such as neuroleptics, antipsychotics and antihistamines that can cause NK should be discontinued. The ocular surface can be preserved through the use of artificial tears without preservatives every 2–4 h and a lubricant ointment at bedtime. The goal at this stage is to improve the quality of the corneal epithelium, prevent an epithelial breakdown and preserve corneal transparency. Comorbidities such as exposure keratitis or limbal deficiency worsen the prognosis and should be treated before beginning NK symptoms.

The goal of treatment for Mackie stage 2 NK is to avoid the development of a corneal ulcer and promote healing of the epithelial defect. In addition to the discontinuation of all topical medications and the instillation of artificial tears without preservatives, as in the previous stage, it is essential that the patient be monitored frequently. The presence of asymptomatic disease may enable rapid progression to corneal perforation without the patient noticing it. In these cases, prophylactic antibiotic eye drops can be administered, and where microbiological examination is positive, it is essential to block concurrent keratitis with an effective antibiotic therapy. Corneal or scleral contact lens therapy can be used to promote healing while paying attention to the increased risks of secondary infection and lens-related sterile hypopyon [35–37]. The function of the lens is to provide a fluid cushion for the cornea and protect it from the rubbing effects of the lids [38–40]. Some authors have no-

ticed an improvement in the cornea through the use of temporary silicone plugs to help increase tear volume [41].

In the event of large epithelial defects or corneal ulcers that do not respond to treatment with artificial tears or contact lens treatment (Mackie stage 3), it is useful to stop all treatment except artificial tears and prescribe antibiotic prophylaxis, as in previous stages. The main goal of treatment at this stage of NK is to prevent corneal thinning and perforation, and tarsorrhaphy has traditionally been considered the treatment of choice because it can be easily performed and is widely used. Alternatives to tarsorrhaphy include injection of botulinum toxin A to induce temporary ptosis of the upper eyelid or the use of a conjunctival flap to cover the corneal surface, but this compromises aesthetics and visual function [42–45].

New surgical and medical alternatives have recently been introduced. The surgical treatments are transplantation of amniotic membranes (AMs), conjunctival flaps and sympathectomy, but the most recent research considers that medical therapy can restore the nerve damage that forms the basis of the pathology. These new medical treatments include autologous serum eye drops, umbilical cord serum eye drops and neurotrophin eye drops [46].

Autologous serum contains many growth factors and tear components, such as epidermal growth factor, vitamin A, transforming growth factor- β , fibroblast growth factors, platelet-derived growth factor, hepatocyte growth factor, fibronectin, and serum antiproteases such as α -2-macroglobulin; all these substances are suitable for facilitating the proliferation, migration and differentiation of the ocular surface epithelium. These properties have made autologous serum eye drops an effective treatment for severe dry eye in Sjögren's syndrome, persistent epithelial defects, superior limbic keratoconjunctivitis, and recurrent corneal erosion [18, 25]. Autologous serum also harbours neurotrophic substances such as SP, IGF-1 and NGF and can be useful for the restoration of ocular surface integrity in patients with NK. Matsumoto et al. [47] first noted the presence of neurotrophic substances in autologous serum eye drops and their usefulness for the restoration of ocular surface integrity in patients with NK [47–53].

Umbilical cord serum also contains essential tear components, growth factors and neurotrophic factors and can be used in many ocular surface diseases, including dry eye syndrome, persistent epithelial defect and NK [54].

Topical steroids and sympathectomy have been suggested for NK therapy, because adrenergic neurotransmitters and prostaglandins lead to an increase in cAMP and reduce corneal epithelial mitosis, whereas Ach causes an increase in cyclic guanosine monophosphate and stimulates the growth of the corneal epithelium. Topical steroids may reduce the activity of inflammatory mediators and are particularly useful in patients with chemical burns [4, 5]. However, the same topical steroids can inhibit stromal healing and increase the risk of stromal melting and corneal perforation [55]. The presence of inflammation in conjunction with a neurotrophic corneal ulceration further complicates treatment because the inflammatory response, together with the absence of sensory innervation, inhibits corneal epithelial growth [4, 5, 56]. The use of topical corticosteroids is indicated in cases in which inflammation is the driving cause of the persistent defect. Although theoretically, the use of topical nonsteroidal agents blocks the influence of prostaglandins on corneal epithelial growth, their clinical use has not been shown to have a relevant trophic effect on wound healing [55]. Diclofenac sodium in particular should be avoided because of its tendency to cause corneal hypoesthesia with topical use [57]. In studies on rabbits, sympathectomy has conferred improvement after damage to sensory nerves [58]; however, sympathectomy after chemically induced sensory nerve damage in humans did not yield the same results [59, 60].

The AM, a thin, avascular membrane comprising the innermost layer of the foetal membranes, is composed of 3 layers: epithelium, basement membrane (BM) and stroma. Each layer has specific biological properties that can be applied in different corneal diseases. The epithelium provides growth factors and cytokines useful for maintaining an undifferentiated epithelial phenotype during culture of limbal stem cells. Collagen IV/VII, laminin 1/5 and fibronectin of the BM improve epithelial cell migration and adhesion to basal cells, induce epithelial differentiation, including goblet cells in the conjunctiva, and prevent apoptosis. Transforming growth factor- β , anti-inflammatory and anti-angiogenic proteins, and protease inhibition factors of the stromal matrix can suppress corneal myofibroblasts, proliferation and differentiation of normal and pathological conjunctival fibroblasts (inhibition of cicatrization), and inhibit inflammation and neovascularization. In NK, the AM is used to support epithelial adhesion, growth and differentiation and to prolong the lifespan of the epithelial progenitor cells [61–64].

Ortuno-Prado and Alio [65] reported that the use of a Tutopatch with platelet-rich plasma was advantageous in a patient with neurotrophic ulcer, suggesting the use of Tutopatch as an alternative to AM transplantation. However, other studies are required to verify its effect.

Therapy with topical reductase inhibitors in diabetic patients produced improvement in corneal sensitivity and corneal epithelial cell morphology [66].

Several recent studies have proposed the use of neuropeptides and growth factors for the treatment of NK. Topical treatment with SP and IGF-1 induced healing in 2 patients who had disease recurrence within 1 year of follow-up [15, 67]. Epidermal growth factor has been used in human clinical trials with conflicting results [68, 69]. Topical treatment with NGF represents a promising therapy in the prevention of onset and progression of NK. Both in vivo and in vitro studies have shown that NGF induces the recovery of sensory neurons and the production of Ach in the central nervous system and of SP in the peripheral nervous system [70]. NGF also plays an important role in the balance between sensory and sympathetic innervations, modulating their functions [71]. Bonini et al. [18] demonstrated the restoration of epithelial integrity and corneal sensitivity in patients with NK treated with NGF. Other recent studies have shown the ability of NGF to induce healing of corneal ulcers by modulating epithelial tropism [19, 72].

Some authors have suggested use of collagenase inhibitors such as N-acetylcysteine, tetracycline or medroxyprogesterone for corneal thinning [73]. Small perforations can be treated with application of cyanoacrylate glue and a soft contact lens or bandage [74, 75], but lamellar or penetrating keratoplasty is necessary to treat large perforations [75]. The success rate of these corneal transplants is low because of poor wound healing and the persistent risk of corneal epithelial defects from anaesthesia. Reed et al. [76] suggest that partial tarsorrhaphy can improve the success rate of keratoplasty, although the severity of sensory impairment is not reported [18, 19, 72, 77, 78].

Prognosis

The prognosis of NK depends on several factors, namely, the cause of impairment of corneal sensitivity, the degree of corneal hypoaesthesia and the presence of concomitant diseases of the ocular surface. Obviously, the more severe the corneal sensory impairment, the greater the likelihood of disease progression [79].

Follow-Up

Patients with Mackie stage 1 NK should be monitored closely, with re-evaluation after 3–7 days. Patients with stage 2 disease should be evaluated every 1–2 days until significant improvement is seen, then every 3–5 days until resolution; those with stage 3 disease should be checked every day or hospitalized until significant improvement is seen. If tarsorrhaphy was performed, the opening between the eyelid margins can be enlarged after a couple of weeks, but attention must be paid because premature opening of tarsorrhaphy can cause recurrent corneal epithelial breakdown. At each visit, it is useful to perform staining to evaluate the corneal surface, a corneal sensitivity test and a Schirmer test; the best corrected visual acuity should also be evaluated.

Conclusion

NK is a degenerative corneal disease that occurs as a result of partial or total impairment of trigeminal innervations, leading to a reduction in or loss of corneal sensitivity. The aim of therapy is to treat the aetiopathogenesis and, at the same time, to promote the healing of the corneal epithelium, preventing the progression of corneal damage. In order to assess a correct treatment, the microbiological examination of large, persistent epithelial defects must be performed to exclude bacterial, fungal or viral infection. The neurotransmitters play a key role in the potential treatment of NK. The topical administration of NGF has actually demonstrated the ocular surface healing and immune-modulating actions in patients with infective and non-infective diseases of the ocular surface.

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