



XLIX CONGRESSO REGIONALE S.O.Si.

PRESIDENTE: PROF. PASQUALE ARAGONA

10-12 APRILE 2025

UNAHOTELS - NAXOS BEACH SICILIA (ME)



University of Messina
Dep. of Biomedical Sciences

EYE CLINIC

SCHOOL OF OPHTHALMOLOGY

EXCELLENCE REGIONAL CENTER FOR OCULAR SURFACE DISORDERS

EXCELLENCE REGIONAL CENTER FOR RARE DISEASES IN OPHTHALMOLOGY

Head: Prof. Pasquale Aragona

CHERATITE NEUROTROFICA

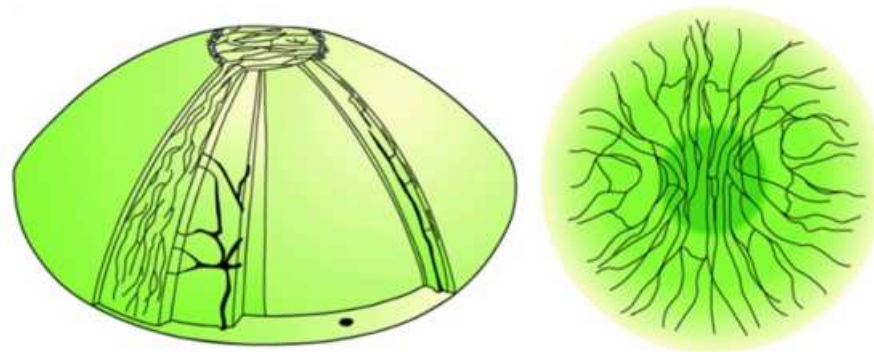
Elisa Imelde Postorino

Cornea Innervation

- The cornea is the most densely innervated tissue in the human body
- Multiple receptors of the cornea and their fibers protect it from damage by modulating the blink response, stimulating the production of tears and maintaining the cornea in a healthy state through the production of trophic factors

Corneal Innervation

- Corneal innervation is primarily sensory and derived from the ciliary nerves of the ophthalmic branch of the trigeminal ganglion
- Nerve fibers penetrate the cornea at the limbus, proceed toward the corneal center remaining below the anterior third of the stroma, penetrate Bowman's membrane, and create the subbasal nerve plexus between Bowman's layer and basal membrane of epithelial cells

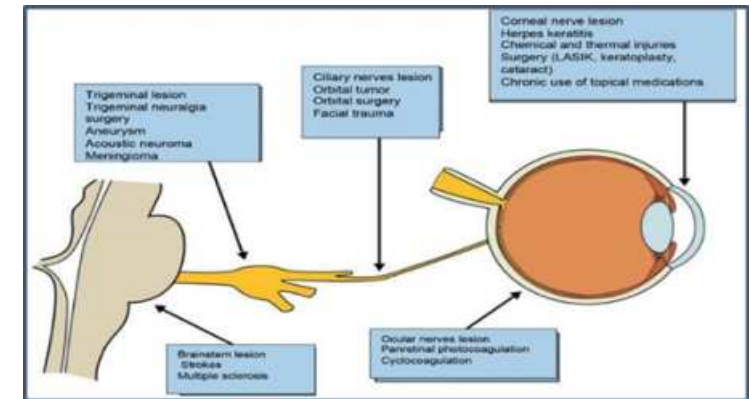


Neurotrophic keratopathy

- Neurotrophic keratopathy (NK) is defined as a disease related to alterations in corneal nerves leading to impairment in sensory and trophic functions with a consequent breakdown of the corneal epithelium, affecting health and integrity of the tear film, epithelium, and stroma (Dua et al., 2018).

Etiopathogenesis

- In healthy cornea when the epithelium is damaged, cells surrounding the wound migrate onto the wound bed to cover and regrowth of axons to repopulate the denervated tissues occurs
- This repair requires a controlled and collaborative system of communication between epithelial and neuronal cells to facilitate the resynthesis of the damaged matrix, cell migration, and restoration of architecture
- If epithelial healing is impaired, the exposed stroma becomes vulnerable to enzymatic degradation, melting and eventually perforation



Etiologies of neurotrophic keratitis.

A list of common etiologies that result in NK and their relationship to pathophysiological pathways is presented

Genetics

- Goldenhar-Gorlin syndrome
- Moebius syndrome
- Familial corneal hypoesthesia
- Congenital insensitivity to pain with anhidrosis
- Riley-Day syndrome
- Ectodermal dysplasia

CNS

- Neoplasm (acoustic neuroma, Meningioma, orbital tumour)
- Aneurysm
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures (trigeminal neuralgia, other surgical injury to trigeminal nerve)

Systemic

- Diabetes
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis
- Sjogren syndrome
- Dry eye disease
- Post-herpetic infections

Iatrogenic

- Surgery (LASIK, keratoplasty, cataract, orbital surgery)
- Panretinal photocoagulation
- Cyclocoagulation
- Benzalkonium chloride exposure
- Abuse of topical anesthetics

Injury

- Ocular nerve lesion, corneal nerve lesion
- Trauma to the ciliary nerve
- Facial trauma
- Chemical and thermal injury
- UV light injury
- Radiation
- Prolonged overuse of contact lenses
- Drug-induced (eg. Steven-Johnson syndrome)

Other conditions

- Chronic use of topical medication
- Vernal keratoconjunctivitis
- Atopic keratoconjunctivitis
- Ocular cicatricial pemphigoid

Symptoms

Due to the corneal sensation impairment, a **discrepancy between the clinical severity of NK and complained symptoms of patients** is often observed

A spectrum of different symptoms can be present:

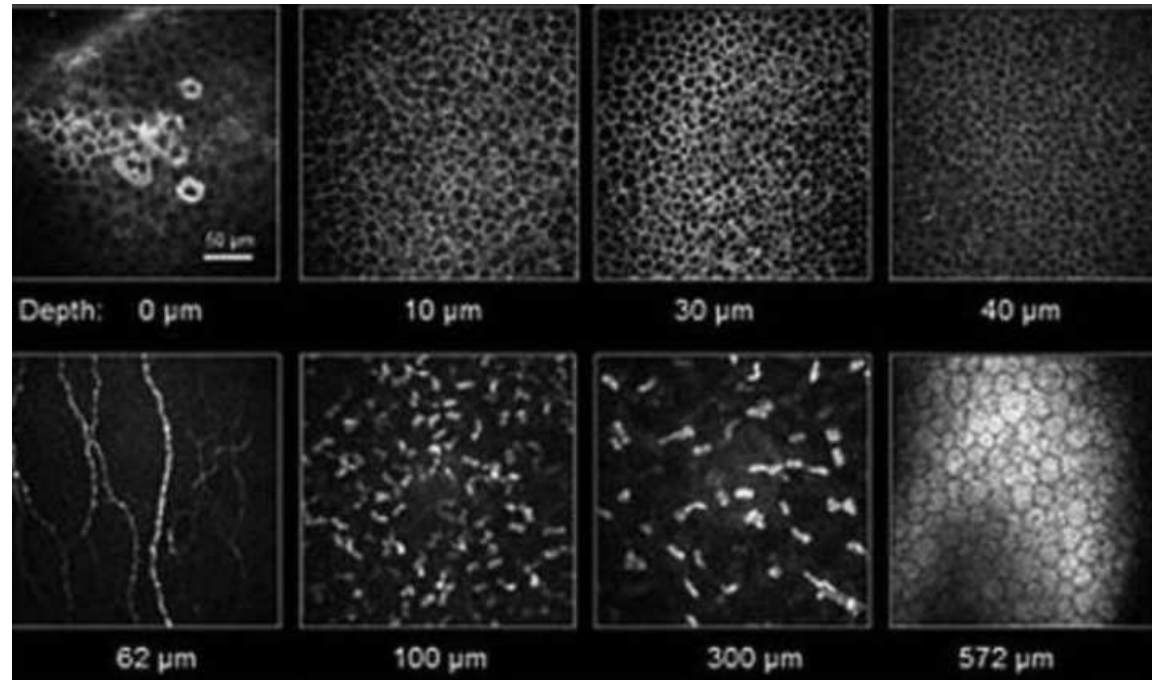
- Burning
- stinging
- tearing
- foreign-body sensation
- photophobia
- visual disturbance or impairment.

The diagnosis of NK

Is a multistep process that starts with:

- Clinical history condition associated with trigeminal impairment.
- The slit lamp examination
- Corneal sensitivity (Cochet– Bonnet aesthesiometer)
- In vivo confocal microscopy
- The anterior segment optical coherence tomography (AS-OCT)
- Keratograph 5M

In vivo cornea confocal microscopy (HRT)



- It allows to **visualize all corneal layers**, cells and nerves on a histological level.
- It provides a **qualitative and quantitative analysis of the subbasal nerve plexus**, with a fast and repeatable method, allowing the visualization of this in healthy and diseased corneas, in particular it allows to visualize the alterations of this plexus in the course of neurotrophic keratitis

The anterior segment optical coherence tomography

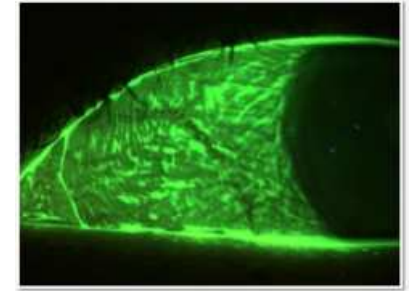
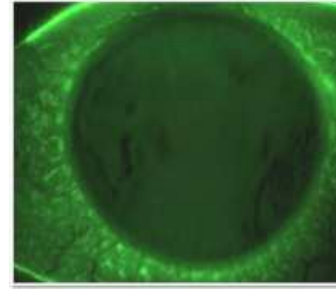
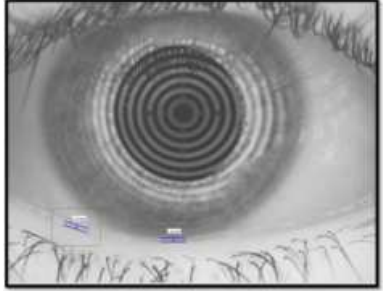
(AS-OCT)

**Follow up
Corneal thickness**



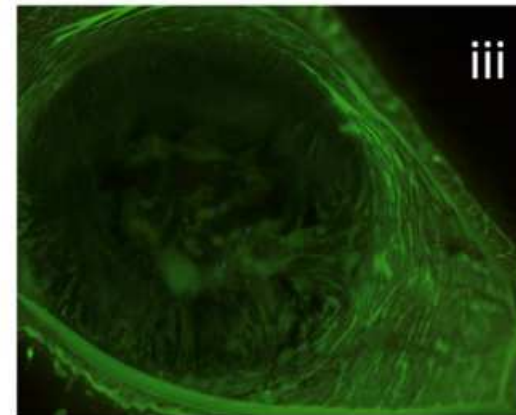
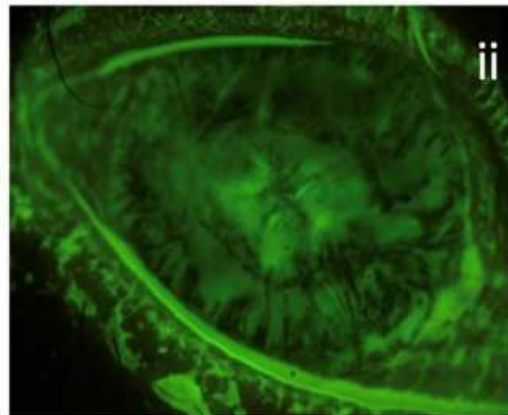
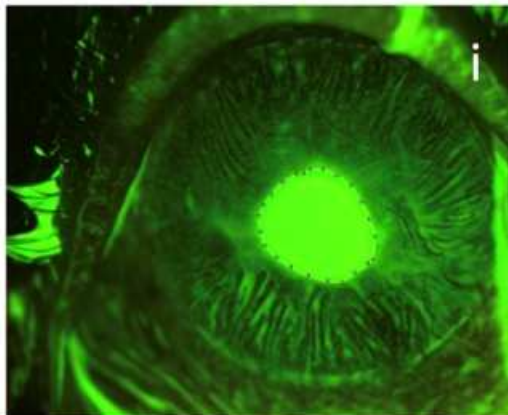
Keratograph 5M

(OCULUS Optikgeräte GmbH, Wetzlar, Germany)



- **videotopographer and a non-invasive, repeatable and reproducible tool for the assessment of the ocular surface**
- It combines corneal topography and dry eye study in a single tool and represents the gold standard for ocular surface investigation .

Follow up
Area of corneal defect

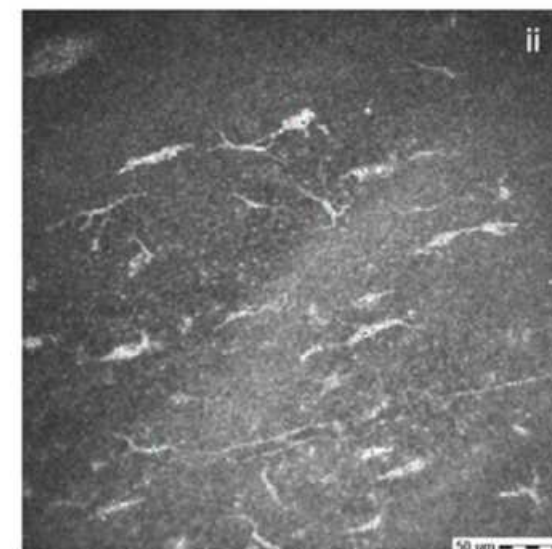
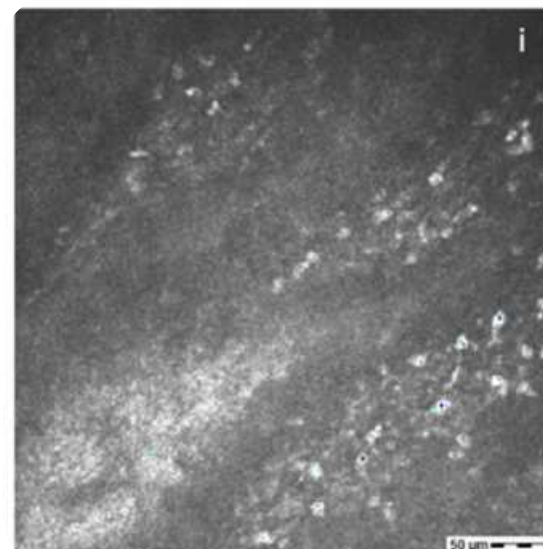




Article

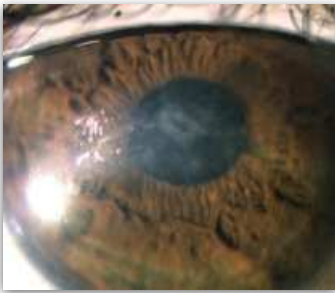
The Role of Hi-Tech Devices in Assessment of Corneal Healing in Patients with Neurotrophic Keratopathy

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The Mackie classification

NK: Stage 1(mild)



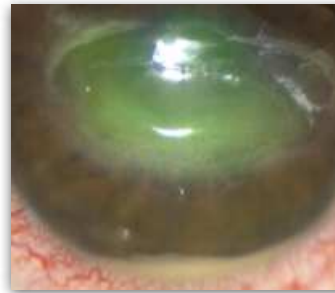
Epithelial irregularity, such as punctate keratopathy.

NK: Stage 2 (moderate)



Recurrent or persistent epithelial defects (PED) without stromal involvement.

NK: Stage 3 (severe)



Stromal involvement with ulcer, melting, and perforation.

- Dua et al. (2018)

[Review](#) > [Prog Retin Eye Res.](#) 2018 Sep;66:107-131. doi: 10.1016/j.preteyeres.2018.04.003.

Epub 2018 Apr 23.

Neurotrophic keratopathy

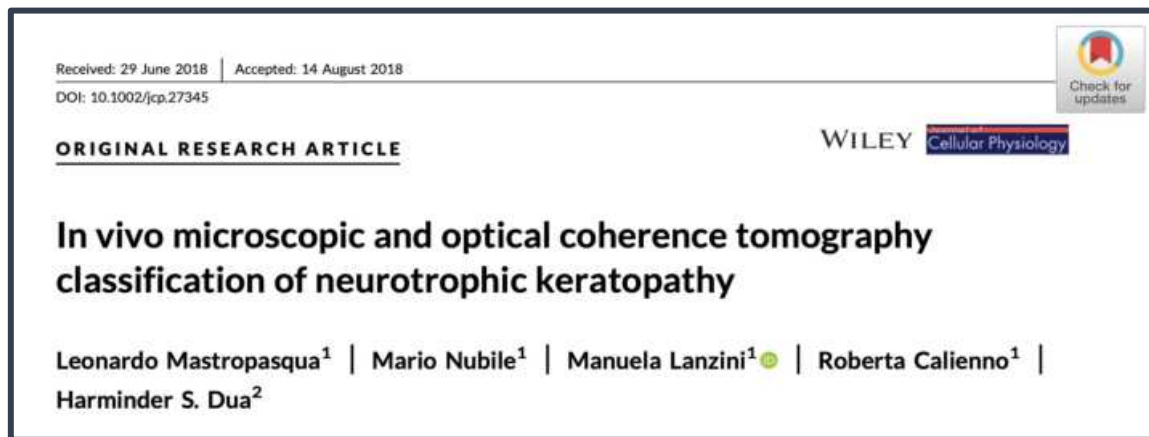
Harminder S Dua ¹, Dalia G Said ², Elisabeth M Messmer ³, Maurizio Rolando ⁴, Jose M Benitez-Del-Castillo ⁵, Parwez N Hossain ⁶, Alex J Shortt ⁷, Gerd Geerling ⁸, Mario Nubile ⁹, Francisco C Figueiredo ¹⁰, Saaeha Rauz ¹¹, Leonardo Mastropasqua ¹², Paolo Rama ¹³, Christophe Baudouin ¹⁴

Affiliations + expand

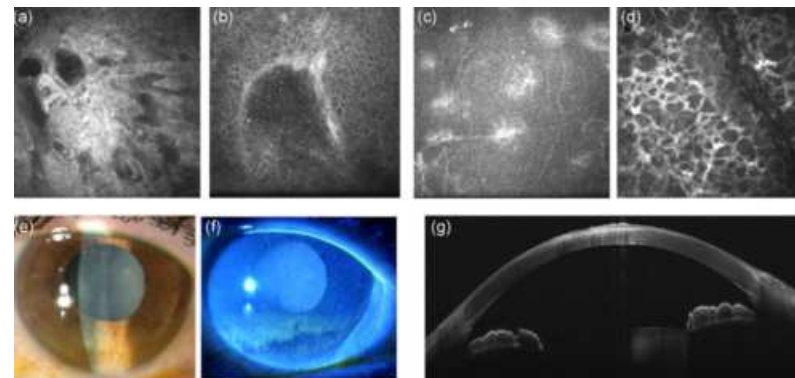
PMID: 29698813 DOI: [10.1016/j.preteyeres.2018.04.003](#)

- Mackie (1995)

Additional classification based on Anterior Chamber Optical Coherence Tomography (AC-OCT) and in vivo confocal microscopy (IVCM)



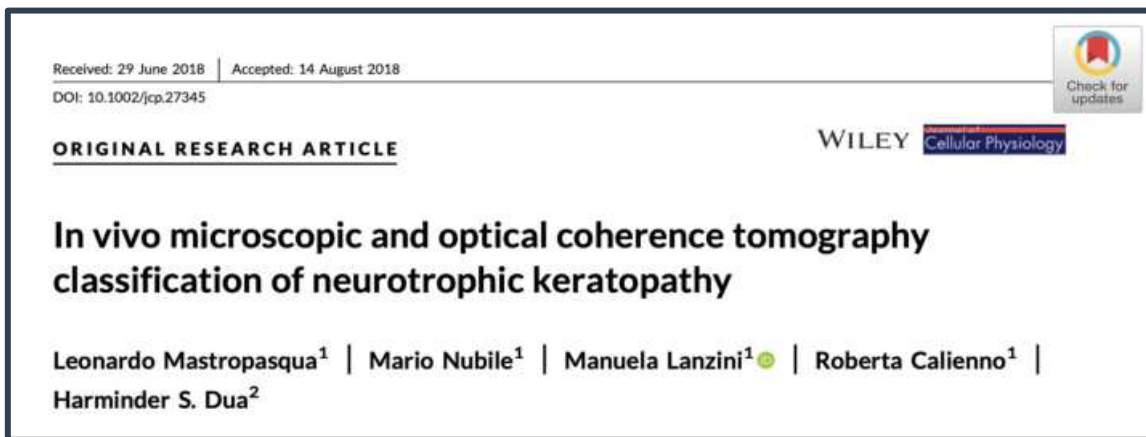
- Mastropasqua et al. (2019)



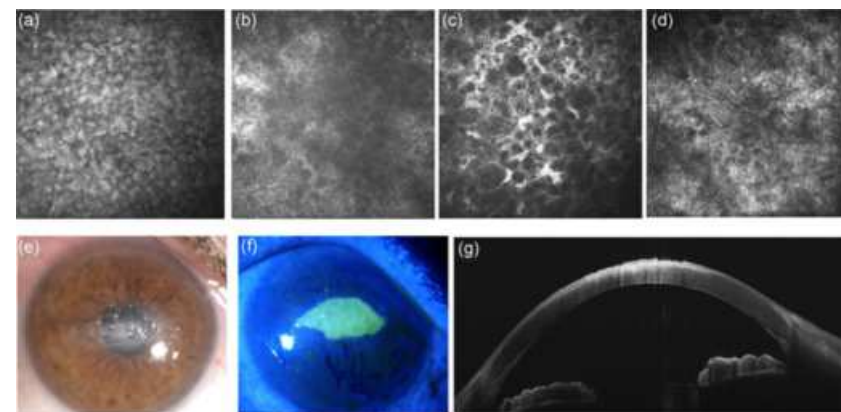
Stage 1

- **Stage 1A:** Punctate corneal epithelial fluorescein staining, possible corneal hypoaesthesia, subbasal nerve fiber density $\geq 5 \mu\text{m}/\text{mm}^2$, and the number of total nerve fibers ≥ 1 per mm^2
- **Stage 1B:** Punctate corneal epithelial fluorescein staining, possible corneal hypoaesthesia, subbasal nerve fiber density $\leq 5 \mu\text{m}/\text{mm}^2$, and number of total nerve fibers ≤ 1 per mm^2 .

Additional classification based on Anterior Chamber Optical Coherence Tomography (AC-OCT) and in vivo confocal microscopy (IVCM)



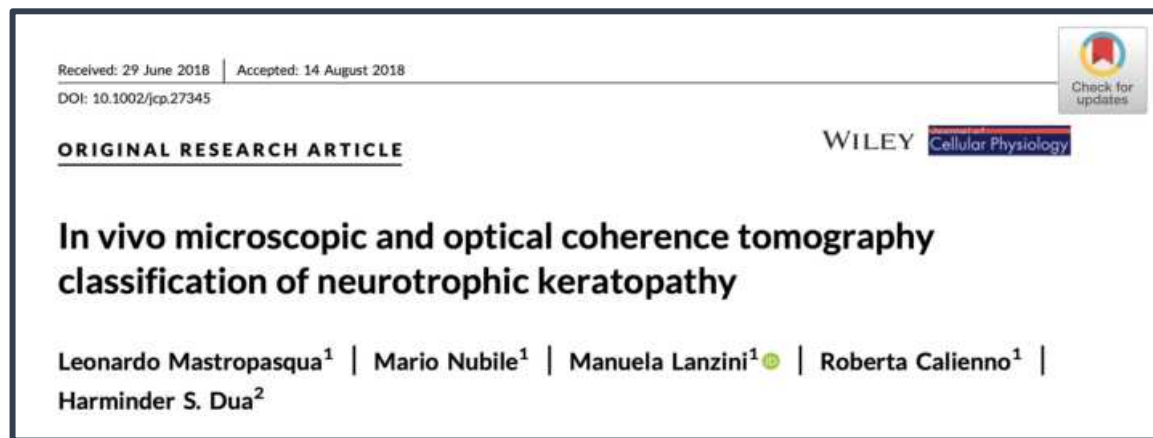
- Mastropasqua et al. (2019)



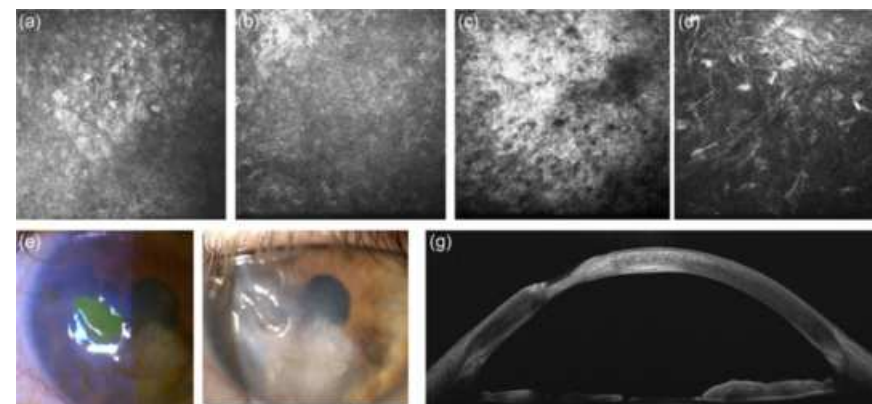
Stage 2

- **Stage 2A:** Epithelial defect with smooth and rolled edges, corneal hypoaesthesia or total corneal anesthesia, subbasal nerve fiber density $\geq 3 \mu\text{m}/\text{mm}^2$, and the number of total nerve fibers ≥ 0.5 per mm^2
- **Stage 2B:** Epithelial defect with smooth and rolled edges, corneal hypoaesthesia or total corneal anesthesia, subbasal nerve fiber density $\leq 3 \mu\text{m}/\text{mm}^2$, and the number of total nerve fibers ≤ 0.5 per mm^2

Additional classification based on Anterior Chamber Optical Coherence Tomography (AC-OCT) and in vivo confocal microscopy (IVCM)



- Mastropasqua et al. (2019)



Stage 3

- **Stage 3A:** Corneal ulceration with stromal thinning $\leq 50\%$ of the total corneal thickness
- **Stage 3B:** Corneal ulceration with stromal thinning $\geq 50\%$ of the total corneal thickness.

Medical Management

Iatrogenic Ocular Toxicity: is related to the concentration, frequency, and duration of administration of the drug:

- Toxicity is often associated with preservatives such as benzalkonium chloride (BAK)
- Topical nonsteroidal antiinflammatory drugs (NSAIDs) may also be involved in the development of serious corneal complications
- Topical medications commonly employed for the clinical management of glaucoma

All preserved therapy should, wherever possible, be discontinued

Detection of drug-induced corneal deposits must be considered

Medical Management

Preservative-free artificial tears: can play a similar role to human tears and can be vital in NK for their lubricating, mechanical, but also epitheliotropic and antimicrobial properties, for the ocular surface

Therapeutic contact lens in the management of NK is to improve epithelial integrity, thereby stabilizing corneal thinning and minimizing the risk of corneal perforation:

- **Soft contact lenses** are used more commonly
- **Scleral lenses** : in complicated corneal and ocular surface conditions; can also be employed to aid healing by providing protection against abrasive forces of the eyelid on a desiccated ocular surface

Blood-derived products

Blood-derived eye drops are formulated from either the patient's own peripheral blood serum (autologous source), or from donors (homologous source), such as allogeneic peripheral blood serum and umbilical cord blood serum

Autologous source: including autologous serum, platelet-rich plasma, plasma rich in growth factors, and platelet lysate

- Risk of potentially instilling circulating antibodies or pro-inflammatory mediators in patients with systemic diseases

Homologous source such as allogeneic peripheral blood serum and umbilical cord blood serum

These ocular eye drops have many kinds of different **biochemical components** that play a main role in maintaining ocular surface integrity:

- epidermal growth factor (EGF)
- fibroblast growth factor (FGF)
- transforming growth factor beta (TGF- β)
- nerve growth factor (NGF)
- platelet-derived growth factor (PDGF)
- insulin-like growth factor (IGF)

Advantage over traditional ocular treatments by not only acting as a substitute for tears to lubricate the ocular surface, but also containing various biochemical components, thereby closely resembling natural tear

Be Careful: potential microbial contamination

Matrix metalloproteinases inhibitors

The first ophthalmic matrix regeneration therapy developed a **polycarboxymethylglucose sulfate solution** :

- Efficacy on corneal healing, including, not only neurotrophic ulcers, but also re-epithelialization after penetrating keratoplasty and chronic corneal dystrophies

A variety of agents are proposed as potential inhibitors of MMPs, such as:

- **Tetracyclines** including drugs like doxycycline and minocycline possess a natural ability to inhibit MMPs
- **Acetylcysteine** in regulating MMP-9 production was investigated in vitro, acetylcysteine is commonly employed in the management of conditions like filamentary keratitis and melting ulcers
- **Ascorbate**: the application of 10% topical ascorbate eye drops can be beneficial in averting ulceration and expediting the healing process. Elevating vitamin C levels in the anterior chamber via systemic supplementation, is expected to increase vitamin C levels in the corneal epithelium, potentially accelerating corneal epithelial healing and reducing corneal opacity. Additionally, vitamin C may reduce corneal opacity size by influencing collagen synthesis.

Other therapies

Nicergoline: is a semisynthetic ergoline derivative that is used to treat cognitive impairment after dementia and stroke; helping epithelial healing by increasing nerve growth factor (NGF) or acetylcholine levels

Recombinant human nerve growth factor therapy (rhNGF): apart from corneal healing, the use of rhNFG also showed a restoration of the ocular surface homeostasis in the aspect of corneal epithelial stability, tear film production, corneal sensitivity and significant improvement in best corrected distant visual acuity (BCDVA)

Insulin which is closely related to insulin-like growth factor (IGF), has been found to aid in the closure of small corneal wounds by promoting cell migration. Importantly, topical insulin is well-tolerated, does not cause ocular side effects, and is accessible for use in cases like NK.

Surgical Management

Punctal occlusion: mechanical treatment that blocks the tear drainage system with punctal plugs composed of either collagen or silicone; can be a less invasive option than a tarsorrhaphy or conjunctival flaps

Correction of lid abnormalities (e.g. lagophthalmos): a proper eyelid closure is crucial for a normal ocular surface and corneal anaesthesia exacerbates risk of corneal damage

Epithelial debridement: The edges of the healing epithelium may thicken and become stagnant, impeding subsequent growth across the defect

Tarsorrhaphy can be categorized as temporary or permanent and may involve partial or complete closure. Partial tarsorrhaphies can be performed nasally, medially, laterally or centrally, to allow for drop medications and eye examinations. There are alternatives to suturing:

- adhesive tape (transpore)
- the use of botulinum toxin on the upper eyelid inducing ptosis
- lid opposition with cyanoacrylate glue

Surgical Management

Amniotic membrane transplantation: often requires multiple applications in NK, but it can be effective for healing NK ulcers when traditional measures have failed.

- Inner layer of the placenta;
- potential risk of transmitting blood-borne pathogens from pooled blood, but this can be minimized if the donors are healthy

Conjunctival flaps: Covering the affected corneal tissue prevents tears, proteolytic enzymes, and proinflammatory mediators from reaching the corneal ulcer and causing stromal lysis

Corneal grafts: penetrating keratoplasty (PK), lamellar keratoplasty (LK), and deep anterior lamellar keratoplasty (DALK)

Corneal Neurotization: complex surgical technique with the purpose of redirecting a sensory nerve from another part of the body to the cornea (e.g. cross face technique)

Current clinical trials

- Various studies **rhNGF**
- **Thymosin beta 4 (Tb4)**, a synthetically produced 43-amino acid peptide that is naturally found in most tissue types but with the highest concentration in platelets, white blood cells; it has been demonstrated to promote corneal wound reepithelization
- **Autologous adipose-derived mesenchymal stem cells**: possible secretion of trophic factors and cytokines to neighboring cells or even direct differentiation into corneal stromal cells

Conclusion

- NK is a challenging condition with the potential for permanent vision loss in affected patients
- Significant advances medical and surgical to promote corneal reinnervation are available
- There are also several ongoing studies

Our Reference Center for Ocular Surface Diseases works daily in the research of new therapeutic approaches

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Grazie per l'attenzione