Acta Clin Croat 2007; 46 (Suppl 1): 117-120 Case Report

NEUROTROPHIC KERATOPATHY: CASE REPORT

Rajko Kordić, Tomislav Kuzman, Smiljka Popović-Suić, Miro Kalauz and Tihomir Ćurković

University Department of Ophthalmology, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – Neurotrophic keratopathy is a degenerative disease characterized by decreased corneal sensitivity and poor corneal healing. This often results as corneal ulceration with a high risk of corneal perforation. A 36-year-old female presented with perforated neurotrophic corneal ulcer and eyelash in the anterior chamber of the right eye and non-perforated corneal ulcer in the left eye, decreased corneal sensitivity, absent corneal reflex and normal lacrimation. History of previous herpetic keratitis episodes was positive. Medical record review showed heredodegenerative encephalopathy with localized brain atrophy and internal hydrocephalus. The patient has mild mental retardation. Eyelash from the anterior chamber of the right eye was surgically removed through limbal incision using a viscoelastic solution. On the first postoperative day the depth of anterior chamber was normal. Treatment was continued with eye patching and application of antibiotic and vitamin ointments. Perforation and ulcers healed ten days after the surgery and visual acuity improved. After the treatment residual corneal scarring remained on both eyes. The pathophysiology of the neurotrophic ulcer in our patient could be explained by corneal denervation caused by previous herpetic keratitis. Denervation results in decreased cell metabolism, levels of acetylcholine and mitosis. Sensory nerves have a favorable effect on corneal epithelialization *via* neuromediators such as acetylcholine, substance P, and calcitonin gene-related peptide. This can lead to an epithelial defect even in the absence of direct injury. Early diagnosis and prompt treatment of neurotrophic keratopathy are mandatory to prevent corneal complications such as scarring and perforation.

Key words: *neurotrophic keratitis*, *corneal ulcer*, *medical treatment*, *surgical treatment*

Introduction

Neurotrophic keratopathy is a degenerative disease characterized by decreased corneal sensitivity and poor corneal healing. This often results in corneal ulceration, a lesion that involves degradation of the stroma with a high risk of corneal perforation[1]. To fully understand the pathophysiologic aspects of sterile corneal ulceration, we must consider mechanisms of epithelial and stromal corneal healing and tear film. Enzymes, cytokines and corneal innervation are very important for the maintenance of strong and healthy cornea[2].

Corneal hypesthesia is the main event in neurotrophic corneal ulceration. The most common reasons for corneal hypesthesia are previous herpetic keratopathy or history of herpes zoster ophthalmicus, previous injury of trigeminal nerve by surgery or trauma, diabetes mellitus, use of contact lenses or chemical corneal injuries[3]. When diagnosing neurotrophic keratopathy, medical history should be coupled by careful ophthalmologic examination, including corneal smear cultures and corneal sensitivity test. Corneal sensitivity can be assessed using a piece of cotton or more reliable Cochet-Bonnet esthesiometer. It is sometimes useful to include neurological examination, e.g., in case of trigeminal neuralgia, nerve palsies and systemic diseases such as diabetes mellitus, vitamin A deficiency and multiple sclerosis. Also, topical medications such as timolol, betoxolol, ketorolac and diclofenac sodium may sometimes cause corneal hypesthesia[4,5]. Treatment of neurotrophic ulceration treatment consists of conservative and surgical methods.

Correspondence to: *Rajko Kordić, MD, PhD*, University Department of Ophthalmology, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia

Received January 30, 2007, accepted March 26, 2007

Table 1. Mackie classification for neurotrophic keratopathy

Stage	Clinical findings
1	– Rose bengal staining of the inferior palpebral conjunctiva – Decreased tear break-up time – Increased mucous viscosity Punctate epithelial fluorescein staining
2	– Epithelial defect, usually oval and in the su perior cornea – Defect surrounded by rim of loose epithelium – Edges may become smooth and rolled – Stromal swelling with folds in Descemet mem brane – Sometimes associated with anterior chamber inflammatory action
3	– Stromal lysis/melting – May result in perforation

Case Report

We present a bizarre case of neurotrophic keratopathy stage 3 according to Mackie classification, which resulted in corneal perforation and eyelash in the anterior chamber (Table 1). A 36-year-old female presented with both red eyes and blurred vision, and with mild discomfort without major pain. Examinations indicated perforated neurotrophic corneal ulcer and eyelash in the anterior chamber of the right eye and non-perforated corneal ulcer in the left eye (Fig. 1). BCVA was 0.05 and 0.1 for the right and left eye, respectively. The anterior chamber of the right eye was very shallow with positive Seidel test. The depth of the left anterior chamber was normal. There was normal tear lacrimation by Schirmer I test 14/15 mm, although tear break up test could not be performed. Corneal sensitivity, tested with a piece of cotton, was found to be reduced. Corneal reflex was absent. Intraocular pressure was measured digitally and showed hypotonia on the right eye and normal pressure on the left eye. It was not possible to perform applanation tonometry. Retinas of both eyes were normal but without good visualization. Medical history revealed two previous episodes of herpes simplex keratitis on both eyes with nubeculas on both corneas. Medical record review showed the patient to have heredodegenerative encephalopathy with localized brain atrophy and internal hydrocephalus. The patient suffered mild mental retardation.

Eyelash from the anterior chamber of the right eye was surgically removed through limbal incision using a viscoelastic solution. Normal depth of anterior chamber was obtained immediately. On the first postoperative day, the depth of anterior chamber of the right eye was normal. Further treatment consisted of the use of eye patching and application of mydriatics, antibiotic and vitamin ointments. Ten days after the surgery, perforation and ulcers had healed. The anterior chamber of the right eye was normal and visual acuity improved. After the treatment residual corneal scarring remained on both eyes (Fig. 2).

Discussion

Neurotrophic keratitis and persistent epithelial defect represent clinically challenging, frequently misdiagnosed, yet commonly presenting members of the ocular surface disease family[6]. Corneal ulceration in neurotrophic keratopathy is difficult to treat and can result in significant vision loss. The progression of clinical findings can be classified by Mackie classification of neurotrophic keratopathy (Table 1). The cornea is innervated by approximately one thousand axons of the nervus ophthalmicus, which is the first branch of trigeminal

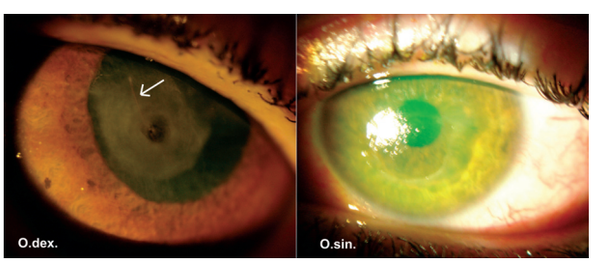

Fig. 1. Perforated corneal ulcer with eyelash in the anterior chamber (white arrow) in the right eye, and corneal ulceration in the left eye.

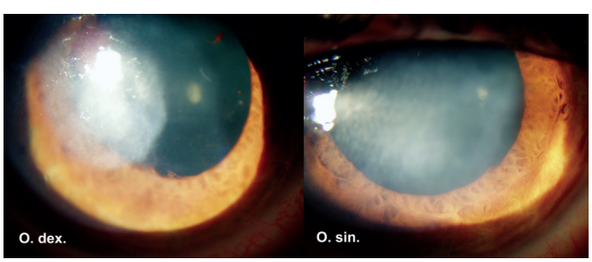

Fig. 2. Healed corneal ulcers and perforation after surgical and conservative treatment in the right and left eye, respectively.

nerve. Sensory nerves have a favorable effect on corneal epithelialization *via* neuromediators such as acetylcholine, substance P, and calcitonin gene-related peptide[7]. We think that the pathophysiology of neurotrophic ulcer in our patient could be explained by corneal denervation caused by previous herpetic keratitis. Some investigators demonstrated that ocular surface changes associated with neurotropic keratitis in denervated animals persisted despite tarsorrhaphy, suggesting a trophic effect of corneal nerves[8]. This effect could be explained by depletion of acetylcholine resulting in a relative decrease in epithelial cell growth. Corneal hypesthesia also results in decreased tearing and blink rate, absence of protective reflexes, and pain. This might be the reason why our patient presented to our department in the late stage of corneal ulceration.

Current medical treatments for neurotrophic ulcers include artificial tears, lubricants, experimental fibronectin, insulin-like growth factor type I and substance P application[9-11]. Recent clinical trials showed beneficial effects of the nerve growth factor (NGF) in promoting corneal epithelial wound healing in patients with neurotrophic keratitis[12]. Also, aldose reductase inhibitor, CT-112, has been shown to reverse abnormal morphology of corneal epithelial cells and increase corneal sensitivity[13]. Some authors suggest that oral tetracycline 250 mg *per os* twice daily or doxycycline 100 mg *per os* every other day can speed corneal healing by combining antibiotic therapy with matrix metalloproteinase inhibitors[14]. Other available conservative treatments include eye patching, contact lens and cyanoacrylate glue application.

If other than conservative treatment is required, several surgical treatments such as botulinum A toxin injections, conjunctival flap and amniotic membrane transplantation, and lateral tarsorrhaphy are available[15,16]. In our patient, surgical treatment was ineluctable. After the removal of eyelash from the anterior chamber of the right eye, cornea showed good stability, requiring only further conservative treatment using eye patching. In addition, it should be noted that certain topical medications that can decrease corneal sensitivity such as timolol, diclofenac, ketorolac, sulfacetamide or contain preservatives should be discontinued from therapy[4,5].

Laboratory findings of corneal smears in our patient were sterile. In some cases when herpes simplex or herpes zoster is suspected, viral cultures or immunofluorescence staining may clarify the diagnosis. In some countries impression cytology is available and helpful to rule out limbal deficiency. Limbal deficiency requires corneal epithelium to be positive for cytokeratin 3 and negative for cytokeratin 19, and conjunctival epithelium to be negative for cytokeratin 3 and positive for cytokeratin 19[17].

In daily practice, more effort should be made to educate our patients with corneal hypesthesia about their condition. Good evaluation of patients with herpes simplex or herpes zoster keratitis for corneal hypesthesia is equally important. Furthermore, we should pay special attention to those patients who had undergone surgery for trigeminal neuralgia or acoustic neuroma as they might be prone to development of postoperative corneal hypesthesia. We should instruct these patients to seek for emergency medical attention in case that redness of the eyes or blurred vision changes occur, and they should be aware that their condition may not cause them any pain. Only early diagnosis and prompt treatment of neurotrophic keratopathy can prevent corneal complications such as scarring and perforation.

References

1. BAZAN HE. Cellular and molecular events in corneal wound healing: significance of lipid signalling. Exp Eye Res 2005;80:453-63.
2. BONINI S, RAMA P, OLZI D, LAMBIASE A. Neurotrophic keratitis. Eye 2003;17:989-95.
3. KANSKI JJ. Clinical ophthalmology: a systematic approach. 5th ed. Oxford: Butterworth-Heinemann, 2003.
4. YAMADA M, OGATA M, KAWAI M, MASHIMA Y, NISHIDA T. Substance P in human tears. Cornea 2003;22:48-54.
5. HOH H. Local anesthetic effect and subjective tolerance of 0.5% levobunolol in normal eyes. Klin Monatsbl Augenheilkd 1990;197:20-6.
6. AFFELDT JC. Neurotrophic keratitis and persistent epithelial defect. In: YIU SC, ed. Epithelial cell biology: implications for the ocular surface. Los Angeles: Doheny Eye Institute, 2003:13-6.
7. CAVANAGH HD, COLLEY AM. The molecular basis of neurotrophic keratitis. Acta Ophthalmol 1989;192:115-34.
8. SIGELMAN S, FRIEDENWALD JS. Mitotic and wound healing activities of the corneal epithelium: effect of sensory denervation. Arch Ophthalmol 1954;52.
9. McCULLEY JP, HOROWITZ B, HUSSEINI ZM, HOROWITZ M. Topical fibronectin therapy of persistent corneal epithelial defects. Fibronectin Study Group. Trans Am Ophthalmol Soc 1993;91:367-86.
10. PHAN TM, FOSTER CS, SHAW CD, ZAGACHIN LM, COLVIN RB. Topical fibronectin in an alkali burn model of corneal ulceration in rabbits. Arch Ophthalmol 1991;109:414-9.

11. BROWN SM, LAMBERTS DW, REID TW, NISHIDA T, MURPHY CJ. Neurotrophic and anhidrotic keratopathy treated with substance P and insulin-like growth factor 1. Arch Ophthalmol 1997;115:926-7.
12. BONINI S, LAMBIASE A, RAMA P. Topical treatment with nerve growth factor for neurotrophic keratitis. Ophthalmology 2000;107:1347-51.
13. NAKAHARA M, MIYATA K, OTANI S, MIYAI T, NEJIMA R, YAMAGAMI S, AMANO S. A randomised, placebo controlled clinical trial of the aldose reductase inhibitor CT-112 as management of corneal epithelial disorders in diabetic patients. Br J Ophthalmol 2005;89:266-8.
14. BROOKS DE, OLLIVIER FJ. Matrix metalloproteinase inhibition in corneal ulceration. Vet Clin North Am Small Anim Pract 2004;34:611-22.
15. LUGO M, ARENTSEN JJ. Treatment of neurotrophic ulcers with conjunctival flaps. Am J Ophthalmol 1987;103:711-2.
16. CHEN HJ, PIRES RT, TSENG SC. Amniotic membrane transplantation for severe neurotrophic corneal ulcers. Br J Ophthalmol 2000;84:826-33.
17. SACCHETTI M, LAMBIASE A, CORTES M, SGRULLETTA R, BONINI S, MERLO D, BONINI S. Clinical and cytological findings in limbal stem cell deficiency. Graefes Arch Clin Exp Ophthalmol 2005;243:870-6.

Sažetak

NEUROTROFIČNA KERATOPATIJA: PRIKAZ SLUČAJA

R. Kordić, T. Kuzman, S. Popović-Suić, M. Kalauz i *T. Ćurković*

Neurotrofična keratopatija je degenerativna bolest rožnice koju obilježava smanjena osjetljivost rožnice i slabo cijeljenje epitela koje vrlo često rezultira nastankom upale, ulkusa ili perforacije. Prikazan je slučaj žene stare 36 godina s perforiranim neurotrofičkim ulkusom rožnice i trepavicom u prednjoj sobici desnog oka i neperforiranim ulkusom rožnice lijevog oka. Obostrano je bila odsutna osjetljivost rožnica, kornealni refleksi su bili ugašeni, a sekrecija suza normalna. U mladosti je preboljela više epizoda obostranog herpetičnog keratitisa. Od ostalih bolesti u djetinjstvu je bila prisutna heredodegenerativna encefalopatija s manjom atrofijom mozga i internim hidrocefalusom. Bolesnica je blaže mentalno retardirana. Operativnim zahvatom odstranjena je trepavica iz prednje očne sobice uz pomoć viskoelastika, te je liječenje nastavljeno zatvaranjem oka i primjenom antibiotskih i vitaminskih masti. Nakon desetak dana dolazi do zacijeljenja i epiteliziranja ulkusa obostrano, uz uredan izgled prednje očne sobice desno i poboljšanja vidne oštrine. Nakon liječenja ostaju makule na rožnicama oba oka. Patofiziološki mehanizam nastanka neurotrofičkog ulkusa kod naše bolesnice možemo objasniti denervacijom rožnice koja je posljedica herpetičkog keratitisa. Denervacija uzrokuje smanjivanje staničnog metabolizma, razine acetilkolina i mitoze. Osjetni živci imaju povoljan učinak na regeneraciju epitela rožnice putem neuromedijatora kao što su acetilkolin, tvar P i peptid srodan genu kalcitonina. Stoga je oštećenje epitela rožnice moguće i bez izravne ozljede. Rana dijagnoza i pravodobno liječenje neurotrofičke keratopatije ključni su u prevenciji komplikacija kao što su zamućenje ili perforacija rožnice.

Ključne riječi: *neurotrofični keratitis, ulkus rožnice, terapija lijekovima, kirurška terapija*