DOI: https://doi.org/10.17816/OV79199
Scientific article

Neurotrophic keratopathy and Wallenberg – Zakharchenko syndrome: a clinical case

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BACKGROUND: Degenerative changes of cornea after transection of the trigeminal nerve were first described by F. Magendie in 1824. Neurotrophic keratopathy is considered to be an orphan disease which lately has been recognized more and more often. According to literature data, neurotropchic keratopathy affects 5 individuals in 10,000. The diagnosis is difficult due to the lack of information about this condition, the rare occurrence and the presence of a large number of etiological factors.

AIM: To determine the causes of the neurotrophic keratopathy development and the treatment tactics in a patient with a neurological disease. The article presents a case of neurotrophic keratopathy in a patient with Wallenberg – Zakharchenko syndrome.

Because of the fact that neurotrophic keratopathy was diagnosed late and the correct treatment did not start in time, further progression of the pathological process in the cornea could not be avoided. Periodic recurrence of neurotrophic keratopathy is associated with an underlying chronic neurological disease.

CONCLUSIONS: Neurotrophic keratopathy requires early diagnosis. In certain clinical cases, for the successful treatment of this pathology, it is necessary to prescribe systemic therapy.

Keywords: cornea; neurotrophic keratopathy; neurotrophic keratitis; Wallenberg – Zakharchenko syndrome; corneal erosion; recurrent corneal erosion; persistent epithelial defect; *in vivo* confocal microscopy.

To cite this article:
Ezugbaya MB, Astakhov SYu, Riks IA, Papanyan SS, Boutaba R, Mikhalchenko YuG, Yakushenko AR. Neurotrophic keratopathy and Wallenberg – Zakharchenko syndrome: a clinical case. *Ophthalmology Journal*. 2021;14(3):83-90. DOI: https://doi.org/10.17816/OV79199

Received: 14.07.2021 **Accepted:** 10.08.2021 **Published:** 29.09.2021

DOI: https://doi.org/10.17816/OV79199
Научная статья

Нейротрофическая кератопатия и синдром Валленберга – Захарченко: клинический случай

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Актуальность. В 1824 г. F. Magendie впервые описал дегенеративные изменения роговицы после пересечения тройничного нерва. Нейротрофическая кератопатия считается орфанным заболеванием, которое в настоящее время диагностируют всё чаще. Частота встречаемости по данным литературы составляет 5 на 10 000 населения. Постановка диагноза вызывает сложности из-за недостаточности знаний о данной патологии, редкого возникновения и наличия большого количества этиологических факторов.

Цель — определить причины развития нейротрофической кератопатии и тактику лечения у пациента с неврологическим заболеванием.

В статье представлен случай развития нейротрофической кератопатии у пациента с синдромом Валленберга – Захарченко. Поскольку заболевание было поздно диагностировано и правильное лечение было начато несвоевременно, не удалось избежать дальнейшего прогрессирования патологического процесса в роговице. Периодическое обострение нейротрфической кератопатии связано с основным хроническим неврологическим заболеванием.

Заключение. Нейротрофическая кератопатия требует ранней диагностики. В определённых клинических случаях для успешного лечения данной патологии необходимо назначение системной терапии.

Ключевые слова: роговица; нейротрофическая кератопатия; нейротрофический кератит; синдром Валленберга – Захарченко; эрозия роговицы; рецидивирующая эрозия роговицы; персистирующий эпителиальный дефект; конфокальная микроскопия *in vivo*.

Как цитировать:
Эзугбая М.Б., Астахов С.Ю., Рикс И.А., Папанян С.С., Бутаба Р., Михальченко Ю.Г., Якушенко А.Р. Нейротрофическая кератопатия и синдром Валленберга – Захарченко: клинический случай // Офтальмологические ведомости. 2021. Т. 14. № 3. С. 83–90. DOI: https://doi.org/10.17816/OV79199

Рукопись получена: 14.07.2021 **Рукопись одобрена:** 10.08.2021 **Опубликована:** 29.09.2021

BACKGROUND

Neurotrophic keratopathy (NTK) is considered to be a rare disease, but it is now increasingly diagnosed. In 1824, Magendie for the first time described similar degenerative changes in the cornea after the intersection of the trigeminal nerve [1]. Several interchangeable terms are used for this pathology, namely, "neurotrophic keratopathy," "neurotrophic keratitis," and "persistent epithelial defect."

In 2018, Dua et al. [2] proposed a new definition: "NTK is a disease associated with pathological changes in the nerve fibers of the cornea, leading to impaired sensory and trophic function, with subsequent destruction of the corneal epithelium, and also affecting the health and integrity of the lacrimal film, epithelium, and stroma." According to international and Russian literature, NTK affects 5 per 10,000 population, so this disease is considered as a rare disease [2]. NTK has diverse causes, including systemic and ophthalmic conditions (Table 1) [3].

CLINICAL CASE

In October 2019, the 59-year-old patient I. visited the ophthalmology clinic of the Pavlov State Medical University of Saint Petersburg with complaints of burning, periodic redness, and blurred vision of the left eye. He considered himself sick for approximately 4.5 years. The first episode was noted at the end of 2014. Subsequently, he was diagnosed with keratitis of the left eye of unclear etiology. Conservative treatment with frequent instillation of antiviral, antibacterial, nonsteroidal anti-inflammatory, trophic, and reparative drugs was prescribed. The patient noted a temporary improvement in the condition of the left eye. The patient also reported similar episodes once a year, and for the last 1.5 years, they have become more frequent up to 3–4 times.

Along with visual impairment, periodic redness, and burning of the left eye, there were paresthesias and burning throughout the left half of the face and head. The visual acuity of both eyes was 1.0, and the intraocular pressure was normal. Biomicroscopy revealed the heterogeneity of the epithelium, point defects of the epithelium within the optical zone, stained with fluorescein (Fig. 1), a decrease in tear production (Schirmer's test was 15 mm in the right eye and 9 mm in the left eye), a decrease in the tear film break-up time according to Norn (8 s in the right eye and 1 s in the left eye), and absence of corneal sensitivity in all quadrants, determined using a moistened cotton wick.

To determine the depth of point defects, optical coherence tomography of the anterior segment was performed. Hyperreflective local foci were determined at the level of the epithelium, with the maximum depth of 50 μm, and the thickness of the cornea in the center was 520 μm (Fig. 2).

Confocal microscopy *in vivo* of the left eye revealed the altered morphology and damage of epithelial cells (Fig. 3, *a*), reduction of fibers of the subbasal nerve plexus, uneven fiber thickness of this plexus, and local repetitive thickenings in the form of "beads" (Fig. 3, *b*), Langerhans cells,

Table 1. Etiology of neurotrophic keratopathy
Таблица 1. Причины развития нейротрофической кератопатии

General	Ophthalmic
In the central nervous system: • degenerative disorders (Alzheimer's disease, Parkinson's disease); • neurosurgical interventions (removal of acoustic neuroma) • craniocerebral injury; • neoplasms; • aneurysms; • stroke	Associated directly with ocular pathology: • herpetic keratitis; • acanthamoeba keratitis; • corneal burns; • corneal dystrophy
Genetic [4]: • familial corneal hypoesthesia; • Riley–Day syndrome; • Goldenhar–Gorlin syndrome; • Möbius syndrome	Due to ophthalmic surgery: • keratoplasty (penetrating and anterior lamellar) [5]; • phacoemulsification; • excimer surgery [6]; • collagen crosslinking [7]
Systemic [8]: • Diabetes mellitus; • Wallenberg–Zakharchenko syndrome; • multiple sclerosis; • vitamin A deficiency; • amyloidosis; • leprosy	Others: • prolonged instillation of drops containing preservatives [9]; • contact lens wear [10]

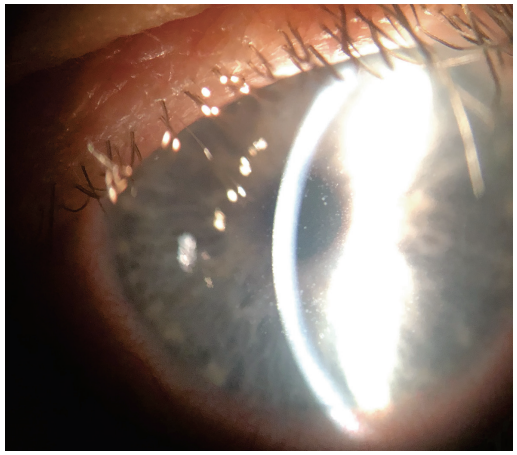


Fig. 1. Clinical case of neurotrophic keratopathy. Biomicroscopy of the left eye: epithelial irregularity, dot-like epithelial defects within the optical zone
Рис. 1. Клинический случай нейротрофической кератопатии. Биомикроскопия левого глаза: неоднородность эпителия, точечные эпителиальные дефекты в пределах оптической зоны

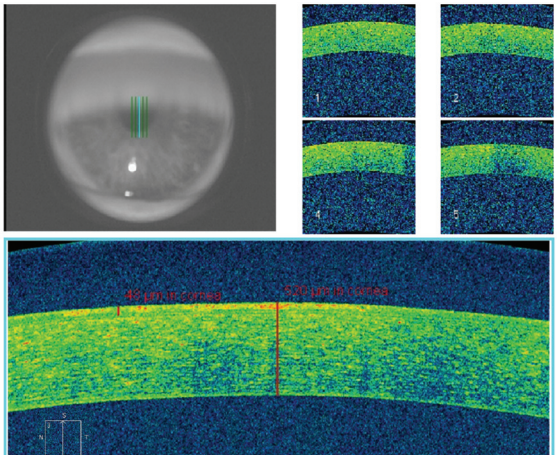
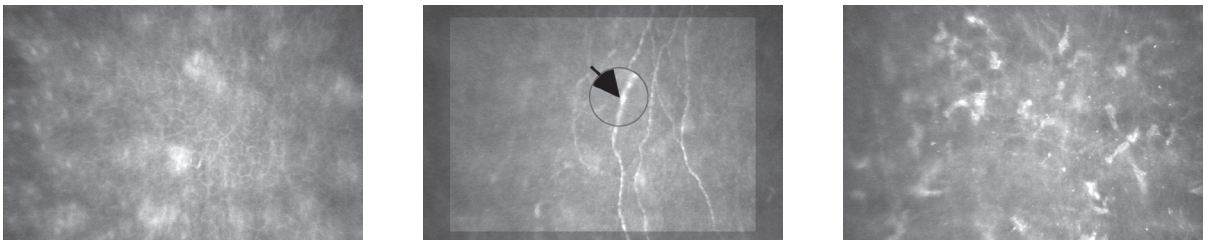


Fig. 2. Optical coherence tomogram of the left cornea (explanation in the text). Examined by ophthalmologist S.G. Belekhova
Рис. 2. Оптическая когерентная томограмма роговицы левого глаза (объяснение в тексте). Исследование проводила врач-офтальмолог С.Г. Белехова



a *b* *c*

Fig. 3. *In vivo* confocal microscopy: *a* – desquamated epithelial cells; *b* – subbasal plexus (arrow); *c* – changes in the corneal stroma (explanation in the text)
Рис. 3. Конфокальная микроскопия *in vivo*: *a* — слущенные эпителиальные клетки; *b* — суббазальное нервное сплетение (стрелка); *c* — изменения стромы при нейротрофической кератопатии (объяснения в тексте)

enhanced anterior stroma pattern, stromal edema, and hyperreflective cells (inflammatory and "enhanced" keratocytes) (Fig. 3, *c*).

The case history revealed that in November 2014, the patient experienced an acute ischemic cerebrovascular accident in the vertebrobasilar artery with alternating syndrome. The multispiral computed tomography revealed chronic cerebrovascular accident, post-ischemic cystic-gliotic changes in the left cerebellar hemisphere, and focal changes in the white matter of the brain, probably of vascular origin. Magnetic resonance imaging revealed signs of thrombosis of the intracranial part of the left vertebral artery with uniform extension. The posterior inferior left cerebellar artery was not visible. In 2014, the patient was diagnosed with cerebrovascular disease and stage II dyscirculatory encephalopathy. Specifically, in November 13, 2014, the patient was diagnosed with acute cerebrovascular accident of ischemic type in the vertebrobasilar system with alternating Wallenberg–Zakharchenko syndrome.

Wallenberg–Zakharchenko syndrome was named after the two doctors who described it at different times independently of each other. The German neurologist A. Wallenberg described this disease in 1895, and the Russian neuropathologist M. Zakharchenko described it in 1911. This disease is included in the group of alternating syndromes, which are characterized by paralysis on the side of the body opposite from the lesion. This syndrome is induced by the blockage of the cerebellar artery, which leads to an insufficient supply of nutrients to the cerebellum and the development of associated neurological problems. Our patient had signs of this syndrome manifested as hemihypesthesia of the right extremities, hypesthesia of the left half of the face, and left-sided prosopalgia.

According to existing classifications, the patient was diagnosed with stage I NTK. Antibacterial, antiviral, and anti-inflammatory eye drops were discontinued. Instillations of lubricants and administration of group B vitamins were prescribed. Following the treatment, the patient noted a significant improvement in the condition of the left eye. However, due to the presence of a chronic concomitant disease, the condition of the left eye deteriorated, and complaints characteristic for NTK were periodically noted.

At the re-examination in March 2020, the patient presented with an increase in the number of punctate

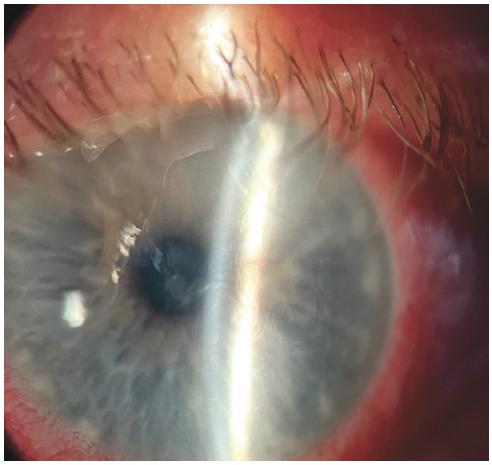


Fig. 4. Biomicroscopy of the cornea: extensive persistent epithelial defect in the optical and paraoptic zones
Рис. 4. Биомикроскопия роговицы: обширный персистирующий эпителиальный дефект в оптической и параоптической зонах

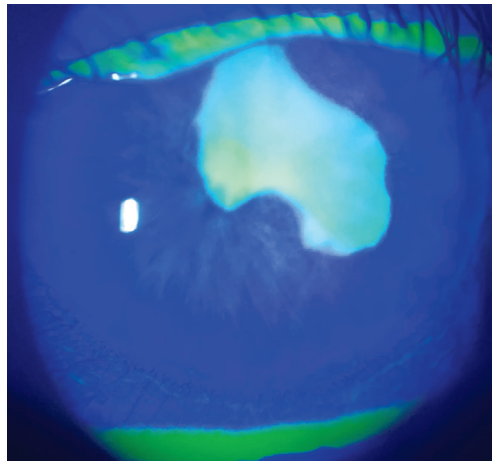


Fig. 5. Corneal biomicroscopy. Fluorescein staining
Рис. 5. Биомикроскопия роговицы. Окраска флюоресцеином

epithelial defects and the emergence of small corneal erosions; therefore, installation of punctal plugs was recommended. However, because of the COVID-19 pandemic, this was not possible to perform. In June 2021, the patient complained again of severe redness and cloudy vision in the left eye, accompanied by paresthesia of the entire left half of the face, right arm, and leg. On examination, a pronounced mixed injection of the eyeball was detected, along with a persistent extensive epithelial defect with complete anesthesia of the cornea (Figs. 4 and 5).

Given the pathological changes, a diagnosis of stage II NTK was made. A soft contact lens was installed. Antiseptic and nonsteroidal anti-inflammatory drugs and frequent instillation of lubricants were prescribed. After 1 week, a significant improvement in the condition of the cornea was revealed, showing healing of corneal erosion. After removal of the soft contact lens, the patient had only punctate epithelial defects characteristic of stage I NTK.

DISCUSSION

In 2018, Dua proposed a new clinical classification of NTK (Table 2) [2, 11]. With the modern instrumental examination methods, it became possible to visualize and analyze *in vivo* the histological structure of the cornea, which plays an important role in the differential diagnostics of its various pathologies. Therefore, many researchers propose a classification of various nosologies based on the results of corneal confoscanning [12, 13].

In 2018, Mastropasqua et al. [14] proposed a new classification of NTK stages based on corneal confoscanning, which indicated the density of the subbasal nerve plexus and the total number of nerve fibers (Table 3). This classification also considers corneal sensitivity.

According to the new classifications, we diagnosed our patient with stage I NTK and prescribed appropriate treatment.

Throughout the follow-up of patients with NTK, we were aware that the condition of the cornea largely was dependent on the general condition and comorbidities of the patient. The principles of NTK treatment differ depending on the disease stage (Table 4) [2, 15–19].

The main aspect in the treatment of patients with NTK is the cessation of drugs containing preservatives and frequent instillations of lubricants without preservatives. In the case of stage II NTK with signs of a secondary bacterial infection, eye drops with antibiotics may be prescribed. Autohemotherapy has also become a widespread

Table 2. Classification of neurotrophic keratopathy with consideration of corneal sensitivity
Таблица 2. Классификация нейротрофической кератопатии с учётом чувствительности

Stage	Clinical manifestations
I	Changes within the epithelial layer without an epithelial defect: heterogeneity of the epithelium, lacrimal film instability, and corneal hypo- or anesthesia in one or more quadrants
II	Epithelial defect without stromal involvement: persistent epithelial defect with hypo- or anesthesia of the cornea
III	Stroma involvement: from central ulcer to lysis leading to perforation with hypo- or anesthesia of the cornea

Table 3. Clinical classification of neurotrophic keratopathy [14]
Таблица 3. Клиническая классификация нейротрофической кератопатии [14]

Stage	Biomicroscopic data	Corneal sensitivity	Density of the sub-basal nerve plexus, μm/mm^2	Total number of nerve fibers per 1 mm^2
1A	Punctate staining of the corneal epithelium with fluorescein	Possible hypoesthesia	⩾5	⩾1
1B	Punctate staining of the corneal epithelium with fluorescein	Possible hypoesthesia	⩽5	⩽1
2A	Epithelial defect with smooth and rounded edges	Hypoesthesia or anesthesia of the entire cornea	⩾3	⩾0.5
2B	Epithelial defect with smooth and rounded edges	Hypo- or anesthesia	⩽3	⩽0.5
3A	Superficial stromal ulcer. Stroma thinning by ⩾50% of the total corneal thickness	Anesthesia	–	–
3B	Superficial stromal ulcer. Stroma thinning by ⩾50% of the total corneal thickness	Anesthesia	–	–

Table 4. Treatment of neurotrophic keratopathy according to stages [2]
Таблица 4. Лечение нейротрофической кератопатии по стадиям [2]

Stage	Treatment
I	Cancellation of agents containing preservatives!!! Anti-inflammatory therapy in the presence of signs of inflammation (nonsteroidal anti-inflammatory drugs can be toxic). Prescription of lubricants!!! Installation of punctal plugs. Removal of damaged epithelium. Correction of the eyelid position anomalies
II	In case of secondary infection, antibiotics (without preservatives) are prescribed. NTGF (neurotrophic growth factor). With the probability of melting, citrate/tetracycline/macrolides. Q10 co-enzyme. Cacicol20/RGTA (regenerating agent technology). Autohemotherapy (platelet-rich plasma and autologous serum instillation). Autoconjunctival plasty
III	Transplantation of the amniotic membrane (may be combined with tarsorrhaphy). Plastic reconstruction of the conjunctiva. Neurotrophic growth factor. Keratoplasty. Corneal neurotization. **In perforation:** Acrylate and fibrin glue [20]

treatment of NTK. Autoconjunctivoplasty can also be performed; however, this procedure leads to a significant decrease in visual functions. In stage III NTK, instillations of drugs containing neurotrophic growth factor is advised, but is not currently available in many countries, including the Russian Federation. The surgical treatment for stage III NTK includes transplantation of the amniotic membrane, lamellar and penetrating keratoplasty, and corneal neurotization, which is a long and expensive complex surgical procedure performed together with neurosurgeons, as well as the use of cyanoacrylate glue [20].

In this clinical case, secondary infection was not observed. It was possible to stop the neurotrophic process by frequent instillations of lubricants at stage I NTK, and by wearing a soft contact lens in the case of stage II NTK.

CONCLUSION

For the diagnosis of NTK, it is important to collect a case history and identify concomitant somatic pathology, which can be a key in clarifying the diagnosis and thus timely prescribing an effective therapy.

Currently, long-term symptomatic treatment of patients with NTK is performed in the Russian Federation and other countries, since etiotropic drugs are not available in these countries. In some cases, NTK requires the prescription of systemic therapy, depending on the etiological factors.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with the international ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article, read and approved the final version before its publication.

Conflict of interest. The authors declare no conflict of interest.

Funding. The study had no external funding.

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