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Sublimbal orbital fat transposition in neurotrophic keratopathy: a case series

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ABSTRACT

Neurotrophic keratopathy is a progressive condition resulting from corneal denervation, leading to the development and persistence of corneal ulcers. Among the pathogenetic treatment methods there are corneal neurotization, a technically challenging approach associated with a prolonged rehabilitation period, and the usage of recombinant human nerve growth factor (cenegermin), which is practically inaccessible due to its high cost and lack of registration in Russian Federation. We propose a technique of orbital fat transposition to the sclerocorneal pocket for the treatment of persistent ulcers associated with neurotrophic keratopathy. This method is based on neuronal embryology of orbital adipose tissue, as well as the abundance of neurotrophic factors and stem cells. This method was applied to three patients with different etiologies of neurotrophic keratopathy, reaching the observation endpoint in two months after the operation. Visual acuity was ranging from 0.005 to 0.01. All patients received standard therapy for 1–2 months without significant improvement. Surgery was then performed using the proposed technique, which involves repositioning the medial and central orbital fat pads into the sclerocorneal pocket. In the postoperative period, partial epithelialization was observed in all patients during the first week, followed by complete healing and scar formation. The maximum visual acuity in 2 months ranged from 0.06 to 0.3.

Keywords: neurotrophic keratopathy; orbital fat; neurotrophic factors; stem cells.

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Перемещение орбитальных жировых пакетов при нейротрофической кератопатии: серия клинических случаев

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АННОТАЦИЯ

Нейротрофическая кератопатия — заболевание, обусловленное нарушением иннервации роговицы, ведущее к возникновению и персистенции язвенных дефектов. К патогенетическим методам лечения относят невротизацию роговицы, которая технически трудновыполнима и сопряжена с длительным реабилитационным периодом, а также применение рекомбинантного человеческого фактора роста нервов (ценегермин), который практически недоступен ввиду высокой стоимости и отсутствия регистрации в Российской Федерации. Нами предложена методика сублимбального перемещения жировых пакетов орбитальной клетчатки. В основе метода лежат данные о смешанном происхождении орбитальной жировой клетчатки, обилии в ней нейротрофических факторов и стволовых клеток. Прооперировано 3 пациента с нейротрофической кератопатией, достигших конечной точки наблюдения через 2 мес. после вмешательства. Все предварительно получали терапию в течение 1–2 мес. без значимой динамики. Острота зрения составляла от 0,005 до 0,01. Проведено оперативное лечение в объёме сублимбального перемещения жировых пакетов орбитальной клетчатки, заключающееся в перемещении медиального и центрального орбитальных жировых пакетов в сформированный склеро-роговичный карман. В послеоперационном периоде у всех пациентов наблюдалась частичная эпителизация язвенного дефекта в течение первой недели с дальнейшим полным заживлением и формированием рубца. Полученная максимальная острота зрения в срок 2 мес. после проведённой операции составляла от 0,06 до 0,3.

Ключевые слова: нейротрофическая кератопатия; орбитальная клетчатка; нейротрофические факторы; стволовые клетки.

Как цитировать

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INTRODUCTION

Neurotrophic keratopathy (NTK) is a disease that leads to the occurrence and persistence of corneal ulcerative defects, often leading to organ-threatening conditions such as descemetocele and perforation [1].

The development of NTK is preceded by conditions affecting the structures of the trigeminal nerve at various levels: the brain stem with the nucleus of the trigeminal nerve (stroke, multiple sclerosis), pathways (aneurysms, tumors, injuries), the subbasal nervous plexus of the cornea (excimer laser surgery in the anamnesis, dystrophy and degeneration, injuries, inflammatory diseases, burns) [2].

Among the approaches to the treatment of NTK, there are both conservative and surgical methods. Optimistic results of randomized clinical trials of the drug cenegermin, which is a recombinant human nerve growth factor, are described. The drug acts directly on the links of the NTK pathogenesis, contributing to the epithelialization of the ulcerative defect and increased corneal sensitivity [3]. However, the use of the drug in the Russian Federation is limited by its high cost and lack of registration.

In the surgical treatment of NTK, various types of corneal coatings and blepharography are currently common methods. It is worth noting that all these interventions are symptomatic, facilitating the course of the disease, but not affecting its pathogenesis. In the case of perforations, microkeratoplasty is indicated, however, neurotrophic disorders can lead to rejection of the allograft [4, 6]. Corneal neurotization, despite the positive outcomes, is a rather aggressive surgical intervention that requires active interdisciplinary interaction of specialists in ophthalmological, neurosurgical and maxillofacial specializations and is associated with a long rehabilitation period and therefore has not been widely used in the Russian Federation to date [2, 4, 5].

Ko-Jo Lin and co-authors studied the effectiveness of epibulbar application of mesenchymal stem cells (SC) isolated from orbital adipose tissue in corneal defects induced by chemical burn in an experiment in mice. As a result of the study complete healing of the ulcer was achieved in a short time. The possible mechanism of the effect is based on data on the mixed origin of orbital fiber — mesenchymal and neuroectodermal. It is also known that orbital fatty tissue is a source of SC having more than 260 surface markers similar to bone marrow [7–9]. The prospects of using the technology of autotransplantation of SC have been demonstrated by the example of transplantation of autologous mesenchymal SC for the treatment of degenerative diseases of the optic nerve and retina [10]. At the same time, the authors note several mechanisms of influence on neurodegenerative processes including the production of growth factors and neurotrophic factors, immunomodulatory effect, antiapoptotic effect and direct cell differentiation [11–13].

We have proposed a technique for sublimbal transfer of orbital fiber fat packages (Sub-Limbal Orbital Fat Transposition, S-LOFT) for the treatment of persistent ulcers associated with neurotrophic keratopathy. An application for the patent “Method of surgical treatment of neurotrophic keratopathy” No. 2023135504 dated 12/26/2023 has been filed.

MATERIALS AND METHODS

A total of 3 patients with stage III neurotrophic keratopathy were operated in the 5th ophthalmological department of the City Multidisciplinary Hospital No. 2. Previously, for a month, patients received conservative therapy without significant effect. The dynamics were evaluated using visometry, optical coherence tomography (OCT, Optovue RTVue 100, Optovue, USA), photofixation using a retinal camera in biomicroscopy and fluorescence modes (TRC-NW7SF Mark II, Topcon, Japan). One patient underwent HRT with a corneal module (HRT 3 RCM, Heilderberg Engineering, Germany).

Description of the S-LOFT technique (Fig. 1)

1. The conjunctiva is cut off from the limb and detached to the vault for 5–8 hours (Fig. 1, *a*)
2. Form of a sclero-corneal tunnel to the transparent layers of the cornea using a delaminator (*b*).
3. Open the tarzoorbital fascia (*c*).
4. Isolate the medial and/or middle packages of orbital fatty tissue (*d*).
5. Move the fatty tissue into the sublimbal space (*e*).
6. Fix the orbital fat by three U-shaped sutures (nylon 10/00) (f).
7. Suture the scleral flap and conjunctiva (silk 8/00).

In the postoperative period all patients receive 0.5% levofloxacin instillations as well as moisturizing drops. The sutures from the conjunctiva are removed after 2 weeks with the subsequent cancellation of antibacterial drops. If necessary after removing the seams, the instillation of moisturizing drops continues.

CLINICAL CASE No. 1

Patient O., 68 years old, was admitted to the emergency room with a grade III alkaline burn of the cornea of the left eye in the late reparative phase (Fig. 2).

A history of lime getting into the eye a month before hospitalization. She was admitted to an ophthalmologist at the place of residence, where, against the background of anti-inflammatory and antibacterial therapy, there was no positive dynamics during the month. Due to the ineffectiveness of therapy, the ophthalmologist at the place of residence prescribed instillation of moisturizing drops, corneal reparants, which, however, did not improve the condition of the cornea. The use of soft contact lenses was hampered by the patient’s condition.

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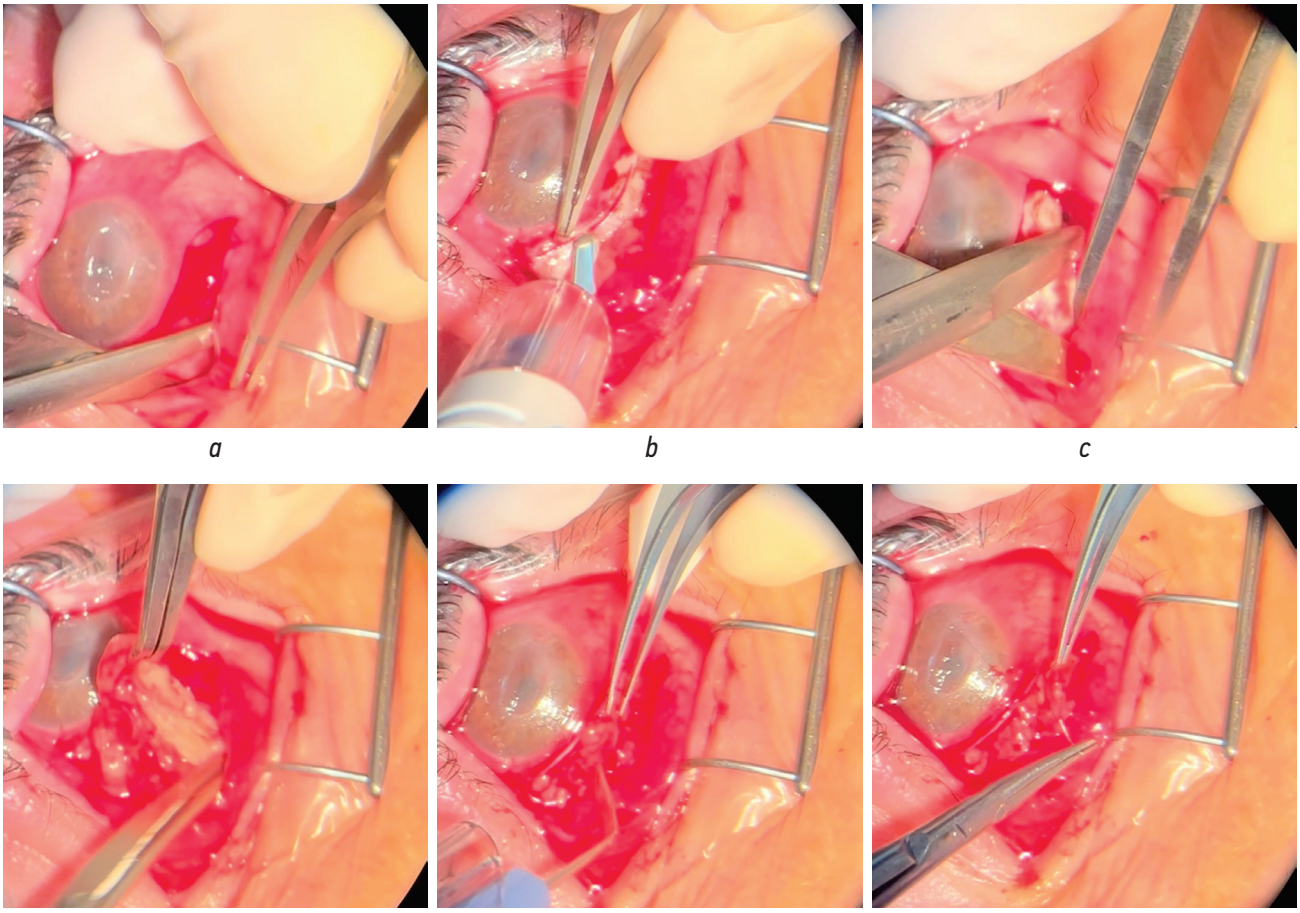


Fig. 1. Stages of operation: *a* — dissection and separation of the conjunctiva towards the fornix; *b* — formation of the sclerocorneal pocket; *c* — incision of the tarsoorbital fascia; *d* — dissection of the orbital fat; *e* — transposition of the fat into the sclerocorneal pocket; *f* — fixation of fat using sutures
Рис. 1. Этапы операции: *a* — отсечение и отсепаровка конъюнктивы к своду; *b* — формирование склеро-роговичного тоннеля; *c* — вскрытие тарзоорбитальной фасции; *d* — выделение жирового пакета; *e* — перемещение клетчатки в сублимбальное пространство; *f* — фиксация клетчатки П-образными швами

Upon admission, the visual acuity of the left eye was 0.005, it was not corrected. According to OCT data, the cornea is thickened in the area of the epithelial defect to 599–635 microns, the defect size is 2.58 × 2.67 mm (Fig. 3).

Sensitivity was assessed by 9 points according to the index of M. Ezugbai et al. The points of hypesthesia are 0.5 points, anesthesia is 1.0 points, the data obtained from 9 points are summarized, thus the value is inversely proportional to the sensitivity of the cornea [14]. In this

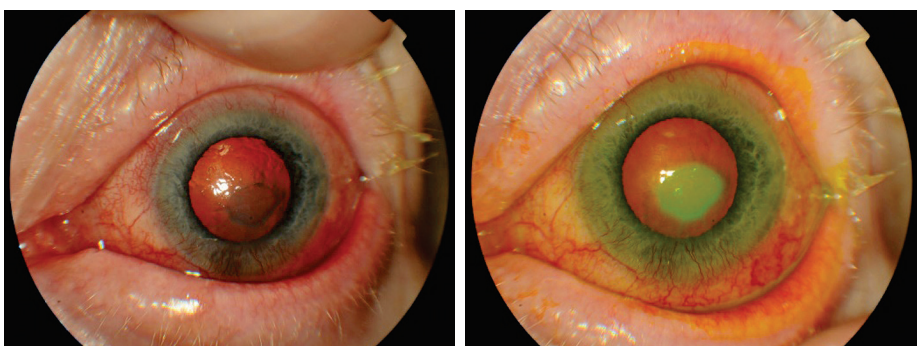


Fig. 2. Photo of the anterior segment with fluorescein in patient O.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 2. Фотография переднего отрезка глаза пациентки О. с применением флуоресцеина: *a* — в цветном режиме; *b* — в режиме флуоресценции

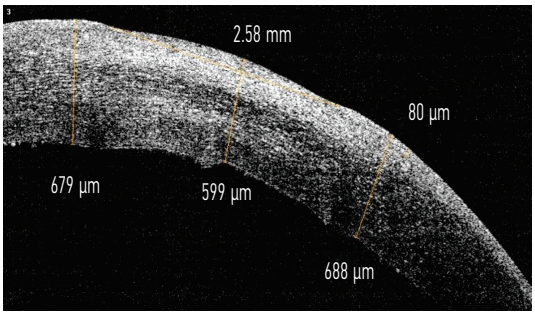


Fig. 3. Optical coherence tomography image of the cornea in patient O. upon hospitalization
Рис. 3. Снимок оптической когерентной томографии роговицы пациентки О. при поступлении

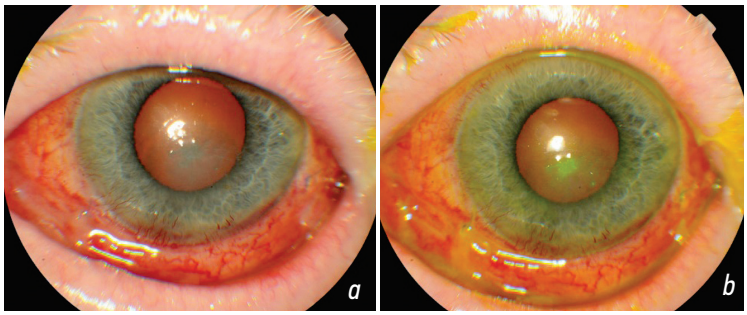


Fig. 4. Photo of the anterior segment with fluorescein 4 days post-op in patient O.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 4. Фотография переднего отрезка глаза пациентки О. с применением флуоресцеина через 4 дня после операции: *a* — в цветном режиме; *b* — в режиме флуоресценции

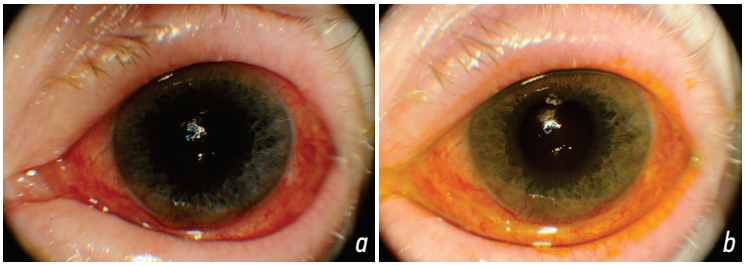


Fig. 5. Photo of the anterior segment with fluorescein 2 weeks post-op in patient O.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 5. Фотография переднего отрезка глаза пациентки О. с применением флуоресцеина через 2 нед. после операции: *a* — в цветном режиме; *b* — в режиме флуоресценции

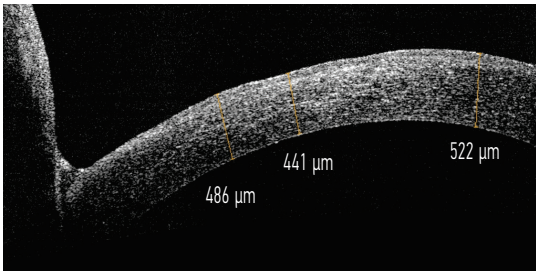


Fig. 6. Optical coherence tomography image of the cornea in patient O. 2 weeks post-op
Рис. 6. Снимок оптической когерентной томографии роговицы пациентки О. через 2 нед. после оперативного лечения

patient anesthesia was determined in the area of the defect by an approximate method, and significant hypesthesia was detected throughout the rest of the surface. According to the above-described index — 5 points. Pronounced folds of the descemet membrane, edema of the stroma around the ulcerative defect and newly formed vessels in the superficial and deep layers were revealed biomicroscopically. Taking into account the development of neurotrophic changes and the ineffectiveness of conservative therapy it was decided that surgical treatment in the amount of sublimbal displacement of orbital fat packages according to the method described above was advisable.

On the 4th day after surgery partial epithelialization of the ulcerative defect, a decrease in the folds of the descemet membrane and resorption of corneal edema were noted (Fig. 4).

After 1 week the patient was discharged with a visual acuity of 0.1 in the left eye and was not corrected. According to OCT data a decrease in corneal thickness to 541–559 microns was detected due to resorption of edema of the stroma and epithelium, while the epithelium is uneven.

After 2 weeks complete epithelialization of the defect was observed, fluorescein staining was absent and persistent corneal opacity was formed (Fig. 5).

The need for instillation of moisturizing drops remained. After 1.5 months the corneal epithelium was uniform over the entire surface, corneal sensitivity was 3 points, visual acuity was 0.2 and it was not corrected.

Dynamics according to OCT data: the thickness of the cornea is 400–450 microns, hyperreflective turbidity in the surface layers is noted, corresponding to the formed scar (Fig. 6).

CLINICAL CASE No. 2

Patient S., 77 years old, was hospitalized with the diagnosis: "Stage III neurotrophic keratopathy associated with keratouveitis of herpetic etiology of the left eye on the background of stage II Fuchs corneal endothelial dystrophy, manifested by bullous keratopathy. Fuchs' endothelial dystrophy is also less pronounced in the right eye."

Anamnesis: conservative treatment of glaucoma for 10 years. During 2 months before hospitalization, the instillation of moisturizing drops and the laying of corneal reparants behind the lower eyelid were carried out.

Upon admission the visual acuity of the left eye was 0.01 eccentrically, not corrected, which is associated with stage II glaucoma. Biomicroscopy revealed bilateral subepithelial bulls, moderate edema of the stroma,

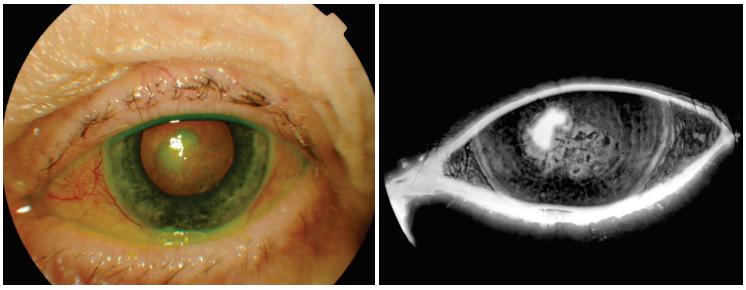
epithelium, pronounced folds of the descemet membrane (Fig. 7). A rounded epithelial defect was detected in the optical zone of the cornea of the left eye, the sensitivity index was 5 points.

According to OCT data, the thickness of the cornea was increased to 640–748 microns due to edema, erosion with dimensions of 230 × 100 microns in the center, the epithelium on the periphery was thickened, partially detached, dust-like precipitates were visualized on the endothelium (Fig. 8).

Surgical treatment was performed according to the proposed method. The patient was discharged the next day. After 1 week, epithelialization of the defect was observed but diffuse fine-point staining with fluorescein persisted, as well as the accumulation of dye around the bull (Fig. 9).

After 1 month keratopathy became less pronounced but the bulls in the optical zone persisted (Fig. 10), against which the visual acuity was 0.06 eccentrically, not corrected. The sensitivity index is 4 points.

During OCT there was a decrease in edema, complete epithelialization of the ulcerative defect and the thickness of the cornea reached 588–614 microns (Fig. 11).



a *b*

Fig. 7. Photo of the anterior segment with fluorescein in patient S.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 7. Фотография переднего отрезка глаза пациентки С. с применением флуоресцеина: *a* — в цветном режиме; *b* — в режиме флуоресценции

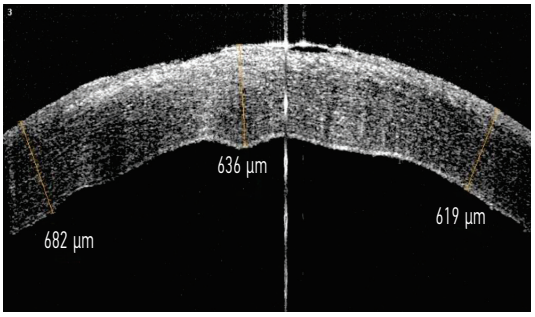
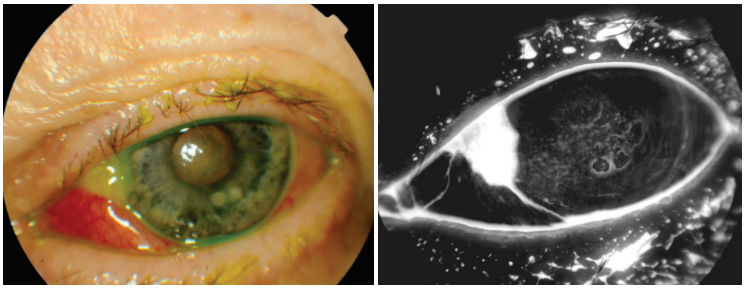


Fig. 8. Optical coherence tomography image of the cornea in patient S. upon hospitalization
Рис. 8. Снимок оптической когерентной томографии роговицы пациентки С. при поступлении



a *b*

Fig. 9. Photo of the anterior segment with fluorescein week post-op in patient S.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 9. Фотография переднего отрезка глаза пациентки С. с применением флуоресцеина через 1 нед. после операции: *a* — в цветном режиме; *b* — в режиме флуоресценции

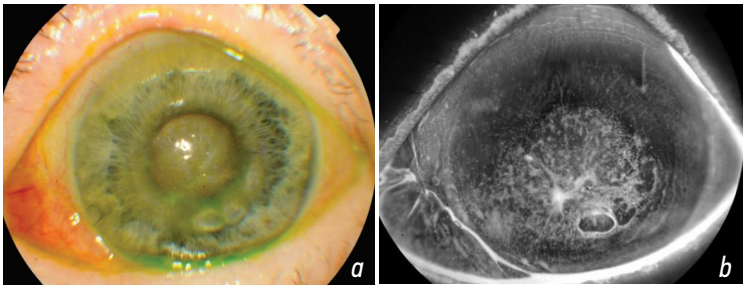


Fig. 10. Photo of the anterior segment with fluorescein 1 month post-op in patient S.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 10. Фотография переднего отрезка глаза пациентки С. с применением флуоресцеина через 1 мес. после операции: *a* — в цветном режиме; *b* — в режиме флуоресценции

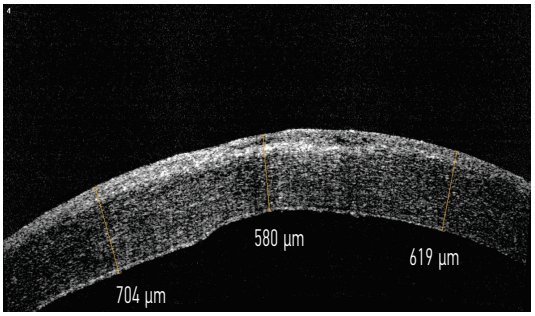


Fig. 11. Optical coherence tomography image of the cornea of patient S. in 1 month
Рис. 11. Снимок оптической когерентной томографии роговицы пациентки С. через 1 мес.

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CLINICAL CASE No. 3

Patient D., 34 years old, was hospitalized with an ulcer of the cornea of the left eye. Anamnesis: removal of vestibuloschannoma 6 months before the hospitalization. In the postoperative period, neuropathy of the facial and trigeminal nerves on the left developed and, despite an attempt to perform plastic surgery with the hyoid nerve, paralytic lagophthalmos and inversion of the lower eyelid persisted; for which 3 months later lateral suspension of the tarsal plate was performed in combination with a recession of aponeurosis of the muscle lifting the upper eyelid (Fig. 12).

In the postoperative period the patient received a course of antibacterial therapy (levofloxacin 0.5%, tetracycline 1.0%), continued to use moisturizing drops, reparants for 2 months. Nevertheless, in the presence of complete closure of the ocular slit, corneal ulcer persisted. Visual acuity at admission was 0.001, was not corrected, corneal sensitivity was estimated at 7 points.

An ulcerative defect was biomicroscopically visualized with clear edges and a clean bottom in the optical zone of the cornea, measuring 5 × 3 mm with edematous stroma and epithelium around it (Fig. 13). According to OCT data, the thickness of the cornea in the area of ulceration reached 402 microns (Fig. 14).

Heidelberg retinal tomography (HRT) with a corneal module made it possible to determine a pronounced depletion of the subbasal nerve plexus, the fibers are thinned (Fig. 15).

The sublimbal displacement of the orbital fiber was performed according to the above-described method. The postoperative period was uneventful. It is worth noting the absence of changes in the profile of the lower eyelid in the projection of the displaced fat pack. After 2 weeks there was a significant decrease in the area of fluorescein staining, newly formed superficial vessels have appeared (Fig. 16).

After 1 month complete epithelialization of the defect was observed, after 2 months a turbidity of the type of an corneal spot was formed, the newly formed vessels partially desolated (Fig. 17). The sensitivity of the cornea by the approximate method is 7 points.

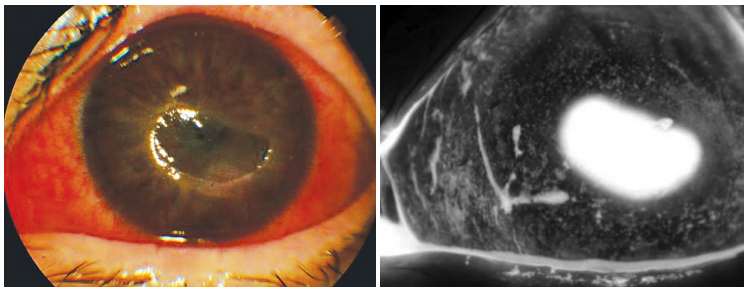
Visual acuity after 2 months was 0.06, it was not corrected. According to OCT data, the thickness of the cornea was restored to 599 microns, hyperreflective opacity corresponding to scar tissue was determined (Fig. 18).

During HRT with the corneal module thickening of nerve fibers is visualized (Fig. 19).

a *b*

Fig. 12. Patient D.: *a* — preoperative condition before lateral tarsal strip combined with levator aponeurosis recession; *b* — postoperative condition after lateral tarsal strip combined with levator aponeurosis recession

Рис. 12. Пациентка Д.: *a* — состояние до латерального подвешивания тарзальной пластинки в сочетании с рецессией апоневроза леватора верхнего века; *b* — состояние после латерального подвешивания тарзальной пластинки в сочетании с рецессией апоневроза леватора верхнего века



a *b*

Fig. 13. Photo of the anterior segment with fluorescein in patient D.: *a* — color mode; *b* — angiography mode of retinal camera

Рис. 13. Фотография переднего отрезка глаза пациентки Д. с применением флуоресцеина: *a* — в цветном режиме; *b* — в режиме флуоресценции

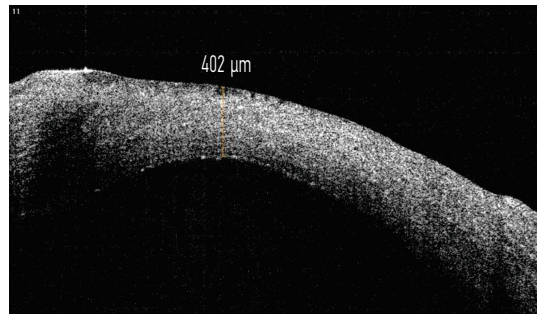


Fig. 14. Optical coherence tomography image of the cornea of patient D. upon hospitalization

Рис. 14. Снимок оптической когерентной томографии роговицы пациентки Д. при поступлении

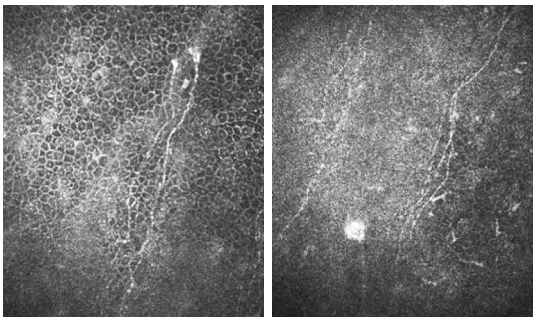
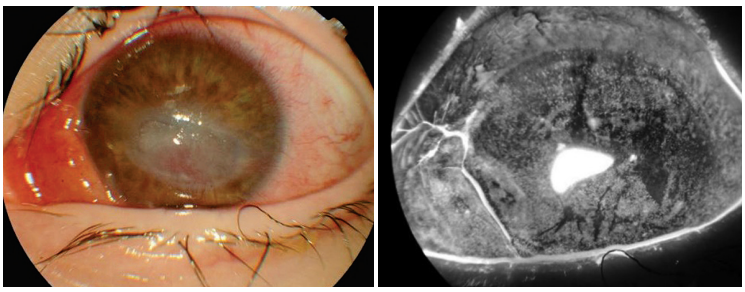
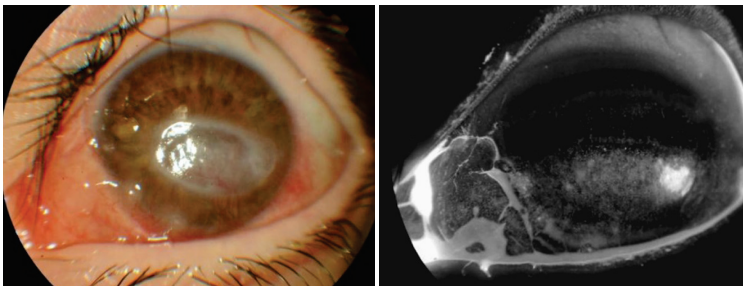


Fig. 15. Photo of the Patient D., upon admission. Heidelberg retinal tomograph (HRT) with corneal module
Рис. 15. Пациентка Д., при поступлении. Гейдельбергская ретинальная томография (Heidelberg retinal tomography, HRT) с роговичным модулем



a *b*

Fig. 16. Photo of the anterior segment photo with fluorescein 2 weeks post-op in patient D.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 16. Фотография переднего отрезка глаза пациентки Д. с применением флуоресцеина через 2 нед. после операции: *a* — в цветном режиме; *b* — в режиме флуоресценции



a *b*

Fig. 17. Photo of the anterior segment photo with fluorescein 2 months post-op in patient D.: *a* — color mode; *b* — angiography mode of retinal camera
Рис. 17. Фотография переднего отрезка глаза пациентки Д. с применением флуоресцеина через 2 мес. после операции: *a* — в цветном режиме; *b* — в режиме флуоресценции

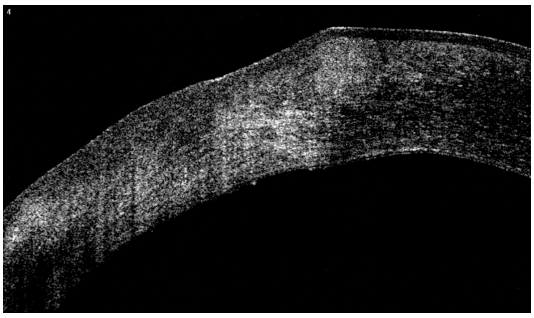


Fig. 18. Optical coherence tomography image of the cornea in patient D. in 2 months
Рис. 18. Снимок оптической когерентной томографии роговицы пациентки Д. через 2 мес.

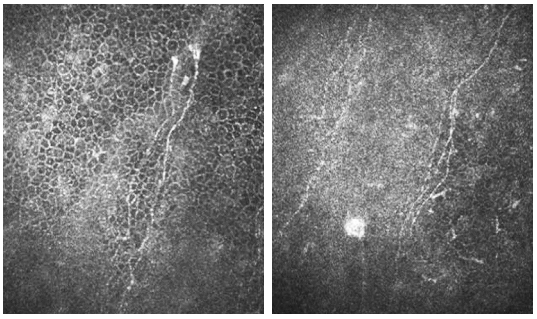


Fig. 19. Patient D., 2 months post-op. Heidelberg retinal tomograph (HRT) with corneal module
Рис. 19. Пациентка Д., через 2 мес. после оперативного лечения. Гейдельбергская ретинальная томография (Heidelberg retinal tomography, HRT) с роговичным модулем

CONCLUSION

The described technique is a promising method for the treatment of corneal ulcers associated with NTK. This method of treatment is advisable for various causes of NTK. It allows influencing the pathogenetic links in the development of the disease, while it is more economically advantageous in comparison with treatment with cenegermin and does not require the involvement of specialists in related fields, and also has a shorter rehabilitation period, unlike corneal neurotization.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: V.V. Potemkin — experimental design, writing the main part of the text, literature review, making final edits; V.S. Prokopchuk — literature review, collecting and preparation of samples, writing the main part of the text; S.Yu. Astakhov — literature review, writing the main part of the text; L.K. Anikina — provision of study materials literature review; V.P. Petukhov, T.S. Varganova — provision of study materials.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Личный вклад каждого автора: В.В. Потемкин — концепция и дизайн исследования, проведение исследований и операций, сбор материала, анализ данных и литературы, написание текста статьи; В.С. Прокопчук — анализ данных и литературы, сбор и обработка материалов, написание текста; С.Ю. Астахов — анализ данных и литературы, сбор и обработка материалов; Л.К. Аникина — проведение исследований, анализ полученных данных, анализ данных и литературы; В.П. Петухов, Т.С. Варганова — проведение исследований, сбор и обработка материалов.

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