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Corneal reinnervation in patients with severe neurotrophic keratopathy secondary to herpes zoster ophthalmicus after treatment with autologous serum tear drops

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Abstract

Purpose: To study potential corneal reinnervation and recovery of corneal sensation in patients with severe neurotrophic keratopathy (NK) secondary to herpes zoster ophthalmicus (HZO) after treatment with topical autologous serum tears (AST).

Method: Four cases of HZO with severe NK were followed clinically and by serial laser *in vivo* confocal microscopy (IVCM, HRT3/RCM, Heidelberg Engineering) before and during treatment with 20% AST drops eight times a day. Two masked observers reviewed the IVCM images and assessed corneal nerve alterations.

Results: At baseline, all patients had complete loss of corneal sensation. In addition, IVCM showed complete lack of the subbasal corneal nerve plexus in all patients. All four patients were refractory to conventional therapies and were treated with AST drops. All patients demonstrated significant nerve regeneration by IVCM within 3–7 months of treatment. The total nerve density increased to a mean ± SEM of 10,085.88±2,542.74 μm/mm^2 at the last follow up. Corneal sensation measured by Cochet-Bonnet esthesiometry improved to a mean ± SEM of 3.50±1.30 cm. Interestingly, 3 of 4 patients developed stromal keratitis with ulceration within weeks of corneal reinnervation, which was reversed by adding topical steroids.

Conclusion: Autologous serum tears are effective in restoring corneal subbasal nerves and sensation in patients with severe NK secondary to HZO. However, this group of patients may require concurrent topical immunomodulation and antiviral therapy while on AST to prevent stromal keratitis.

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Keywords

Herpes zoster ophthalmicus; neurotrophic keratopathy; autologous serum tears; in vivo confocal microscopy; cornea; nerves

INTRODUCTION

Herpes zoster is a common disease with over one million new cases per year in the United States.[1] According to the Centers for Disease Control and Prevention (CDC), nearly 1 in 3 people develop shingles during their lifetime.[2] It has been estimated that 8 to 20% of cases of herpes zoster involve the first branch of the trigeminal nerve, resulting in herpes zoster ophthalmicus (HZO).[2–4] After primary infection with varicella, the virus remains dormant in neurosensory ganglia and can reactivate due to multiple risk factors, including increasing age or an immunocompromised state. Around 50% of patients with HZO have been shown to demonstrate ocular involvement. [4–6] One of the common ocular complications of HZO is neurotrophic keratopathy (NK), which can present in 8.6% to 31.5% of patients with HZO.[7]

Corneal nerves protect the ocular surface through an elaborate mechanism of sensation and induction of the blink reflex, as well as release of numerous neurotrophic factors that regulate the epithelial integrity, proliferation, and wound healing.[8–10] NK can result from damage to corneal nerves, subsequent diminished tear secretion, protective blink reflex, and the loss of trophic factors provided by corneal nerve fibers. Corneal anesthesia may be evident at the time of HZO onset or may develop over weeks to years, with the highest rate within the first 1–2 years after the onset of HZO.[11] Corneal nerves can be directly visualized by *in vivo* confocal microscopy (IVCM), a non-invasive, high-resolution, real-time device that allows visualization of the cellular structures of the anterior segment with 800 times higher magnification.[12] IVCM is widely used to evaluate corneal nerves in different ocular and systemic conditions, including neurotrophic keratopathy, HZO,[13, 14] HSV keratitis,[15, 16] as well as other ocular surface diseases and infectious keratitis.[17, 18] Our previous studies have shown significant decrease or complete loss of the subbasal nerve plexus in both the affected and contralateral eyes of patients with unilateral HZO.[13,19] In addition to nerve loss, persistent inflammation plays a role in HZO, and correlation of an increased immune response to decreased innervation has been noted in HZO patients.[19] As NK may lead to serious complications, such as severe ocular surface disease, persistent corneal epithelial defect (PCED), corneal melting, and perforation, various topical agents have been tried to treat these patients.[20–24] These treatments aim at promoting corneal nerve regeneration as well as reducing ocular inflammation.[25, 26]

Despite the pervious dogma that corneal nerves do not regenerate after HZO, recent studies have shown that nerve regeneration can occur after HZO.[27, 28] As autologous serum tears (AST) contains a variety of neurotrophic factors,[22] we hypothesized that treating HZO patients with AST may promote corneal reinnervation. In this case series, we aimed at further investigating corneal nerve regeneration via serial IVCM and esthesiometry in 4 patients with severe HZO-induced NK and complete loss of subbasal nerves and corneal sensation treated with AST.

SUBJECTS AND METHODS

This is a retrospective, case series of four patients with severe NK secondary to HZO treated with 20% AST 8 times a day after having failed other conventional treatments including discontinuation of all preserved eye drops and frequent use of preservative free tear drops, who were followed at the Cornea Service of the Massachusetts Eye & Ear Infirmary, Boston, Massachusetts between January 2010, and October 2012. The study was approved by the Institutional Review Board and complied with the Health Insurance Portability and Accountability Act (HIPAA) and adhered to the tenets of the Declaration of Helsinki. All patients were diagnosed with HZO based on the history of unilateral vesicular rash in dermatomal distribution of the first branch of trigeminal nerve and at least one episode of characteristic epithelial or stromal keratitis or keratouveitis. Only patients with complete loss of corneal sensation and subbasal nerve plexus on IVCM were included in the study. Patients with active infectious keratitis, previous ocular surgery, contact lens use, diabetes, and immune compromised state were excluded. Records were reviewed for slit lamp biomicroscopy findings, corneal esthesiometry results, and IVCM images at baseline and follow-up.

Corneal Sensation

Corneal sensation was measured in the central cornea with a Cochet-Bonnet esthesiometer (Luneau Ophthalmologie, Chartres, France) as previously described.[15] This test mechanically stimulates corneal nerves by touching the tip of a retractable 6 cm long monofilament nylon thread of 0.12-mm diameter against the corneal surface, decreasing in steps of 1.0 cm if a positive response was not obtained or advancing by 0.5 cm if a positive response was obtained. The longest filament length resulting in a positive response was recorded. Measurements were repeated twice and averaged.

In Vivo Confocal Microscopy

Laser scanning IVCM (Heidelberg Retina Tomograph 3 with the Rostock Cornea Module; Heidelberg Engineering GmbH, Heidelberg, Germany) was performed centrally in all eyes as described previously.[17] IVCM provides images that represent a coronal section of the cornea measuring 400×400 μm, at a selectable corneal depth. Each image is separated from adjacent images by approximately 1 to 4 μm, with lateral resolution of 1 μm/pixel. The three best focused images of the subbasal nerve plexus for each eye were chosen for analysis in a blind fashion. The images were selected from the layer immediately at or posterior to the basal epithelial layer and anterior to the Bowman's layer. The subbasal nerve plexus was quantified using a semi-automated tracing program NeuronJ (http://www.imagescience.org/meijering/software/neuronj/), a plug-in of ImageJ. Two masked observers evaluated the confocal images and analyzed the subbasal nerve plexus. Total nerve density was assessed by measuring the total length of all the nerve fibers, including the length of main nerve trunks and branches in one frame, and converted to $\mu m/mm^2$. The number of total nerves was defined as the absolute count of all nerves, including the number of main nerve trunks and number of branches in one image.

Autologous Serum Tears

Serum tears were prepared by a local compounding pharmacy. In summary, 30 ml of the patient's blood was obtained in a sterile vacutainer tube. Blood was left to clot at 4°C for 10 to 12 hours before centrifuging at 4500 rpm for fifteen minutes. The serum was separated in a laminar flow cabinet and diluted with 0.9% sterile saline to a 20% concentration and transferred to 2 ml vials. The vials were kept frozen at −20°C. A fresh bottle was thawed by the patient and used every 24 hours. Blood draw was repeated every 3 months.

Statistical Analysis

Statistical Package for the Social Sciences V.27.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Wilcoxon signed rank test was used to compare corneal sensation and IVCM parameters at baseline and the last follow-up. A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographic Data

Four patients with severe NK secondary to HZO were included in the study. All patients were female. Three patients were white and one African American. The mean ± SEM age was 77.75±2.00 years old. The mean ± SEM follow-up was 11.75±3.01 months with a range of 4 to 22 months (Table 1).

Corneal Sensitivity and IVCM

All four cases had completed loss of sensation at baseline and did not show any nerves on IVCM (Fig. 1, Table 2). Patient 1 was followed for 22 months. Despite being completely neurotrophic at baseline, her corneal nerve density and sensation improved remarkably to normal levels during the follow-up (Fig. 2A–C, Table 2). Her corneal sensation increased from 0 cm to 1.5 cm, 5 cm, and 6 cm at 7.5, 11, and 22 months respectively (Fig. 2C, Table 2). Her corneal nerve number and density measured zero at 7.5 months, 9.3 n/frame and 16,732.52μm/mm^2 at 11 months, and 12.7 n/frame and 17,250.61 μm/mm at 12 months (Fig. 2A–B, Table 2). Patient 2 was followed for 12 months. During this time, her corneal sensation increased from 0 to 3 cm at 3 and remained stable until 12 months follow-up (Fig. 2C). Her corneal nerve number and density increased from zero to 2.7 n/frame and 4,346.91 μm/mm^2 at 3 months, 6.3 n/frame and 8,489.86 μm/mm^2 at 4 months, 11 n/frame and 9,719.84 μm/mm at 12 months (Fig. 2A–B). Patient 3 was followed for 4 months. Her corneal sensation increased from 0 to 4.5 cm at 4 months (Fig. 2C), corneal nerve numbers increased to 7.5 n/frame, and corneal nerve density increased to 7,912.50 μm/mm^2 (Fig. 1A–B, Fig. 2A–B). Patient 4 was followed for 9 months. Despite some improvement in her corneal nerve numbers from 0 to 5 n/frame, and corneal nerve density to 5,460.60 μm/mm^2 (Fig. 1C–D, Fig. 2A–B), her corneal sensation did not change (Fig. 2C).

While IVCM showed complete loss of the subbasal corneal nerve plexus in all patients at baseline, the mean total nerve number increased from 0 to 9.05±1.72 n/frames at the end of follow-up. Further, the total nerve density increased from 0 to 10,085.88±2,542.74 μm/mm^2 at the last follow-up (4 to 22 months). IVCM demonstrated increased corneal nerve count

and density at the last follow up in all patients. The mean corneal sensation increased from 0 to 3.50±1.30 cm at the last follow-up. Three eyes (75%) had an improvement of corneal sensitivity. One eye did not show any increase in corneal sensitivity, despite increased nerve density. A summary of corneal sensitivity and nerve parameters for each patient is presented in Fig. 2 and Table 2.

All patients except patient 4 developed stromal keratitis with ulceration within 1 to 3 weeks after nerve regeneration in the absence of topical steroid use. Patients were not on steroid drops prior to AST therapy. Slit lamp examination showed focal or multifocal stromal opacities accompanied by haze with or without stromal edema. Patients subsequently were treated with prednisolone acetate 1% drop 4–8x/day, along with prophylactic oral antiviral. Prednisolone was tapered over the course of 4–8 weeks and then switched to loteprednol daily, which was continued throughout the course of treatment with AST. After adding topical steroids, stromal keratitis resolved in all 3 patients and did not recur for the duration of follow-up.

Two patients were followed beyond the duration of the study. Patient one's last follow up was in March 2022. She has remained stable with good visual acuity. Patient 2 developed a severe infectious keratitis later. She subsequently had multiple ocular surgeries including type I Boston keratoprosthesis. Patients 3 and 4 were lost to longer follow up.

DISCUSSION

In this case series of four patients with HZO-induced severe NK, the use of AST alone was effective in restoring corneal subbasal nerve plexus and sensation in patients. All of our patients showed some degree of subbasal nerve plexus regeneration, and 3 out of 4 patients had improvement in their corneal sensation.

It was previously believed that spontaneous nerve regeneration does not occur in patients with HZO. A study of 57 zoster patients showed no recovery in cutaneous innervation by 6 months.[29] However, our group recently reported spontaneous corneal nerve regeneration and partial recovery of corneal sensation in a patient with severe NK 5 years after the onset of HZO.[27] In addition, Rao et al. showed an increase in subbasal corneal nerve density by IVCM after treatment with autologous plasma drops in 3 NK patients secondary to HZO,[28] while our study demonstrate the effect of 20% AST. AST contains a variety of factors including nerve growth factor (NGF), vascular endothelial growth factor (VGEF), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF) that promote nerve regeneration.[22, 30] Because of harboring neurotrophic factors, as well as factors that promote epithelial healing, AST drops have been successfully used in the treatment of NK and resulted in improvement of corneal epithelial healing and sensitivity.[22] In addition, previous IVCM studies have shown corneal nerve regeneration following treatment with AST drops in patients with NK,[28] neuropathic corneal pain,[31] and photoallodynia.[32] The current study confirms the efficacy of AST drops in corneal nerve regeneration in severe NK patients secondary to HZO, shown by improvement in corneal nerve count and density through serial IVCM.

Three of our patients had significant improvement in corneal sensation. Our group has previously reported that abnormal corneal sensation (<5.5cm) develops when the central corneal nerve density drops below 1,032.6 μm/frame (6,450 μm/mm^2) using slit-scanning IVCM,[13, 15] and 2,570.7 μm/frame (16,067.4 μm/mm^2) using laser IVCM.[19] The three patients, who had nerve regeneration with density values greater than 7,000 μm/mm^2 (nerve density correlated with corneal sensation of 3 cm),[19] demonstrated improvement in corneal sensitivity over 3 cm. One patient with nerve density lower than 7,000 μm/mm^2 did not report any improvement in corneal sensation. Our study confirms that a cutoff of nerve density needs to be reached before corneal sensation improves. Therefore, both baseline severity of nerve loss prior to treatment and the length of treatment will impact when this threshold could be reached. Based on our current study, serial IVCM not only can be used to monitor the response to AST drops in NK patients but can also tailor the length of treatment until corneal density reaches this cut off before therapy can be discontinued or frequency of neuroregenerative therapy decreased.

One of the important findings of our series is the development of stromal keratitis with ulceration in 3 patients within weeks after nerve regeneration in the absence of topical steroid use (Fig. 3). However, when treatment with AST drops was continued with concurrent use of low dose topical steroids, stromal keratitis resolved and did not reoccur. This finding suggests that nerve regeneration may potentially result in inflammation in neurotrophic corneas secondary to HZO. Previous studies have shown that neurons express functional receptors for cytokines, and immune system cells may recognize, and are modulated by, neuropeptides.[33] Moreover, stimulation of nociceptors releases sensory neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP), which contribute to the inflammatory response following tissue injury (neurogenic inflammation).[34] In addition, neural signaling with SP and/or VIP has been shown to promote resistance to infection by stimulating immune system effectors. Whether this inflammatory response following nerve regeneration can be extrapolated to NK due to other etiologies, or to other neuroregenerative treatments needs further study. Regardless, our findings suggest that use of anti-inflammatory therapies in conjunction with neuro-regenerative therapies in NK may be of benefit. Future randomized trials are needed to answer this question. Thus, based on findings of our current study, we suggest adding topical mild steroids and prophylactic dose of systemic antiviral during the phase of the nerve regeneration induction to control the inflammation and prevent necrotizing stromal keratitis in HZO-induced NK.

Our study has several limitations. First, this case series has a small sample size. It would be desirable to conduct a larger prospective study to monitor corneal nerve regeneration via serial IVCM in NK patients treated with AST drops or other neuroregenerative treatments, particularly assessing the factors that have a role in nerve regeneration and inflammation. Second, the patients were not categorized according to the layers of the cornea affected by HZO. Third, we did not assess the peripheral corneal nerve density and peripheral corneal sensation. Fourth, we used the Cochet-Bonnet esthesiometer that assesses only mechanoreceptors, although it is considered the gold standard for corneal sensitivity assessment, is rapid, non-invasive, and it allows obtaining repeatable measurements. Fifth, we did not have a control group to compare with patients treated with AST. A recent study

showed spontaneous improvement in corneal nerve density measured by IVCM in HZO patients 6 months after presentation.[35]

In conclusion, we demonstrate that treatment with AST drops results in corneal reinnervation and improvement of sensation in severe NK patients secondary to HZO. However, corneal nerve regeneration may result in stromal keratitis in HZO patients. Therefore, treatments to improve corneal regeneration may require concurrent systemic antiviral therapy and local immunosuppression with mild topical steroids.

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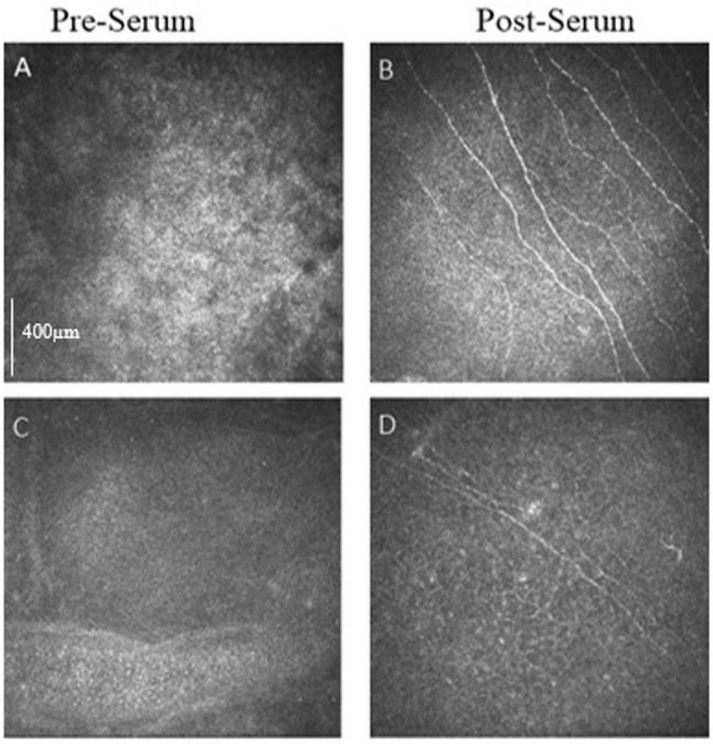

Figure 1.

Complete subbasal nerve plexus loss in patients 3 (**A**) and 4 (**C**) and nerve regeneration (**B, D**) after treatment with 20% autologous serum drops for 4 months.

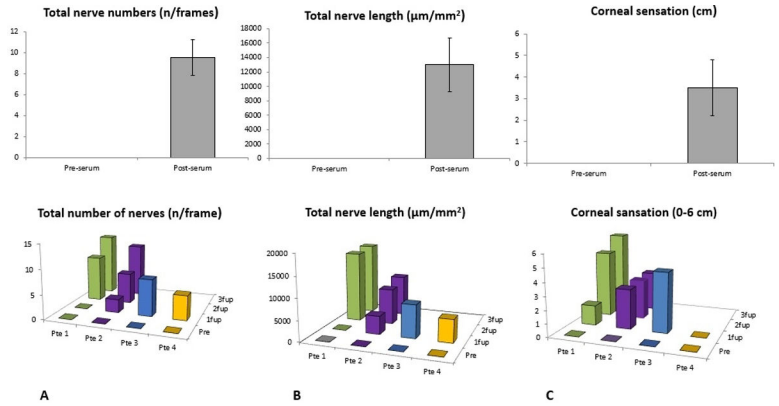

Figure 2.

Average number of corneal nerves per frame (**A**), corneal nerve density (**B**), and corneal sensation (**C**) with standard error of mean for all patients. The total nerve number and density increased in all patients. Corneal sensitivity increased in three of the four patients. Patient 1 follow-ups 1–3 represent 7.5, 11, and 22 months after baseline. Patient 2 follow ups 1–3 represent 3, 4, and 12 months after baseline. Patient 3 and 4 follow ups were 4 and 10 months after baseline respectively.

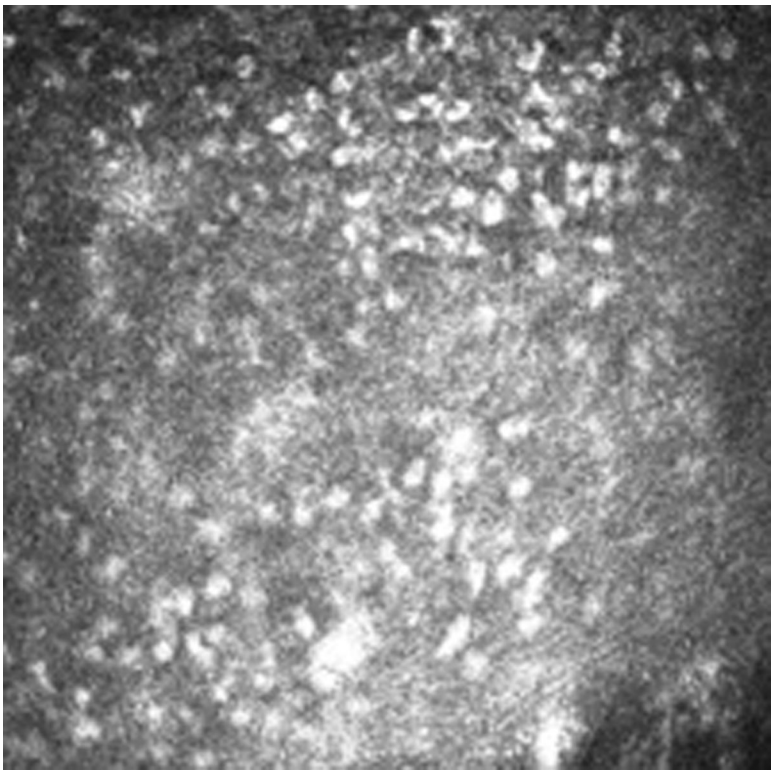

Figure 3.
Increased number of inflammatory cells on IVCM in patient 2 who developed stromal keratitis without epithelial ulceration 3 weeks after corneal reinnervation. The slit lamp examination was remarkable for multifocal stromal opacities with haze and mild edema.

Table 1-

Demographics of patients with severe HZO neurotrophic keratopathy treated with AST.

Number of patients/eyes	4/4
Age (years)	77.75±2.00
Sex, male/female	0/4
Duration of follow-up (months)	11.75±3.01

Table 2-

Corneal sensation, measured by Cochet-Bonnet esthesiometer, and central corneal nerve density by *in vivo* confocal microscopy at baseline and follow ups.

	Baseline	1–3 month follow up	4–8 month follow up	9–12 month follow up	12–24 month follow up
Corneal sensation (cm)					
Patient 1	0		1.5	5	6
Patient 2	0	3	3	3	
Patient 3	0		4.5		
Patient 4	0			0	
Corneal nerve density (μm/mm^2)					
Patient 1	0		0	16,732.52	17,250.61
Patient 2	0	4,346.91	8,489.86	9,719.84	
Patient 3	0		7,912.52		
Patient 4	0			5,460.61	