Blink Reflex in Neurotrophic Keratopathy: An Electrophysiological Evaluation

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Purpose: Neurotrophic keratitis (NK) is a rare condition which may result in visual loss. This case review investigates if there may be an association between NK and the blink reflex in the absence of facial nerve palsy and lagophthalmos.

Methods: This is a retrospective case review of 5 patients with trigeminal nerve damage referred to the oculoplastic department with suspected anesthetic corneae. Information on etiology, symptoms, duration, associated medical conditions, medications, examination findings including Mackie stage of keratopathy, management of keratopathy, and blink electrophysiology results was obtained.

Results: All 5 patients demonstrated absence of corneal sensation. All patients had preserved facial nerve function with no evidence of lagophthalmos. Keratopathy ranged from Mackie stage 0–2. Management ranged from ocular lubricants to Botulinum-toxin-induced ptosis. Blink studies demonstrated reduction in amplitude as well as increased latency in 2 patients, conferring reduced blink strength. Two patients demonstrated an absent blink reflex on the affected side. One patient had blink latency within the normative range; this patient recovered corneal sensation and was discharged.

Conclusions: Our finding of reduced amplitude in blink studies offers both a factor in pathogenesis of NK and a potential therapeutic target. Additionally, blink studies may provide prognostic information for recovery and therefore guide management. We suggest performing blink electrophysiology in patients with trigeminal nerve damage to assess nerve function.

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Neurotrophic keratitis (NK) is a rare condition with the hallmark feature of reduced or absent corneal sensation, which can lead to corneal damage that confers a significant risk of visual loss.[1,2] In our clinical practice, we have observed that patients' corneal condition can deteriorate even in the presence of full eyelid closure and hence the current management of NK mirrors that of lagophthalmos. The authors are unaware of any known association between NK and the BR in the absence of facial nerve palsy and lagophthalmos. To better understand, the mechanisms that may lead to corneal damage and poor healing in patients with NK, we retrospectively reviewed 5 consecutive patients presenting to a tertiary oculoplastic clinic. In particular, we focused on the effect of corneal anesthesia on the BR, including the results of electrophysiological BR studies.

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MATERIALS AND METHODS

This work was discussed with the Hospital Research and Innovation team. This work did not meet the criteria for research as per the HRA as the results generated were not transferable, no question was asked or answered, and robust research methods have not been utilized. Ethical approval was therefore not required. The work adhered to the tenets of the Declaration of Helsinki.

We retrospectively reviewed the case records of 5 consecutive patients referred to a tertiary center oculoplastic department with absent or reduced corneal sensation. All patients were previously diagnosed with unilateral damage to the trigeminal nerve secondary to a variety of etiologies. Data on etiology, symptoms, duration, associated medical conditions, medications, and current and prior treatments for keratopathy were abstracted.

Ophthalmic examination included assessing visual acuity, facial movement, eyelid position and presence of lagophthalmos, anterior segment examination via slit-lamp biomicroscopy, corneal staining with 2% Fluorescein eye drops and Mackie grading if keratopathy was present.[3] Corneal anesthesia was confirmed by testing with a cotton bud and comparing the patients' response with the fellow eye. Corneal confocal microscopy and a Cochet-Bonnet aesthesiometer and were not available in our clinic.

Blink Reflex Testing. All patients underwent electrophysiological testing of their blink reflex (BR). This was performed using a 4-channel Dantec Keypoint electromyography machine. Patients were sat with their eyes open in a quiet room. The BR was recorded bilaterally using adhesive silver-silver chloride surface electrodes on both orbicularis oculi. Electrical stimuli were delivered to the supraorbital and mental nerves using a small bipolar electrode (13L35 Medtronic Functional Diagnostics A/S, Skovlunde, Denmark). The stimulus intensity was gradually increased from 1 mA in 1 mA steps to evoke both the R1 and the R2 components. The recording of the BR has been described in detail elsewhere.[4–6]

The normality of the BR was determined based on the shortest latency values of the R1, R2i, and R2c components out of 8 consecutive responses on each side. The recorded shortest BR latencies were compared with the reference values of our laboratory (healthy adults, N ¼ 44). The BR was judged abnormal when the latencies of one or several components were prolonged over the 99% upper reference limit or when the components were totally missing. In addition, the presence of constant ultra-late R3 components was noted. The habituation of the BR, that is, the area attenuation of the consecutive R2i components in a series of responses, was studied with 8 repeated stimuli given at a constant

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TABLE 1. Results

Patient	Age (years)	Gender	Laterality	Etiology of trigeminal nerve damage	Corneal findings	Mackie stage	Blink reflex electrophysiology						Other trigeminal nerve electrophysiology	Keratopathy management
							Mental nerve stimulation			Supraorbital nerve stimulation				
							Description	Threshold values (milliAmps (mA))		Description	Threshold values (milliAmps (mA))			
1	50	Female	Left	Cerebello-pontine angle meningioma excision	Dry cornea, inferior superficial punctate keratopathy, reduced TBUT (5 seconds)	I	Absent blink reflex on the left. Right blink reflex normal.	Right R1 = No response Right R2 = 14mA	Left R1 = Absent response Left R2 = Absent response	Absent blink reflex on the left. Right blink reflex normal.	Right R1 = 7mA Right R2 = 4mA	Left R1 = Absent response Left R2 = Absent response	Absence of temperature sensation on the left and reduced masseter reflex on left; right normal	Ocular lubricants, inferior punctal plug
2	63	Female	Right	Microvascular decompression of trigeminal nerve for trigeminal neuralgia	No corneal staining, reduced TBUT (5 seconds)	I	Right sided latencies in the normal range but delayed compared with the left.	Not available	Not available	Right sided latencies in the normal range but delayed compared with the left.	Right R1 = 10mA Right R2 = 2mA	Left R1 = 7mA Left R2 = 2mA	Normal masseter reflexes. Subtle impairment of temperature reflexes on the right.	Ocular lubricants
3	63	Male	Right	Trigeminal schwannoma excision	Reduced visual acuity (6/48), red eye with a central round corneal abrasion with healing edges	II	Absent orbital blink on right side, normal on left.	Right R1 = Not available Right R2 =Absent response	Left R1 = Not available Left R2 = 15mA	Increased latency and reduced amplitude on stimulation on right; normal on the left.	Right R1 = Absent response Right R2 = 7mA	Left R1 = 7mA Left R2 = 5mA	Significant impairment of masseter reflex on the right.	Ocular lubricants, topical antibiotic, botulinum injection (induced ptosis), inferior punctal plug
4	56	Male	Right	Trigeminal nerve decompression, neurectomy and glycerol injection for trigeminal neuralgia	Dry cornea, sore eye with blurred vision	I	Absent blink reflexes on the right; normal on the left.	Right R1 = Not available Right R2 = 25mA	Left R1 = Not available Left R2 = 7mA	Increased latency and reduced amplitude on stimulation on the right side; normal on the left side.	Right R1 = Absent response Right R2 = Not available	Left R1 = Not available Left R2 = Not available	Masseter reflex: normal latency on both sides, but reduced amplitude on the right.	Ocular lubricants, inferior punctal plug
5	79	Female	Left	Glycerol injections (×3) for trigeminal neuralgia.	No corneal staining, bilateral ptosis	0	Slight delay in all responses, most likely secondary to central nervous system (CNS) demyelination.	Right R1 = Absent response Right R2 = 14mA	Left R1 = Absent response Left R2 = 14mA	Stimulation of the left side shows completely absent blink reflex. Slight delay in right side, likely secondary to CNS demyelination	Right R1 = 8mA Right R2 = 2mA	Left R1 = Absent response Left R2 = Absent response	Masseter reflexes normal bilaterally.	Ocular lubricants

CNS, central nervous system; TBUT, tear break up time.

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frequency of 1 Hz on each side to the SON. Throughout the habituation test, the stimulus intensity was kept at the constant level determined in the first BR test on each side. The onset and offset of the rectified R2 components of the BR were assessed and manually marked on the computer screen. The habituation was considered abnormal when the area under R2i response did not attenuate at least 50% between the first and the third of 8 consecutive responses. (In normal control subjects, the 50% area decrement always occurred before or at the third stimulus.) The ordinal number of the response to which the R2 area had diminished at least 50% was indicated as the habituation index on each side.[5,7]

In addition to the BR, masseter reflexes were also recorded.

RESULTS

The patient demographics, laterality, etiology, Mackie stage of corneal involvement, electrophysiology results, and management of the keratopathy are outlined in Table 1. Figures 1 and 2 exemplify the electrophysiology results of trigeminal testing for patient 1 and patient 2, respectively.

All patients had complete absence of corneal sensation on initial testing. Patients 1–4 had normal eyelid closure and facial movements. No patients had lagophthalmos.

No patients had repeat electrophysiology testing, as this was not clinically indicated.

DISCUSSION

In this case series, all 5 patients demonstrated absence of corneal sensation secondary to trigeminal nerve damage. The etiology was tumor-related, or iatrogenic from surgery or glycerol injection to the nerve. All patients had preserved facial nerve function with no evidence of lagophthalmos.

With the exception of Patient 5, they developed NK, ranging from Mackie stage 1 to 2. All patients were managed with ocular lubricants: 3 patients also required inferior punctal plug insertion, and 1 patient underwent Botulinum A toxin injection to the upper eyelid to induce therapeutic ptosis. The absence of keratopathy in Patient 5 was likely secondary to the corneal protection conferred by her concurrent ptosis.

Electrophysiology blink studies demonstrated some interesting findings in 3 of the patients, which may confer a role for blink studies in evaluating prognosis in NK. In 2 patients, stimulation of the supraorbital nerve displayed not only increased latency, but also reduced amplitude. This reduction in amplitude implies that not only is the BR delayed but, despite the absence of lagophthalmos and facial nerve damage, the strength of the blink is also reduced. Diminished blink strength may be an additional contributor to poor corneal protection and subsequent keratopathy, so may offer a therapeutic target. Potential treatments could focus on improving the speed and amplitude of the blink using electrical stimulation or eyelid surgery to enhance the blink.

Patient 2 with a history of microvascular trigeminal nerve decompression had a blink latency that fell within the normative range, albeit with an increased latency compared with the contralateral side. This patient recovered corneal sensation within a year, perhaps suggesting a correspondence between normative latency and recovery of trigeminal nerve function. Usually, neurosurgery-induced NK confers impairment of corneal morphology and function even years after the initial event.[8]

Intact corneal innervation, via the ophthalmic branch of the trigeminal nerve,[9] and nerve function play a fundamental role in corneal protective mechanisms such as the BR, reflex tear production, release of trophic neuromodulators, and maintenance of corneal endothelial function.[1,10,11] The afferent arm of the BR is carried via the trigeminal nerve and the efferent component is conveyed via the facial nerve to the orbicularis oculi.[12] Blink studies involve the electrophysiological assessment of this reflex and therefore provide information about the function of the trigeminal nerve. They involve the stimulation of the supraorbital nerve, a branch of the ophthalmic nerve, or the mental nerve, a branch of the inferior alveolar nerve.[5,12] In our patients, the BR was assessed by stimulation of both supraorbital and mental nerves: latency, threshold, and maximum amplitudes were compared against both normative values and the contralateral response.

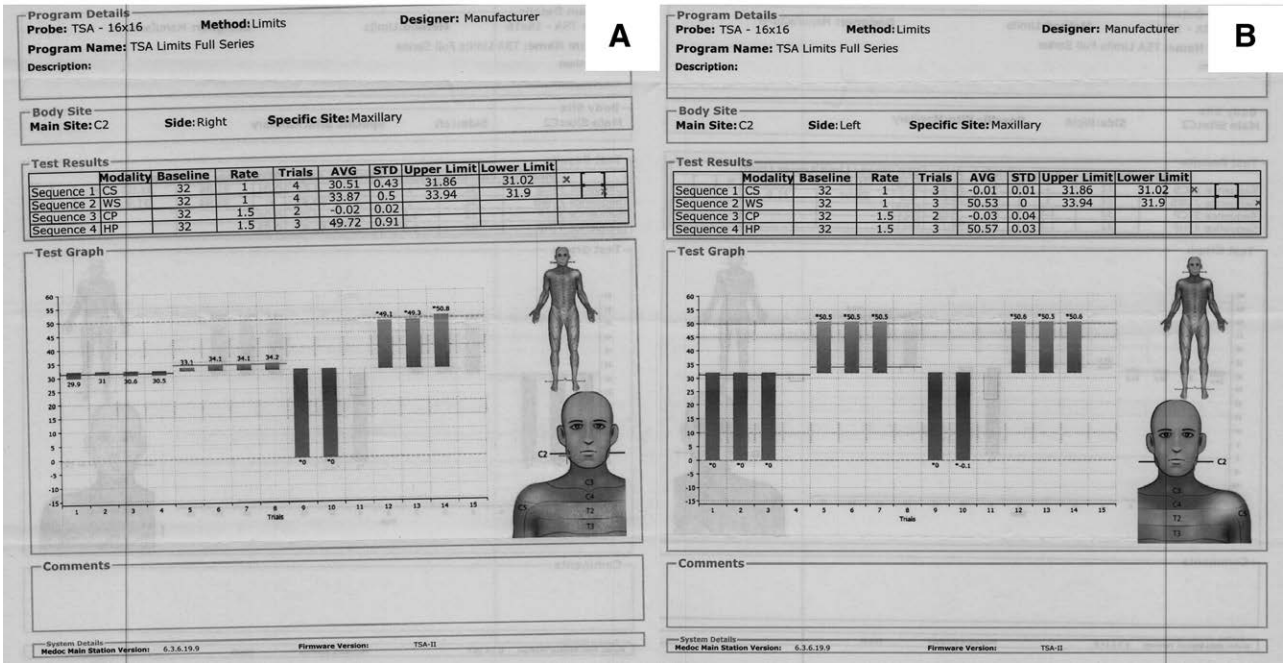

FIG. 1. Electrophysiology of maxillary branch of trigeminal nerve of patient 1. A, Normal electrophysiology response on the right side. B, Left-sided trigeminal reflexes demonstrate reduced masseter reflex.

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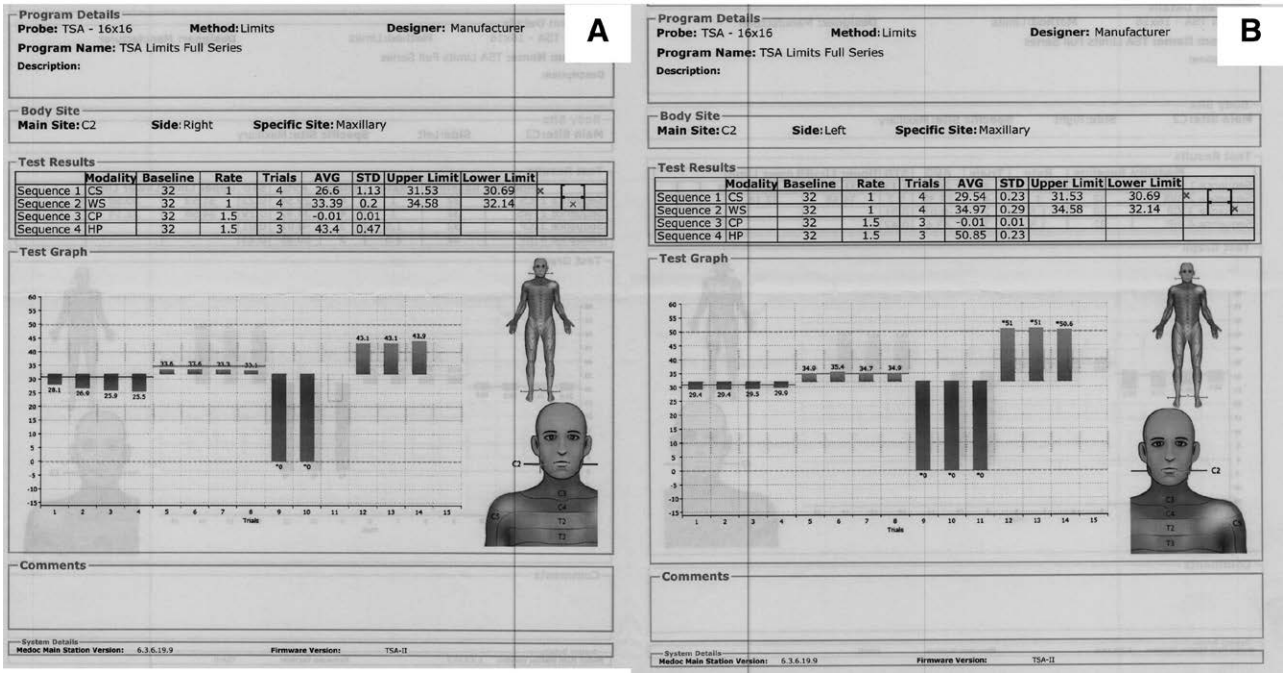

FIG. 2. Electrophysiology of maxillary branch of trigeminal nerve of patient 2, demonstrating normal masseter reflexes on the right (A) and left (B) sides.

Mackie's 3-stage classification system was used to describe the severity of corneal damage in NK.[1–3,10] Stage 1 describes alterations to the corneal epithelium such as punctate epitheliopathy, while stage 3 is defined by the presence of a corneal ulcer. The classification helps guide management in a stepwise fashion.[2,10]

There are no nonsurgical treatments to rapidly restore corneal sensation and NK remains a difficult and challenging condition to manage.[1,2] Management is aimed at corneal protection and prevention/progression of keratopathy. Surgical techniques carry the limitations of reduced visual function and esthetic compromise.[10] Neuroregenerative treatments are currently being investigated. Autologous serum eye drops are thought to have neuroregenerative properties[2,13] and the recombinant human nerve growth factor Cenegermin has been shown to be safe and effective in treating moderate to severe NK in phase 2 trials.[14] Tersiz et al showed good results with corneal neurotization, the surgical restoration of corneal innervation.[2,15] Although initially performed with direct transfer of contralateral supraorbital and supratrochlear nerves, transfer of the ipsilateral nerves is possible where loss of sensation only affects the cornea and sensation of the ipsilateral forehead is intact. The latter is quicker as it requires a smaller procedure to access the nerves rather than a bicoronal flap. Since then, other modifications have been made including indirect neurotization using the sural nerve,[16] as well as a less invasive endoscopic approach to mobilize the nerve to be transferred,[17] and the use of acellular nerve allografts to act as the conduit for neurotization.[18] Over time, patients usually have improved visual acuity, corneal sensation, and corneal clarity.[15] Complete neurotization of the basal and central cornea may be seen from 6 months to 2 years postoperatively while the restored corneal sensation may last even up to 20 years postoperatively.[15] Additionally, the corneal nerves may initiate a BR for maintenance of corneal health.[15]

This review has limitations. As neurotrophic cornea is a rare diagnosis, the cohort size is small, and this was a retrospective review. Corneal sensation was assessed by a cotton bud not a Cochet-Bonnet esthesiometer as the latter was not available in our clinic. While the former is recognized as an alternative method of establishing loss of corneal sensation, it is less sensitive, and the esthesiometer is the better assessor.[1,10,19] Corneal nerve damage is likely more precisely assessed by corneal confocal microscopy[20]; this was not obtainable in our setting. There were no repeat measurements of electrophysiology testing upon improvement of keratitis or corneal sensation: this had not been performed as there was no clinical requirement.

Our review suggested a role for diminished blink strength in the pathophysiology of NK, potentially offering further management options, and that blink electrophysiology studies may allow insight in prognosis. Serial electrophysiology testing, especially if any alteration in corneal sensation or keratitis occurred, could give valuable information.

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