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Original Research

Neurotrophic keratitis: Frequency, etiologies, clinical management and outcomes

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ABSTRACT

Purpose: To determine neurotrophic keratitis (NK) frequency, etiologies and prognostic factors, and evaluate the outcome of its management.
Methods: In this retrospective epidemiologic study, we reviewed the electronic records of all patients consulting our tertiary referral eye hospital between November 2009 and October 2017. NK was defined as corneal hypoesthesia or anesthesia associated with epithelial irregularities.
Results: Among the 305,351 patients' files screened for eligibility, 335 (354 eyes) were included, yielding an NK frequency of 11/10,000 (0.11%). Their mean ± SD age was 63.1 ± 21.0 years. Eyes were equally divided among the Mackie classification 3 stages. The most frequent etiology was herpetic eye disease (114 eyes; 32.2%). A multifactorial cause was found for 121 (34.2%) eyes. Surgery required for 118 eyes (33.3%). Respective success rates for amniotic membrane transplantation (AMT) or matrix-regeneration of stages 2 and 3, and autologous serum of stage 1 were 57.2%, 63.6% and 21.7%, with mean healing times of 15.0, 16.3 and 85 days. The overall healing rate was 79.5%, with a mean of 44.8 days to healing. Advanced initial stage, diminished corrected-distance visual acuity (CDVA) and advanced age correlated with worse final CDVA.
Conclusions: NK was more frequent than previously reported in the literature. Delayed diagnoses indicated we must increase ophthalmologists' awareness of this disease for patients with decreased corneal sensitivity and abnormal epithelium. To improve prognosis and final CDVA, NK-specific treatment should be initiated as soon as the diagnosis is suspected. Patient-centered combinations of different therapeutic components and close monitoring achieved promising results.

The cornea is an avascular, transparent tissue that is densely innervated by the ophthalmic branch of the trigeminal nerve. Corneal innervation is essential for protective functions of the eye, such as blinking and tearing, and exerts trophic support for epithelial cells by releasing neuromediators and growth factors. Therefore, corneal nerves play an important role in maintaining corneal epithelial integrity, proliferation and homeostasis, and in wound healing [1,2]. Consequently, alteration of its innervation is associated with the breakdown of the corneal epithelium, leading to persistent epithelial defects, corneal ulceration, melting and ultimately perforation [3,4].

Neurotrophic keratitis (NK) is defined as a rare neurodegenerative corneal disease characterized by decreased or absent corneal sensitivity [4]. Local or systemic disease damaging the fifth cranial nerve at any level, from the trigeminal nucleus to corneal nerve endings, may result in NK [2,5]. To our knowledge, no report has been published on NK epidemiology, demography and therapeutic outcomes. Hence, the precise NK frequency in a specific population has never been directly determined, as it was only calculated from data on conditions associated with NK. Indeed, its prevalence of 1.6/10,000 patients [4] was estimated based on data indicating that NK affects 6% of patients with herpetic keratitis [6], 12.8% with herpes varicella-zoster keratitis [7] and 2.8% undergoing surgical procedures for trigeminal neuralgia [8].

Abbreviations: NK, neurotrophic keratitis; AMT, amniotic membrane transplantation; CDVA, corrected distance visual acuity; CNS, central nervous system; RGTA, matrix-regeneration therapy

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This study was undertaken to evaluate NK frequency, identify its etiologies, and shed a light on clinical management and visual outcomes of these patients consulting a tertiary referral eye hospital.

Methods

Patient selection

This retrospective, observational, monocenter study included patients examined at the Fondation Ophtalmologique Adolphe de Rothschild Hospital, a tertiary referral center, between November 1, 2009 and October 31, 2017. Retrospective chart-review approval was obtained from the hospital's Institutional Review Board. The study adhered to the tenets of Helsinki.

The electronic records of all patients consulting during that period were reviewed for NK-related search words ("neurotroph-", "hypoesthésie", "anesthésie", "ulcère", "défect epithelial"). Retrieved records were then manually double-checked for NK presence or absence. Included patients' files were retrieved for collection of demographic characteristics (age, sex and NK laterality), NK etiology, visual acuity at first consultation, time to diagnosis, NK stage, complications (e.g., perforation and/or bacterial infection), management and evolution.

NK was diagnosed based on slit-lamp examination with a typical clinical picture of corneal hypoesthesia or anesthesia (evaluated by a cotton wisp or Cochet–Bonnet esthesiometer) associated with punctate keratopathy, cloudy and irregular epithelium, persistent epithelial defects or corneal ulcer. Mackie's classification [9] was used to categorize NK into 3 stages, characterized as follows: stage 1, mainly superficial punctate keratopathy; stage 2, recurrent or persistent, oval or circular persistent epithelial defects; and stage 3, corneal ulcer with stromal involvement. Eyes for which Mackie staging was not possible were included only in the etiology and management analyses.

Therapeutic success rate and time to complete healing were recorded separately for the following treatment options: overlay and/or inlay amniotic membrane transplantation (AMT), autologous serum and matrix-regeneration therapy (RGTA). Complete healing was defined as negative fluorescein staining of the corneal ulcer for Mackie stage-2 or -3 NK and the absence of punctate epithelial fluorescein staining for stage 1. A treatment was considered successful if it achieved complete healing without requiring subsequent intervention.

Statistical analyses

Statistical significance was computed with *SPSS software® Version 22.0 (SPSS INC, Chicago, IL)* and Microsoft Excel 2011 (Microsoft Office, Seattle, WA). Descriptive statistics are reported as mean ± standard deviation (SD) or 95% confidence interval (95% CI) for continuous variables and numbers (percentages) for categorical variables. Spearman's correlation coefficient was computed for multiple regression analyses between different variables. A 2-tailed *P* value ≤ 0.05 was considered significant.

Results

Patient characteristics

Among 305,351 patient consultations during the observation period, 392 pertinent medical records were identified for a final total of 354 NK eyes (335 patients) included (Fig. 1). NK frequency in our facility was 11/10,000 patients. The average age at consultation was 63.1 ± 21.0 (range, 6–101) years. NK was equally distributed between sexes. Nineteen patients (5.7%) had bilateral NK.

At first consultation, eyes were fairly equally distributed among the 3 Mackie stages classified as follows (Table 1): 34.5% stage 1, with 6/122 patients progressing rapidly to stage 2; 30.5% stage 2, with 12/108 progressing rapidly to stage 3; and 32.5% as stage 3. Notably, 14 (3.94%) stage-3 eyes were at a pre- or perforated state. Because of missing clinical information in the patients' records, 9 (2.5%) eyes could not be staged. Mean initial corrected-distance visual acuity (CDVA) was 0.61 ± 0.49 LogMAR (95% CI, 0.54–0.69).

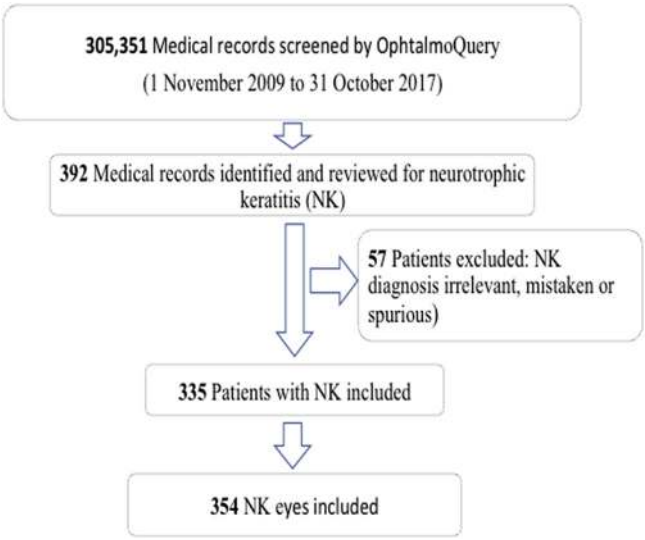

Fig. 1. Flowchart of the study inclusion protocol.

Table 1
Characteristics of neurotrophic keratitis patients.

Characteristic	Value[a]
Patients	
Reviewed medical records	392
Excluded	57 (14.5%)
Included	335 (85.5%)
Sex	
Male	166 (49.6%)
Female	169 (50.4%)
Age in years	63.1 ± 21.0
Eyes	
Included	354
Lost-to-follow-up	47 (13.3%)
Side affected	
Right	167 (47.2)
Left	149 (42.1)
Bilateral	19 (5.4)
Initial Mackie stage (eyes)	
1	122 (34.5%)
2	108 (30.5%)
3	115 (32.5%)
Pre-perforated or perforated ulcer	14 (4%)
Not reported	9 (2.5%)
CDVA (LogMAR)	0.61 ± 0.49

This table represents initial characteristics of included cases.
CDVA = corrected distance visual acuity.
[a] Results are expressed as number (%) or mean ± standard deviation.

Etiology

NK was multifactorial for 121 (34.2%) eyes and idiopathic for 29 (8.2%). Dividing etiologies according to ocular or systemic origin, the former were slightly more frequent, as detailed in Table 2. Ocular etiologies were mostly herpes infections, responsible for 114 NKs (predominantly herpes simplex, followed by varicella zoster) or iatrogenic interventions. Systemic etiologies found for 98 NK eyes were mostly tumors and/or surgeries, strokes and cerebral hemorrhage or arteriovenous malformation.

Nineteen (5.7%) patients had bilateral NK, which was multifactorial

Table 2
Neurotrophic keratitis etiologies for the 354 eyes.

Etiology	No. of eyes (%)
Ocular	
Herpetic eye disease	**114 (32.2)**
Herpes simplex virus	91 (25.7)
Varicella-zoster virus	23 (6.5)
Iatrogenic[a]	**113 (31.9)**
Vitrectomy with endolaser	36 (10.2)
Multiple ocular surgeries	18 (5.1)
Corneal grafting (penetrating or lamellar keratoplasty)	17 (4.8)
Radiotherapy sequelae	16 (4.5)
Eye drops toxicity	39 (11.0)
Antiglaucoma	14 (4)
Antibiotics	14 (4)
Nonsteroidal anti-inflammatory	9 (2.5)
Anesthetics	2 (0.6)
Systemic neurotoxic chemotherapies	11 (3.1)
Refractive surgery	6 (1.7)
Pan-retinal photocoagulation	4 (1.1)
Chronic ocular surface disease	**62 (17.5)**
Chronic severe blepharitis and/or rosacea	38 (10.7)
Entropion	9 (2.5)
Ocular injuries or chemical burns	9 (2.5)
Graft-versus-host disease	4 (1.1)
Sjögren's syndrome	3 (0.8)
Trachoma	3 (0.8)
Ocular cicatricial pemphigoid	2 (0.6)
Systemic causes	
Central nervous system diseases[a]	**98 (27.7)**
Intracerebral tumors and/or surgeries	62 (17.5)
Stroke	13 (3.7)
Cerebral hemorrhage or arteriovenous malformation	9 (2.5)
Trigeminal ophthalmic branch damage due to cerebral surgery	6 (1.7)
Trigeminal thermocoagulation	3 (0.8)
Carotid–cavernous fistula	3 (0.8)
Degenerative or infiltrative central nervous system disease	2 (0.6)
Cerebral infection	2 (0.6)
Multiple sclerosis	2 (0.6)
Cerebral leukodystrophia	2 (0.6)
Tuberous sclerosis	1 (0.3)
Multiple endocrine neoplasia type IIB	1 (0.3)
Neurofibromatosis (type I)	1 (0.3)
Neurofibromatosis (type II)	1 (0.3)
Guillain–Barré syndrome	1 (0.3)
Diabetes mellitus	**37 (10.5)**
Diabetes without vitrectomy or pan-retinal photocoagulation	25 (7.1)
Other rare conditions	9 (2.5)
Severe alcoholism or vitamin B_{12} deficiency	3 (0.8)
Acanthamoeba keratitis sequelae	2 (0.6)
Leprosy	2 (0.6)
Vitamin A deficiency	1 (0.3)
Goldenhar syndrome	1 (0.3)
Unknown	29 (8.2)

This table represents etiologies of neurotrophic keratitis in included cases.
[a] Some patients had more than one etiology.

for 7 patients and idiopathic for 3. The most frequent etiologies were: iatrogenic (7; 36.8%), chronic ocular surface disease (i.e., chronic severe blepharitis and/or ocular rosacea (5; 26.3%)), herpes infection (4; 21.1%), CNS origin or diabetes (3; 15.8% each).

Global management

Among the 354 eyes included, 220 (62.1%) were diagnosed with NK at the first consultation, while remaining initial misdiagnoses were rectified after a mean of 38.8 days, as detailed in (Table 3). Because 45 patients (47 eyes) were lost-to-follow-up post-diagnosis, the analysis of therapeutic responses and outcomes (success rate and time to complete healing) was based on 307 eyes.

Overall, patients had a mean of 15.0 consultations over a mean of 21 months. Seventy-three patients required hospitalization, lasting a mean of 11.5 days. During follow-up, NK recurred in 70 eyes, for a mean of 1.5 recurrences per eye.

Table 3
Global management.

Parameter	Value[a]
Diagnosis	
1st consultation	220 (62.1%)
Days to revision	38.8 (29.6–48.0)
Lost-to-follow-up	
Patients, no.	45
Eyes[b]	47 (13.3%)
Stage 1	24
Stage 2	8
Stage 3	7
Consultations, no.	15.0 (13.3–16.6)
Follow-up in months	21.4 (13.7–29.1)
Patients hospitalized, no.	73 (21.8%)
Length of stay, days	
Mean	11.5 (8.9–14)
Median	7
Eyes with recurrences	10
Mean no.	1.5 (1.3–1.8)
Complete healing	
Stage 1 eyes, no;	56
Consultations	9.9 (7.1–12.6)
Over no. days	77.8 (14.1–69.1)
Days to healing	
< 7	7%
7–14	14%
> 14	79%
Stages 2&3	188 (90.4%)
Consultations	16.9 (14.6–19.1)
Over no. days	35.0 (19.7–32)
Days to healing	
< 7	13%
7–14	27%
> 14	60%

This table represents global management of neurotrophic keratitis.
[a] Values are expressed as No. (%) or mean (95% CI), unless stated otherwise.
[b] Stages missing for 6 eyes.

Fifty-six stage-1 eyes healed completely after a mean of 9.9 visits, over a mean of 77.8 days, with 79% requiring > 14 days to do so. For stages 2 & 3 combined, 188 eyes healed after a mean of 16.9 visits, over a mean of 35.0 days, with 60% requiring > 14 days to do so. Hence, time to complete healing was significantly longer for stage-1 NK than stages 2 & 3 ($P < 0.001$).

Medical management

At first consultation, 344 (97.2%) NK eyes were already benefiting from medical interventions, as detailed in Table 4. The most frequently prescribed treatments were: hyaluronic acid, topical vitamin A, systemic antiherpes agent, matrix-metalloprotease inhibitor, topical, fortified or prophylactic antibiotics and RGTA.

Fortified antibiotics, prescribed at the first consultation for 58 (16.4%) eyes, were discontinued at the follow-up visit because the cornea specialist considered them unnecessary.

Surgical management

Overall, 118 (33.3%) eyes required surgical procedures (Table 4), including overlay and/or inlay AMT, partial or complete tarsorrhaphy, other eyelid interventions, therapeutic penetrating or lamellar keratoplasty, botulinum-A toxin injection into the levator palpebrae, debridement of epithelial hyperplasia, conjunctival flap or cyanoacrylate glue application. Fourteen eyes with a pre- or perforated ulcer at first consultation underwent emergency surgeries.

Table 4
Medical and surgical treatments.

Treatment	No. of eyes (%)
Medical, n	344
Artificial tears with hyaluronic acid	287 (81.1)
Topical vitamin A ointment	274 (77.4)
Systemic antiherpetic therapy	156 (44.1)
Matrix-metalloprotease–inhibitor therapy	91 (25.7)
Oral doxycycline	44 (12.4)
Topical azithromycin	44 (12.4)
Topical N-acetyl-cysteine	3 (0.8)
Fortified antibiotics	81 (22.9)
Unnecessary	58 (16.4)
Culture-proven secondary bacterial infection	23 (6.5)
Topical prophylactic antibiotics	70 (19.8)
RGTA	49 (13.8)
Patch occlusion	44 (12.4)
Autologous serum	39 (11.0)
Scleral contact lenses	25 (7.1)
Bandage contact lens	22 (6.2)
Punctal occlusion	7 (2.0)
Surgical, n	118
Overlay AMT	82 (23.2)
Inlay AMT	43 (12.1)
Tarsorrhaphy, partial or complete	26 (7.3)
Other eyelid interventions	11 (3.1)
Therapeutic penetrating or lamellar keratoplasty	8 (2.3)
Botulinum-A toxin injection	7 (2.0)
Epithelial hyperplasia debridement	5 (1.4)
Conjunctival flap	4 (1.1)
Cyanoacrylate glue application	2 (0.6)
Pre- or perforated ulcer at 1st consultation	14 (11.9)

This table represents medical and surgical treatments of included cases.
AMT: Amniotic membrane transplantation; RGTA: matrix-regeneration therapy.

NK-specific therapies

The NK-specific surgical arsenal includes autologous serum, RGTA and overlay and/or inlay AMT. Eighty-seven eyes were treated with only one of the above, while 42 received a combination of those treatment modalities. Most eyes that received an inlay AMT had stage-2 or -3 NK at first consultation (27.9% and 69.8%, respectively), as did eyes treated with overlay AMT (36.4% and 57.1%, respectively). Six eyes with initial Mackie stage 1 required overlay AMT and 12 eyes with initial stage 2 needed overlay and inlay AMTs during follow-up because of rapid deterioration.

Healing rates with NK-specific therapies as a function of Mackie stage 1 or 2 & 3 combined are reported in Table 5. Healing rates for stage 2 & 3 AMT- or RGTA-treated eyes were 57.2% or 63.6%, respectively, while those for RGTA- or autologous serum-treated stage-1 eyes were 0% or 21.7%, respectively. Specific healing times for stage-2 or -3 NKs were the fastest with AMT procedures but were non-significantly shorter than with RGTA ($P = 0.70$). The autologous serum healing time for stage-1 NK was the longest, exceeding 5 times that for AMT procedures. The mean number of AMT procedures per eye was of 1.44 ± 0.70 (range, 1–5).

Healing times (< 7, 7 < −14 or > 14 days, respectively) for stage-2 & −3 eyes after AMT were 31%, 40% or 29%, while after RGTA, they were 33%, 29% or 38%. Autologous serum was used exclusively to treat stage-1 NK eyes and all healing times exceeded 14 days. Seven (17.9%) eyes treated with autologous serum alone progressed from stage 1 to stage 2 or 3.

Healing rates and etiologies were available for 33 stage-2 or -3 NK eyes treated with RGTA alone. According to Spearman's rank correlation analysis, the healing rate was positively correlated with CNS etiologies ($r = 0.36$, $P = 0.04$) and negatively with a herpes origin ($r = -0.39$, $P = 0.026$). No correlations were found between healing rate and diabetes, iatrogenic causes or chronic ocular surface diseases.

Visual outcomes

Final CDVA (LogMAR) was available for 229 eyes. Overall, mean CDVA significantly improved from initial 0.61 ± 0.49 (95% CI, 0.54–0.69) to 0.38 ± 0.49 (95% CI, 0.30–0.45]), at last follow-up visit. For stages 1, 2 and 3, respectively, mean initial CDVAs were 0.44 ± 0.41, 0.70 ± 0.43 and 0.89 ± 0.29; mean final CDVAs were 0.35 ± 0.37, 0.45 ± 0.36 and 0.55 ± 0.38. Stage-3 NK eyes had significantly worse final CDVAs than stages 1 and 2. Overall, mean CDVA gain was 0.19 ± 0.34 (almost 2 ETDRS lines): 0.09 ± 0.25 for stage 1, 0.25 ± 0.42 for stage 2 and 0.44 ± 0.34 for stage 3. Initial CDVA for 121 (34.2%) eyes was counting fingers or worse; that number declined to 97 (27.4%) after treatment. CDVA improved for 104 (45%) eyes, remained stable for 75 (33%) and deteriorated for 50 (22%).

According to Spearman's rank correlation analyses (Table 6), significant correlations were found between initial CDVA and stage but not with etiology or lagophthalmos. Final CDVA was significantly correlated with baseline CDVA, initial Mackie stage and age. Final CDVA improvement was correlated with baseline CDVA and initial Mackie stage.

Discussion

Demographics

To our knowledge this is the largest observational study on NK epidemiology, etiologies, treatments and outcomes. Over 8 years, 335 NK patients were referred to our tertiary eye hospital, corresponding to 11 NKs/10,000 patients. Compared to estimates extrapolated from NK-associated diseases, such as herpes eye disease, our frequency was higher. That finding can be explained by patient identification in our specialized facility's database, which could represent a selection bias, but previously reported rates were based on estimations for only some of the possible NK etiologies and, therefore, probably underestimated the real frequency.

We think that NK occurs more frequently than previously thought. As result, a low threshold should be established for suspected NK diagnosis and patients with corneal ulcer, epithelial defect and/or irregular epithelium, and/or corneal sensitivity must be assessed.

Prognosis

Initial low CDVA, advanced Mackie stage and older age negatively impacted the final CDVA. However, time to NK diagnosis apparently

Table 5
Specific neurotrophic keratitis treatments and their efficacies.

NK-specific treatment	Total, no.	Failures, no. (%)	Successes, no. (%)	Mean ± SD [95% CI] healing time, days
AMT procedures (stages 2 & 3)	145	62 (42.8)	83 (57.2)	15.0 ± 14.9 [12.5–17.4]
RGTA (stages 2 & 3)	33	12 (36.4)	21 (63.6)	16.7 ± 13.9 [14.4–19.0]
RGTA (stage 1)	11	11 (100)	0 (0)	–
Autologous serum (stage 1)	23	18 (78.3)	5 (21.7)	85.0 ± 72.8 [73.2–96.8]

This table represents efficacy of specific neurotrophic keratitis treatments and mean healing time.
AMT: Amniotic membrane transplantation; RGTA: matrix-regeneration therapy; SD: standard deviation.

Table 6
Rank-Correlation Analyses of Initial, Final and Initial vs Final Differential Affected-Eye Corrected-Distance Visual Acuity (LogMAR).

Independent variable	CDVA (LogMAR)					
	Baseline		Final		Change	
	r[a]	P	r[a]	P	r[a]	P
Herpes simplex sequelae	0.04	0.60	0.07	0.42	0.11	0.23
Varicella-zoster sequelae	0.03	0.73	0.13	0.10	−0.03	0.73
Iatrogenic causes	0.07	0.38	0.07	0.36	−0.02	0.82
Central nervous system causes	−0.07	0.38	−0.13	0.10	−0.03	0.75
Chronic ocular surface diseases	0.006	0.94	0.08	0.34	0.0003	1
Diabetes	0.10	0.20	0.08	0.33	0.15	0.10
Unknown etiology	−0.04	0.61	−0.09	0.30	−0.03	0.77
Initial Mackie stage	0.40	< 0.001^	0.24	0.002^	0.40	< 0.001^
Age	0.15	0.04^	0.24	0.003^	−0.06	0.53
Lagophthalmos	0.11	0.17	0.08	0.33	0.03	0.79
Late diagnosis			0.09	0.28	0.02	0.80
Days to late diagnosis			0.15	0.38	−0.10	0.29
No. of visits to late diagnosis			0.12	0.47	−0.05	0.63
Initial affected-eye visual acuity (LogMAR)			0.66	< 0.001^	0.56	< 0.001^

This table represents correlation between independent variables and initial CDVA, final CDVA and CDVA change.
CDVA: corrected distance visual acuity.
^ significant P < 0.05.
[a] Spearman's correlation coefficient.

did not influence outcome, but could be explained by the rapid initiation of adequate treatment for many patients, despite missed initial diagnoses (mostly stage 1), and that topical antibiotics erroneously prescribed for corneal abscess (16.4% of eyes) were discontinued shortly thereafter and had no consequences. Importantly, referral times were short and monitoring frequent.

Once the NK diagnosis is established, treatment should be initiated, along with close monitoring. In their randomized phase II study, Bonini et al. [10] found untreated stage-2 or -3 NK healing rates of 13.7% at 4 weeks and 33.3% at 8 weeks. Those rates were improved with the use of recombinant nerve-growth factor, reaching 55% at 4 weeks and 74% at 8 weeks. Our healing rate for stage-2 & −3 NKs was 87.9% at 5 weeks. A different medical approach, applying a low threshold to AMT and very close monitoring may have contributed to this higher rate.

Etiologies

Herpes infection was the most frequent NK etiology, followed by iatrogenic or CNS causes and diabetes. Our results are in accordance with those of Bonini et al., based on 43 NK cases, with herpetic eye disease and repeated corneal surgeries being the most frequent etiologies, representing, respectively, 27% and 21.6% [11]. According to Hsu and Modi, the most frequent NK etiologies for 46 eyes were diabetes mellitus, herpes simplex and CNS causes [12]. Our rate of CNS origins seems to be higher than previously reported, perhaps reflecting that our hospital is also a referral center for neurologic diseases and neuroradiology.

Medical management

In light of our results and those of others, we propose an NK-treatment algorithm using an incremental approach as a function of the Mackie stage (Fig. 2). Once NK is suspected, etiologies should be carefully sought and drugs with potential corneal toxicity should be stopped. Clinical examination, signs of dryness, ocular surface disease and lagophthalmos should be sought, and NK should be classified according to Mackie stage, which will help guide management. All patients should be treated promptly and closely monitored.

For almost 70% of our series, medical therapy was sufficient. Lubrication, such as hyaluronic acid, should be prescribed for all patients, because ocular dryness is a factor aggravating NK [4]. Matrix-

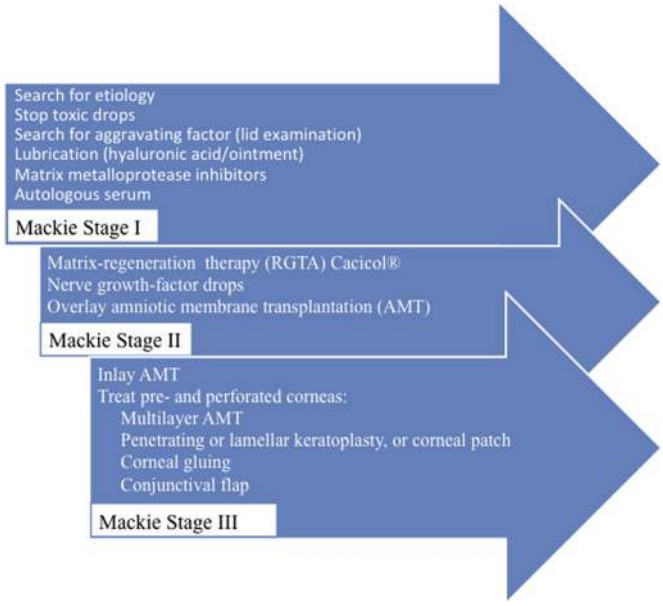

Fig. 2. Incremental algorithm approach to the treatment of neurotrophic keratitis as function of the Mackie stage.

metalloprotease inhibitor therapy can be an option for patients with ocular surface disease. However, the use of unnecessary topical antibiotics should be limited. Eyelid abnormalities should be sought and treated adequately.

Because progression of stage-1 NK is frequent, despite initiating therapy, Guadilla et al. suggested that autologous serum be started early during the disease course [13]. Punctal occlusion was also shown to be effective against severe dryness [14]. Our main indication for autologous serum was persistent stage-1 NK, despite nonspecific therapy, and prior stage-2 or -3 NK.

In this study, AMT and RGTA were used to treat stage-2 or -3 NKs with good efficacy. However, RGTA obtained no healing of stage-1 NKs, perhaps because of the molecule's action [15,16]. Our results suggest that RGTA should not be used to treat stage-1 NKs, reserving it for stage-2 or -3 NKs, particularly for CNS etiologies.

Bacterial infections were treated with fortified antibiotic eyedrops,

taking into account their ocular surface toxicity in this neurotrophic context. Depending on the extent of corneal ulceration and affected corneal surface, AMT surgery (including multilayer inlay graft) or lamellar keratoplasty was the treatment of choice, but when the defect was too large and AMT surgery not feasible, emergency corneal graft was chosen.

Conclusion

NK frequency in our study was higher than that previously estimated, and an advanced Mackie stage was associated with worse outcomes and lower final CDVAs. Therefore, we plead for increased ophthalmologists' awareness of this disease, especially during its early stages. Pertinently, corneal sensitivity should be assessed for all eyes with superficial keratitis, corneal epithelial defect or ulceration. NK must be considered a disease requiring emergency intervention, and the diagnosis and etiology must be determined rapidly to optimally adapt therapeutic management. The place of new therapies, like topical nerve-growth factor, remains to be clarified and changes in the management of NK can be forseen. Concerning treatment, more data, especially long-term outcomes, are needed to evaluate risks and benefits.

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Declaration of competing interest

No conflicting relationship exists for any author.

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