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The THINK Study: Testing Hypoesthesia and the Incidence of Neurotrophic Keratopathy in Cataract Patients with Dry Eye

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Purpose: This study was designed to determine the frequency of neurotrophic keratopathy (NK) among patients presenting for cataract surgery consultation in a suburban US practice.

Methods: Patients presenting for cataract consultation were evaluated with corneal staining without anesthetic. Those with grade 1 or greater corneal stain and a tear breakup time (TBUT) of ≤10 underwent corneal sensitivity testing with a Cochet Bonnet esthesiometer. The study also evaluated patient SPEED score symptoms, corrected distance visual acuity (CDVA), corneal higher-order aberrations (HOAs), and conjunctival hyperemia.

Results: Among the 31 patients enrolled, mean corneal esthesiometry was 40 ± 9.5 mm (range 13 to 55). Esthesiometry of ≤40 mm, indicating neurotrophic keratopathy, was detected in 18 (58%, 95% CI 39–75%) patients. Corneal higher-order aberrations were significantly worse at 0.83 ± 0.22 μ in the group with NK vs 0.67 ± 0.16 among patients without NK ($P < 0.028$). A nonsignificant correlation was found between reduced corneal sensitivity and reduced symptoms. Older patients had slightly reduced sensation, but this trend was not statistically significant. No trend was seen between reduced sensation and either CDVA or corneal staining.

Conclusion: More than half of patients presenting for cataract evaluation with dry eye had stage 1 neurotrophic keratopathy. These patients had significantly worse higher-order aberrations than patients with normal sensitivity. Among patients with NK, symptoms were milder and age was higher, but neither trend was statistically significant. No trend was observed between corneal sensation and either corneal staining or CDVA.

Plain Language Summary: We performed this study to determine how common reduced corneal sensation is among patients who present for cataract surgery evaluation when they also have signs of dry eye. Fifty-eight percent of patients met criteria for Stage 1 reduced sensation, and they also had significantly more corneal irregularity than those without reduced sensation. Further study is needed to determine whether patients with reduced sensation should be treated differently from other dry eye patients when preparing their eyes for preoperative biometry.

Keywords: neurotrophic keratopathy, corneal sensation, dry eye, cataract surgery

Introduction

Ocular surface and dry eye disease (DED) affects as many as 30 million people in the United States, with prevalence and severity increasing with age.[1,2] Among patients presenting for cataract surgery in an observational study, 77% had signs of DED, of which only 25% had been previously diagnosed, and only 30% reported more than occasional symptoms.[3] Management of DED in these patients is commonly accomplished by artificial tears, warm compresses, and eyelid hygiene,[2] as well as immunomodulating drugs and can improve signs, symptoms (where they exist), and decrease higher-order aberrations, which leads to more accurate preoperative biometry and refractive outcomes.[4,5] Therefore, the identification of DED and its effective treatment is highly important for achieving patient satisfaction.

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The high prevalence of DED among patients presenting for cataract consultation along with the low rate of symptom complaints suggests that reduced corneal sensation may be present in this population. The finding of neurotrophic keratopathy among cataract patients with DED would be important because normalizing the ocular surface in neurotrophic keratopathy typically requires more aggressive intervention than typical DED. More advanced and necessary treatments may include serum tears, placement of amniotic membrane grafts, or recombinant human nerve growth factor.[6,7]

This study sought to determine the incidence of Stage 1 or greater neurotrophic keratopathy among patients presenting for consultation for cataract surgery with coexisting dry eye in a suburban US population.

Materials and Methods

This study was registered on ClinicalTrials.gov as NCT 06482164. It was also approved by WCG IRB (Puyallup, Washington) as study # 1372701 and adhered to both the Declaration of Helsinki and good clinical practices as defined by the US Food and Drug Administration. Dompé farmaceutici SpA provided funding for this study. Informed consent was obtained in writing from patients enrolled in this study.

This study involved consecutive patients who presented for cataract consultation to the author's private practice. As part of routine testing, patients underwent corneal fluorescein staining (CFS) prior to administration of anesthetic. When staining of grade 1 or greater (Oxford Scale)[8] was identified in at least one eye along with a TBUT ≤ 10seconds, patients who met the inclusion and exclusion criteria were invited to enroll in the study and provided informed consent in writing. Inclusion criteria included the following:

- Patients presenting for cataract consultation in the practice of the author.
- Central or inferior corneal fluorescein staining defined by the Oxford Scale
- Reduced tear break-up time (TBUT) ≤10 seconds.
- Able to comprehend and sign a statement of informed consent.
- Willing and able to complete all required testing.

Exclusion criteria included the following:

- Ocular surgery (eg, intraocular, oculoplastic, corneal, or refractive surgical procedure) performed within the last 3 months or at any time in the investigator's clinical judgment if it would interfere with the outcome measures of this study.
- Evidence of BAK or other chemical toxicity that, in the best judgment of the investigator, could cause reduced corneal sensitivity
- Concomitant use of daily contact lenses that, in the best judgment of the investigator, is causing reduced corneal sensitivity
- Clinically significant ocular trauma.
- Active or past ocular herpes simplex virus (HSV) or herpes zoster infection in the evaluated eye
- Ocular inflammation (uveitis, iritis, scleritis, episcleritis, keratitis, conjunctivitis).
- Ocular infection (eg, viral, bacterial, mycobacterial, protozoan, or fungal infection or the cornea, conjunctiva, lacrimal gland, lacrimal sac, or eyelids including hordeolum/stye).
- Active, systemic, or local disease condition that causes clinically significant ocular surface irritation such that it could interfere with the study findings.
- Moderate to severe (Grade 2–4) allergic, vernal, or giant papillary conjunctivitis.
- Inflammation of the eyelid (eg, blepharochalasis, staphylococcal blepharitis, or seborrheic blepharitis)
- Eyelid abnormalities that significantly affect the lid function (eg, entropion, ectropion, tumor, edema, blepharospasm, lagophthalmos, severe trichiasis, severe ptosis).
- Ocular surface abnormality that may compromise the corneal integrity (eg, prior chemical burn, recurrent corneal erosion, map dot fingerprint dystrophy, or the effect of any other ophthalmic medication that might in the opinion of the investigator compromise the ocular surface integrity).
- Participation in this trial in the same patient's fellow eye
- Patients who are under age 18, pregnant or breastfeeding, or who may become pregnant during participation in the study.

Further data collection included measurement of corneal sensitivity with a Cochet Bonnet corneal esthesiometer (Luneau Technology, Esthesiometer 12/100 mm, Ref 8630–1490-29, Pont-de-l'Arche, France), medical history, medications, concurrent illnesses, evaluation of dry eye symptoms with the validated standard patient evaluation of eye dryness (SPEED) questionnaire, evaluation of conjunctival hyperemia (Schulze Scale)[9] score, uncorrected distance visual acuity (UCDVA), manifest refraction and corrected distance visual acuity (CDVA), RMS corneal higher-order aberrations measured in the central 6.0 mm with a Pentacam (Oculus, Wetzlar, Germany).

Corneal sensitivity was tested in one eye, choosing the eye with the higher-grade corneal staining. If both eyes had similar staining severity, the right eye was tested. At the beginning of testing, the filament of the corneal esthesiometer was extended to 60 mm, and the filament was gently touched to the quadrant of the cornea with most prominent staining. Testing was repeated, reducing the filament length by 5 mm each time, until the patient reported feeling the touch of the filament on the eye. This testing was repeated in an area of the cornea outside the area of staining.[10] Sensitivity was recorded according to the longest length of filament that was detectable by the patient in either quadrant.

The widely accepted Mackie Classification System for neurotrophic keratopathy describes Stage I neurotrophic keratopathy as "epithelial irregularity most commonly in the form of punctate keratopathy without epithelial defect" when accompanied by a reduced corneal sensitivity.[11] Decreased corneal sensation was defined in this study as a reading of less than or equal to 4 cm in the quadrant of staining with a Cochet-Bonnet esthesiometer, based on previous studies which have used this threshold.[6,12,13]

Confidence intervals for binomial proportions were calculated using the normal approximation with a confidence interval of 95%. Standard deviations were calculated for parametric variables, and a Students *T*-test was used for calculation of significance of means.

Results

The study included 31 patients of average age 71 ± 8.8 (range 36–84) years. Of these, 19 (61%) were female. Four patients (12%) had diabetes or prediabetes that was reported as well controlled with no significant systemic complications, and our testing revealed that none of these patients had reduced corneal sensitivity. No patients wore daily contact lenses.

Among the 31 total enrolled dry eye patients, mean corneal esthesiometry was 40 ± 9.5 mm (range 13 to 55). Esthesiometry of ≤40 mm was detected in 18 (58%, 95% CI 39–75%) patients and ≤35 mm in 13 (42%, 95% CI 25–61%) of patients. Figure 1 shows the distribution of readings in 5 mm increments. Corneal staining of at least Grade 1

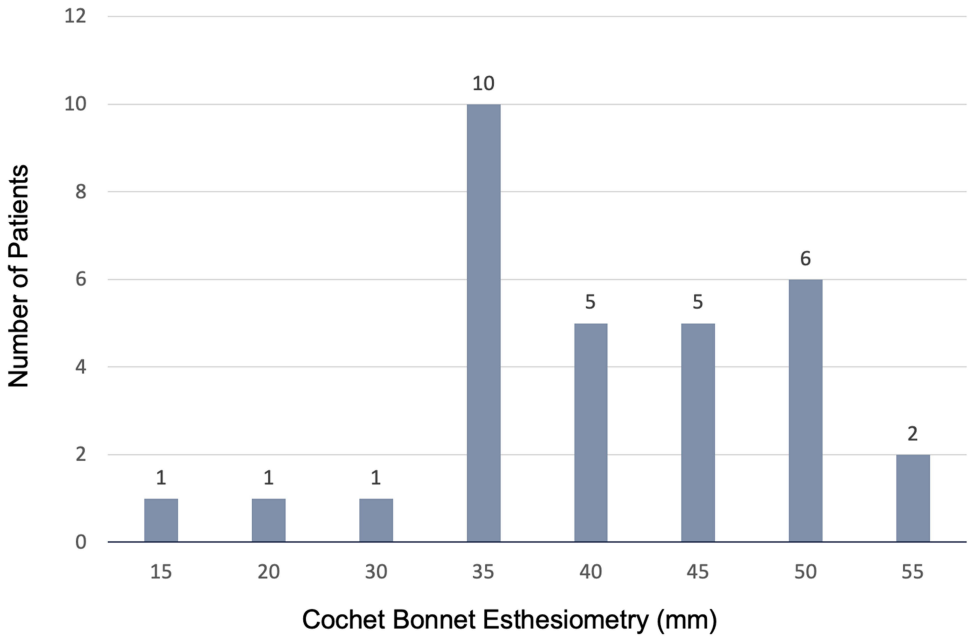

Figure 1 Distribution of corneal esthesiometry readings.

(Oxford Scale) was present in all patients as a condition of enrolling in this study. Thus, all patients with esthesiometry ≤40 mm would qualify for a diagnosis of at least Stage 1 NK by the Mackie Classification System.

Corneal staining was grade 1 in 9 (29%) patients, grade 2 in 19 (61%), and grade 3 in 3 (10%) patients. No patient had a full thickness epithelial defect or ulceration. Therefore, no patient in this study had Stage 2 or greater NK. Among all 31 patients enrolled, corneal staining did not show a consistent trend or correlation with corneal sensitivity (Figure 2).

Corneal higher-order aberrations in the central 6.0 mm were 0.83 ± 0.22 μ in the group with NK vs 0.67 ± 0.16 among patients without NK. This difference was statistically significant (P < 0.028, Student's *t*-test with two-tailed distribution). (Figure 3)

Age is correlated inversely and weakly with esthesiometry values, with a correlation coefficient of −0.09 (Figure 4).

The best-corrected visual acuity among these patients with cataract was 20/20 in 15 (48%) subjects, 20/25 in 4 (13%), and 20/30 or worse in 12 (39%) patients. Mean logMAR CDVA was 0.1 ± 0.14 (range 0 to 0.5) among patients with NK vs 0.15 ± 0.20 (range 0 to 0.7) among those with no NK (non-significant P < 0.38, Student's *t*-test). Likewise, a nonsignificant (P < 0.47, Chi-squared test) trend toward a lower incidence of NK among patients with worse BCVA

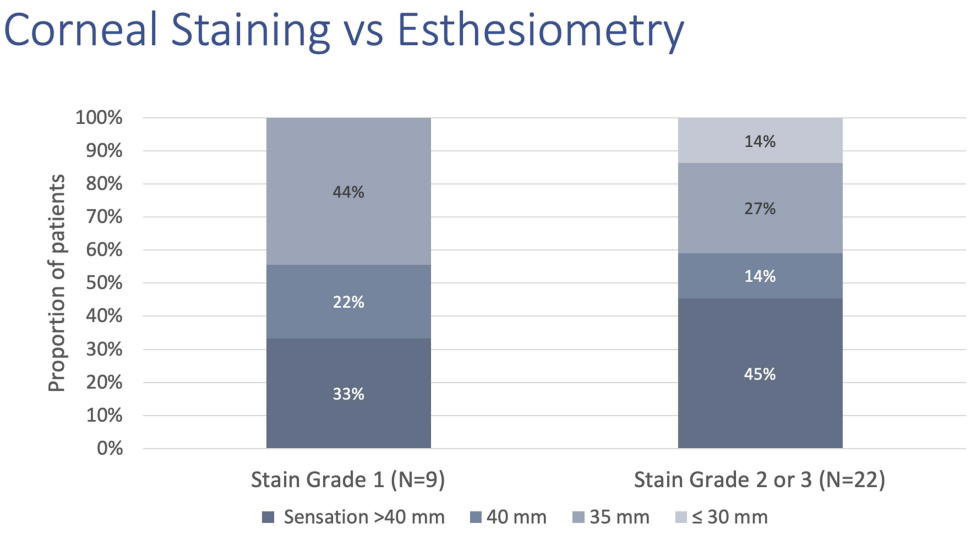

Figure 2 Those with more severe, grade 3 corneal staining showed a trend toward lower corneal sensitivity, but this was not statistically significant.

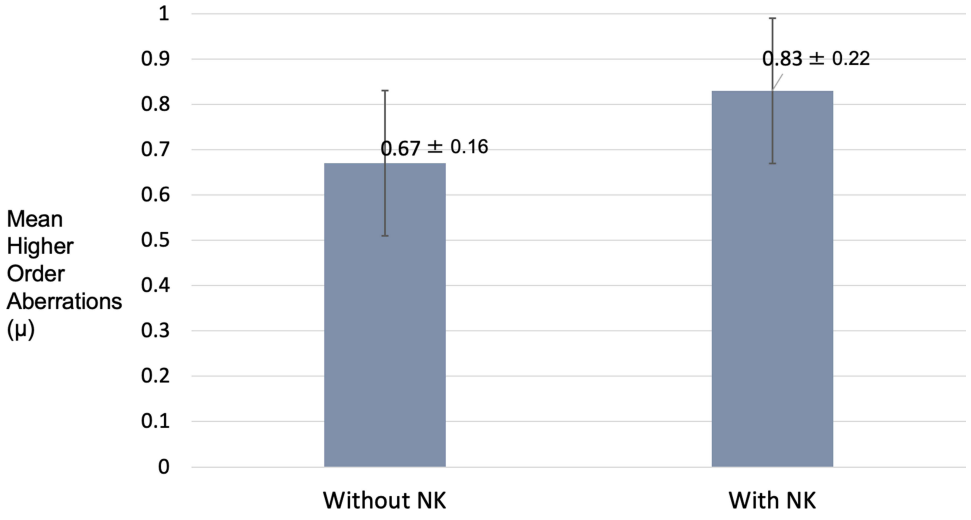

Figure 3 Corneal higher order aberrations were significantly worse among patients with NK.

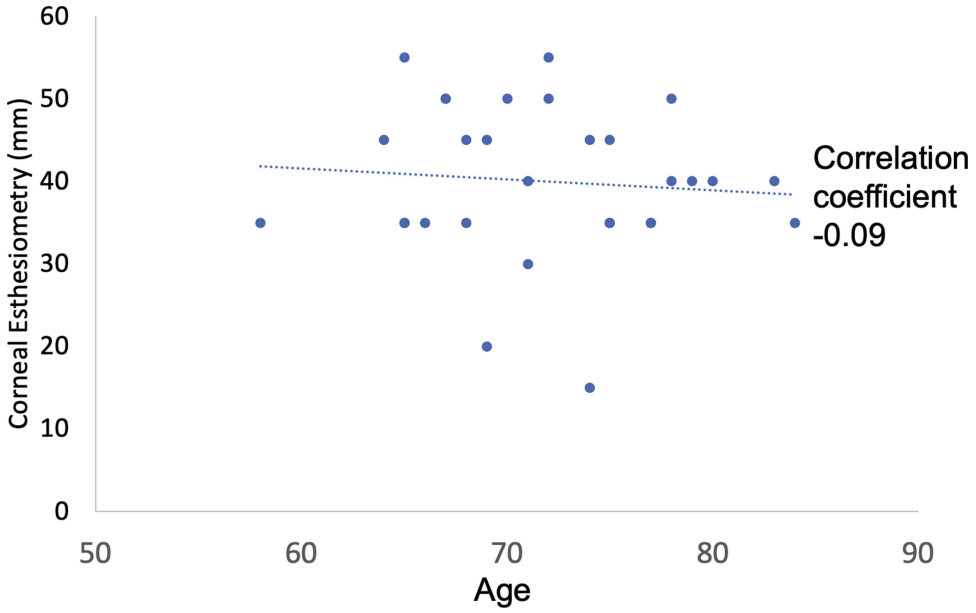

Figure 4 Age correlated inversely and weakly with esthesiometry values, with a correlation coefficient of −0.09.

was found with 5 of 12 (41%) patients with BCVA worse than or equal to 20/30 having NK vs 13 of 19 (69%) patients with BCVA better than 20/30 having NK.

SPEED questionnaires revealed no/mild DED symptoms scores of <8 in 10 (32%) patients, moderate symptom scores (8–10) in 11 (35%), and severe symptom scores (>10) in 10 (32%) of subjects. The prevalence of NK in these three groups was 60%, 73%, and 40%. These differences were not statistically significant.

Discussion

To our knowledge, this is the first paper describing the prevalence of neurotrophic keratopathy among patients with dry eye presenting for cataract surgery.

In recent years, the US FDA approval of cenegermin has raised awareness of reduced corneal sensitivity, which has been found as a more common comorbidity of DED than was previously expected.[13] The high incidence of NK in this study certainly raises questions for future study. Should NK testing should be considered in all cataract patients? Should dry eye treatment be altered when NK is found? If tested with in vivo confocal microscopy, would many of these patients show a loss of corneal nerve tissue? Should a special definition of NK apply when reduced corneal sensation is found in patients without known predisposing factors other than dry eye?

A number of conditions can be predisposed to NK, such as diabetes.[14.] In this study, four patients had diabetes, but none with NK. This study also attempted to exclude patients with as many predisposing conditions, such as HSV, daily contact lens wear, eyelid abnormalities, etc, as could be identified.

Testing for corneal sensitivity takes time and induces a mild degree of patient discomfort, though the latter is minimized with careful technique. This testing also must be performed prior to the administration of topical anesthetic, which means applanation tonometry, if it is desired, must be delayed until after the examination. This can create operational inefficiencies for some busy practices, and some may hesitate to perform sensitivity testing at the initial cataract visit. Delaying sensitivity testing until a later visit may be more efficient operationally but will delay the identification of this important diagnosis, which could otherwise guide DED treatment to be more aggressive.

Corneal staining severity did not correlate with the presence of NK in this study, suggesting that the underlying cause of the staining in these patients was DED rather than NK. While a larger study might reveal a more obvious trend, this lack of correlation suggests that clinicians should not rely on the severity of dry eye findings as a prompt to suspect NK.

In this study, the reduced CDVA did not correlate with the presence of NK. This is not surprising given that in a cataract population, the most important contributor to reduced CDVA would likely be lens opacity rather than corneal irregularity. Anticipating this, the design of this study included corneal higher-order aberrations as an outcome measure, which is a more sensitive indicator of corneal surface disruption than corrected visual acuity. Corneal HOAs were high in all enrolled patients, which would be expected in the presence of corneal staining from dry eye, which was an inclusion criterion for the study. And indeed the values for HOAs were significantly higher in eyes with NK.

The reduction of corneal sensitivity with advancing age has been well described in the past,[15] so an increased incidence of NK among older dry eye patients compared to a younger population is not surprising, even if the trend in this small study was not statistically significant. Still, the presence of NK in such a large proportion of enrolled patients suggests that this condition, previously considered uncommon, is worthy of attention among cataract patients.

Symptoms of dry eye correlated inversely with the presence of NK but not significantly. Directionally, this agrees with previous studies and implies that clinicians cannot rely on patient symptoms either to identify patients with either a dry eye or an NK diagnosis.[7]

No universal definition has been accepted for reduced corneal sensitivity as measured with a Cochet Bonnet esthesiometer.[16] However, for purposes of defining the Mackie Classification System stage 1 NK, this study needed a threshold. A number of studies have shown that a range of sensitivity of 5–6 cm is commonly seen in healthy corneas,[17,18] and others have shown that readings in the range of 2 to 4 cm were commonly observed in abnormal eyes.[19] Additionally, a number of drug registration studies with the US FDA[12,13] have used 4 cm as the threshold for reduced sensitivity, and this same level was chosen for this study.

The most commonly used clinical method for testing corneal sensitivity is with a thin wisp of cotton from a cotton tip applicator.[20] This method is simple, inexpensive, and fairly reliable, especially for comparing corneal sensitivity between fellow eyes, as is useful in cases of herpes simplex keratitis. A cotton wisp gives a less clear result when both eyes have reduced sensitivity, while a Cochet-Bonnet esthesiometer or other quantitative instrument might be better suited to screening cataract patients.

This study is not without limitations. The sample size of 31 patients precluded a more rigorous study of the significance of age, symptoms, and correlation with corneal staining. A larger study might also allow subgroup analysis to determine what subtypes of dry eye were most associated with NK. However, the primary purpose of this study—to measure the prevalence of NK in patients presenting for cataract evaluation with signs of DED—is adequately served even with a small patient cohort.

This study also did not examine the most effective treatment options for patients identified with NK, which will be the subject of further study, along with the timeline of how cataract surgery, once performed, affects corneal sensitivity.

Data Sharing Statement

Reasonable requests for de-identified patient data relating to the study findings will be available through the corresponding author for 5 years following the publication date.

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This paper is scheduled for presentation at the 2025 annual meeting of the American Society of Cataract and Refractive Surgery.

Disclosure

Dr John Hovanesian reports grants, personal fees from Dompe, during the conduct of the study; personal fees from Dompe, outside the submitted work. The author reports no other conflicts of interest in this work.

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