Research Square

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Prevalence and clinical characteristics of neurotrophic keratopathy in hispanic population in northeastern Mexico

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Abstract

Purpose

To evaluate the prevalence and clinical characteristics of neurotrophic keratopathy (NK) in northeastern Mexico.

Methods

Cross-sectional study in which NK patients admitted to our ophthalmology clinic between 2015–2021 were consecutively enrolled. Data regarding demographics, clinical characteristics, and comorbidities were collected at the time diagnosis of NK was made.

Results

In the period from 2015 to 2021, a total of 74,056 patients were treated and of these 42 had a diagnosis of neurotrophic keratitis. The prevalence found was 5.67 [CI95 3.95 ~ 7.38] in 10,000 cases. The mean age observed was 59 ± 17.21 years (Table 1), occurring more frequently in males in 59% and with corneal epithelial defects in 66.7% (Table 1). The most frequent antecedents were the use of topical medications in 90% (Table 1), the presence of diabetes mellitus 2 in 40.5% (Table 1) and systemic arterial hypertension in 26.2% (Table 1). A higher proportion of male patients with corneal alterations and a higher proportion of female patients with corneal ulcerations and/or perforation were observed (Table 2).

Conclusion

Neurotrophic keratitis is an underdiagnosed disease with a broad clinical spectrum. The antecedents that were contracted corroborate what was reported in the literature as risk factors. The prevalence of the disease in this geographical area was not reported, so it is expected to increase over time when searching for it intentionally.

Introduction

Neurotrophic keratitis (NK) is a degenerative corneal disease characterized by loss of trigeminal innervation causing hypoesthesia or a total loss of corneal sensitivity. The injury occurs due to damage to fibers of the ophthalmic nerve, decreasing local sensitivity to stimuli, causing a loss of functioning of autonomic protective reflexes, resulting in constant epithelial alteration with inability to regenerate [1].

NK is a disease of multiple etiology with diverse clinical manifestations, which causes its intentional search to be overlooked [2]. It has currently been classified as an orphan/rare disease (ORPHA137596), causing it to present no specific epidemiological data reported in the literature [3] A prevalence and

incidence of less than 5 per 10,000 inhabitants have been estimated based on data obtained from the diseases associated with its development. One of the most common is the development after herpetic keratitis and after surgical procedures. Worldwide, the incidence of herpetic keratitis is 6.8 per 100,000 inhabitants per year. In the US, the incidence of herpetic keratitis is 31.5 per 100,000 population per year and the prevalence is estimated at 150 per 100,000 population per year. The prevalence of patients who develop neurotrophic keratitis after herpetic keratitis is 149/100,000 [4]. Surgical ablation of the trigeminal ganglion can cause trigeminal nerve injury in 2.8% of patients, causing a prevalence of neurotrophic keratitis after surgery in 0.02/10,000 [5]. Regarding systemic diseases, no data reported in the literature have been found.

One of the characteristics of neurotrophic keratitis is decreased tear production [6, 7]. The purpose of tears is to provide a surface that allows regular light refraction, maintain the metabolism of the ocular surface, and lubricate the ocular surface to facilitate blinking. The tear components are water (98.3%), salts (1%), proteins/glycoproteins (0.7%), carbohydrates, lipids, and enzymes [8]. Within the tear proteins are immunoglobulins and neuropeptides that regulate the processes of proliferation, migration, and differentiation of corneal and conjunctival epithelial cells, in addition to presenting antimicrobial properties, stimulating lymphocytes and macrophages to secrete enzymes such as peroxidase, lactoferrin and lysozyme. The complex interactions between the corneal epithelium, tears, and nerve stimulation are essential for proper epithelial function and regeneration. Alterations in corneal sensitivity generate an imbalance in these complex relationships, producing the pathological changes observed in neurotrophic keratitis [9, 10, 11].

Clinical characteristics

Neurotrophic keratitis is usually the expression of congenital or iatrogenic systemic or ocular diseases culminating in damage to the fifth cranial nerve [1]. The most common causes of loss of corneal sensitivity are herpetic keratitis, chemical burns, use of contact lenses for prolonged periods, corneal surgery, ablative procedures for trigeminal neuralgia and systemic diseases including diabetes, multiple sclerosis, and leprosy. Clinically, its main characteristic is the absence of pain [12]. Among the antecedents to be investigated are previous corneal surgery, previous trauma, abuse of topical anesthetics, use of topical medications and contact lenses for prolonged periods. The symptoms reported are diverse and depend on the triggering antecedents, but the common denominator is dry eye symptoms and in conjunction with reduced visual acuity [13]. The diagnosis is based on the clinical history, intentionally looking for antecedents associated with trigeminal lesions, ulcers and decreased corneal sensitivity [14]. Comprehensive evaluation includes physical examination and the use of tests such as the sensitivity test, which is performed by touching the central and peripheral portion of the cornea with the Cochet-Bonnet anesthesiometer, which locates and quantifies the loss of corneal sensitivity in response to stimulation with a nylon thread (less than 5 mm is clinically significant hyposensitivity) [15]. Clinical classification is based on changes in corneal epithelium. There are many classifications and currently the most recent is the one proposed by Mastropasqua [16]. The severity is related to corneal sensory loss. The treatment will depend on its staging and is based on improving the

quality of the corneal epithelium based on the use of artificial tears and treating the underlying disease that caused it, however, there are currently multiple experimental treatments [17].

The objective of the study is to identify the prevalence of neurotrophic keratitis in the Hispanic population. Also, we wanted to determine the main clinical characteristics of patients with neurotrophic keratitis at the time of receiving ophthalmological clinical care, underlying diseases presented by patients with neurotrophic keratitis at the time of diagnosis, staging of the disease at the time of diagnosis of patients with neurotrophic keratitis and correlate the data obtained to find possible associations.

Method

An observational, descriptive, and cross-sectional study was carried out where data will be obtained from the clinical file of patients diagnosed with neurotrophic keratitis from the Institute of Ophthalmology and Visual Sciences at Hospital Zambrano-Hellion and the Integral Health Center of the Santos y de la Garza Evia foundation (CAM) in the period from March 2015 to November 2021. The inclusion criteria are patients with a diagnosis of neurotrophic keratitis, in an age range between 20 and 85 years, in any clinical stage and both sexes. Exclusion criteria were patients with a doubtful or uncertain diagnosis of neurotrophic keratitis. The variables to collect from the clinical file of patients diagnosed with neurotrophic keratitis are age, sex, medical history, symptoms, and clinical staging according to Mackie´s clinical staging system. For clinical purposes, Mackie´s clinical stages 1 and 2 were grouped into the superficial corneal alterations group and stage 3 was classified as the corneal ulcer/perforation group. General descriptive analyzes were performed using measures of central tendency and comparative analysis were performed using Student's T test or Mann Whitney for quantitative data and Fisher's test or χ^2 distribution for qualitative data. A p-value of < 0.05 was considered significant. The software used was IBM SPSS version 26.

Results

In the period from 2015 to 2021, a total of 74,056 patients were treated and of these 42 had a diagnosis of neurotrophic keratitis (Fig. 1).

The prevalence found was 5.67 [CI95 3.95 ~ 7.38] in 10,000 cases. The mean age observed was 59 years (**Table 1**), occurring more frequently in males in 59% and with corneal alterations in 66.7% (**Table 1**). The most frequent antecedents were the use of topical medications in 90% (**Table 1**), the presence of diabetes mellitus 2 in 40.5% (**Table 1**) and systemic arterial hypertension in 26.2% (**Table 1**). The associated clinical characteristics that were observed more frequently were visual acuity deficiency in 81% (**Table 1**) followed by foreign body sensation in 50% (**Table 1**).

Table 1. Clinical characteristics

		Mean	SD
Age		59	17.21
		N (42)	%
Sex	Female	17	40.50%
	Male	25	59.50%
Clinical staging	I	19	45.20%
	II	9	21.40%
	III	14	33.30%
Severity	Corneal ulceration and/or perforation	14	33.30%
	Superficial corneal alterations	28	66.70%
Eye	Right	15	35.70%
	Left	18	42.90%
	Both	9	21.40%
Diabetes Mellitus		17	40.50%
Systemic arterial hypertension		11	26.20%
Previous corneal surgery		8	19.00%
Topic medicine		38	90.50%
Contact lenses		3	7.10%
Herpes virus infection		8	19.00%
Eye redness		13	31.00%
Without ocular pain		33	78.60%
Visual acuity deficency		34	81.00%
Foreign body sensation		21	50.00%
Constant tearing		8	19.00%

A higher proportion of male patients with corneal alterations and a higher proportion of female patients with corneal ulcerations and/or perforation were observed (**Table 2**). Diabetes mellitus was observed more frequently in patients with corneal alteration **(Table 2).** Among the clinical characteristics, the absence of ocular pain and visual acuity deficiency were the most observed (**Table 2**).

Table 2. Comparison between clinical characteristics and superficial corneal alterations

		Corneal ulceration and/or perforation	Superficial corneal alterations	P
		M, DE	**M, DE**	
Age	Years	51.93 ±20.1	62.54 ±14.71	0.0587
		N, %	**N, %**	
Sex	Female	8, 57.14%	9, 32.14%	0.1836
	Male	6, 42.86%	19, 67.86%	0.1836
Clinical staging	I	0, 0%	19, 67.86%	
	II	0, 0%	9, 32.14%	0.0186
	III	14, 100%	0, 0%	
Eye	Right	6, 42.86%	9, 32.14%	0.5159
	Left	7, 50%	11, 39.29%	0.5298
	Both	1, 7.14%	8, 28.57%	0.2302
Diabetes mellitus		2, 14.29%	15, 53.57%	0.0204
Systemic arterial hypertension		1, 7.14%	10, 35.71%	0.0668
Previous corneal surgery		1, 7.14%	7, 25%	0.2328
Topic medicine		14, 100%	24, 85.71%	0.2829
Contact lenses		2, 14.29%	1, 3.57%	0.2537
Herpes virus infection		4, 28.57%	4, 14.29%	0.4064
Eye redness		6, 42.86%	7, 25%	0.298
Without ocular pain		10, 71.43%	23, 82.14%	0.4508
Visual acuity deficency		11, 78.57%	23, 82.14%	0.9999
Foreign body sensation		6, 42.86%	15, 53.57%	0.7442
Constant tearing		4, 28.57%	4, 14.29%	0.4064

Discussion

NK is a disease with a prevalence of less than 5 cases/10,000 population, being more precise than 4.2 cases/10,000 inhabitants, although it should be noted that the exact incidence and prevalence are not yet available in the literature, and that even these approximations seem to overestimate the real numbers. [3] In fact, said prevalence was estimated and extrapolated from the available evidence regarding the conditions most associated with said pathology, being reported as low as 1.6 cases/10,000 inhabitants, with respect to estimates on herpetic keratitis (1.22/ 10,000) and the post-surgical state with damage to the trigeminal nerve (0.02/10,000) [2]. Currently, neurotrophic keratitis develops on average in 6% of herpetic keratitis, which in turn have a prevalence of 149/10,000 [4] as well as in 12.8% of herpes zoster keratitis, the latter presenting a prevalence of 26/100,000 [5]. Other common causes are neurosurgical procedures to treat neuralgia of the trigeminal nerve, which tends to damage said nerve in 2.8% of cases, with a prevalence of 1.5/10,000 and therefore the previously mentioned estimated prevalence (0.02/10,000) [1]. Unfortunately, there is still no evidence in the literature on the incidence and/or

prevalence of other common associated conditions such as chemical burns, diabetes, contact lens wear, as well as less frequent associated causes such as intracranial masses, space occupants, multiple sclerosis, or leprosy [12, 18]. A recent retrospective, observational study at an ophthalmology center in Paris, France screened more than 300,000 patients and reported an incidence of 11/10,000 patients. [19]. Similar to what has been reported in the literature was found in our population. Likewise, age was also expected from what was reported. It is important to mention that the antecedent that occurred most frequently was the use of topical medications, which represents an important focus of attention for treating physicians since these patients could present a higher risk of developing neurotrophic keratitis.

Any condition that alters the innervation of the trigeminal nerve towards the cornea at any of the levels of this circuit, from the nucleus to the free nerve endings, can eventually generate neurotrophic keratitis, an entity with specific diagnostic characteristics and totally independent of the basic medical history of the patient at that time [3], and it can include causes as diverse as those concerning ocular surface diseases, systemic pathologies and both peripheral and central nerve damage [2, 20]. The most common causes of neurotrophic keratitis are attributed to both herpes simplex virus as well as herpes zoster virus with a proportion ranging from 27–32% of cases [6, 7, 8]. In our population we found a higher proportion of herpes virus infection, with 19% of patients diagnosed with neurotrophic keratitis. Other local conditions associated with this disease are chemical, thermal, and traumatic ocular burns, the use of contact lenses, corneal dystrophies, and the chronic use of topical medications such as anesthetics, beta-blockers, antivirals, antibiotics, NSAIDs and glaucoma treatment [2, 17]. Surgical procedures that involve the cornea, such as refractive surgery, keratoplasty and its derivatives, and cataract surgery, are also associated with their respective alteration to the trigeminal innervation of the treated area [9, 10, 20]. In addition, therapeutic surgeries for trigeminal neuralgia are strongly related to the disease, such as microvascular decompression, balloon compression, radiofrequency thermocoagulation, and gamma laser knife radiosurgery.

NK is a chronic disease with an insidious evolution, which is interesting due to the diversity of clinical characteristics it presents. In our study population, it was found that 40% of patients with neurotrophic keratitis had a history of diabetes mellitus, which is important to keep in mind when treating this disease. Regarding the progress of the disease, it is important to keep in mind the clinical variety of presentation. We found the absence of eye pain, redness and constant tearing as clinical symptoms associated with the progress of the disease, which is consistent with what is reported in the literature [20], so this pathology should be sought intentionally when encountering the clinical symptoms described above. One of the limitations of this study is the size of the sample, which although it exceeds what was expected, could be increased even more if the registry of patients from both public and private hospitals in the locality is analyzed.

Conclusion

Neurotrophic keratitis is an underdiagnosed disease with a broad clinical spectrum. The antecedents that were contracted corroborate what was reported in the literature as risk factors. The prevalence of the

disease in this geographical area was not reported, so it is expected to increase over time when searching for it intentionally.

Abbreviations

ACh: Acetylcholin

NK: Neurotrophic keratitis

SP: Substance P

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of School of Medicine and Health Sciences of Monterrey Institute of Technology and Higher Education (October 5, 2021/No. **P000581-PQN3543-CEIC-CR002**).

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Figures

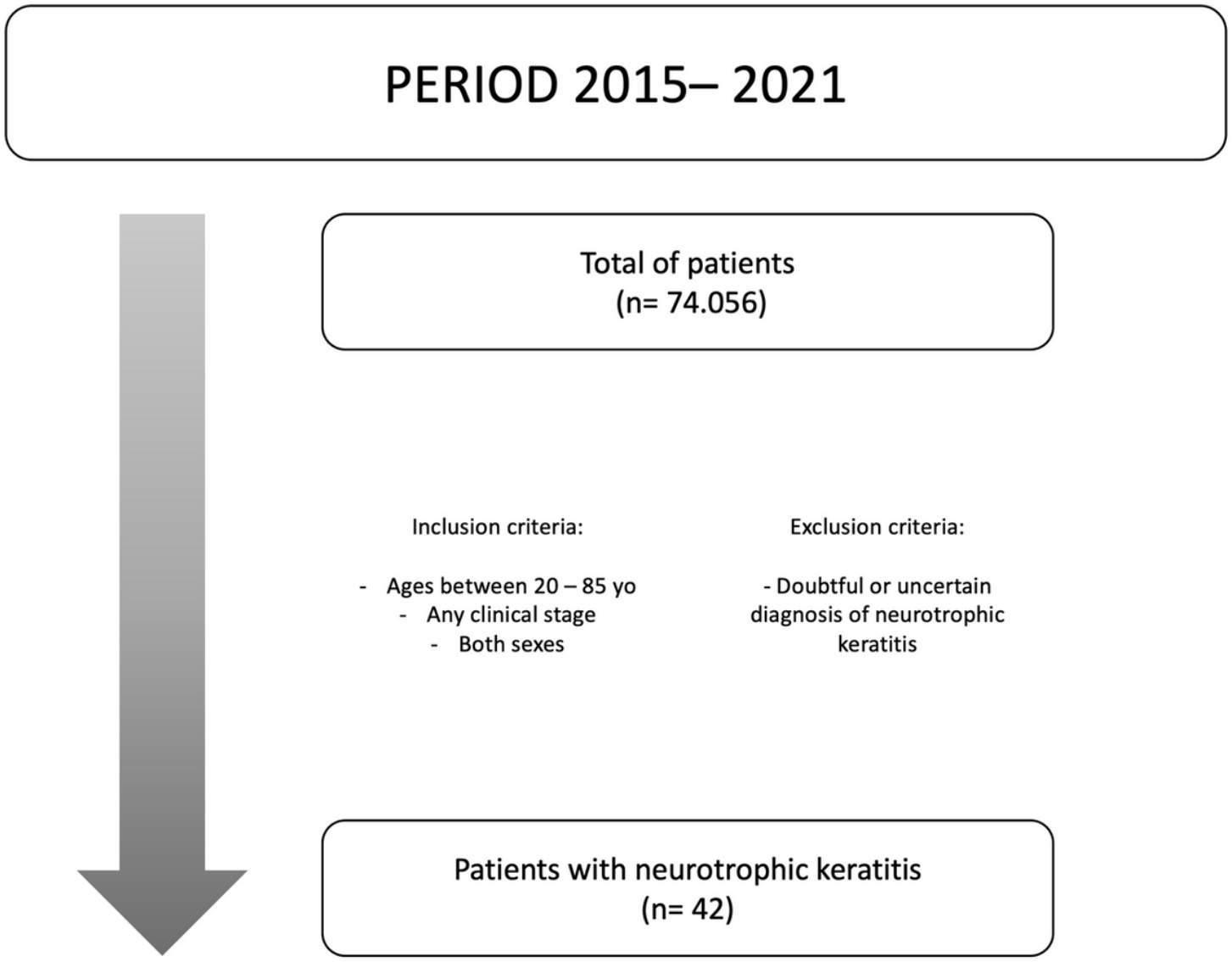

Figure 1

Patients included in the study