Corneal epitheliopathy under diagnosed: toxic, nutritional and diabetic epitheliopathy

Epiteliopatías corneales subdiagnosticadas: epiteliopatías tóxica, nutricional y diabética

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Abstract

There are many causes of corneal epitheliopathies, however, the rare causes are underdiagnosed due to the little knowledge that exists about them. Among these the most frequent is undoubtedly the toxic epitheliopathy, due to the misuse or treatment of some topical medication, exerting its toxic effects directly to cause a superficial punctate keratopathy, or indirectly causing inflammation and interfering with the migration of the epithelial limbal cells. There is a wide range of agents that can cause toxic epitheliopathy, the most known benzalkonium chloride (BAK), highly toxic to the corneal epithelium, strongly associated with toxic epitheliopathy, allergic conjunctivitis and blepharitis. There have been described toxic epitheliopathies secondary to chemotherapy specifically with monoclonal antibodies that inhibit the epidermal growth factor receptor (EGFR). The epitheliopathy secondary to vitamin A deficiency is a very important clinical aspect in this pathology, causing an instability of the precorneal tear layer causing a punctate epitheliopathy, which can progress to epithelial defects, stromal edema and keratinization. Diabetes mellitus can lead to several ocular complications, among which is the diabetic epitheliopathy that includes superficial punctate keratopathy and persistent epithelial defects, having an important clinical impact due to the symptoms produced from foreign body sensation to visual impairment. It is important to know this entities for its proper diagnosis and treatment. Search intentionally in ophthalmological practice in cases of persistent epitheliopathies or treatment resistant.

Key words: Corneal Epithelium. Benzalkonium Compounds. Allergic Conjunctivitis. Blepharitis. Inflammation. Diabetes Mellitus.

Resumen

Existen muchas causas de epiteliopatías corneales; sin embargo, las causas poco frecuentes son infradiagnosticadas debido al poco conocimiento que existe acerca de ellas. Dentro de éstas la más frecuente es, sin duda, la epiteliopatía tóxica, debida al mal uso o sobretratamiento de alguna medicación tópica. Ejerce sus efectos tóxicos directamente ocasionando una queratopatía punteada superficial o indirectamente provocando inflamación e interfiriendo en la migración de células basales epiteliales del limbo. Existe un amplio rango de agentes que pueden provocar epiteliopatía tóxica, el más conocido de los cuales es el cloruro de benzalconio (BAK), altamente tóxico en el epitelio corneal y fuertemente asociado con epiteliopatía tóxica, conjuntivitis alérgica y blefaritis. En la literatura se han reportado epiteliopatías tóxicas secundarias a quimioterapias específicamente con anticuerpos monoclonales que inhiben el receptor del factor de crecimiento epidérmico (EGFR). En cuanto a las causas nutricionales, la epiteliopatía secundaria a deficiencia de vitamina A es un aspecto clínico muy

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Date of reception: 04-10-2017

Date of acceptance: 20-02-2018

DOI: 10.24875/RMOE.M18000024

Available online: 16-07-2018

Rev Mex Oftalmol (Eng). 2018;92(4):145-151

www.rmo.com.mx

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importante en esta enfermedad, que ocasiona una inestabilidad de la capa lagrimal precorneal provocando una epiteliopatía punteada, que puede progresar a defectos epiteliales, edema estromal y queratinización. La diabetes mellitus (DM) puede llevar a varias complicaciones oculares, entre las cuales se encuentra la epiteliopatía diabética que comprende la queratopatía punteada superficial y defectos epiteliales persistentes, con un impacto clínico importante debido a los síntomas que produce, desde sensación de cuerpo extraño hasta baja visual. Es importante conocer este tipo de enfermedades para su adecuado diagnóstico y tratamiento. Deben buscarse intencionadamente en la práctica oftalmológica en los casos de epiteliopatías persistentes o refractarias al tratamiento convencional.

Palabras clave: Epitelio corneal. Compuestos de benzalconio. Conjuntivitis alérgica. Blefaritis. Inflamación. Diabetes mellitus.

Introduction

Corneal epitheliopathy has a diverse range of causes and clinical presentations that generate a challenge in the ophthalmological practice. Uncommon causes are under-diagnosed due to little awareness. Therefore, it is very important to recognize and diagnose them in a timely manner for an effective treatment.

Toxic epitheliopathy

Topical medication is a very specific treatment in ophthalmological clinical practice. Ophthalmic drops have several factors that can affect the ocular surface. Because the volume of a drop is too high for the conjunctival sac, the components of the tear, including electrolytes, proteins and mucin, are removed from the tear film. These drops can also alter the pH and osmotic pressure. In addition, it is known that they inhibit the proliferation, regeneration and renewal of the corneal epithelium¹.

Self-medication is a common practice in Mexico, especially in people of low socioeconomic status who rarely seek a specialist for proper management of their medical problems. In addition to this, some patients borrow topical medications from relatives or friends. When they apply them and obtain unfavorable results, patients seek professional help.

It has been shown that the risk of having adverse drug reactions is related to the number of prescribed medications². Consequently, the use of multiple medications increases the probability of drug interactions, toxicity, and combinations that may be synergistic. However, the ophthalmologists may be the culprits of the overtreatment of patients, with certain topical medications that can have deleterious effects on ocular tissues.

Pathophysiology

A toxic substance can be defined as any substance that due to its chemical reaction causes structural

damage or alteration in the function, above any therapeutic effect³. Drugs can be directly toxic to the corneal epithelium, damaging its structure and altering its function, accompanied or not by an inflammatory response⁴. Most of these drugs exert their toxic effects through multiple proposed mechanisms: directly by causing superficial punctate keratopathy or indirectly causing inflammation as ring-like stromal infiltrates in cases of overuse of anesthetics or anti-inflammatories⁵. Some topical medications may interfere with the migration of limbal basal epithelial cells, especially if epithelial defects exist, causing a delay in epithelialization and promoting stromal infiltrates.

Ophthalmic drops are composed of the active drug, as well as preservatives and buffer solutions. BAK has been used as a conservative for many years⁶. It is very soluble in water and easy to handle. Because BAK has a strong antibacterial activity, these drops can be safe for very long periods. However, BAK is highly toxic to the corneal epithelium and is strongly associated with toxic epitheliopathy and allergic conjunctivitis or blepharitis⁷.

Toxicity induced by ophthalmic drugs

Toxicity to the corneal epithelium secondary to topical medications commonly occurs after the use of antiglaucoma drugs, anesthetics and, to a lesser extent, topical antibiotics^{5,8} (Fig. 1).

Non-steroidal anti-inflammatory drugs (NSAIDs) can also cause severe ocular surface complications⁹. There is a wide range of agents that can cause toxic epitheliopathy; however, there are some known specifically for this characteristic, including antibiotics such as aminoglycosides (neomycin and gentamicin), fluoroquinolones (especially ciprofloxacin), ocular hypotensives (especially timolol and dorzolamide), NSAIDs (particularly diclofenac) and topical anesthetics. Ophthalmic preservatives such as thimerosal and BAK have been extensively associated with toxic epitheliopathy. While thimerosal is no longer contained in most ophthalmic

Figure 1. Slit lamp photograph of the corneal surface (A) and with fluorescein staining (B) of a patient with toxic epitheliopathy secondary to topical drops of 0.3% ciprofloxacin (image taken from the photographic archive of the Cornea and Refractive Surgery Department of the Institute of Ophthalmology “Fundación Conde de Valenciana”).

drugs and contact lens solutions in the US, BAK is the most commonly used conservative in ophthalmic drugs, despite its recognized hypersensitivity potential⁴.

Toxicity secondary to other causes

There may be a toxic epitheliopathy because of accidental or unwanted contact of caustic substances with the ocular surface. This variety ranges from substances that can be found at home (chlorine, ammonium, alcohol and kerosene) to chemical weapons (pepper spray [*Oleoresin capsicum*] or tear gas [ortho chloro-benzylidene malononitrile]) and toxic substances produced by animals or plants (poison, plant and animal toxins)^{2,10}. These agents are less likely to cause a simple type I hypersensitivity reaction and more commonly cause damage to the epithelial cells due to direct toxicity, followed by secondary inflammatory effects¹¹.

In the literature, epitheliopathies and corneal perforations secondary to chemotherapy have been reported, specifically with monoclonal antibodies that inhibit EGFR, a transmembrane protein with a domain for the binding of the extracellular ligand associated to an intracellular protein tyrosine kinase, which regulates proliferation, differentiation, migration and cellular apoptosis. This treatment is used in carcinomas refractory to treatment or in patients intolerant to chemotherapy. Due to the increased interest in new chemotherapies, it is important that ophthalmologists recognize and manage the potential side effects of these treatments¹².

Clinical features

There is a wide variety of corneal manifestations associated with toxic keratitis, ranging from minimal

punctate epitheliopathy to corneal ulceration and necrosis.¹³ Patients often recognize a causal agent, and report a history of inadvertent (cleaning chemicals) or intentional (instillation of a topical medication) eye contact.

Toxic epitheliopathy can be uni- or bilateral and affect any individual, regardless of age, race or gender. Patients may commonly present some degree of ocular discomfort, which may manifest as itching, burning, photophobia, foreign body sensation or pain. Blurred vision and tearing are also often associated with this entity¹⁴.

The classic clinical finding is punctate epitheliopathy, which may or may not be confluent and show a specific pattern by fluorescein staining, predominantly in the inferonasal quadrant, where the maximum contact time between the drug and the ocular surface occurs¹³ (Fig. 2). Filamentous keratopathy or pseudo dendrites are also observed in some cases¹⁵.

The corneal epithelium can be opaque and edematous, and sometimes a hurricane keratopathy may be observed¹⁶. In more advanced cases, occasionally a spiral pattern is observed (vortex keratopathy) (Fig. 3). Severe or prolonged exposure can lead to persistent epithelial defects, ulcerative keratitis (Fig. 4), corneal thinning and perforation^{13,17}.

Diagnosis

There are several tests designed to evaluate the toxic effects of ophthalmic preparations on the ocular surface, but most of them are not practical, not available or difficult to perform in the clinical context¹⁸.

Impression cytology

Impression cytology with topical anesthesia provides a homogenous cell layer for histological studies with an almost intact architecture and preserved cell junctions. Immunostaining protocols are able to differentiate epithelial, goblet and inflammatory cells. In addition, they can be used for cytometry analysis. Some studies have shown that the HLA-DR (human leukocyte antigens) class II antigens and IL-(interleukin) 6, 8 and 10 are highly expressed in the conjunctival epithelium of patients with history of prolonged antiglaucoma treatment¹⁹.

The diagnosis of toxic epitheliopathy is commonly based on the clinical history and evolution of the disease, as well as on current clinical manifestations. It should be taken into consideration as a differential

Figure 2. Fluorescein corneal staining with cobalt blue filter of a patient with toxic epitheliopathy secondary to difluprednate, showing inferonasal location (*image taken from the photographic archive of the Cornea and Refractive Surgery Department of the Institute of Ophthalmology "Fundación Conde de Valenciana"*).

Figure 4. Slit lamp photograph of an ulcer secondary to prolonged use of topical tetracaine hydrochloride (*image taken from the photographic archive of the Cornea and Refractive Surgery Department of the Institute of Ophthalmology "Fundación Conde de Valenciana"*).

Figure 3. Slit lamp photograph with diffuse illumination of the corneal surface of a patient with vortex keratopathy associated to systemic amiodarone (*image taken from the photographic archive of the Cornea and Refractive Surgery Department of the Institute of Ophthalmology "Fundación Conde de Valenciana"*).

diagnosis when patients report initiating a new ophthalmic treatment, cosmetic agent or contact lens product in the previous weeks²⁰.

Treatment

When establishing a toxic agent, the most important consideration for treatment is to discontinue the substance or causal drug. Treatment will depend on the time of exposure, as well as the severity of the ocular surface disease. The drug must be discontinued, if possible, or replace it with preservative-free formulations. Contact lenses should be used with caution, as they

can act as a toxic reservoir. In case of moderate illness, preservative-free lubricants can be used to alleviate symptoms. A topical steroid can be used in most symptomatic patients¹³. A more advanced disease such as a persistent epithelial defect may require other types of procedures such as tarsorrhaphy, amniotic membrane graft or conjunctival flaps. Keratoplasty may be an option for corneal ulcerations with impending risk of perforation or necrosis²¹.

Nutritional epitheliopathies

Introduction

Nutrition-related corneal diseases have been recognized for a long time and are a very common cause of new cases of blindness every year.

Manifestations of vitamin A deficiency remain the leading cause of childhood blindness in developing countries²². The deficiency of this fat-soluble vitamin or its metabolites manifests in two ways: night blindness and a spectrum of ocular disorder known as xerophthalmia, including epidermal keratinization and squamous metaplasia of the cornea and conjunctiva²³. Epitheliopathy secondary to vitamin A deficiency is a very important clinical aspect in this disease.

For a long time vitamin A has been recognized for improving skin healing. Numerous studies have shown that it accelerates epithelial migration and the formation of granulation tissue, and reverses the delay in healing induced by corticosteroids^{24,25}.

Clinical features

Vitamin A deficiency promotes instability of the pre-corneal tear film that causes punctate epitheliopathy, which can progress to epithelial defects, keratinization and stromal edema²³. Without treatment, epithelial defects progress to partial or full-thickness ulcerations and may predispose to bacterial infections. Keratomalacia is a full-thickness liquefactive necrosis of the cornea that, together with vitamin A deficiency, is frequently associated with a preceding systemic factor such as measles or severe protein malnutrition.²⁶

When the disease is active, the cornea may have a ground-glass appearance on retro illumination (Fig. 5). This is more prominent in areas of dense punctate keratopathy, the same sites where the tear film break-up time is shorter. Dense, irregular patches suggesting an agglomeration of bacteria or fragmented keratin can be observed, as in Bitot's spots. Plaques, xerosis, and corneal opacity usually occur in both eyes (Fig. 6).

Treatment

Recommended treatments include 0.01-0.1% trans retinoic acid^{27,28}. Effectiveness does not increase with higher doses (0.25%)²⁹. By increasing the dose and frequency of application, the likelihood of developing Meibomian gland dysfunction and blepharoconjunctivitis also increases, although this is reversible after discontinuing retinoic acid. Studies have shown that treatment must start with three or four applications per day, decreasing up to once a day or every two days as symptoms improve (usually in 2-3 weeks)³⁰.

Diabetic epitheliopathy

Introduction

DM can lead to several ocular complications, among which diabetic epitheliopathy encompasses superficial punctate keratopathy, recurrent corneal erosions and persistent epithelial defects³¹ (Fig. 7). In addition to this, most diabetic patients suffer from dry eye syndrome.

In some cases, diabetic epitheliopathy is difficult to treat and can induce abnormalities in the quantity and quality of tear secretion, a decrease in corneal sensitivity and poor adhesion of regenerated epithelial cells³².

Clinical features

Corneal diseases are a common condition that include several alterations, especially epithelial and

Figure 5. Corneal surface photograph showing a ground-glass appearance on retro illumination in a patient with an epitheliopathy secondary to vitamin A deficiency (image taken from the photographic archive of the Cornea and Refractive Surgery Department of the Institute of Ophthalmology "Fundación Conde de Valenciana").

Figure 6. Ocular surface photograph of a patient with vitamin A deficiency and a diagnosis of xerophthalmia (image taken from the photographic archive of the Cornea and Refractive Surgery Department of the Institute of Ophthalmology "Fundación Conde de Valenciana").

endothelial. Corneal epitheliopathy manifests as punctate keratitis, decreased adherence to the basement membrane and corneal hypoesthesia. It is of clinical interest due to the symptoms it produces: foreign body sensation, red eye, pain and visual fluctuations³³.

The most important damage to the cornea occurs in the cells of the epithelial basement membrane (with regenerative abilities). The diabetic cornea also suffers

Figure 7. Slit lamp photograph with diffuse illumination of the corneal surface showing a persistent epithelial defect of a patient with uncontrolled type 2 DM (image taken from the photographic archive of the Cornea and Refractive Surgery Department of the Institute of Ophthalmology "Fundación Conde de Valenciana").

from nerve dysfunction, which contributes to the epitheliopathy. Limbal stem cells are also affected in sustained hyperglycemia, which hinders the normal regeneration of the epithelium.

The decrease in corneal sensitivity contributes to the severity of dry eye and predisposes patients to corneal trauma, which entails an increased risk of developing neurotrophic corneal ulcers and can adversely affect corneal healing³⁴.

Diagnosis

In the literature, some researchers describe that in diabetic patients corneas have a tendency to show a statistically significant higher central thickness,³⁵ due to pleomorphism and polymegatism compared to corneas of patients without DM.

Treatment

Diabetic epitheliopathy can be treated with lubricants, antibiotics, therapeutic contact lenses and tarsorrhaphy; all this treatments generate favorable conditions for healing. Failures of conventional methods to improve epithelial repair relate to greater symptoms of pain and discomfort in patients and they also provide an opportunity for infections that can lead to devastating visual problems. Furthermore, none of these therapies aims at the pathophysiology of the delay in corneal

reepithelialization secondary to DM, which is why metabolic control of the patient is essential³⁶.

Some studies have shown that growth factors and cytokines can significantly improve epithelialization (epithelial proliferation and migration) and, consequently, accelerate epithelial healing. More recently, improvement and a significant increase in healing corneal rate were demonstrated with the topical administration of insulin, naltrexone and nicergoline³⁷.

Conclusion

There are several causes of corneal epitheliopathy, so it is important to consider the most frequent ones for proper diagnosis and treatment. Among the rare causes of corneal epitheliopathy are the toxic, nutritional and inflammatory, from which diabetic epitheliopathy is the most important one. These conditions must be intentionally sought out in ophthalmological practice in cases of persistent epitheliopathies or those refractory to conventional treatment.

The ophthalmologist must be aware and identify these causes for proper management and to avoid complications that can affect vision irreversibly.

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