REVIEW ARTICLE

Allergic conjunctivitis

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Received: 09/06/2022 - Approved: 12/11/2022

ABSTRACT

Introduction: allergic conjunctivitis is a group of diseases that affect the conjunctival surface and are associated with type I hypersensitivity reactions generated by various allergens to which the affected individual reacts, after sensitization to it.
Objective: to review this disease in order to gather criteria and treatments and to guide in the integral management of this health problem.
Methods: a search was made with the keywords allergic conjunctivitis, hypersensitivity, diagnosis and treatment. Scientific journals were consulted in academic Google and in scientific literature databases.
Conclusions: allergic conjunctivitis is a worldwide public health problem and is a very frequent disease that increases its incidence in combination with an increase in atopy. The importance of a good control of the ocular allergic process lies in the impact it has on the quality of life of patients because it affects sleep, work and school activities, social interactions and the psychological state of the patient.
Key words: allergic conjunctivitis; hypersensitivity; diagnosis; treatment

RESUMEN

Introducción: la conjuntivitis alérgica constituye un grupo de enfermedades que afectan la superficie conjuntival y que están asociadas a reacciones de hipersensibilidad tipo I y generadas por diversos alérgenos a los que el individuo afectado reacciona, previa sensibilización con el mismo.
Objetivo: realizar una revisión sobre esta enfermedad que permita reunir criterios y tratamientos y orientar en el manejo integral de este problema de salud.
Métodos: se realizó una búsqueda con las palabras clave conjuntivitis alérgica, hipersensibilidad, diagnóstico y tratamiento. Se consultaron revistas científicas en Google académico y en bases de datos de literatura científica.
Conclusiones: la conjuntivitis alérgica es un problema de salud pública a nivel mundial y es una enfermedad muy frecuente que aumenta su incidencia en combinación con un incremento de la atopía. La importancia de un buen control del proceso alérgico ocular radica en el impacto que tiene en la calidad de vida de los pacientes debido a que afecta al sueño, a las actividades laborales y escolares, a las interacciones sociales y al estado psicológico del paciente.
Palabras clave: conjuntivitis alérgica; hipersensibilidad; diagnóstico; tratamiento

INTRODUCTION

Ocular allergy is a disease characterized by an inflammation that directly affects the conjunctiva, which is a thin mucous membrane that covers and lines the ocular surface, except for the cornea, thus providing the eye with a primary barrier against environmental, chemical and infectious allergens.[1,2]

The conjunctiva is made up of three parts: the first is the palpebral conjunctiva, which covers the inner part of the eyelids, in which there are small elevations called papillae; the second, called ocular or bulbar conjunctiva, which covers the anterior portion of the eyeball and is attached to the sclera and the third part is the fundus of the conjunctival sac, which is the intermediate portion that forms a very loose fold that ensures the mobility of the eye, it is very rich in blood vessels, which explains its tendency to swelling and, in this portion, the tear ducts open and by two layers: a basal and a superficial one. The superficial layer is formed by three layers of cells: the first deep, by cylindrical cells; the second is the middle, by polygonal cells and the third, superficial, by squamous cells, which have microvelloci on their free surface. Among the conjunctival epithelium are scattered mucus-secreting cells that preserve the humidity, surface tension and stability of the lacrimal layer[2].

Allergic conjunctivitis, although it is not a serious condition or an ophthalmologic emergency, has become a very frequent disease in Ophthalmology Offices; its evolution and response to treatment sometimes make them patients with a long stay in the office and difficult to manage, even with levels of dissatisfaction due to the time of treatment.

The first to define allergic conjunctivitis as a clinical disease was the Englishman Bortock, in 1819. Almost a century later, in 1928, Mac Culloch associated this condition with hay growers, but it was not until the 1940s that, thanks to the work of several groups of French, German and North American researchers, the concept of allergy was definitively detached from the infectious origin to which it had been linked until then. Vernal conjunctivitis was described by Arlt in 1846 and was characterized as a clinical disease in 1876 by Saenrsch, who called it spring catarrh due to its periodicity.[3] It is an ophthalmoreaction at conjunctival level that frequently accompanies asthma, rhinitis and other allergic diseases, but can also be an isolated disease.[4] It is an allergic disease that is becoming increasingly common.

It is an increasingly common allergic disease, with the same clinical severity as asthma and allergic rhinitis. Epidemiological studies of allergic conjunctivitis are scarce, despite its frequent association with other diseases of this type.[5]

In recent decades it has been documented that the prevalence of allergic diseases has increased considerably. It is estimated that about 30% of the population has allergic symptoms and of these 40 to 80% may have ocular symptoms. The prevalence is considered to be higher in Western countries than in Asia or Africa.[1]

In the pediatric population atopic diseases range from 25 to 30%, among them atopic dermatitis (15 to 20%), asthma (seven to 10%) and rhinitis and conjunctivitis (15 to 20%).[6]

Allergic conjunctivitis is present in 30 to 71% of patients with allergic rhinitis and has been estimated in six to 30% of the general population and up to 30% of children, with or without association with allergic rhinitis.[5]

The term ocular allergy is used to encompass a group of diseases characterized by inflammation of the conjunctiva which can be divided into seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis, atopic keratoconjunctivitis and contact blepharoconjunctivitis, in which there may be involvement of the eyelids, conjunctiva or cornea as a result of hypersensitivity reactions triggered by exposure to certain substances in the anatomical structures.[7,8]

The significance of allergic conjunctivitis lies more in its frequency than in its severity. In its different forms of presentation, seasonal or perennial, it is the most common form of ocular allergy, accounting for approximately 66% of all ocular allergic diseases.[9]

Vernal keratoconjunctivitis accounts for only 0.5% of ocular allergy and occurs in children, with a peak incidence between the ages of 11 and 13 years. Atopic keratoconjunctivitis accounts for less than 1% of ocular allergies and primarily affects young adults, with a peak presentation between 30 and 50 years of age.[10]

Although most cases are mild forms, they can interfere with the patient's quality of life. There are differences between the different types of ocular allergy, in age of onset, prevalence and morbidity. There is also a geographic distribution because in Europe, for example, mild forms are frequent, while severe and vision-threatening forms are very rare.[9]

In Cuba, allergy behaves as in other countries; allergic diseases constitute more than 15% of the visits to consultation rooms and reach a high national prevalence. The World Health Organization places it in the sixth position among the most frequent diseases and it has come to be considered as a health problem in modern society.[11]

The review of patients seen in consultation, the interaction with other Ophthalmology Specialists regarding the increase of patients with allergic conjunctivitis and the opportunity to perform other diagnostic tests in patients seen at the Ophthalmology Center of Villa Clara constituted the motivation to carry out a review on this disease that allows not only to gather criteria and treatments, but also to orient in the integral management of this health problem.

METHODS

The following keywords/descriptors provided by the MeSH Database of PubMed were chosen for the search and localization of the information: allergic conjunctivitis in relation to hypersensitivity, diagnosis and treatment. An extensive literature review of documents obtained through Google Scholar, TripDatabase and Cochrane was performed.

DEVELOPMENT

Allergic conjunctivitis is a group of acute, recurrent and sometimes persistent inflammatory diseases of the ocular surface that can affect the eyelids, conjunctiva and cornea to different extents. They are hypersensitivity reactions generated by various allergens to which the affected individual reacts, after sensitization to the same allergen.[1,7,8]

Pathophysiology

Regarding immunopathological mechanisms, allergic conjunctivitis is produced by a mechanism mediated by immunoglobulin E (IgE) or immediate hypersensitivity by direct contact of the allergen on the conjunctival surface of sensitized patients, which causes mastocyte activation and the release of inflammatory mediators.[5,7]
Allergic conjunctivitis occurs from multiple causes and is linked to conjunctival sensitization to an allergen (pollen, proteins, vegetables, oak wood, flour, animal scales, feathers, mushroom spores, dusts, occupational allergens, chemicals, drugs, foods, soaps, face powders, and nail polish) or to fungal and infectious causes, especially bacterial and viral. This is a classic example of the type I allergic reaction.[4]
Exposure to a given allergen elicits both a cellular (T-cell) and humoral (IgE) response; these two mechanisms culminate in the release of inflammatory mediators, responsible for the characteristic symptoms of allergic conjunctivitis.[12]
The severity of these conditions is reflected in the type of cells that mediate the allergic reaction: mild forms are characterized by the presence of mast cells (acute, seasonal and perennial allergic conjunctivitis), whereas severe forms are associated with a preponderance of T cells (vernal and atopic keratoconjunctivitis and giant papillary conjunctivitis).[9]

Classification

According to the last European Academy of Allergy & Clinical Immunology (EAACI) classification of 2012, ocular allergy is classified according to the immunological mechanism involved and, in a simple way, two major groups could be considered: that mediated by immunoglobulin E (IgE) and that not mediated by IgE (Figure 1).[7]

Clinical picture

The most important symptoms are ocular pruritus, burning, red eye, epiphora and mucous secretion. According to severity, there may be extensive conjunctival edema that alarms the patient and eyelid edema. In general, visual acuity is not compromised and it is not associated with tissue damage or scarring. It is very often accompanied by nasal pruritus, mucous discharge and pharyngeal pruritus. Symptoms are usually bilateral, but may be asymmetric.[13]

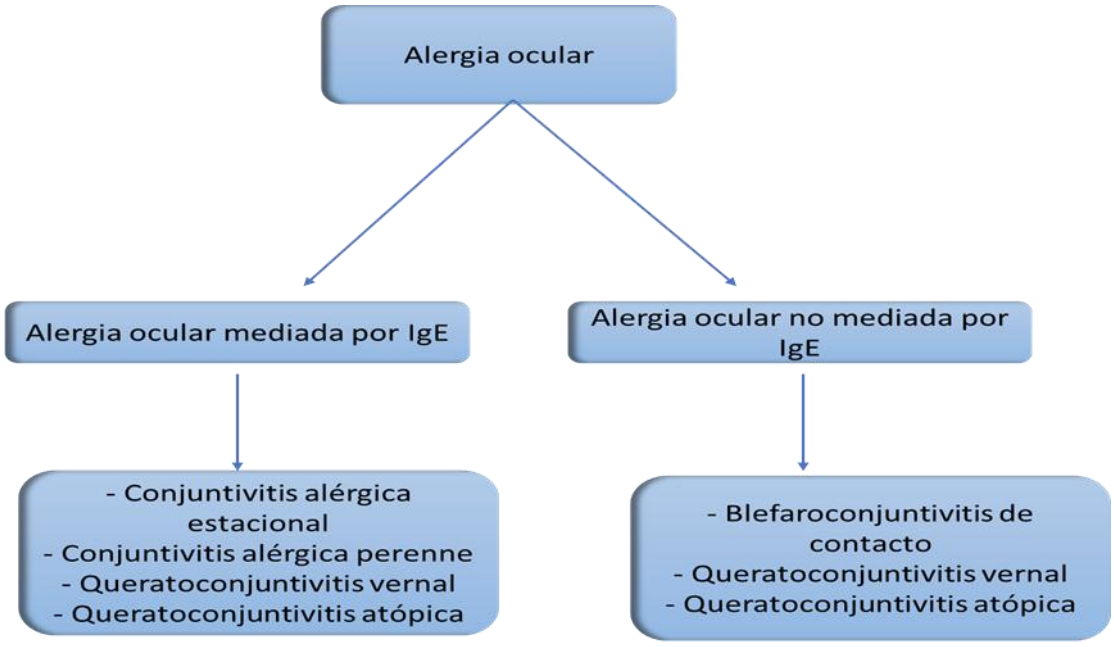

Figure 1. Classification of ocular allergy
Modified from Navarrete Rodríguez et al.[7]

In severe cases, photophobia and blurred vision may occur due to an alteration in the composition and stability of the tear film. Tear film disruption may also appear in atopic children with rhinitis and asthma.[8]
Clinical signs can be explored with a slit lamp or, alternatively, with a spotlight and fluorescein staining if ocular surface epithelial changes are suspected. Mild to moderate conjunctival hyperemia or conjunctival injection and edema or chemosis may be observed in the conjunctiva. Ocular secretion is watery or mucoid.[8]
Depending on the form of presentation there are other specific clinical features (Table 1).

Diagnosis

The diagnosis of allergic conjunctivitis is clinical and is integrated by the symptoms and findings found during the ophthalmologic physical examination present in the patient at the time of consultation.[7]
Patients may present a clinical history suggestive of allergic conjunctivitis at any age, with no gender predominance and its association with other allergic diseases such as rhinitis, atopic dermatitis and asthma is frequent.[8]
The main demographic data such as age at onset, sex, geographic location and environmental situation are very important to discern the type of ocular allergic disease, as well as the season of the year in which symptoms begin or are exacerbated, the form of presentation and evolution. The most useful way to obtain all the information about the conditions and quality of life, the environment surrounding the patient and the potential sources of allergens that provoke the allergic response, is the completion of allergy questionnaires.[14]

Table 1. Most important clinical features of ocular allergy[1,2,7,13,15]

Type	Frequency	Physiopathology	Triggering factor	Age of presentation	Clinical picture
Seasonal allergic conjunctivitis (SAC)	Most common 25 to 50% of all cases	Hypersensitivity reaction Type I hypersensitivity reaction (IgE-mediated)	Specific circulating aeroallergens, more frequently in spring, summer and early autumn, when there is a greater amount of pollen in the environment	It occurs at any age	Pale pink or milky palpebral conjunctiva (related to edema); corneal involvement is less frequent, although punctate epithelial keratitis may be found
Perennial Allergic Conjunctivitis (PAC)	Second most frequent most frequent presentation	IgE-mediated reaction	Allergens, which are present throughout the year (dust mites, animal epithelium and fungi)	Occurs at any age	Discrete papillary reaction in the conjunctiva, corneal involvement is rare, may be associated with dry eye
Vernal Keratoconjunctivitis (VKC)	Relative rare (0.5%)	Type I and type IV hypersensitivity	Seasonal character, worsens with warmer months	Minors from 15 to 21 years of age, with a peak incidence between 11 and 13 years of age	Presence of giant papillae (7-8mm) affecting mainly the upper tarsal conjunctiva (cobblestone); Horner-Trantas spots, micropannus, superficial punctate keratopathy, corneal macroerosions and ulcerations, subepithelial fibrosis (Arlt's line) and pseudogerontoxon.
Atopic Keratoconjunctivitis (AKC)	Occurs in 25 to 40% of patients with atopic dermatitis	Type I and type IV hypersensitivity.	It is associated with atopic dermatitis.	Adults between 20 and 50 years of age	Eczematous lesion of the eyelid, tending to thicken, harden and fissure, madarosis.

					Papillary hypertrophy < 1mm in diameter in the lower tarsal region, punctate epithelial keratitis, pannus and frank ulceration; corneal neovascularization, symblepharon, herpetic keratitis, *Staphylococcus* palpebral infections, meibomitis, trichiasis, ectropion and entropion
Blepharoconjunctivitis (CB)	Infrequent	Type IV hypersensitivity	Exposure to cosmetics, chemicals, pharmaceuticals and some intradomestic plants	Occurs at any age	Blepharitis with acute eczematous appearance, folds, crusts and fissures on the eyelids, with thickening of the skin and eventual lichenification. The conjunctiva may have a papillary or follicular appearance; lower superficial punctate keratitis.
Giant papillary conjunctivitis	Affects 1% to 5% of soft contact lens wearers and 1% of rigid lens wearers	Repetitive mechanical stimulus and an abnormal inflammatory response of the conjunctiva	It is associated with continuous use of contact lenses, ocular prosthesis, sutures or foreign bodies	Occurs at any age	Superior tarsal conjunctival papillary hypertrophy, with cobblestone appearance, papillae are usually > 1mm and do not show corneal involvement

Ocular cytology was performed on the patients studied (more than 60) at the Ophthalmologic Center of the "Arnaldo Milián Castro" University Clinical Surgical Provincial Hospital of Santa Clara City, Villa Clara Province. This technique offers sensitivity because, from very small amounts of genetic material, it detects the presence of viral, bacterial and fungal deoxyribonucleic acid (DNA), among others; specificity due to the fact that, under strict conditions, it is possible to amplify only the DNA to be detected. In the sample studied it was found that the predominant cell population was that of neutrophils and eosinophils.

The diagnosis is confirmed by skin testing with the suspected allergens or by determination of serum IgE specific to complete allergens or their purified molecular components, which should be positive. Sometimes skin tests or specific IgE values (or both) are not decisive because up to 24% of patients may present polysensitizations and, in some allergic conjunctivitis, skin tests are negative, especially if they are not associated with rhinitis.[8]

Small excoriations are made on the skin surface, on which a small sample of the antigens that most frequently produce allergy will be deposited.[15]

A complete blood test will reveal a slight eosinophilia and an increase in serum IgE. Determination of serum ICAM-1 (Intercellular Adhesion Molecule-1) is important in the limbic forms, in which a considerable increase is seen.[15]

Measurement of serum sVCAM-1 (Soluble Vascular Cell Adhesion Molecule-1) can be used as a marker to differentiate vernal keratoconjunctivitis from other allergic processes because values are elevated in vernal keratoconjunctivitis.[15]

In patients with atopic dermatitis, elevated serum sICAM-1 (Soluble Intercellular Adhesion Molecule-1) and sIL-2R (soluble IL-2 receptor) values are frequently found.[15]

It is useful to know the function of the tear film and in tears it is also possible to measure levels of free specific IgE, total IgE, cytokines, inflammatory mediators such as eosinophil cationic protein (ECP) or conjunctival cytodiagnostic studies can be performed, but these are not useful techniques for routine practice and are mainly used in research.[8]

The differential diagnosis of ocular allergies should exclude other diseases that involve red eye with associated symptoms of itching, burning and tearing, such as autoinflammatory dry eye syndrome, blepharitis, and bacterial and viral infectious conjunctivitis because the clinical presentation and symptoms may be common among some. Chlamydia conjunctivitis should also be considered because of the increase in sexually transmitted diseases. Another cause of chronic conjunctivitis is flaccid eyelid syndrome.[10]

Treatment

The best way to avoid the development of allergic conditions is to prevent and reduce contact with the substances to which the patient reacts in an altered way, that is, to strictly comply with environmental control measures. First, it is necessary to diagnose the allergen to which the individual reacts, and second, it is possible to perform clinical laboratory tests to determine antibodies in blood (dosage of immunoglobulins IgA, IgG, IgM, IgD, and IgE, total and specific)[11]

The main goals of treatment are to minimize and control the signs and symptoms of the disease. In addition, interventions aim to interrupt and prevent the cycle of inflammation, mainly in those with chronic symptoms.[7]

To improve adherence to treatment requires a multi-pronged approach based on pharmacological and non-pharmacological measures, in addition to education for the patient and their caregivers about the chronic nature of the condition. All measures taken should be based on the duration, frequency, and severity of symptoms.[7]

Cold compresses (five to 10 minutes, once or twice a day) provide symptomatic relief of ocular pruritus and can be used as an adjunct in treatment.[7]

Pharmacological treatment becomes necessary when there is inadequate relief of symptoms by allergen avoidance and lifestyle modification; its main goal is always to prevent or relieve symptoms as quickly as possible, with the fewest number of pharmacological agents.[7]

Several drugs are available for treatment including vasoconstrictors, antihistamines, mast cell stabilizers and anti-inflammatory agents; the efficacy of these agents varies from patient to patient and the choice of agent used should be individualized for each patient (Table 2).[7]

The use of artificial tears (two to six times a day according to the needs) is a fundamental part of the management of allergic conjunctivitis because it reduces the symptoms associated with dry eye such as itching and foreign body sensation, besides helping to stabilize the tear film and to eliminate, or at least dilute, the allergen from the ocular surface, so they are frequently used long-term.[7]

In the event that artificial tears are insufficient, ointments that provide lubrication to the ocular surface while the patient sleeps can be used at night.[7]

Table 2. Characteristics of drugs for the treatment of allergic conjunctivitis [1,2,7,13,15]

Category	Presentations	Characteristics and use
Vasoconstrictors	Naphazoline/pheniramine Naphazoline/antazoline	They are alpha-adrenergic agonists, their main effect is to decrease conjunctival hyperemia.
Antihistamines	Levocabastine (Livostin®) Pheniramine Antazoline	Competitive and reversible blockade of H1 receptors. Use for acute attacks.
Mast cell stabilizers	Sodium Chromoglycate (Cromolin® Osmocrom®) Lodoxamide (Alomide®) Neodocromil (Alocromil®)	These agents stabilize the mast cell membrane, thereby preventing degranulation and reducing the influx of inflammatory cells. Use for chronic conjunctivitis.
Antihistamine + mast cell stabilizer	Olopatadine (Patanol S®) Fumarate de Ketotifeno (Zaditen®, Kenaler®) Azelestine (Faraler® Sophistina®, Azel®)	H1 and H2 receptor binding, mast cell stabilization, down-regulation of inflammatory markers, eosinophils, neutrophils, adhesion molecules, interleukins and other cytokines affecting the early and late phases of the conjunctival allergic response.
Topical steroids	Loteprednol (Lotesoft®)	They inhibit intracellular synthesis

	Fluoromethalone (Aflarez®, Efemolina®, Flumex®) Dexamethasone 0.1% (Maxidex®) Prednisolone (Pred F®, Prefox T®)	of proteins and phospholipase A2. These drugs do not act effectively in the early phase of the allergic reaction but suppress the late phase by inhibiting the production or release of inflammatory mediators.
Topical NSAIDs	Ketorolac (Acular®) Diclofenac (Voltaren®, Diclanex®)	It inhibits the production of prostaglandins and reduces pruritus.
Oral antihistamines	Fexofenadine, loratadine, cetirizine levocetiricine, desloratadine	Useful when systemic allergic symptoms are present.
Immunosuppressants	Cyclosporine A Tacrolimus	Modulates mast cell activity by reducing calcium influx, degranulation and gene expression of some cytokines. Suppresses T-cell activation and subsequent B-cell proliferation.

Immunotherapy

Allergen-specific immunotherapy has been shown to provide an improvement of signs and symptoms of allergic conjunctivitis, used both in its subcutaneous and sublingual form, with an effect that persists even after discontinuation of treatment.[7]

Subcutaneous administration of the allergen causing the allergic reaction in these patients is intended to desensitize them and reduce the allergic reaction as much as possible. These are long and expensive treatments but they improve the patients' symptoms, both in chronic and acute forms, by reducing the frequency and severity of outbreaks.[15]

Local desensitization by conjunctival instillation of the allergen in increasing concentrations has been attempted.[13]

Follow-up of the allergic patient should be coordinated between the different levels of care. Due to the prevalence of allergic disease, it is imperative that there are common protocols and easy communication between Primary Care and the Specialist, in the interest of greater benefit for the patient.[16]

CONCLUSIONS

Allergic conjunctivitis is a worldwide public health problem and is a very frequent disease that is increasing in incidence in combination with an increase in atopy. The importance of a good control of the ocular allergic process lies in the impact it has on the quality of life of patients because it affects sleep, work and school activities, social interactions and the psychological state of the patient.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.