MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt22307

Major considerations and clinical findings on the allergic conjunctivitis: a narrative and systematic review

Malú Inês Perez Moura[1], Ana Cristyna Saad Murad[1], Rafaella Scalabrini Ferrari[1], Isabelle Dalloul Daher[1], Eneidia Batista Neiva[1], Fernanda Soubhia Liedtke[1]*

[1] Unioftal - Ophthalmology And Eye Plastic, São José do Rio Preto, São Paulo, Brazil.

*Corresponding author: Dr. Fernanda Soubhia Liedtke, Unioftal- Ophthalmology And Eye Plastic, São José do Rio Preto, São Paulo, Brazil.
E-mail: drafernandaliedtke@unioftal.com.br
DOI: https://doi.org/10.54448/mdnt22307
Received: 05-11-2022; Revised: 07-25-2022; Accepted: 08-05-2022; Published: 08-23-2022; MedNEXT-id: e22307

Abstract

Introduction: Allergic conjunctivitis (AC) is a disease of increasing prevalence, affecting children and adults, with progressive loss of quality of life. It has been reported that about 20 % of the entire human population undergoes a form of allergy. The prevalence of allergic conjunctivitis (AC) varies around the world, usually ranging from 15 to 40 %. In Japan, the prevalence of allergic diseases is the conjunctiva is estimated to be as high as 15% -20% of the population is on the rise. **Objective:** the present objective was to carry out a narrative and systematic review of the major clinical considerations of allergic conjunctivitis, as well as the main treatments, immunological aspects, and allergic conjunctivitis classification. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from May to June 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 20 years were selected. The quality of the studies was based on the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results:** A total of 512 articles were found, and 35 articles were included in the systematic review. Allergic conjunctivitis (AC) is an inflammation of the conjunctiva secondary to an immune response to foreign antigens, usually called allergens. This inflammation can be mediated or non-IgE and atopy could play a significant role in the outcome. These forms include seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis and atopic keratoconjunctivitis. Giant papillary conjunctivitis and contact or induced by dermatoconjunctivitis drugs are considered to be allergic conjunctivitis subtypes. **Conclusion:** It was concluded that allergic conjunctivitis is a frequent comorbid with many undiagnosed patients. Then, an additional specific questioning and a therapeutic challenge in suspected patients may help identify patients who may benefit from treatment of Allergic conjunctivitis.

Keywords: Allergic Conjunctivitis. Immunological Aspects. Allergic Eye Diseases. Monoclonal Antibodies. Immunotherapy.

Introduction

In the scenario of eye diseases, allergic conjunctivitis (AC) is a disease of increasing prevalence, affecting children and adults, with progressive loss of quality of life. There are several forms of the disease [1], some are allergen-induced, such as seasonal and perennial allergic conjunctivitis, giant papillary conjunctivitis, and allergic contact blepharoconjunctivitis, while others are not always explained by exposure to allergens, such as spring keratoconjunctivitis and atopic keratoconjunctivitis [2,3].

In this sense, it has been reported that about 20% of the entire human population undergoes a form of allergy. The prevalence of AC varies around the world, usually ranging from 15 to 40% [4]. These variations can be attributed to both genetic and environmental factors (including hot and dry climate degree of pollution). According to statistical data, the incidence of AC in developed countries is 20% with a high degree of co-morbidity of allergic rhinitis (AR). AC recognition is declared even in patients with known RA. In Japan, the prevalence of allergic diseases in the conjunctiva is estimated to be as high as 15% -20% of the population is on the rise [5].

In an attempt to mitigate this epidemiological picture of the incidence and prevalence of allergic

conjunctivitis, are proposed various treatments involving pharmacological treatment, nonpharmacological, immunotherapy, and monoclonal antibodies. Most of these treatments are reducing the effects of AC, with significant improvement in comorbidities. The treatment offers benefits that can even eliminate the problem [4-6]. The non-pharmacological treatment, although it offers less risk to the patient, it is sometimes less effective. As the treatments by immunotherapy and monoclonal antibodies allow a natural response to allergens. However, despite the benefits of these treatments, the answers are often not significant, and other adverse effects, making it necessary to increase the combination of treatments through randomized multicenter studies [7,8].

As a corollary, antihistamines first generation are not recommended because of their sedative and anticholinergic activity. Antihistamines second-generation (bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, and Rupatadine) have similar efficacy but sedation profile more manageable and less adverse effects. Furthermore, keratoconjunctivitis has been reported with oral antihistamines and antimuscarinic activity which causes abnormalities in the film. These changes in the conjunctival epithelium may enhance the inflammatory response to allergen [1-3, 9].

Furthermore, few studies assessed the changes in sensitivity to allergen using a conjunctival challenge before and after immunotherapy but in all cases, the sensitivity threshold is increased. Although significant relief of ocular symptoms was observed with omalizumab in patients with seasonal allergic rhinitis caused by the pollen of Japanese cedar, the drug has not been authorized for the treatment of AC [1-3].

Therefore, the present objective was to carry out a narrative and systematic review of the major clinical considerations of allergic conjunctivitis, as well as the main treatments, immunological aspects, and allergic conjunctivitis classification.

Methods

Study design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): *"Allergic Conjunctivitis. Immunological Aspects. Allergic Eye Diseases. Monoclonal Antibodies. Immunotherapy"*. The research was carried out from May to June 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study quality and risk of bias

The quality of the studies was based on the GRADE instrument. The highest ratings were for controlled clinical studies with a sample size with statistical significance. The risk of bias was analyzed using the Cochrane instrument, based on the effect size of each study versus the sample size.

Results and Discussion

Major findings

A total of 512 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 125 articles. A total of 85 articles were evaluated and 35 articles were included and developed in this systematic review study (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 13 studies with a high risk of bias and 27 studies that did not meet the GRADE that was removed.

Figure 1. Flowchart showing the article selection process.

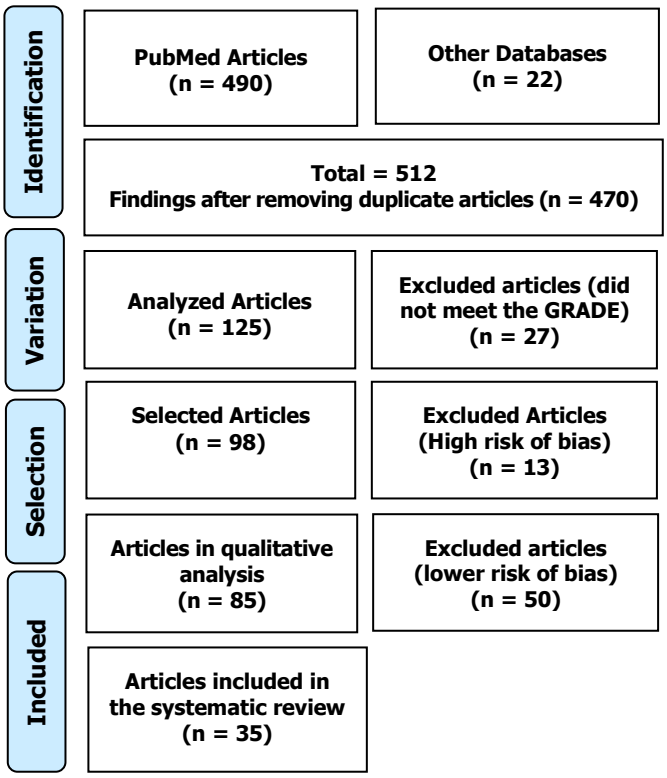

Figure 2. Major types of journals that publish on allergic conjunctivitis were research targets for this work.

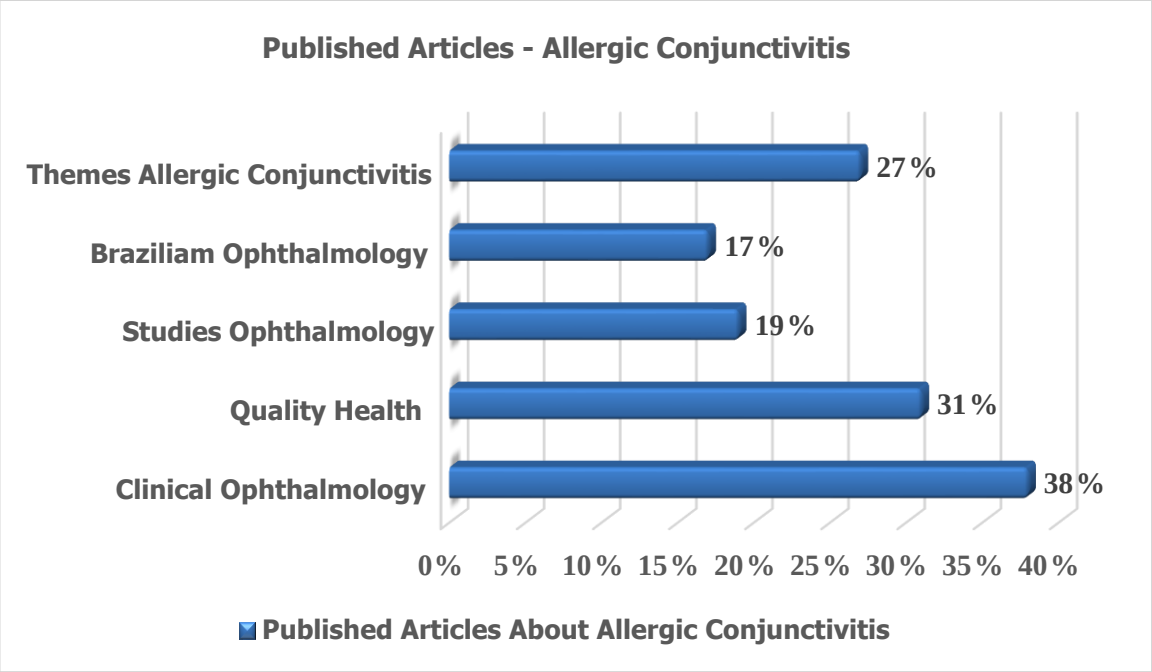

Figure 2 presents the rate of the main scientific publications on AC, as well as the main themes published on the subject in the world.

Immunological aspects

By definition, allergic conjunctivitis (AC) is an inflammation of the conjunctive secondary to an immune response to foreign antigens, usually called allergens. This inflammation can be mediated or non-IgE and atopy could play a significant role in the clinical evolution [1-3]. AC is a syndrome that affects the whole ocular surface, including the conjunctiva, eyelids, cornea, and lacrimal film. Signs and symptoms of AC harm the quality of life of the patient and are influenced by genetics, environment, eye microbiota, and mechanisms for regulating the immune system, which works together in a complex immune response [7-9].

Two stages were set up in the pathophysiology of immune AC. The first phase is called the sensitization phase reaction and preferential starts the activation polarization and the immune response to environmental antigens resulting in Th2 immune response and the production of IgE antibodies. The second phase, termed the effector phase of reaction is initiated by an antigen (Ag) [7-10].

Studies have shown that in patients with asthma or allergic rhinitis, bronchial tubes and nasal mucosa can capture Ag Langerhans cells. Thus, these cells could process and present Ag in the context of MHC II molecules and stimulate CD4 + cells to induce specific secretion of interleukin (IL) -4, IL-13, and CD154 expression. This process enables genetic recombination in B cells and IgE class switching. Thus, a similar mechanism may be involved in the ocular mucosa, since it has been reported that the IgE may be detected in human tears and B cells located in the lymphoid follicles of the conjunctiva are CD23 + CD21 + CD40 +, suggesting that they may be precursors B cells producing IgE, and contribute to the local synthesis of IgE [10-13].

The crosslinking of IgE receptors induces the release of mediators such as histamine, proteases, chemotactic factors and, activation of transcription factors and cytokine gene expression, production of prostaglandins and leukotrienes via phospholipase. The activation of mast cells by IgE conjunctiva is important since it is well known that there are up to 6000 cells / mm3 in the conjunctiva and the density of mast cells is increased in acute and chronic conjunctivitis patients, contributing to increased local inflammatory Th2 response [14-17].

Added to this, cellular infiltration is characteristic of late-phase reaction (LPR). LPR involves the infiltration of inflammatory cells, basophils, neutrophils, eosinophils, and T Lymphocytes. In preclinical studies, AC has shown that migration is directed by inflammatory Tcells The role for T cells has been suggested, since there was a reduction of clinical signs and eosinophil infiltration compared to the control group. However, the involvement of T cells in the human AC is still unknown. However, during the active phase of inflammatory disease, multiple types of Th1 and Th2 cytokines are expressed and contribute to

increasing ocular inflammation [18-21].

Although other allergies are well known for the involvement of cytokines Th9, Th17, Th22 and T cells in effector responses, a long way in the investigation is still pending in the AC of humans and animals [22-24]. Additionally, other molecules such as Toll-like receptors (TLR) and Nucleotide Olimerization domain (NOD) that are expressed in epithelial cells could modulate the immune response unexpectedly depending on ocular microflora thus must be an AC field extensive research [25-28].

Clinical Aspect And Allergic Conjunctivitis Classification

Allergic conjunctivitis presents some conditions ranging from intermittent and persistent symptoms signals with levels of gravity and presentation. These forms include seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. Giant papillary conjunctivitis and contact-induced drugs keratoconjunctivitis are considered allergic conjunctivitis subtypes [1,3].

The main ocular allergy symptom is itching. The clinical manifestations of the effects of friction of the eye include vascular bed conjunctival injection due to vascular dilation evoked by vasoactive amines liberated during the degranulation of mast cells, followed by an influx of water from the intravascular space into the vascular extra space, resulting in edema tissue and eyelid swelling, progressing from milky or pale conjunctiva to swelling of the conjunctiva. Swelling appears after 15-30 minutes of exposure to antigen [5,6]. Furthermore, in chronic forms fibrosis occurs in vascularization that can be easily identified with the slit lamp.

Furthermore, keratoconjunctivitis relates to contact T cell-mediated delayed hypersensitivity reaction to the hapten-carrier complex such as cosmetics, chemicals, and metals, as well as topical drug preparations or preservatives involved [7,8]. The eyelid symptoms of itching, eczema, conjunctival redness, and punctate keratitis can be seen. A role of Langerhans cells of the skin or eyelid conjunctiva and presented to T-helper cells in regional lymph nodes, which in turn react with cytokines sensitized cells, resulting in allergic conjunctivitis processes [5,29].

The main types of AC may be presented as seasonal allergic conjunctivitis which is caused by type I hypersensitivity reaction, often associated with rhinitis or asthma, and is closely related to direct exposure to the allergen [6,30]. It is the most common form of ocular allergy. The pathogenesis is based on the degranulation of mast cells, which are previously stimulated by IgE, they release chemical mediators that trigger symptoms - itching, hyperemia, edema, and formation of buds in the upper tarsal conjunctiva, which are smaller than 1 mm, in rare cases corneal involvement [31].

Another type of AC is atopic keratoconjunctivitis which is caused by hypersensitivity reaction type I and IV, crises are more frequent in winter, and there is an association with atopic dermatitis. The most common symptoms are itching, tearing, mucous discharge, redness, blurred vision, photophobia, and pain [1]. The eyelid involvement is because of secondary blepharitis, which can reach scar entropion. Madarosis is frequent, as microcalazius. Conjunctival hyperemia, chemosis, limited, papillary hypertrophy in the upper tarsal conjunctiva, and points of Tranta are signals present [32]. The corneal involvement is most common in dotted keratitis which may be accompanied by peripheral neovascularization. Chronic epithelial defects can result in decreased visual acuity [5,33].

Still, there is the type conjunctivitis spring (vernal) which is caused by hypersensitivity reaction types I and IV; crises are more frequent in the spring, in hot and dry climates. It is more common in male children, between 2 and 10 years of age, and usually resolves spontaneously at puberty. Histopathology reveals the presence of an abnormal amount of mast cells in the conjunctiva [34].

Also, vernal conjunctivitis presents clinically in two forms: palpebral and limbal. The characteristic of the eyelid is the way papillary hypertrophy in the upper tarsal conjunctiva. In severe cases, there is a coalescence of the papillae, forming giant papillae [1]. Commonly their mucous secretion is disposed between the papillae. The limbal form has buds in limbo, which becomes thickened and gelatinous, often with points Tranta. The cornea has diffuse punctate keratitis, which is exacerbated by the mechanical trauma of buds. The coalescence of points inflammatory corneal epithelial defect oval shape with fibrin deposits in the upper third of the cornea termed ulcer shell [35].

Besides, allergic rhinitis may be present during allergic conjunctivitis. Thus, the swelling of the mucosa of the upper airways induces changes in nasal physiological balance and intrinsic factors such as allergies, metabolic disorders, and anatomical changes, as well as extrinsic factors such as humidity, temperature, pollution, and barometric pressure, induce the inflammatory processes that can be limited or persistent. The mucosal inflammation also stimulates mucin hypersecretion and inflammation continues to develop dysfunction and sinus occlusion of the tear duct. Thus, serious eye complications of sinus infection

include periorbital cellulitis and cavernous sinus thrombosis. Occlusion of the tear duct is associated with persistent epiphora and eye infections [13-15].

Furthermore, there is giant papillary conjunctivitis is caused by hypersensitivity reaction types I and IV, and has as a characteristic the formation of giant papillae on the upper tarsal conjunctiva. The most frequent cause of this conjunctivitis is prolonged use of contact lenses, particularly soft, but also occurs in sutures exposed, use of ocular prostheses, and scleral exposure range [1,2,6].

The most common symptoms are intolerance to contact lenses, with abundant mucous secretion especially in the morning (after removal of the lenses the day before), and feeling strange and itchy body. The characteristic signs are conjunctival hyperemia and papillary hypertrophy in the upper tarsal conjunctiva. With progression, the discharge becomes thicker and the papillae coalesce, forming giant papillae. When combined with exposure sutures or scleral band, the reaction is located adjacent to stimulation [7].

Scale Severity of Allergic Eye Diseases

The degrees of severity to identify the severity of involvement in the conjunctiva are mild, moderate, and severe; however to better assess clinical proposed a classification system based on a scale of 0 to 4, where 0 = absent, 1 = mild, 2 = moderate, 3 = moderately severe and 4 = severe for both signals and symptoms, taking into account the frequency of symptoms such as itching, tearing, light sensitivity, gritty sensation and burning sensation and transmission of signals involved in the changes that accompany inflammation of the ocular surface, such as the position of the eyelid and appearance skin or eyelid margin mucocutaneous junction state with involvement of meibomian gland disease, aspect unloading implication limbal stem cell deficiency and even keratoconus [1,2].

The total score of symptoms and signs after a degree of severity scale was 48 points, twenty of them corresponding to the symptoms, and twenty-eight of them corresponding to signs. Thus, a classification system has been proposed to recognize the progress of allergic eye disease, which could be defined as follows: 0 = absent, points 1-12 points (light) 13-24 points (moderate), 25-36 points (moderately severe) and 36-48 points (severe). The score of the most severe side in bilateral cases could be used as a clinical score [1].

Pharmacological Treatments, Immunotherapy, and Monoclonal Antibodies

Systemic Antihistamines block ocular symptoms induced by histamine and interact with H1 receptors on nerve endings. Some antihistamines have anti-inflammatory effects because they inhibit the expression of intercellular adhesion molecules and affect platelet-activating factors. However, antihistamines first generation is not recommended because of their sedative and anticholinergic activity [5,6]. Already antihistamines second-generation (bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, and Rupatadine) have similar efficacy but a more manageable sedation profile and fewer side effects [1,6].

The antihistamine drugs are generally administered to control nasal and ocular symptoms in patients with allergic rhinoconjunctivitis. However, keratoconjunctivitis sicca has been reported with oral antihistamines which cause pellicular tear antimuscarinic activity [6,7]. These changes in the conjunctival epithelium can increase the inflammatory response to an allergen. Moreover, antihistamines first generation topical ocular (antazoline and pheniramine) are poorly tolerated, since their effects are short-lived and their power is limited. They are often combined with a vasoconstrictor to increase the duration of the effect [3].

Also, the topical antihistamines second-generation (emedastine and levocabastine) have a longer half-life and a good safety profile and effectiveness even in children. When symptoms are ocular, topical antihistamines are preferred over oral medications because the onset of action is faster. Pose make up the combination of antihistamine and topical oral use, to increase efficiency. Moreover, mast cell stabilizers (0.1% lodoxamide, nedocromil 2% sodium cromoglycate 2% and 4%, 4% spaglumic acid) block the release of mediators and activation of the arachidonic acid. However, these agents must be administered every 6 to 8 hours for at least 2 weeks [1-3].

Added to this, the double-acting agents (azelastine, epinastine, ketotifen, and olopatadine) have the advantage that they act as stabilizing mast cells and selective H1 receptor antagonists (olopatadine and ketotifen). Some, such as epinastine, may act on both H1 (pruritic receptors), and reduce the H2 receptors (decrease vasodilation). These agents act quickly with a lasting effect, they suppress the release of mediators and inhibit the recruitment of inflammatory cells. Furthermore, vasoconstrictors (naphazoline, oxymetazoline, phenylephrine, tetrahydrozoline) are α adrenergic agonist which alleviates redness caused by conjunctival vasodilation. Medicines should be administered with caution in patients with glaucoma, hyperthyroidism, or cardiovascular disease [5-8].

Furthermore, nasal corticosteroids are not the first

choice for the treatment of AC, but they can improve ocular symptoms by decreasing nasal-ocular reflex in patients who also have rhinitis. Thus, mometasone furoate and fluticasone furoate may relieve the symptoms of allergic rhinoconjunctivitis. Still, prolonged use does not seem to generate a significant risk of ocular hypertension or glaucoma, although there are few studies. When inflammation is severe, the drugs of choice are betamethasone, dexamethasone, and prednisolone. It should be given in low doses and for short periods in all cases. The potential adverse effects such as increased intraocular pressure, cataract formation, and viral, bacterial, and fungal infections which mean the diligent research of ophthalmologists [6-9].

Moreover, anti-leukotrienes (particularly montelukast) are included as a possible treatment for nasal symptoms of allergic rhinoconjunctivitis, as they block leukotriene activity. A metaanalysis demonstrated that montelukast was more effective than placebo in seasonal BC, however, less effective than oral antihistamines in adults [23,24].

The World Health Organization recommends an effective approach to immunotherapy in patients with allergic diseases such as asthma and rhinoconjunctivitis. Both sublingual, and subcutaneous administration appear to be capable of inducing tolerance, short and long term by the same mechanism: high doses of allergens induce deviation of immune response in favor of Th1 lymphocytes with the release of IFN-γ producing cells, and regulatory T. Both play a key role in the secretion of IL-10 and transforming growth factor β, which suppress the TH2 response specific to the allergen [1-3].

So with specific immunotherapy, the ocular symptoms improve in patients with allergic rhinoconjunctivitis, even after treatment discontinuation. When the specific immunotherapy is analyzed for each patient, the ocular symptoms are relieved both overall and type of patient, reducing the use of drugs up to 63% in patients with seasonal rhinoconjunctivitis or AC [1,2]. To support the US Agency for Health Research and Quality published a systematic review of the results of randomized controlled studies in patients (adults and children) with allergic rhinoconjunctivitis or asthma treated with sublingual and subcutaneous immunotherapy. The analysis of the efficacy of immunotherapy for subcutaneous immunotherapy showed that AC alleviated ocular symptoms. In addition, the evidence was strong for adults but weak for children and adolescents [2,3].

In addition to this, Omalizumab is a humanized IgG antibody that binds to free IgE and prevents it from interacting with high affinity for receptors on the surface of mast cells, thereby inhibiting the inflammatory cascade triggered by the degranulation of mast cells. Although there was a relief of ocular symptoms in patients with seasonal allergic rhinitis caused by the pollen of Japanese cedar, the drug has not been authorized for the treatment of AC [6,7].

Another study examined the relationship between hormones in children and adolescents with vernal keratoconjunctivitis (VKC) [5]. Results Showed serum estrone levels were significantly increased in all groups of patients with VKC Compared with healthy controls. Prepubertal and early puberty VKC showed a significant decrease in dihydrotestosterone and sexhormones binding globulin when compared to controls. These results suggest the role played by sex- hormones in the pathogenesis and/or VKC activity [1,2,5].

Conclusion

It was concluded that allergic conjunctivitis is a frequent comorbid with many undiagnosed patients. Then, an additional specific questioning and a therapeutic challenge in suspected patients may help identify patients who may benefit from treatment of Allergic conjunctivitis.

Acknowledgement
Not applicable.

Funding
Not applicable.

Ethics approval
Not applicable.

Informed consent
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

References

1. Bielory L, Delgado L, Katelaris CH, Leonardi A, Rosario N, Vichyanoud P. ICON: Diagnosis and management of allergic conjunctivitis. Ann Allergy Asthma Immunol. 2020 Feb;124(2):118-134. doi: 10.1016/j.anai.2019.11.014.
2. Villegas BV, Benitez-Del-Castillo JM. Current Knowledge in Allergic Conjunctivitis. Turk J Ophthalmol. 2021 Feb 25;51(1):45-54. doi: 10.4274/tjo.galenos.2020.11456.
3. Bielory L, Delgado L, Katelaris CH, Leonardi A, Rosario N, Vichyanoud P. ICON: Diagnosis and management of allergic conjunctivitis. Ann Allergy Asthma Immunol. 2020 Feb;124(2):118-134. doi: 10.1016/j.anai.2019.11.014.
4. Sánchez-Hernández MC, Montero J, Rondon C, Benítez del Castillo JM, Velázquez E, Herreras JM, Fernández-Parra B, Merayo-Lloves J, Del Cuvillo A, Vega F, Valero A, Panizo C, Montoro J, Matheu V, Lluch-Bernal M, González ML, González R, Dordal MT, Dávila I, Colás C, Campo P, Antón E, Navarro A. Consensus Document on Allergic Conjunctivitis (DECA). J Investig Allergol Clin Immunol; 2015, 25(2): 94-106.
5. Sacchetti M, Lambiase A, Moretti C, Mantelli F, Bonini, S. Sex Hormones in Allergic Conjunctivitis: Altered Levels of Circulating Androgens and Estrogens in Children and Adolescents with Vernal Keratoconjunctivitis. Journal of Immunology Research, 2015, Article ID 945317.
6. De Bruin Weller MS, Rockmann H, Knulst AC, Bruijnzeel- Koomen FM. Evaluation of the adult patient with atopic dermatitis. Clin Exp Allergy. 2013;43:279-91.
7. O'Brien TP. Allergic conjunctivitis: an update on diagnosis and management. Curr Opin Allergy Clin Immunol; 2013, 13:543- 9.
8. Lin SY, Erekosima N, Suarez-Cuervo C, Ramanathan M, Kim JM, Ward D, Chelladurai Y, Segal JB. Allergen- Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013, Mar. Report No.: 13-EHC061EF.
9. Demoly P, Calderon MA, Casale T, Scadding G, Annesi- Maesano I, Braun JJ, Delaisi B, Haddad T, Malard O, Trebuchon F, Serrano E. Assessment of disease control in allergic rhinitis. ClinTransl Allergy; 2013, 3:1-7.
10. Gomes PJ, Ousler GW, Welch DL, Smith LM, Coderre J, Abelson M. Exacerbation of signs and symptoms of allergic conjunctivitis by a controlled adverse environment challenge in subjects with a history of dry eye and ocular allergy. Clin Ophthalmol; 2013, 7:157-65.
11. Gane J, Buckley R. Leukotriene receptor antagonist sine allergic eye disease: A systematic review and meta-analysis. JAllergy Clin Immunol: In practice; 2013, 1:65-74.
12. Fujishima H, Satake Y, Okada N, Kawashima S, Matsumoto K, Hirohisa S. Effects of diesel exhaust particles on primary cultured healthy human conjunctival epithelium. Ann Allergy Asthma Immunol; 2013, 110:39-43.
13. Bielory L. Allergic conjunctivitis: the evolution of therapeutic options. Allergy Asthma Proc; 2012, 33:129-39.
14. Lightman S, Scadding GK. Should intranasal corticosteroids be used for the treatment of ocular symptoms of allergic rhinoconjunctivitis? A review of their efficacy and safety profile. Int Arch Allergy Immunol; 2012, 158:317-25.
15. Bilkhu PS, Wolffsohn JS, Naroo AS. A review of nonpharmacological and pharmacological management of seasonal and perennial allergic conjunctivitis. Cont Lens Anterior Eye; 2012, 35:9-16.
16. Friedlaender MH. Ocular allergy. Curr Opin Allergy Clin Immunol; 2011, 11:477-82.
17. Sanchez MC, Fernandez Parra B, Matheu V, Navarro A, Ibanez MD, Davila I, Dordal MT, Lluch Bernal M, Rondon C, Montoro J, Anton E, Colas C, Valero A. (SEAIC Rhinoconjunctivitis Committee 2010). Allergic Conjunctivitis. J Investig Allergol Clin Immunol. 2011, ;21 Suppl 2:1-19.
18. Bousquet PJ, Bachert C, Canonica GW, Casale TB, Mullol J, Klossek JM, Zuberbier T, Bousquet J. Uncontrolled allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial. J Allergy Clin Immunol; 2010, 126:666-8.
19. Palmares J, Delgado L, Cidade M, Quadrado MJ, Filipe HP (2010). Allergic conjunctivitis: a national cross-sectional study of clinical characteristics and quality of life. Eur J Ophthalmol. ;20:257-64.
20. Picado C, Badiola C, Perulero N, Sastre J, Olaguibel JM, Lopez -Vina A, Vega JM. Covalair Investigator Group. Validation of de Spanish version of the Asthma Control Questionnaire. Clin Ther. 2008, 30:1918-31.
21. Singh K, Bielory L, Hackensack NJ, Newark NJ. Epidemiology of ocular allergy symptoms in United States adults (1988-1994). Ann Allergy Asthma Immunol.; 2007, 98:A22:34.

22. S. Bonini, M. Sacchetti, F. Mantelli, and A (2007). Lambiase, "Clinical grading of vernal keratoconjunctivitis," Current Opinion in Allergy and Clinical Immunology, vol. 7, no. 5, pp. 436–441.
23. Vega JM, Badia X, Badiola C, Lopez-Vina A, Olaguibel JM, Picado C, Sastre J, Dal-Re R. Covalair Investigator Group. Validation of the Spanish version of the Asthma Control Test (ACT). J Asthma; 2007, 44:867-72.
24. Murphy PJ, Lau JS, Sim MM, Woods RL. How red is a white eye? Clinical grading of normal conjunctival hyperemia. Eye. 2007, 21:5:633-8.
25. Valero A, Alonso J, Antepara I, Baro E, Colas C, del Cuvillo A, Ferrer M, Herdman M, Marti-Guadano E, Monclus L, Navarro- Pulido AM, Sastre J, Izquierdo I, Mullol J (2007). Health-related quality of life in allergic rhinitis: comparing the short form ESPRINT-15 and MiniRQLQ questionnaires. Allergy; 62:1372-8.
26. Martinez CF. Caracteristicas generales de la muestra: descripcion sociodermografica y sanitaria de la poblacion de estudio. In: Alergologica 2005. Factores epidemiologicos, clinicos y socioeconomicos de las enfermedades alergicas em Espana en 2005. SEAIC and Schering-Plough eds. Madrid: Luzan, 2006, 5; p. 71-106.
27. Leonardi A, Busca F, Motterle L. "Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study," Acta Ophthalmologica Scandinavica, 2006, vol. 84, no. 3, pp. 406–410.
28. Uekert, SJ, Akan, G, Evans, MD (2006). "Sex-related differences in immune development and the expression of atopy in early childhood,"The Journal of Allergy and Clinical Immunology, vol. 118, no. 6, pp. 1375–1381, 2006.
29. Leonardi, A (2002). "Vernal keratoconjunctivitis: pathogenesis and treatment," Progress in Retinal and Eye Research, vol. 21, no. 3, pp. 319–339.
30. Efron N, Morgan PB, Katsara SS (2001). Validation of grading scales for contact lens complications. Ophthal Physiol Opt; 21:17-29.
31. Bonini, A. Lambiase, S. Marchi (2000). "Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup," Ophthalmology, 2000, vol. 107, no. 6, pp. 1157–1163.
32. Bielory L. "Allergic and immunologic disorders of the eye. Part II: ocular allergy," The Journal of Allergy and Clinical Immunology, 2000, vol. 106, no. 6, pp. 1019–1032.
33. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. J Allergy Clin Immunol; 1999, 104(2 Pt 1):364-9.
34. Willingham FF, Cohen KL, Coggins JM, Tripoli NK, Ogle JW, Goldstein GM. Automatic quantitative measurement of ocular hyperemia. Curr Eye Res; 1995, 14: 1101-08.
35. McMonnies CW, Ho A. Conjunctival hyperemia in non-contact lens wearers. Acta Ophthalm; 1991, 69:6:799-801.