

Pathogenetic mechanisms of allergen influence with ocular manifestations: the relationship between allergens and symptoms

Mecanismos patogênicos da influência dos alérgenos nas manifestações oculares: a relação entre alérgenos e sintomas

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Lisiecka MZ. Pathogenetic mechanisms of allergen influence with ocular manifestations: the relationship between allergens and symptoms. Rev Bras Oftalmol. 2026;85:e0093.

doi:

<https://doi.org/10.37039/1982.8551.20260093>

Keywords:

Immunoglobulins; Mast cells;
Conjunctivitis

Descritores:

Imunoglobulinas; Mastócitos;
Conjuntivite

Received on:

December 23, 2025

Accepted on:

June 2, 2026

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Conflict of interest:

no conflict of interest.

Financial support:

no financial support for this work.

Data Availability Statement:

The datasets generated and/or analysed
during the current study are included in the
manuscript.

Associated editor:

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ABSTRACT

Objective: To conduct a comprehensive analysis of the pathogenetic mechanisms through which various groups of allergens cause ocular manifestations.

Methods: A systematic review of scientific publications from 2010 to 2024 is conducted, incorporating data from PubMed®, Scopus, Web of Science, and Google Scholar. The selection of literature is based on peer-reviewed studies with clear methodologies, ensuring a high level of result reliability.

Results: The analysis demonstrates that the primary triggers of allergic conjunctivitis are aeroallergens, contact allergens, and food allergens. Aeroallergens most commonly provoke IgE-mediated reactions, characterised by typical symptoms of allergic conjunctivitis, such as itching, hyperaemia, and lacrimation. Food allergens can cause ocular symptoms, particularly in cases of sensitisation to specific foods, such as nuts or shellfish. The analysis of cross-reactive allergic reactions between pollen and food allergens is of particular importance.

Conclusion: For effective management of allergic reactions with ocular manifestations, it is recommended to use specific allergy diagnostic methods, including the determination of IgE levels to key allergens, conducting elimination diets, and using antihistamine medications. Individualised treatment approaches, including allergen-specific immunotherapy, reduce sensitivity to pollen allergens and can alleviate the course of the disease.

RESUMO

Objetivo: Realizar uma análise abrangente dos mecanismos patogênicos pelos quais diferentes grupos de alérgenos causam manifestações oculares.

Métodos: Foi realizada uma revisão sistemática de publicações científicas de 2010 a 2024, incorporando dados do PubMed®, Scopus, Web of Science e Google Scholar. A seleção da literatura baseou-se em estudos revisados por pares com metodologias claras, garantindo um alto nível de confiabilidade dos resultados.

Resultados: A análise demonstra que os principais desencadeadores da conjuntivite alérgica são os aeroalérgenos, os alérgenos de contato e os alérgenos alimentares. Os aeroalérgenos provocam mais frequentemente reações mediadas pela IgE, caracterizadas por sintomas típicos de conjuntivite alérgica, como prurido, hiperemia e lacrimejamento. Em contraste, os alérgenos de contato induzem reações mais prolongadas associadas à hipersensibilidade tardia, levando a inchaço e irritação ocular. Os alérgenos alimentares também podem causar sintomas oculares, particularmente em casos de sensibilização a determinados alimentos, como nozes ou frutos do mar. A análise das reações alérgicas de reatividade cruzada entre pólen e alérgenos alimentares é de especial importância.

Conclusão: Para a gestão eficaz das reações alérgicas com manifestações oculares, recomenda-se a utilização de métodos específicos de diagnóstico de alergias, incluindo a determinação dos níveis de IgE para alérgenos-chave, a realização de dietas de eliminação e o uso de medicamentos anti-histamínicos. Abordagens terapêuticas individualizadas, incluindo a imunoterapia específica com alérgenos, reduzem a sensibilidade aos alérgenos do pólen e podem aliviar o curso da doença. A relevância prática do estudo reside no fato de que a compreensão desses mecanismos é essencial para o desenvolvimento de abordagens diagnósticas e terapêuticas mais eficazes para alergias oftálmicas, reduzindo a carga sobre os pacientes e melhorando sua qualidade de vida.

INTRODUCTION

The diagnosis of allergic diseases of the ocular organs is a critical component of ophthalmology, encompassing immunological, allergological, and ophthalmological aspects. These diseases represent a challenge due to their high prevalence, diverse clinical forms, and impact on patients' quality of life. Immunopathological processes in allergic ophthalmic diseases form a complex interplay between allergens, immune system cells, and inflammatory mediators. This necessitates a detailed analysis of systemic and local allergy mechanisms for their effective diagnosis and treatment.

The literature places emphasis on the mechanisms of immune reactions and their clinical manifestations in the form of ophthalmic diseases. For example, Rodrigues et al.⁽¹⁾ highlight the wide variety of allergic conjunctivitis phenotypes, including seasonal and persistent types, which require a differentiated approach to diagnosis. The authors stress the importance of developing standardised diagnostic criteria that allow for more accurate identification of specific phenotypes and appropriate therapeutic strategies. Khatri et al.⁽²⁾ focused on the role of low-molecular-weight ligands in immunoglobulin E (IgE)-mediated processes, particularly in the context of allergic reactions. The authors examined the mechanisms through which these ligands interact with the immune system, leading to the activation of inflammatory processes in allergies. Meanwhile, Bielory et al.⁽³⁾ underscored the importance of exploring seasonal fluctuations in the prevalence of allergic ophthalmic diseases, especially in the context of climate change, which increases the duration of pollen allergen exposure. Their findings suggest a rise in the complexity of symptom prediction in patients due to the extended pollen season. This highlights the need for new methods to monitor environmental factors and their impact on allergic eye diseases. Bonini et al.,⁽⁴⁾ in turn, delved into the analysis of endotypes and phenotypes of allergic conjunctivitis, defining their impact on the course of the disease. In particular, they noted that understanding the endotypic characteristics of patients improves the selection of individualised therapy, tailored to the pathophysiological features of each case. This opens the way for personalised medicine, which is especially relevant for diseases with polymorphic manifestations.

The authors also highlight various aspects of allergic diseases, particularly those with ophthalmic manifestations. For instance, Wróbel-Dudzińska et al.⁽⁵⁾ analysed the prevalence of dry eye symptoms among students at Polish universities, investigating factors that may contribute to

the development of this condition. They identified a correlation between socio-economic conditions and environmental factors, which could have a substantial impact on the eye health of students. Another aspect of allergic diseases is addressed by Bubyř,⁽⁶⁾ who investigated the optimisation of food allergy diagnostics in children with gastrointestinal disorders. This study focused on the importance of accurate prediction and early detection of food allergies in children with concomitant digestive organ diseases, which can affect the treatment.

Attention is also drawn to animal allergens. Min et al.⁽⁷⁾ conducted a study on the structure of dog (Can f 1) and cat (Fel d 7) allergens and their ability to bind with ligands. The results of this study may aid in the further development of therapeutic agents and the identification of new approaches for treating animal allergies.

The issue of allergic conjunctivitis was explored by Dupuis et al.,⁽⁸⁾ who investigated the mechanisms behind its development and clinical manifestations. They emphasised the importance of timely diagnosis and effective treatment of this condition, which is one of the most common among patients suffering from allergies. Another important aspect is the relationship between allergic rhinitis and conjunctivitis. A meta-analysis conducted by Iordache et al.⁽⁹⁾ investigated this phenomenon, describing the mechanisms of their concurrent development, which allowed for the identification of key aspects in the diagnosis and treatment of allergic rhinoconjunctivitis. The authors stressed the need for a comprehensive approach in treating patients suffering from both conditions simultaneously. The issue of individual approaches was also addressed by Knyziak-Mędrzycka et al.,⁽¹⁰⁾ who analysed the sensitisation profile to food allergens among children in Poland using molecular diagnostics. This approach enabled a more precise identification of allergens and the development of personalised allergy treatment methods, which is particularly important for children.

Despite achievements in allergic ophthalmic disease research, gaps remain that require further investigation. In particular, the role of cross-allergic reactions between different types of allergens, including pollen, food, and contact allergens, in the formation of the clinical picture of the disease is insufficiently explored. Their impact on the development of chronic inflammation and exacerbation of the pathology remains a subject of ongoing debate. These aspects remain relevant for the development of comprehensive diagnostic and therapeutic strategies that consider phenotypic and endotypic characteristics of patients. The purpose of this study is to analyse the

current data regarding the pathogenetic mechanisms through which different types of allergens influence the onset and progression of ophthalmic allergies. Special emphasis is placed on the systematisation of knowledge about cross-reactions between pollen and food allergens, which contributes to improving the effectiveness of the diagnosis and treatment of these conditions.

So, the objective of this study was to conduct a comprehensive analysis of the pathogenetic mechanisms through which various groups of allergens cause ocular manifestations. To achieve this aim, the following research secondary objectives were established: to classify the primary groups of allergens and evaluate their impact on the visual organs; to define the relationship between specific allergens and their distinct ophthalmological manifestations; to assess cross-reactive allergic responses, specifically focusing on the role of food and inhalant allergens; to outline the prevalence of ophthalmic symptoms and provide targeted clinical recommendations.

METHODS

The study aimed to analyse current scientific data regarding the pathogenetic mechanisms through which allergens with ophthalmic manifestations influence clinical symptoms. The study was conducted throughout 2024.

The study was based on the analysis of contemporary scientific literature presented in leading peer-reviewed journals and monographs. The sources of information included publications from databases such as PubMed®, Scopus, Web of Science, and Google Scholar. For the analysis, papers published between 2010 and 2024 were considered.

To analyse the pathogenetic mechanisms through which allergens with ophthalmic manifestations exert their effects, sources that met specific inclusion criteria were selected. The main criterion for relevance was the publication date: only materials published within the last 10 years were considered. This approach ensured the use of up-to-date data reflecting the latest discoveries in immunology, allergology, and ophthalmology. Furthermore, only those studies that highlighted key aspects of immunopathogenetic mechanisms, including IgE activation, the role of target cells (mast cells, eosinophils, T-lymphocytes) in the development of allergies and related ophthalmic reactions, were included. An additional inclusion criterion was the presence of data on specific allergens that trigger ophthalmic manifestations. For the analysis of the pathogenetic mechanisms through which allergens exert their effects, particular attention was paid

to key groups of irritants: aeroallergens, contact allergens, food proteins, chemicals, environmental pollutants, and animal-derived allergens. Special focus was given to studies describing the mechanisms by which these allergens affect the ocular mucosa, conjunctiva, and related structures, which helps identify specific links between the impact of allergens and clinical manifestations. The selected publications included clinical observations or reviews on the mechanisms of interaction between allergens and immune system cells.

To systematise and analyse the data, various types of studies were included, such as peer-reviewed scientific reviews and meta-analyses, which allow for the generalisation of existing data, clinical studies, and experimental models describing the mechanisms of interaction between allergens and the cells and tissues of the visual organs. The sample included publications that address different aspects of allergological and ophthalmological reactions, which were assessed using preliminary screening tools such as the Rayyan software⁽¹¹⁾ for detecting duplicates and specialised tools for evaluating methodology, including Covidence.⁽¹²⁾

The quality of the studies was assessed using appropriate tools and standards, such as the Cochrane Risk of Bias (RoB) for clinical studies, and the Newcastle-Ottawa Scale for cohort and case-control studies. For data synthesis, a qualitative approach was used, which allowed for the identification of key patterns between different types of allergens and clinical manifestations. The quantitative analysis involved the creation of comparative tables to visualise the relationships between allergens and symptoms such as itching, lacrimation, eyelid swelling, and conjunctival redness.

Some studies were excluded from the analysis. This category included papers that had not undergone scientific peer review. Studies with incorrect methodology were also excluded, as the lack of a clear description of the research process or its sample cast doubt on the reliability of the data. Furthermore, studies in which allergic reactions were presented without detailing ophthalmic manifestations were excluded.

After systematising the materials, a final total of 52 studies were selected for the analysis, which allowed for the identification of key patterns between allergens and clinical manifestations. The process of study selection, including identification, screening, eligibility assessment, and final inclusion, is illustrated in figure 1. Particular attention was focused on the relationship between allergen types and the most common symptoms, such as itching,

lacrimation, eyelid swelling, and conjunctival redness. Based on the available publications, a generalised description of the immunopathogenetic mechanisms of allergic reactions was created, with an emphasis on the clinical significance of such manifestations in diagnosis.

The statistical information presented in the analysed sources was systematised in the form of comparative tables, which allowed for a clear representation of data on the impact of specific allergens on the ocular conjunctiva.

RESULTS AND DISCUSSION

Classification and impact of allergens on the visual organs

Allergic conjunctivitis is often caused by aeroallergens. The main categories are pollen, dust mites, mould spores, and domestic dust. Birch pollen, alder, oak, grasses, ragweed, and mugwort are the most powerful plant allergies. Pollen grains in the air increase during these plants' flowering season, causing widespread allergy reactions. Poplar fluff (*Populus trichocarpa*) is commonly mistaken for a severe allergen, but it can carry pollen from other plants and dust particles that cause allergy reactions. Poplar fluff does not cause allergies, although it may irritate and create allergic symptoms in sensitive people. Dust mites *Dermatophagoides pteronyssinus* and *farinae* are the main cause of allergic sensitisation because their excrement contains proteins (Der p 1, Der f 1) that trigger immunological responses. *Aspergillus fumigatus*,

Cladosporium herbarum, *Penicillium chrysogenum*, and *Alternaria alternata* produce mould spores, another common allergen.⁽⁴⁾ These microbes love damp soil, food, and overripe produce. Dust mites, silk and cotton fibres, animal hair and skin, and microscopic wood particles make household dust an allergy.

Contact allergens are critical to the development of visual organ allergic reactions owing to direct chemical or biological irritating exposure. Such compounds might cause localised allergic reactions such itching, redness, lacrimation, and eyelid swelling, lowering patients' quality of life. Cosmetics are a common trigger. Parabens and aromatic compounds like citronellol and limonene, used in facial treatments, makeup removers, eyeshadows, and mascaras, might cause hypersensitivity. Colour pigments like zinc and titanium oxides can also cause skin and eye mucosal irritation and inflammation.

Pharmaceuticals used in ophthalmology can be sensitising due to allergenic components. Ophthalmic solution preservative benzalkonium chloride has been linked to eye irritation. Beta-blockers like timolol and antibiotics like chloramphenicol and gentamicin can also cause sensitisation. Even ocular hydration products like artificial tears might cause allergy reactions if they contain allergenic excipients.

Contact lenses and maintenance items also contribute to ocular allergies. With continuous use, silicone hydrogel polymers in lenses may cause hypersensitivity. Lens cleaning solutions with strong chemicals like

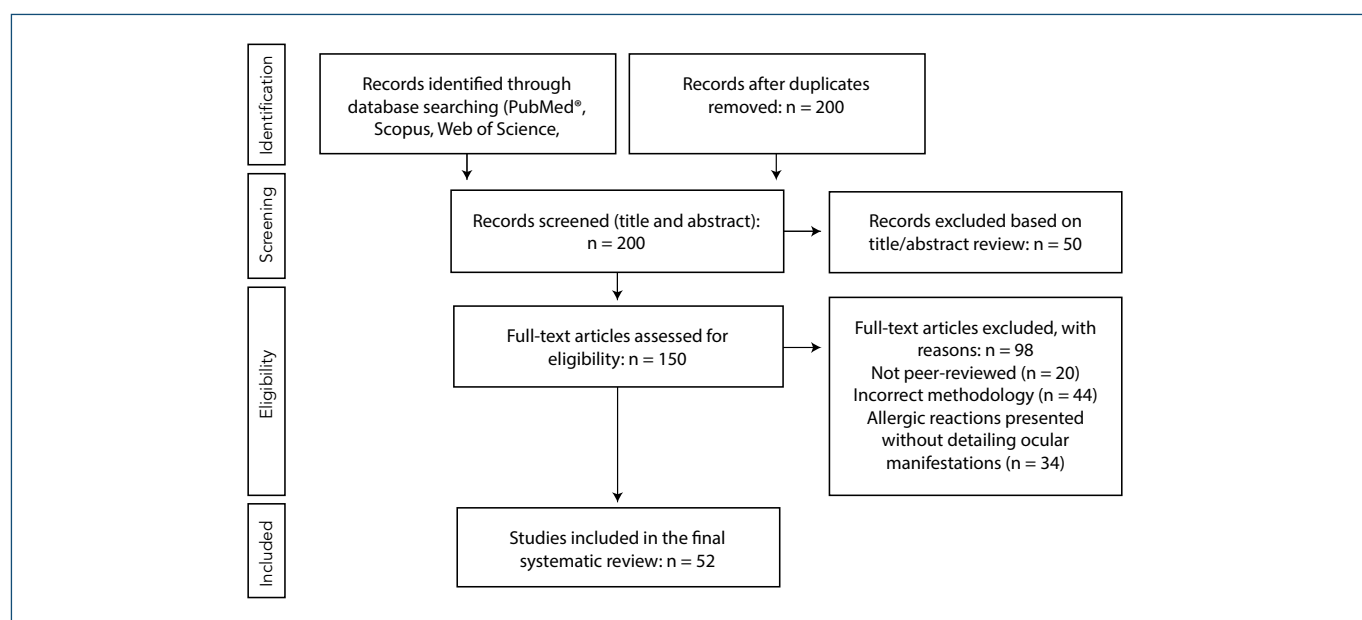


Figure 1. Systematic review literature search and selection process (referred Reporting Items for Systematic reviews and Meta-Analyses – PRISMA flow).

hydrogen peroxide or PAPB can worsen these reactions. Improper lens maintenance strains the ocular mucosa, increasing discomfort and allergic reactions.

Certain food allergies can cause ophthalmologic symptoms. Food sensitisation can cause eyelid puffiness and redness. Almonds and cashews include the strong allergenic proteins Ara h 1 and Ara h 2.

Tropomyosin, a protein in prawns, oysters, and squid, is a common seafood allergy. Milk and eggs, two of the most common dietary triggers in children, cause sensitisation through casein and beta-lactoglobulin and ovalbumin and ovomucoid proteins.⁽⁶⁾ Pollen allergen-protein cross-reactivity in food is also essential. Birch pollen-sensitive people may be allergic to apples, peaches, kiwis, celery, and tomatoes.

Chemical allergies affect eye health, especially in polluted areas. The furniture and construction industry uses formaldehyde, a powerful irritant. Long-term exposure to this chemical may cause conjunctival redness and irritation. PM 2.5 and nitrogen oxides from vehicle exhaust can penetrate ocular tissues and cause inflammation.⁽¹⁾ Resins and paint coats release allergenic volatile chemicals into the air, triggering sensitisation. Tobacco smoke contains ammonia, acetone, and phenols, which can worsen sensitisation reactions and increase mucous membrane permeability to other agents.

Saliva, hair, and dander proteins can cause allergic responses. In particular, Fel d 1, a protein in cat saliva and fur, causes most home allergies. Horse Equ c 1 and dog Can f 1 have similar allergenic characteristics. Dust mite and bee (Api m 1) and wasp (Ves v 5) allergens can cause eyelid oedema and conjunctival irritation.⁽⁷⁾

Understanding each allergen type is essential for developing effective diagnostic and preventive methods for allergic ocular disorders. In conclusion, aeroallergens, contact agents, dietary proteins, chemical pollutants, and animal-derived particles cause ocular allergy reactions, which must be identified to develop appropriate management techniques.

Relationship between allergens and ophthalmological manifestations

A review of the literature identified that the effects of major allergen groups are mediated by complex immunopathogenetic mechanisms that activate the immune response. Particular emphasis was placed on environmental allergens, which are among the most common triggers.

According to systematic sources, pollen from ragweed, birch, and grasses induces acute inflammatory responses

via IgE-mediated sensitisation, resulting in an increase in serum IgE levels to 200 to 500 kU/L in sensitised individuals.^(4,8) Upon allergen exposure, mast cells become activated and release mediators such as histamine (1.2 to 1.8 ng/mL), prostaglandins, and leukotrienes. This process is key to the development of primary symptoms, including itching, conjunctival redness, and lacrimation.⁽⁸⁾

Contact allergens, including cosmetic products and ophthalmic medications, tend to provoke prolonged allergic reactions, frequently associated with delayed-type hypersensitivity. Substances such as benzalkonium chloride, commonly used in eye drops, contribute to inflammatory processes by activating T lymphocytes, which, in turn, induce delayed eyelid oedema and irritation of the ocular mucosa. Studies have shown that benzalkonium chloride increases intercellular adhesion molecule (ICAM)-1 expression on endothelial cells by three- to five-fold, thereby promoting the migration of inflammatory cells into the conjunctiva.^(4,6)

The immune mechanisms underlying allergic reactions that manifest as ophthalmic symptoms exhibit specificity depending on the type of allergen, target cells, and the molecular pathways involved. IgE-mediated immune response is the predominant mechanism in the pathogenesis of allergic conjunctivitis, particularly in response to aeroallergens.^(4,9) This reaction develops in two distinct phases. During the initial exposure to an allergen, sensitisation occurs through the activation of antigen-presenting cells (dendritic cells and macrophages), which present the allergen's antigen on major histocompatibility complex (MHC) class II molecules. This information is relayed to type 2 T-helper (Th2) cells, which subsequently produce cytokines interleukin (IL)-4 and IL-13, stimulating B-lymphocyte differentiation and the production of specific IgE (IL-4 levels increase by a factor of 2-3, and IL-13 by 1.5-2).⁽⁹⁾ These antibodies bind to high-affinity FcεRI receptors on the surface of mast cells, forming a sensitised complex.

Upon subsequent exposure to the allergen, cross-linking of IgE on the surface of mast cells induces their degranulation. This results in the release of key inflammatory mediators, including histamine, tryptase (1.5 to 2.5 ng/mL), prostaglandins, leukotrienes, and cytokines. Histamine interacts with H1 receptors in the vascular endothelium, leading to vasodilation, hyperaemia, oedema, and pruritus, which are the hallmark symptoms of allergic conjunctivitis.⁽⁹⁾ This mechanism is responsible for the acute symptoms of allergic reactions, such as itching, lacrimation, and conjunctival hyperaemia. Aeroallergens,

including birch pollen and house dust mites, are the most common triggers of IgE-mediated reactions.^(4,9)

Delayed-type hypersensitivity (classified as type IV hypersensitivity according to the Coombs and Gell classification) is mediated by T lymphocytes, particularly CD4⁺ (Th1) and CD8⁺ cells, which orchestrate a cellular immune response. This reaction is most associated with contact allergies.

Following the penetration of allergens, such as components of cosmetic products or ophthalmic medications, into the eyelid skin or conjunctival mucosa, dendritic cells present the antigen to T cells. Th1 cells subsequently release cytokines, including interferon-gamma (IFN- γ) and tumour necrosis factor-alpha (TNF- α), which activate macrophages and other immune cells, thereby promoting inflammation. In the effector phase of the immune response, cytotoxic CD8⁺ cells induce apoptosis in target cells, leading to localised tissue damage. This mechanism explains the delayed onset of symptoms, including eyelid oedema, pronounced irritation, and pruritus. Delayed-type hypersensitivity is frequently associated with prolonged use of pharmaceutical agents (e.g., eye drops containing preservatives) or contact lenses.^(6,8)

Cytokine-mediated inflammatory reactions represent a universal mechanism accompanying all allergic responses. Interleukins, particularly IL-4, IL-5, and IL-13, play a central role in this process, being activated through the involvement of Th2 cells. IL-4 and IL-13 enhance IgE production, while IL-5 is responsible for eosinophil activation. The activation of eosinophils leads to the release of toxic proteins, such as major basic protein (MBP, 0.5 to 1.2 ng/ml) and eosinophilic cationic protein (ECP, 5 to 15 ng/ml), which cause damage to the conjunctival epithelium. These processes sustain and prolong allergic inflammation, contributing to chronic allergic conjunctivitis or keratoconjunctivitis.⁽⁹⁾

Elevated levels of pro-inflammatory cytokines, such as TNF- α and IL-1 β , further promote vascular endothelial activation, thereby enhancing the recruitment of immune cells to the site of inflammation. Key aspects of this type of reaction include the increased levels of cytokines (IL-4, IL-5, IL-13) observed in patients with chronic allergic conjunctivitis and the fact that this mechanism plays a crucial role in persistent allergic conditions associated with structural alterations in the mucosal epithelium (Table 1).

An analysis of the mechanisms underlying allergic reactions that lead to ophthalmic manifestations demonstrates certain patterns in the relationship between

Table 1. Relationship between allergen groups, primary mechanisms, and symptoms

Allergen group	Examples of allergens	Response mechanism	Primary symptoms
Aeroallergens	Ragweed, birch, and grass pollen; mould spores, house dust mites	IgE-mediated reaction, mast cell activation, histamine, and other inflammatory mediator release	Itching, lacrimation, hyperaemia, eyelid oedema, seasonal allergic conjunctivitis
Contact allergens	Cosmetics (preservatives, dyes), ophthalmic preparations (benzalkonium chloride), metals (nickel)	Delayed hypersensitivity (type IV), T-cell activation and inflammatory cascade	Eyelid oedema, irritation, redness, delayed allergic dermatconjunctivitis
Food allergens	Dairy products, seafood, nuts, eggs	IgE-mediated systemic reaction, elevated cytokine and eosinophil levels	Conjunctivitis, itching, eyelid oedema
Chemical pollutants	Formaldehyde, exhaust fumes, tobacco smoke, industrial emissions	Cytokine cascade, chronic inflammation, possible delayed-type reactions	Redness, chronic ocular irritation, exacerbation of allergic reactions (allergic conjunctivitis, contact dermatconjunctivitis)

Source: Compiled by the authors based on Buby,⁽⁶⁾ Dupuis et al.⁽⁸⁾ and Iordache.⁽⁹⁾

allergen types and the clinical symptoms experienced by patients. Key factors that may modulate this relationship include the level of patient sensitisation, genetic predisposition, comorbidities, and environmental factors such as air pollution levels. Aeroallergens (pollen, mites, fungal spores) most commonly trigger IgE-mediated reactions. These manifest as acute symptoms such as itching, lacrimation, and conjunctival hyperaemia, which are characteristic signs of allergic conjunctivitis. In patients with high sensitisation levels or a genetic predisposition to allergies, these symptoms may be more pronounced, particularly during seasonal pollen exposure.

Contact allergens, such as cosmetic products and ophthalmic preparations, are more likely to induce delayed-type hypersensitivity, resulting in chronic symptoms such as eyelid oedema and irritation of the ocular mucosa, significantly affecting patients' quality of life. Prolonged use of these substances may increase the frequency of such reactions. Food allergens may also be associated with ophthalmic manifestations, including pronounced eyelid oedema and itching around the eyes. These reactions are particularly pronounced in cases of cross-reactivity with pollen allergens, such as birch pollen. Patients with this type of sensitisation may experience allergic symptoms not only upon exposure to pollen but also following the ingestion of certain foods. Chemical pollutants, such as vehicle emissions or household chemical components, have the potential to activate the cytokine cascade, provoking inflammation and chronic ocular irritation. Patients residing in areas with high levels of pollution tend to exhibit more pronounced

symptoms, which may be compounded by other allergic reactions, leading to chronic forms of conjunctivitis.

Research indicates that the level of sensitisation, as determined by the concentration of specific IgE antibodies in serum, serves as a key predictor of the severity of allergic reactions and their ophthalmological manifestations. For instance, elevated levels of specific IgE to ragweed pollen (> 17.5 kU/L) have been associated with more pronounced conjunctival hyperaemia and lacrimation.^(4,8) High concentrations of IgE also correlate with increased levels of ECP in tear fluid, indicating enhanced eosinophil involvement in the pathogenesis of allergic inflammation.⁽⁹⁾ This supports the observation that patients with high levels of sensitisation exhibit more severe clinical symptoms and face an increased risk of persistent or chronic forms of allergic conjunctivitis.⁽⁸⁾

Beyond immunological factors, genetic predisposition and comorbid conditions, such as bronchial asthma and atopic dermatitis, play a crucial role in the severity of ophthalmological manifestations. In patients with concurrent asthma, the concentration of IL-4 and IL-13 in tear fluid is reported to be two to three times higher than in patients without coexisting allergic conditions.⁽⁹⁾ Furthermore, individuals residing in urban areas with exposure to elevated concentrations of fine particulate matter ($PM_{2.5} > 35 \mu g/m^3$) demonstrated increased levels of TNF- α and IL-1 β in tear fluid, exacerbating inflammatory responses on the ocular surface.⁽¹³⁾

These findings highlight the influence of environmental factors on the development and severity of allergic reactions in ophthalmology. To summarise, the specific clinical manifestations and severity of ocular allergies are dictated by the underlying immune mechanism, ranging from acute IgE-mediated responses to delayed T-cell hypersensitivity, and are significantly modulated by patient sensitisation levels, genetic predisposition, and environmental exposures.

Cross-reactive allergic responses: the role of food and inhalant allergens

Cross-reactive allergy is a complex immunological phenomenon that arises due to structural similarities between proteins from different allergens. The immune system, recognising these similar molecules as identical antigens, mounts a comparable response even when they originate from distinct sources. This phenomenon has been extensively investigated in the context of interactions between pollen and food allergens. However, food allergens exhibit diverse properties that influence their

potential to trigger cross-reactive responses, with thermal processing emerging as a potential strategy for mitigating allergic manifestations.

Cross-reactive allergy is triggered by structural similarities between proteins from different allergens, frequently involving interactions between seasonal pollen and food items. The immune system recognises structurally similar molecules as identical antigens, inducing an allergic reaction even in the absence of direct contact with the primary allergen. The key cross-reactive links and their seasonal dependencies are summarised in table 2.

Table 2. Cross-reactivity between seasonal pollen and food allergens

Primary allergen	Season	Cross-reactive food products	Key allergenic proteins
Birch pollen	Spring	Apple, carrot, peach, peanuts, hazelnuts, celery	Bet v 1; Mal d 1 (apple), Cor a 1 (hazelnuts), Ara h 8 (peanuts)
Grasses	Summer	Melon, watermelon	Not specified
Mugwort pollen	Autumn	Celery, carrot, aromatic herbs, mango; courgette, banana, sunflower seeds, honey	Art v 1
Ragweed pollen	Autumn	Melon, banana, watermelon	Amb a 8 (profilin)

Source: Compiled by the authors based on Cox et al.,⁽¹⁴⁾ Kamath et al.,⁽¹⁵⁾ and Chruszcz et al.⁽¹⁶⁾

Studies confirm that the severity of cross-reactive allergies is directly correlated with the concentration of the primary allergen in the environment.⁽¹⁴⁻¹⁶⁾ During peak pollen seasons (April to May for trees, June to July for grasses), individuals demonstrate increased susceptibility to cross-reactions, even at minimal exposure to dietary triggers. For instance, during ragweed pollen season, clinical symptoms following melon consumption may be more pronounced than out of season, despite identical allergen intake. Seasonality further establishes an optimal setting for the development of multifactorial allergic responses. In pollen-sensitised individuals, additional triggers, such as chemical pollutants or contact with domestic animals, exacerbate the inflammatory response. This is particularly relevant in urbanised areas, where natural allergens are compounded by exposure to vehicle emissions and fine particulate matter.

The identification of seasonal dynamics in allergic manifestations requires a detailed medical history and the application of specific allergy diagnosing methods. The most informative approach involves determining the levels of specific IgE antibodies to seasonal pollen allergens and cross-reactive food components. Effective patient management can be achieved through the use of antihistamines and topical mast cell stabilisers, the development of an individualised elimination diet plan

during high-risk seasons for cross-reactive responses, and the administration of allergen-specific immunotherapy (ASIT) to reduce sensitivity to major pollen allergens.⁽¹⁷⁾ Cross-reactive allergy complicates the diagnosis and treatment of patients with ophthalmological manifestations of allergic diseases. A thorough analysis of the structural similarity of proteins and an understanding of the mechanisms underlying secondary allergens are essential. During peak pollen seasons, such as the flowering periods of birch, ragweed, or mugwort, the immune system of sensitised individuals remains in a state of heightened activity. Elevated airborne pollen concentrations activate large numbers of mast cells and basophils, leading to the extensive release of inflammatory mediators such as histamine, prostaglandins, and leukotrienes. This creates a “hyperactive immune background”, in which even structurally similar proteins present in minimal amounts (e.g., in food) are recognised by the immune system as threats. For instance, the Bet v 1 protein in birch pollen actively interacts with IgE antibodies bound to mast cells. During this period, even a small amount of Mal d 1 from apples may enhance mast cell degranulation, triggering ophthalmic symptoms associated with cross-reactive allergic responses. Understanding the mechanisms of such reactions is crucial for effective treatment and symptom prevention. Personalised approaches to diagnosis and management can improve the quality of life for affected individuals.^(14,15,17)

In conclusion, cross-reactivity between pollen and food allergens substantially complicates the clinical picture of ocular allergies, driven by structural protein similarities and seasonal exposure spikes. Recognising these cross-reactive patterns is therefore essential for implementing effective, personalised dietary and therapeutic interventions.

Prevalence of ophthalmic symptoms and clinical recommendations

The distribution of ophthalmic symptoms among patients with allergic reactions is a key area of research in allergology and ophthalmology. A review of existing literature identified the most common manifestations and their relationship with specific allergen types.⁽¹⁸⁻²⁰⁾ Such insights facilitate a better understanding of pathological processes and support the development of individualised treatment strategies.

Ophthalmic symptoms are common manifestations of allergic reactions and can impact patients' quality of life. The most frequently observed symptoms include

itching, conjunctival redness, and lacrimation, which are associated with various allergen groups, including pollen, household, and food allergens. In some cases, severe eyelid oedema may occur, necessitating particular ophthalmological attention. The frequency and characteristics of these symptoms are influenced by the type of allergen involved (Table 3).

Table 3. Frequency of ophthalmic symptoms in relation to allergen type

Symptom	Frequency (%)	Typical allergens	Manifestation characteristics
Itching and conjunctival redness	80-90	Household (dust, dust mites), food allergens	Often accompanied by lacrimation and photophobia
Lacrimation	60-75	Pollen, household allergens	Typically presenting as isolated ocular tearing or accompanied by photophobia
Angioedema	10-15	Food allergens (in cases of multiple sensitisation)	Characterised by pronounced eyelid swelling and severe ocular irritation

Source: Compiled by the authors based on Klossek et al.,⁽¹⁹⁾ Lee et al.⁽²⁰⁾ and Kari et al.⁽²¹⁾

Analysis of findings enabled not only the identification of the primary ophthalmic symptoms caused by allergens but also the development of a practical diagnostic algorithm. This algorithm aims to improve the diagnosis of ophthalmic allergies, reduce the time required for identifying the underlying causes of symptoms, and optimise treatment strategies. The diagnostic approach is based on a combination of thorough medical history collection, physical examination, and laboratory testing. The analysis of common ophthalmic symptoms enabled the development of a practical, five-step diagnostic algorithm aimed at reducing identification time and optimising treatment strategies for ophthalmic allergies. The recommended clinical approach is outlined in table 4.

Table 4. Diagnostic algorithm for ophthalmic allergic reactions

Step	Objective	Key actions
1	Patient history & examination	Assess symptom frequency, duration, and seasonal dependence Identify manifestations (pruritus, hyperaemia, lacrimation, oedema) and potential triggers (pollen, mites, food) Evaluate comorbid conditions like asthma or rhinitis
2	Laboratory testing	Measure total serum IgE levels to gauge overall allergic predisposition Conduct specific IgE panels for common household, seasonal, and food allergens
3	Skin testing	Perform skin prick tests with allergen extracts to confirm specific sensitisation, provided there are no contraindications
4	Differential diagnosis	Rule out infectious conjunctivitis, dry eye syndrome, and traumatic ocular injury Analyse response to trial treatments, such as antihistamines
5	Advanced testing	Conduct immune response and controlled provocation tests for patients with suspected food sensitisation or angioedema

Based on the synthesis of available data, it is recommended that a comprehensive analysis of common

allergens and timely screening tests be conducted, particularly for patients with systemic allergies or elevated IgE levels. Treatment should encompass pharmacological management, including antihistamines, topical mast cell stabilisers (e.g., sodium cromoglicate), and, where necessary, topical corticosteroids. Immunotherapy is indicated for patients with confirmed sensitisation, such as ASIT. Preventive measures should focus on minimising exposure to triggering allergens and optimising living conditions (e.g., air purification, reducing exposure to dust mites). Therefore, a detailed analysis of the mechanisms underlying ophthalmological symptoms not only enhances diagnostic approaches but also improves the efficacy of prevention and treatment strategies, ultimately reducing the overall burden on patients with allergic diseases.

The studies on allergic reactions and ophthalmological manifestations provide both confirmation and an expanded understanding of the mechanisms underlying allergic responses, their triggers, and clinical manifestations. Hemmer et al.⁽²²⁾ highlighted the correlation between sensitisation to animal allergens and exposure to domestic pets. Their study also indicates a higher prevalence of sensitisation among pet owners, underscoring the importance of considering this factor in the diagnosis and prevention of allergies. Furthermore, Muñoz et al.⁽²³⁾ examined reactive dye allergens, which are significant in occupational settings. The results revealed a sensitisation pattern similar to that of other industrial allergens, necessitating further research in the field of occupational allergology.

The association between atopic dermatitis and ophthalmological complications is explored in a study by Rønnstad et al.,⁽²⁴⁾ which demonstrates that patients with atopic dermatitis are at a higher risk of developing ophthalmological disorders. This finding is corroborated by the present study, which highlights an increase in cases of atopic keratoconjunctivitis and exacerbations of allergic conjunctivitis among patients with concomitant atopy. Food allergy and the multifactorial approach to its management were examined by Sindher et al.,⁽²⁵⁾ who describe food allergy as a complex process involving genetic, environmental, and immunological interactions. Their findings reinforce the importance of a comprehensive treatment approach, including immunotherapy and personalised dietary recommendations. Das et al.⁽²⁶⁾ established a link between air pollution and allergic eye diseases in children and adolescents. The findings indicate a similar mechanism by which pollutants affect the

conjunctiva and exacerbate chronic inflammation, highlighting the importance of environmental factors in the development of allergic eye diseases. Furthermore, the observed seasonal variation in symptoms supports the conclusions of this study. Fukuda et al.⁽²⁷⁾ complemented the present findings by providing a deeper insight into contemporary therapeutic approaches for ocular allergies. Their conclusions confirm the central role of cytokines in the pathological process, particularly in relation to the impact of chemical pollutants. The findings of Fukuda et al. emphasise the need for further research to assess long-term risks and optimise treatment strategies.

The results of this study underscore the importance of cross-reactivity between aeroallergens and food allergens, aligning with the conclusions of Zhao et al.⁽²⁸⁾ These authors suggest that immunotherapy may play a crucial role in reducing cross-reactivity between dust mite allergens and other aeroallergens. However, the effectiveness of this approach remains variable, depending on individual patient characteristics, necessitating further research to optimise immunotherapy protocols.

A meta-analysis conducted by Galor et al.⁽²⁹⁾ emphasised that ocular symptoms such as itching and dryness may have both allergic and non-allergic origins, thereby complicating differential diagnosis. In this context, the findings confirm that allergic mechanisms represent only one of many potential causes of ophthalmological complaints, highlighting the importance of a multifactorial approach to treatment. A meta-analysis conducted by de Groot et al.⁽³⁰⁾ examined sensitisation to 2-hydroxyethyl methacrylate (HEMA) as a factor in the development of contact allergic dermatitis, which is particularly relevant for assessing the risks of occupational sensitisation. Given the widespread use of HEMA in dentistry and cosmetology, there is a need to improve preventive measures and enhance early diagnostic methods for contact allergy to this compound. Villa et al.⁽³¹⁾ analysed the molecular characteristics of sesame allergens, underlining their relevance in assessing cross-reactivity. The findings corroborate the importance of such research in refining the diagnosis of food allergies, as many patients exhibit sensitisation to multiple food products, complicating the identification of the primary allergen. Moreover, the study explored the impact of thermal and technological food processing on allergenicity. Costa et al.⁽³²⁾ focused on allergies to Rosaceae family products, highlighting their clinical significance. As this botanical family includes widely consumed fruits such as apples, peaches, and cherries, some of which were examined in the present study,

greater attention should be devoted to diagnostic approaches that identify hidden allergens in food products.

Barber et al.⁽³³⁾ underscored the significance of molecular allergology in advancing the diagnosis and treatment of allergic diseases. The findings further support the importance of this approach in individualising allergy diagnostics. The study by Wolffsohn et al.⁽³⁴⁾ proposed an alternative method for managing ocular allergic reactions, specifically using contact lenses to mitigate allergen exposure. This approach contrasts with conventional treatments centred on pharmacological therapy, highlighting the potential role of a mechanical barrier in preventing exacerbations. Gomes et al.⁽³⁵⁾ established that controlled environments with elevated exposure to triggers can aggravate allergic conjunctivitis symptoms in patients with concurrent dry eye syndrome. Both studies affirm the necessity of a comprehensive approach to diagnosing ophthalmological allergic manifestations. However, Gomes et al. particularly stressed the influence of external factors. The findings of Scheman et al.⁽³⁶⁾ on contact allergy reinforce the importance of identifying sensitisation threshold levels to prevent allergic reactions. This aligns with the conclusions of de Groot et al.⁽³⁰⁾ regarding occupational allergens, particularly methacrylates, although the latter focuses on a specific chemical agent, whereas the former study encompasses a broader spectrum of potential allergens.

Katellaris⁽³⁷⁾ analysed the specificity of ophthalmic allergic reactions in the Asia-Pacific region and identified an increased prevalence of certain types of allergic eye conditions in relation to climatic factors and air pollution levels. This complements the findings of Das and Basu⁽²⁶⁾, who also established a significant impact of pollution on allergic eye manifestations, although their study focused on the paediatric population. Geraldini et al.⁽³⁸⁾ investigated the epidemiology of ocular allergy among adolescents and associated comorbidities. Their findings suggest that atopic dermatitis, asthma, and rhinoconjunctivitis frequently co-occur in these patients, which supports systemic nature of allergic diseases, as evidenced by the analysed data. Furthermore, the study by Beutner et al.⁽³⁹⁾ examined changes in sensitisation to common inhalant allergens in Germany from 2001 to 2021. Their results demonstrate a substantial increase in sensitisation levels, which may be attributed to urbanisation and environmental changes. These findings partially correlate with the present study, further confirming the role of ecological factors in the rising incidence of sensitisation.

The study by Fauquert et al.⁽⁴⁰⁾ provided detailed recommendations regarding the conjunctival provocation

test, which is a valuable tool for diagnosing allergic conjunctivitis. Their findings support the necessity of standardising testing procedures and considering individual patient sensitisation. Rasmussen et al.,⁽⁴¹⁾ in their meta-analysis, determined the prevalence of allergic sensitisation in patients with vernal keratoconjunctivitis, reporting a high frequency of polysensitisation. This aligns with the present study, highlighting the importance of accounting for multiple allergens in the diagnosis and management of patients with severe forms of allergic conjunctivitis.

A review of the existing literature offers a deeper understanding of the immune mechanisms underlying allergic reactions affecting the eyes and the influence of various allergens on the development of such conditions. Notably, the study by Jacquet⁽⁴²⁾ emphasised the role of allergens such as dust mites in triggering allergic reactions through immune system activation, supporting the conclusion that aeroallergens are contributors to allergic conjunctivitis. The high level of sensitisation to dust mites reported by Almaliotis et al.⁽⁴³⁾ correlates with the analysed data on the primary allergens responsible for allergic conjunctivitis symptoms, underscoring the importance of dust as a trigger in patients with chronic allergic conjunctivitis. The findings of Shaker et al.⁽⁴⁴⁾ further support the relevance of seasonal fluctuations in allergen levels, which may contribute to cross-reactive allergic responses. Their study reinforces the need for diagnostic and predictive approaches that account for seasonal pollen activity. This, in turn, allows for the anticipation of increased sensitivity to food allergens, particularly during peak pollen seasons, and facilitates appropriate adjustments to treatment strategies.

Zeindl et al.⁽⁴⁵⁾ examined the structural characteristics of food allergens, employing nuclear magnetic resonance spectroscopy to elucidate the mechanisms underlying cross-reactivity between pollen and food allergens, which may induce severe ophthalmic symptoms. These findings align with the established similarity between Bet v 1 protein in birch pollen and certain food components, which can trigger cross-allergic reactions. The expanded approach discussed by Aydin et al.,⁽⁴⁶⁾ which incorporated proteomic analysis of tear fluid, represents a promising avenue for the diagnosis of ophthalmic allergies, as alterations in tear composition may facilitate the precise identification of allergens responsible for inflammation. This underscores the importance of investigating not only classical IgE biomarkers but also other molecular participants in allergic processes. Furthermore, Chigbu et al.⁽⁴⁷⁾

highlighted the importance of understanding the immunological mechanisms underlying allergic eye diseases, particularly the activation of T-lymphocytes and cytokine release. These findings support previous conclusions regarding the critical involvement of cytokines in chronic forms of allergic conjunctivitis, which is essential for the development of novel therapeutic approaches. Similarly, Zemba et al.⁽⁴⁸⁾ examined biomarkers of ocular allergy and dry eye syndrome, emphasising the correlation between specific protein levels in tear fluid and the severity of clinical symptoms. Their results reinforce the relevance of biomarker analysis in advancing personalised treatment strategies, which is consistent with existing evidence regarding the substantial impact of inflammatory processes on symptom severity.

A meta-analysis conducted by Lo et al.⁽⁴⁹⁾ explored the relationship between keratoconus and risk factors such as eye rubbing, atopy, and other allergic conditions. Their findings underscore the comorbidity between allergic pathologies and structural alterations in the cornea, further demonstrating that chronic ocular irritation may exacerbate clinical manifestations, a conclusion that aligns with their results. The study by Meng et al.⁽⁵⁰⁾ which investigated neuropeptide interactions in the development of allergic rhinoconjunctivitis, rhinitis, and conjunctivitis, corroborates prior findings on the chronic effects of pollutants, which may activate analogous inflammatory mechanisms. Their study highlighted the pivotal role of interactions between sensory nerves and immune responses. Chong-Neto et al.⁽⁵¹⁾ analysed the manifestations of ocular allergy in children and adolescents. Their data indicate that the paediatric population exhibits a higher prevalence of severe forms of allergic conjunctivopathy, underscoring the importance of early diagnosis and prevention.⁽⁵²⁾ This study identified a predisposition to exacerbated allergic reactions in certain patient groups, consistent with their conclusions.

The findings confirm the importance of a comprehensive approach to the diagnosis and treatment of ophthalmic allergic manifestations, which considers not only classical allergens but also their interactions, seasonality, and cross-reactivity. They also reflect global trends in research on allergic eye diseases, contributing to the development of new therapeutic strategies. Future research areas include interactions between different classes of allergens, particularly pollen, food, and chemical allergens, to enhance the understanding of cross-allergy mechanisms. Moreover, emphasis should be placed on the development of novel diagnostic methods, such as tear

fluid analysis and other biomarkers, to enable the precise identification of specific allergens and the assessment of treatment efficacy.

CONCLUSION

This study indicated that allergic reactions affecting the eyes arise from exposure to various allergens, categorised according to their origin and mechanisms of action. Aeroallergens, including pollen, dust mites, and mould spores, are the primary triggers of allergic conjunctivitis. Contact allergens, such as cosmetic products, pharmaceutical agents, and contact lens care solutions, induce local allergic manifestations. Food allergens can cause ophthalmological symptoms, particularly in cases of sensitisation to specific foods such as nuts or seafood. Chemical and animal-derived allergens also have a considerable impact on ocular health, especially in environmentally polluted conditions.

It was established that key allergens responsible for ophthalmic manifestations elicit complex immune responses involving various components of the immune system. Aeroallergens such as pollen and dust mites predominantly trigger IgE-mediated reactions, characterised by typical symptoms of allergic conjunctivitis, including itching, hyperaemia, and lacrimation. Contact allergens, including cosmetic products and ophthalmic medications, induce more prolonged reactions associated with delayed hypersensitivity, leading to oedema and irritation. The mechanisms underlying these allergic reactions involve the activation of T-lymphocytes, the release of cytokines, and inflammatory mediators such as histamine and prostaglandins, which determine the clinical presentation. Cytokine-mediated inflammatory responses play a predominant role in chronic forms of allergic eye diseases. Understanding these mechanisms is crucial for developing more effective diagnostic and therapeutic approaches for ophthalmic allergies, thereby reducing the burden on patients and improving their quality of life.

Findings regarding cross-reactive allergic reactions highlight the complexity of the immunological mechanisms involved in the interaction between pollen and food allergens. The structural similarity of proteins from different allergens may elicit an allergic response even when the allergenic molecules originate from distinct sources. A prominent example is the cross-reactivity between birch pollen and certain food products, such as apples or peanuts. The Bet v 1 protein in birch pollen and other allergenic proteins found in specific food items share similar epitopes, which can trigger an immune response via an IgE-mediated reaction.

The seasonality of allergic reactions is a significant factor influencing the severity of cross-reactivity. During peak pollen seasons, individuals sensitised to these allergens exhibit an increased likelihood of developing symptoms not only in response to pollen but also to food products containing similar protein components. As a result of heightened sensitisation during plant pollination periods, even minimal exposure to cross-reactive food allergens can elicit pronounced ophthalmological symptoms, such as itching and lacrimation. Effective management of such reactions necessitates the use of specialised allergy diagnostic methods, including the measurement of IgE levels for key allergens implicated in cross-reactivity. Furthermore, timely administration of antihistamines, mast cell stabilisers, and the implementation of elimination diets aimed at reducing exposure to triggers can alleviate the disease course. An individualised treatment approach, including ASIT to reduce sensitivity to pollen allergens, helps to decrease the frequency and severity of allergic reactions and improve the quality of life for patients affected by cross-reactive allergy.

Overall, the analysis of the literature supports the findings of the present study, particularly regarding the impact of seasonality, allergen structure, and the importance of comprehensive diagnostic and therapeutic approaches. The role of conjunctival provocation tests was clarified as a crucial diagnostic method, and the impact of ophthalmic allergy on patients' daily lives, including occupational performance, was emphasised. The consistency of the obtained data with global trends underscores the universality of the immunopathogenic mechanisms underlying allergic eye conditions. This supports the need for further refinement of diagnostic algorithms, adaptation of preventive measures to local environmental and climatic conditions, and the development of personalised therapeutic strategies. Limitations include dependence on the availability of full-text versions of some papers and the absence of specific data on ophthalmic manifestations in certain publications. Also, the limitation of this study is that the analysis of specific allergen classes does not account for the multiple factors that may interact in the development of cross-reactive allergies, such as concurrent exposure to chemical pollutants and other non-specific triggers.

AUTHORS' CONTRIBUTION

Maria Zofia Lisiecka: Conceptualization, writing original draft, writing review & editing, project administration.

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