ALLERGIC CONJUNCTIVITIS

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ABSTRACT

Allergic conjunctivitis is an extremely common condition, occurring in up to 50% of individuals reporting allergic symptoms. Although most of the different forms of the condition have many symptoms in common it is important to be able to distinguish them from one another as this may have important prognostic and management implications. This review first discusses the common symptom complex and then divides the allergic conjunctivitides into acute and chronic forms. The acute forms described are seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), while the chronic conditions detailed are atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC). Giant papillary conjunctivitis (GPC) and contact allergic conjunctivitis (CAC), although not pure examples of allergic conjunctivitis have many features in common with the group, and are therefore also described. The review focuses primarily on the clinical presentation of the conditions, but a brief overview of the pathophysiology and an approach to the management of each condition is also provided.

Allergic conjunctivitis is an extremely common disorder. *The Allergy Report,*[1] a survey published by the American Academy of Allergy, Asthma, and Immunology in 2000, found that 35% of families interviewed had experienced allergies during the previous year, of whom over 50% reported associated eye symptoms. Fortunately the vast majority of these are mild and self-limiting, either not requiring medical attention at all or being very adequately managed at the primary care level. A small minority however may be very difficult to control and may result in chronic sight-threatening complications, caused by secondary corneal involvement.

All classifications have inherent limitations because of the overlap of the classically described conditions. Grouping the allergic conjunctivitides, however, into acute and chronic subtypes is very commonly used, and has significant clinical value.

The two major acute disorders are seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), while atopic keratoconjunctivitis (APC), vernal keratoconjunctivitis (VKC) and giant papillary conjunctivitis (GPC) are recognised as chronic ones. Some authors feel that GPC is not strictly an allergic condition, containing as it does elements of chronic low-grade trauma, but it is traditionally classified with the chronic allergic conjunctivitides and has several features in common with these conditions.

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The above diagnostic groupings do not however cover the full spectrum of allergic conjunctival disease. For example, topical medications may cause either a toxic or allergic conjunctivitis and it may be important, although not always easy, to distinguish between these responses in order to treat the patient effectively. In addition conjunctivitides associated with peripheral corneal infiltrates may have an allergic aetiology as well. Understanding the pathophysiology of these conditions also impacts on their effective management.

The presence of a type I hypersensitivity reaction is usually considered a defining characteristic of an allergic conjunctivitis, distinguishing it from other immune-dependent ocular surface diseases. Within this definition the acute disorders are usually referred to as being purely type I hypersensitivity reactions while the chronic ones are described as having an additional type IV component. Although this classification has some validity, ongoing research has shown it to be a significant oversimplification, and the full complexity of the relationship between the clinical and immunological pictures remains to be elucidated.

COMMON CLINICAL PRESENTATION

Although each condition has typical distinguishing features there are several signs and symptoms that are common to all types of allergic conjunctivitis. Patients usually complain of a burning or itching sensation, which is often associated with an irresistible urge to rub the eyes. Rubbing however provides only transient relief and usually aggravates the itchiness leading to an even greater desire to rub and a consequent perpetually aggravating cycle of itch-rub-itch. Tearing which may be severe is very common although this may be somewhat less prominent as chronicity increases, resulting in the complaint of a slightly thicker, less profuse discharge.

The complaint of red and swollen eyes is also common to all forms of allergic conjunctivitis and this is usually further exacerbated by the above itch-rub-itch cycle. A degree of photophobia is also a common symptom although the pathophysiology of this symptom is not well understood. Examination usually confirms the above with chemosis, hyperaemia, and tearing which is occasionally associated with a fine papillary reaction (Fig. 1).

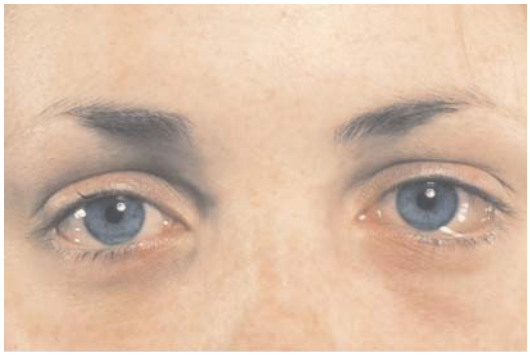

Fig. 1. Acute conjunctival chemosis and hyperaemia.

THE ACUTE CONDITIONS: SEASONAL ALLERGIC CONJUNCTIVITIS (SAC) AND PERENNIAL ALLERGIC CONJUNCTIVITIS (PAC)

SAC and PAC, the two acute conditions, are both usually bilateral although they may be asymmetrical. They are almost always self-limiting on removal of the triggering allergen. They have an equal gender distribution and there is no particular age or racial distribution. A personal or family history of atopy is very common. The simultaneous presence of an allergic rhinitis is typical. The rhinitis will also tend to be seasonal in SAC and perennial in PAC, causing patients to report sneezing and a watery rhinorrhea as well as itching of the nose and ears. Both present with similar symptoms of itching, burning, tearing, red eyes on exposure to allergens, while the major difference between them is related to the variable presence of the sensitising allergens. Both conditions are extremely common, but the incidence of SAC in most population groups is considerably greater, reflecting the epidemiology of the triggering allergens.

In SAC the patients are usually completely asymptomatic when the particular allergen to which they are sensitive is not present in the environment, but some individuals may be sensitive to both seasonal and perennial allergens and will consequently have year-round symptoms with seasonal exacerbations. Seasonal allergens and their timing may differ in different parts of the world, with common allergens being tree and flower pollen in the spring, grass pollen in the late spring and early summer and ragweed during the late summer and early autumn.

In PAC the patients are usually symptomatic throughout the year, reflecting the perennial nature of the triggering allergens. The most common allergens implicated in the pathogenesis of PAC are located indoors and include animal dander, dust mites and feathers, but may also include air pollutants and fungal spores in the external environment.

The pathogenesis of both SAC and PAC involves a type I immune response with the allergens dissolving in the tear film and traversing the conjunctival epithelium to reach the substantia propria. There they bind to the IgE antibodies attached to the mast-cell membranes, resulting in their degranulation and the release of histamine and other cytokines and inflammatory mediators. These result in vasodilatation and increased vascular permeability which are responsible for all the symptoms and signs of the condition. This early phase is typically followed after a few hours by a late phase with the influx of eosinophils and T lymphocytes. The full picture is considerably more complicated than the above desciption and opinions vary considerably on the finer detail. A more detailed analysis of the literature on this subject is beyond the scope of this review and is discussed elsewhere in this issue.

Both SAC and PAC present with the typical allergic symptoms and signs detailed above, with itching being very prominent in this group of patients, resulting in an intense urge to rub the eyes. Rubbing may cause the rupture of subepithelial mast cells, causing their further degranulation and aggravation of symptoms. In this scenario the degree of chemosis may be exaggerated, resulting in conjunctival ballooning. In addition this may aggravate lid swelling and induce superficial skin changes. Because of the self-limiting nature of the condition, there may be only a few residual signs by the time medical attention is sought, but mild chemosis on the bulbar and lower tarsal conjunctiva may persist, and an occasional mild papillary reaction may be noticeable in the lower fornix or upper palpebral conjunctiva.

Various forms of allergen testing may be of value in difficult cases. Skin-prick testing is the most widely used, but patients will often be aware of the allergens that trigger their symptoms. Therefore a good history and examination are all that is indicated in the vast majority of cases. Conjunctival scrapings, looking for the presence of eosinophils, may be useful in diagnostically difficult cases, but this is rarely necessary in routine clinical practice.

Although patients may be extremely symptomatic there is generally no corneal involvement in either SAC or PAC and consequently it is extremely rare for patients to develop sight-threatening complications.

Treatment is initially directed at avoiding or eliminating the causative agent if this is possible. Careful attention to environmental modifications can have a major ameliorative effect. Patients should also be advised not to rub their eyes as this may introduce additional allergens into the eyes in addition to the consequences mentioned above. Artificial tears may provide some relief by diluting the allergens. Inflammatory mediators and cold compresses may provide some relief as well. Topical antihistamines and vasoconstrictors may be of value in the acute stages and mast-cell stabilisers are of value in the prevention of chronic symptoms. The major value of oral antihistamines is in the control of the associated systemic symptoms such as rhinitis.

THE CHRONIC CONDITIONS: ATOPIC KERATOCONJUNCTIVITIS (AKC) AND VERNAL KERATOCONJUNCTIVITIS (VKC)

In both AKC and VKC the allergic process may result in severe sight-threatening complications. Here, in addition to the type I immune response that is active in SAC and PAC, a type IV immune response is also generated which is responsible for these additional complications. VKC is discussed in some detail in a separate article in this issue and will not be discussed further, except in so far as it is important to be able to differentiate it from AKC.

Once again both AKC and VKC present predominantly in patients with a personal or family history of atopy. They are chronic and bilateral, although often asymmetrical, conditions. While AKC presents in all age groups and persists throughout the life of the individual, VKC has its onset in childhood and typically resolves spontaneously in the late teens to early twenties. While most reviews show that AKC has no particular gender, racial or geographic predilection, VKC is known to be more common in males and individuals of African origin. Furthermore while AKC has no particular seasonal predilection, VKC is typically seen in the spring.

The symptoms of AKC are once again those typically seen in all allergic patients, and these are often increased if animals are involved. The prominent feature in AKC however is a significant component of periocular skin and lid changes (Fig. 2). These include a prominent dermatitis with scaling and flaking, and the lids may eventually become thickened, resulting in a cicatricial ectropion and lagophthalmos. There is often a chronic meibomitis, keratinisation of the lid margins and loss of lashes. As opposed to VKC the signs predominantly involve the lower lid. Subepithelial fibrosis of the conjunctiva is a common finding, eventually resulting in shallowing of the inferior fornix and occasional symblepharon formation. Vision loss is a result of subsequent corneal involvement, which starts with a superficial punctate keratitis, and may progress to a persistent epithelial defect with secondary infection, scarring and neovascularisation. The association

between AKC and the early development of cataracts is difficult to determine, because many of these patients are placed on chronic steroid therapy, which is an independent risk factor for cataract formation.

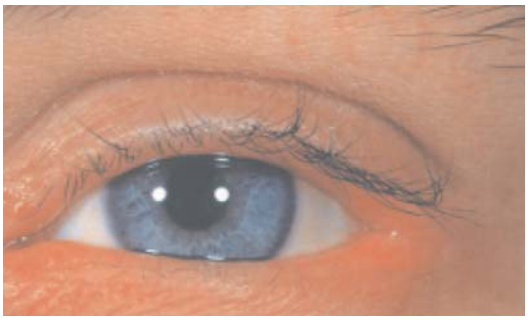

Fig. 2. Atopic conjunctivitis with peri-ocular skin changes.

The immune pathophysiology of VKC and AKC is very complex and incompletely understood. Although there is a very definite increase in the number and activation of mast cells, the overall immune cell profile involves eosinophils, lymphocytes, fibroblasts and a complex array of cytokines and immune modulators in a poorly characterised combination.

Management of AKC requires a careful history to define the sensitising allergen so that measures can be taken to decrease exposure. Because of the chronicity of the problem, care should be taken with the long-term use of topical medications, because it is possible to exacerbate the problem by inducing toxicity. Long-term mast-cell stabilisation is important, and management of acute exacerbations with topical steroids and steroid-sparing agents such as cyclosporin both topically and systemically may sometimes be indicated. Management and prevention of lid complications is necessary and maintenance of an adequate tear film may diminish the severity of corneal complications.

GIANT PAPILLARY CONJUNCTIVITIS (GPC)

GPC is a non-infectious chronic inflammatory process of the conjunctiva, characterised by giant papillae on the tarsal conjunctiva of the upper lids, with no definite age or gender distribution. Strictly speaking it is not an allergic disease but occurs predominantly secondarily to chronic low-grade mechanical trauma of the conjunctiva. However there is a very definite allergic component to the disease, which is more difficult to define. There is evidence of an increased number of mast cells in the conjunctiva and increased levels of IgE in the tear film, but the exact role of these and many other inflammatory mediators is complex and incompletely understood. One of the reasons for its common inclusion with the allergic conjunctivitides is its superficial similarity to VKC, but the classic conditions are very easy to distinguish from one another, especially when history is considered.

GPC is most typically associated with soft contact lens (SCL) wear, but has been described with hard contact lens (HCL) wear, as well as gas-permeable lenses. More rarely it has been recognised in patients wearing ocular prostheses, where exposed sutures chronically irritate the conjunctiva, and with prominent glaucoma filtering blebs. Many different features of contact lens wear have been implicated in its aetiology including lens coatings, lens chemistry, edge design, surface properties, wearing schedule, cleaning routine, fitting characteristics and replacement cycle. As an example, people who sleep wearing their contact lenses are three times more likely to develop GPC than patients who restrict themselves to daily wear only. Although patients wearing HCL and gas-permeable lenses are also prone to develop the condition, the average duration of contact lens wear before symptoms and signs develop with these lenses has been reported to be in the order of 8 years compared with 8 months for SCL wearers.[2]

The development of symptoms and signs is usually slow and progressive. It is important not to ignore the early complaints, as appropriate intervention at this stage is likely to simplify management considerably and avoid chronicity. Early symptoms include tearing and itching even at night once the contact lenses have been removed. A foreign body sensation with increasing contact lens intolerance is also common. Patients may also complain of the accumulation of mucus at the inner canthus on awakening with adherence of the lids. Blurring of vision is usually due to increased protein coating of the lens.

Early signs include mild upper tarsal conjunctival hyperaemia, associated with subtle thickening, and gradually increasing opacification of the conjunctiva. A mucoid discharge is a common feature. Giant papillae on the upper lids are however the characteristic feature of the disease, varying in size from 0.3 mm to over 1.0 mm in diameter (Fig. 3). The appearance and distribution of these may vary considerably. For example, it has been noted that those due to SCL may start superiorly and progress downward while those due to gas-permeable lenses begin inferiorly.

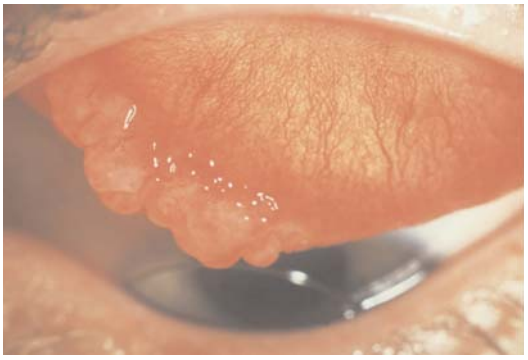

Fig. 3. Giant papillary conjunctivitis.

Treatment involves the removal of the inciting agent, but as the majority of cases are secondary to contact lens wear, and patients are often loath to give up this mode of refractive correction, this complicates the management significantly. A period without lens wear is mandatory, coupled with various topical preparations including mast-cell stabilisers, NSAIDs, antihistamines and steroids. These may be of value while a careful history of the details of contact lens wear is taken so as to guide modifications of contact lens wear technique. This may include varying cleaning, rinsing and storage solutions and modifying wearing schedules, as well as ultimately changing from SCL to gas-permeable lenses.

CONTACT ALLERGIC CONJUNCTIVITIS (CAC)

Prolonged use of many topical medications and other products, such as cosmetics, hair-care products and industrial chemicals may induce toxic effects on the conjunctiva. The pathological effects of these products may also be allergic in nature and distinguishing these

two processes may often be difficult, especially as both processes may be present simultaneously. Often however one or the other process may be predominant; then certain clinical features may be very useful in distinguishing the main culprit.

With allergy, repeated exposure and adequate sensitisation time are needed, which may vary from days to years, while toxicity usually occurs on first exposure. Although papillary reactions may occur in both allergic and toxic reactions, papillary reactions are more common with allergy while a follicular response, which is common with toxic reactions, is very rarely seen with allergy. Hyperaemia secondary to toxicity is usually more pronounced in the inferior conjunctiva, while an evenly distributed hyperaemia is more typical of allergy. A mucoid discharge is a feature of an allergic response, while toxicity is often associated with a more mucopurulent one. The cornea is not usually involved in allergic reactions while a range of corneal signs may be present with toxicity.

It might also be possible to distinguish between toxicity and allergy with skin testing or analysis of conjunctival scrapings, but this is rarely necessary in clinical practice.

Topical medications that have been reported to induce allergic responses include gentamycin, neomycin, atropine and idoxuridine. Preservatives such as benzalconuim chloride, used in commercial eyedrops, are also frequently responsible for CAC.

CONCLUSION

There are other inflammatory conditions which involve the conjunctiva, including certain diseases of the peripheral cornea, Stevens Johnson syndrome and ocular cicatricial pemphigoid which have clinical features suggestive of an allergic aetiology, however IgE and type I hypersensitivity do not appear to play a role in these immune conditions and they are therefore not included in this grouping.

Allergic conjunctivitis is a widespread and common condition and although it only results in significant visual morbidity in a very small minority of affected patients, its symptoms may cause significant discomfort and limit the day-to-day activity of a far greater number, resulting in absenteeism from work and school. It may require major lifestyle adjustments. Although reasonably effective medications exist for managing the acute forms of the condition, the management of the chronic forms remains a major clinical challenge.

Although much of the complex immune pathophysiology remains unclear, significant progress has been made in defining the cellular and molecular processes involved in the allergic conjunctivitides. It is to be hoped that this knowledge will soon be translated into more effective therapies, especially for the more chronic forms of the disease.

Declaration of conflict of interest

The author has no conflict of interest.

FIGURE CREDITS

Figs 1, 2 & 3. Reproduced from Spalton DJ, Hitchings RA, Hunter P. *Atlas of Clinical Ophthalmology*, 3rd ed. Philadelphia: Elsevier Mosby, 2005: pp 118, 119 & 123 respectively.

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