Diagnostic criteria of chronic conjunctivitis: atopic keratoconjunctivitis and vernal keratoconjunctivitis

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Purpose of review
Chronic ocular allergies, vernal (VKC) and atopic keratoconjunctivitis (AKC) are relatively rare conditions that require definite diagnostic criteria to the most appropriate therapeutical approach.

Recent findings
The diagnosis of both VKC and AKC is generally based on clinical history, signs and symptoms, and the results of *allergic* tests, which allow to identify the different diseases phenotypes. However, other subtypes of the two diseases and/or overlaps may occur making the diagnosis non always so clear, such as VKC and AKC overlaps or adult-like VKC disease. Each of these phenotypes may be sustained by different mechanisms which are still not well defined but not only related to a type 2 inflammation. The further challenges will be to correlate clinical or molecular biomarkers to a single subtype or disease severity.

Summary
Definite criteria of chronic allergies will further guide to more specific therapeutical approaches.

Keywords
allergic conjunctivitis, atopic keratoconjunctivitis, endotypes, phenotypes, sign and symptoms, vernal keratoconjunctivitis diagnosis of ocular allergy

INTRODUCTION

Historically, the classification of ocular allergies (OA) includes seasonal (SAC) and perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis (GPC) and contact blepharoconjunctivitis (CBC). These diseases can be divided into immunoglobulin E (IgE)- and non-IgE-mediated, trying to provide a more schematic immunopathological approach to classification [1]. Recently, a new classification has been proposed based on phenotypes and endotypes [2▪▪]. Specific phenotypes may result from different mechanisms of outcomes (endotypes), and may be continuously modulated by the micro/macro-environment that specifically drives the innate and adaptive immune responses [3]. Conversely, the same phenotype (observable characteristics) may have different endotypes (pathobiological mechanisms). Allergic responses in general belong to the type-2 (T2) immune reaction, involving innate lymphoid cell (ILC)2, cytotoxic T-cells (Tc)2, and Th2 producing interleukin(IL)-4, IL-5, and IL-13. T1 immune response consists of interferon gamma (IFNγ)-producing ILC1, Tc1, and Th1 while T3 immunity is composed of ILC3, Tc3, and Th17 cells producing IL-17. SAC and PAC are typical T2 response, while VKC and AKC should be considered severe T2 responses. Since a mixed expression of Th1, Th2 and Th17 cytokines has been reported in AKC and in VKC, probably subtypes of these diseases may be sustained by mixed T1/T2/T3 mechanisms [4▪▪,5▪,6▪▪] with both innate and adapted immunity involved.

Corneal involvement is typically restricted to VKC and AKC, which in fact are defined as *keratoconjunctivitis*. Although the atomical, physiological, and immunological properties of the cornea render this tissue relatively protected from inflammation, most of the problems in VKC and AKC are indeed related to corneal complications. In addition,

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KEY POINTS

- Vernal keratoconjunctivitis (VKC) is a persistent and severe form of ocular allergy, which occurs mainly in areas with a warm climate, affecting male children (male/female sex ratio 3/1) and usually disappearing after puberty.
- Atopic keratoconjunctivitis (AKC) is a chronic allergic conjunctivitis occurring in patients affected by atopic dermatitis usually appearing after puberty but lasting all lifelong.
- Both VKC and AKC are defined as keratoconjunctivitis, therefore the cornea is mostly involved even though without complication.
- Diagnosis of both VKC and AKC is mainly clinical, based on accurate clinical history and evaluation of signs and symptoms.
- Both VKC and AKC range from mild and intermittent to seriously debilitating forms.
- Both VKC and AKC should be considered severe Type 2 immune-reaction, however mixed T1/T2 or T1/T2/T3 endotypes may sustain similar phenotypes.

epithelial barrier dysfunctions might be responsible of corneal involvement in these diseases [7▪▪].

Recognizing VKC and AKC manifestations is extremely important for their management. *Diagnostic tools* have been suggested [8]. More recently, a consensus on clear guidance for primary care physicians and general ophthalmologists involved in the diagnosis of VKC have been produced both in European Union and in Asia [9▪,10▪].

In this review, we highlight different clinical features and diagnostic criteria for VKC and AKC, which may help their diagnosis and eventually their future tailored therapeutical approach.

VERNAL KERATOCONJUNCTIVITIS

Clinical presentation

VKC is a severe OA that occurs predominately in children. Most VKC patients complain of symptoms from early spring to fall, with differences among climate zones. Exacerbations arise triggered by allergen exposure or, more frequently, by nonspecific stimuli such as wind, light and dust. VKC is an IgE- and Th2-mediated disease, however only 50% of patients present a clearly defined allergic sensitization [11,12].

Intense itching, tearing, foreign body sensation and photophobia are the classic symptoms (Table 1), which may be particularly intense upon awakening in the morning causing the typical 'morning misery' [13]. The presence of pain associated with photophobia is indicative of corneal involvement. Foreign body sensation may be caused by mucous hypersecretion, papillae hypertrophy and superficial keratopathy. Signs of VKC (Table 1) involve the conjunctiva, limbus and cornea, but not the eyelids. Various grades of conjunctival hyperemia and chemosis are always present in both limbal and tarsal forms. The *tarsal* VKC is characterized by irregularly sized hypertrophic papillae, named *giant papillae* (GP) if >1 mm in diameter, leading to a cobblestone appearance on the upper tarsal plate. This might appear as diffuse upper tarsal conjunctival thickening with fine and diffuse subepithelial fibrosis without papillary hypertrophy. Abundant mucus may be incarcerated between the GP. The *limbal/bulbar* form is characterized by multiple gelatinous, yellow gray limbal infiltrates and papillae, whose size and location may change over time. The limbus may appear thickened and opacified in a limited area or for 360°, accompanied by a peripheral, superficial neovascularization. The apices of the infiltrates may appear as punctiform calcified concretions called

Table 1. Signs and symptoms of vernal keratoconjunctivitis

Symptoms	Signs	Corneal complications
Itchy	Conjunctival hyperemia	Limbal deficiency
Tearing or 'watery eyes'	Focal limbal inflammation	Pannus
Discharge	Horner-Trantas dots	Macroerosions
Sticky mucous discharge	Anular limbal inflammation	Shield ulcer
Foreign body sensation	Superficial punctate keratitis	Plaques
Photophobia	Papillary hypertrophy	LSCD
Pain	Giant papillae	Keratoconus
	Tarsal scars	Infections

LSCD, limbal stem cell deficiency.

Horner-Trantas dots, which are clumps of necrotic epithelial cells, neutrophils and eosinophils. In the *mixed* form, both tarsal and limbal signs are observed at varying degrees. Blepharospasm, tearing and mucus hypersecretion may be present in all VKC forms, while pseudoptosis is usually secondary to the presence of heavy tarsal GP. Meibomian glands and their orifices appear normal without signs of obstructions or blepharitis.

Corneal involvement is common, more frequently in tarsal and mixed forms, as superficial punctate keratitis, epithelial macroerosion, ulcers, plaque, neovascularization, subepithelial scarring. Pseudogerontoxon is due to increased chronic limbal vasopermeability and peripheral corneal deposition of lipids. Ulcer formation is preceded by a progressive deterioration of the corneal epithelium, which appears irregularly stained and covered with fine filaments. Corneal ulcers are classified based on their clinical characteristics [14]: Grade 1 = shield ulcer with a clear base; Grade 2 = ulcers with visible inflammatory debris at the base; Grade 3 = shield ulcers with elevated plaques.

The ocular complications that may lead to visual loss include steroid-induced cataract, steroid-induced glaucoma, corneal scars, irregular astigmatism, keratoconus, limbal tissue hyperplasia, limbal stem deficiency (LSCD), infections and dry eye [15,16,17▪]. A perilimbal pigmentation has been suggested as a sign of persistent limbal inflammation in Asian and African patients [18,19]. Typical of VKC is the increased length of eyelashes [20]. Both signs may be a consequence of the increased expression of growth factors independently for patients' ethnicity [21].

Diagnosis

Recognizing *signs and symptoms* and their severity is important for the pediatrician, general ophthalmologist, and allergist for taking the decision to refer or not to a referral ophthalmologist or specialized center [9▪,22]. Up to 40–75% of VKC patients suffer from other allergic diseases [23] but negative skin prick test or specific IgE does not exclude the VKC diagnosis. Mild limbal forms might be misdiagnosed especially if seen 'out of season', since limbal signs usually disappear. A careful examination of the limbus might reveal the presence of micro vesicles, mild subepithelial fibrosis or increased limbal vascularization as residual signs of previous limbal inflammation. The most frequent disease that is misdiagnosed with VKC is blepharokeratoconjunctivitis (BKC) in children also called ocular rosacea [1]. A well performed anamnesis and external ocular examination may help to differentiate these two diseases. Symptoms may be similar but are asymmetric and nonseasonal related in BKC. The presence of MGD, blepharitis or history of hordeola, chalazion, the prevalent involvement of lower half of the cornea with epithelial defects, subepithelial opacities, vascularization, and the presence of subconjunctival (cholesterol) oil crystals in BKC should help to distinguish the two diseases [24,25].

Unfortunately, there is no specific laboratory evaluation suitable for the diagnosis of VKC, even though tear levels of eotaxin, ECP, specific IgE, oncostatin and periostin have been proposed as disease biomarkers [26▪▪]. Typical history, the presence of itch, skin prick test and the identification of serum-specific IgE, are the fundamental for the diagnosis of IgE-mediated VKC [27].

Vernal keratoconjunctivitis subtypes

Besides the three VKC phenotypes, tarsal, limbal and mixed, different subtypes can be recognized suggesting that different mechanisms or endotypes may be responsible of the different manifestation. The three main phenotypes have been shown to have relatively differently expressed genes by a recent transcriptomic analysis in VKC [6▪▪]. *Seasonal* and *perennial* forms of VKC may reflect different specific sensitizations to pollens, mites, molds, and animal dander. In addition, local allergy has been proposed in VKC based on the positive results of specific IgE measurement and the positive response to conjunctival allergen provocation test in the absence of positive sensitization by conventional tests [28,29]. *Familiar* VKCs may be related to a genetic predisposition even though only very few studies with limited number of patients [30▪].

Particularly interesting is the *adult VKC-like disease* described as a new onset after puberty or in young adults [31], with an incidence of 0.06/100 000 compared to 7.2/100 000 in children [32]. Adult VKC-like is different from the *recurrent VKC in adulthoods* that may occur after years of disease quiescency after puberty, in patients free of signs of atopic dermatitis (AD), which differently indicate an AKC. Compared to the disease in childhood, adult VKC-like disease has a lower male: female ratio, a lower incidence of corneal ulcer but a similar cytokine profile [31]. Because of the rarity of the disease, it is characterized by a late diagnosis, a high economic and quality of life impact [33], and a frequent cortico-dependency. However, when patients are switched to topical cyclosporine, they report a high treatment satisfaction [31].

The association of *VKC and HIV infection* is also interesting. In a cohort of South African adult VKC-like disease patients, 78.8% were HIV+ (51.5% males

and 48.5% females) with a significant correlation between a lower $CD4^+$ count and the risk of the disease [34▪]. In HIV+ children the prevalence of VKC was 87.5% with a male:female ratio of 61:2 [35▪]. The severity of the disease has been inversely correlated to the $CD4^+$ cell count and the Th1–Th2 shift typical of the HIV infection [36▪]. In our personal experience, we have no HIV+ children or adults with concomitant VKC.

ATOPIC KERATOCONJUNCTIVITIS

Clinical presentation

AKC, originally described by Hogan, is a persistent inflammatory, bilateral condition involving the eyelids, the conjunctiva, and possibly the cornea [37]. It can be defined as the ocular manifestation of AD. AKC is present in up to 40% of AD patients with co-morbidity with AD and asthma around 90% [38]. Generally, it emerges in children with active AD or in young adults and continues through the fifth decade of life, reaching its peak incidence between the ages of 30 and 50. A family history of allergic conditions is common [39].

AKC presents as a chronic bilateral conjunctivitis with seasonal exacerbations corresponding to the offending allergen/s. The common presenting symptoms are bilateral ocular itching, burning, tearing and mucous discharge (Table 2). The hallmark sign is erythematous, exudative lesions of the eyelids. Eyelids tend to be thickened, indurated, erythematous, fissured, due to eczema, with increased pigmentation around the eyes, also called *panda eyes*. AKC is often associated with chronic blepharitis, meibomian gland dysfunction and staphylococcal infection. The lids are colonized with staphylococcus aureus rather than the usual staphylococcal flora, however, their presence does not correlate with the incidence or severity of keratopathy [40]. The limbus may present Trantas dots, and the tarsal conjunctiva may present GP like those observed in VKC patients. Cicatrizing conjunctivitis, subepithelial fibrosis, and symblepharon have also been reported, with the lower fornix possibly shrinking after scarring. Reduced tear function and tear volume may also be observed. Punctate keratitis, persistent epithelial defects and ulcer with plaque formation are possible complications [41].

Herpes keratitis and microbial infections may complicate the disease, particularly if chronic topical steroid therapy is required. Severe keratopathy with corneal neovascularization, pannus formation and stromal keratitis may develop because of repeated corneal inflammation. This can result in marked astigmatic changes and permanent visual impairment. Anterior 'atopic' or posterior subcapsular cataract contributes to the visual deterioration associated with AKC.

Diagnosis

Incidence and prevalence of AKC are probably underestimated since most atopic dermatitis patients have mild and seasonal ocular signs and symptoms. A careful medical history and clinical examination should confirm the preexisting or concomitant presence of AD. If AD was not previously diagnosed, suspected AKC patients should be referred to a dermatology to exclude other diseases such as rosacea, acne vulgaris, and psoriasis. An entire allergy workout should be performed to

Table 2. Signs and symptoms of atopic keratoconjunctivitis

Symptoms	Signs	Complications
Itchy	Conjunctival hyperemia	Herpetic keratitis
Tearing or 'watery eyes'	Lid eczema	Corneal erosions
Discharge	Meibomian gland disfunction	Shield ulcer
Epiphora	Lid margin keratinization	Plaques
Sticky mucous discharge	Danny-Morgan folds	Filamentary keratitis
Foreign body sensation	Pigmented lid skin	Corneal perforation
Photophobia	Horner-Trantas dots	Steroid glaucoma
Pain	Superficial punctate keratitis	Cataract
	Papillary hypertrophy	LSCD
	Giant papillae	Keratoconus
	Lower fornix scars	Infections
	Inferior symblepharon	Retina detachment

LSCD, limbal stem cell deficiency.

evaluate specific allergen sensitizations, which are frequently multiple.

Atopic keratoconjunctivitis subtypes

Different but not-well defined AKC phenotypes or subtypes can be recognized. AKC is not usually divided into tarsal, limbal or mixed, since tarsal, limbal and lower fornix signs may be present at different times in the same patient. There is no consensus if patients with prevalent eyelid involvement and occasional conjunctivitis should be considered as a different subtype or just a mild form of AKC. Finally, AKC may be associated with the hyper-IgE syndrome in patients with multiple sensitizations.

AD patients with ocular signs, may be more at risk to develop a dupilumab-induced ocular surface disease (DIOSD) or blepharoconjunctivitis as a side effect of anti-IL-4/IL-13 treatment [42▪]. There is evidence that a mixed T1/T2 inflammation is predominant in AKC. In fact, only 17% of AKC patients had a IL-4/IL-13-dominant profile (T2), 17% an IFNγ-dominant profile (T1) and 66% a mixed IFNγ/IL-4/13 profile (T1/T2) [43,44]. Blocking the Th2 pathway with dupilumab might result in a shift towards T1-inflammation and/or a dysfunctional mucin production causing the ocular findings associated with dupilumab [45].

Atopic keratoconjunctivitis in children

AKC is defined as the presence of severe allergic conjunctivitis with AD diagnosed before 16 years of age [46]. Hyperemia and eczema are reported in 96% of patients, associated with keratitis (87%), facial thickened dry skin (83%), Dennie-Morgan double folds of the lower lid (78%). Follicles, tarsal papillae, inferior fornix infiltration and blepharitis are also common signs while Trantas dots are reported in less than 40% [46]. GP are more frequent in child AKC compared to the adults. Keratoconus is also often associated with AKC in children. Dennie–Morgan infraorbital folds are considered a mild criterion of both IgE- and non-IgE-mediated AKC [47].

DIAGNOSTIC CRITERIA: VERNAL KERATOCONJUNCTIVITIS/ATOPIC KERATOCONJUNCTIVITIS DIFFERENCES AND SIMILARITIES

Children with allergic keratoconjunctivitis are usually diagnosed as affected by VKC unless they are affected by severe AD. Both VKC and AKC might have GP and Trantas dots, however the eyelid and eyelid margin diseases are typical of AKC and usually never involved in VKC (Table 3). These criteria are similarly reported by the European Academy of Allergy and Immunology (EAACI), International Consensus on Ocular Allergy, and Latin American Society of Allergy, Asthma and Immunology (SLAAI) [8,48▪]. In Japan, VKC is considered a *proliferative* allergic conjunctival disease with either papillary proliferation of the eyelid conjunctiva, swelling, and bank-like elevation of the limbal conjunctiva, while AKC is defined as a chronic allergic conjunctivitis occurring in patients with AD involving the facial skin with or without *proliferative* conjunctival changes [49▪]. Even though some differences in definition exist in different parts of the globe, there is agreement that the clinical diagnosis should be supported by the assessment of the sensitivity to specific allergens by skin prick test and/or serum specific IgE. In addition, local tests such as the identification of eosinophils by different cytodiagnostic techniques, conjunctival allergen provocation test and measurement of total and specific IgE in the tear sample are ancillary test performed in specialized centers accordingly to specific recommendations and the availability of kits and reagents.

Many inflammatory cytokines and chemokines have been found overexpressed in both VKC and AKC with apparently little differences in terms of cytokine profile [50]. In previous studies, we found an IL-4/13-dominant profile in 50% of VKC and in 17% of AKC patients, an IFNγ-dominant profile in 25% of VKC and in 17% of AKC, and a mixed FNγ/IL-4/13 profile in 18% of VKC and in 66% of AKC patients, suggesting that the majority of VKC have a T2 endotype and that the majority of AKC have a mixed T1/T2 endotype [43,44]. In a recent study, severe VKC and AKC patients resistant to topical tacrolimus had the highest expression levels of T1, T2 and T3 mediators, suggesting that endotyping these patients may further predict their responsiveness to targeted drugs [51▪▪].

Regarding other ocular surface biomarkers, higher levels of tear instability, lower corneal sensitivity, up-regulation of MUC1, 2, and 4, and down regulation of MUC5AC were described in AKC compared with VKC [41]. Recently, we described distinct in N-glycome profiles in control, VKC, and AKC tear fluids with peaks with increased intensities referred to glycans from lactotransferrin and serotransferrin and in peaks with decreased intensity associated with immunoglobulins [52▪▪].

CONCLUSION

Specific diagnostic criteria (Table 3) should guide an early diagnosis and prognosis also in relation to specific treatment needs. Even though VKC/AKC

Table 3. Clinical characteristics of vernal and atopic keratoconjunctivitis

Characteristic	VKC	AKC
Age at onset	Children and young adults Rare postpuberty onset (adult VKC-like)	Children and adults all with Atopic Dermatitis
Sex	Male predominance	No difference between sex
Evolution	Frequent (but not always) resolution at puberty	Chronic Frequently complicated by HSV keratitis, cataract and glaucoma
Seasonal variation	Typically, during spring-summer months	Perennial with seasonal exacerbations
Discharge	Thick, mucoid	Watery, clear
Eyelid involvement	Never involved Long eyelashes	Typical eyelid eczema; frequent meibomian gland dysfunction; tendency to ectropion
Limbus involvement	Common Horner-Trantas dots, papillae Rare LSCD	Rare Horner-Trantas dots, papillae and LSCD
Corneal involvement	SPK at the corneal upper third (in tarsal form), perilimbal (in limbal forms) Complicated by macro-erosion and ulcers Corneal nerves abnormalities	Diffuse SPK also in nonactive phases Complicated by macro-erosion and ulcers Corneal nerves abnormalities
Corneal neovascularization	Not present, unless secondary to persistent plaques	Tends to develop
Remodeling	Typical upper tarsal giant papillae and limbal changes	Upper tarsal giant papillae, limbal, lid margin and lower fornix changes
Conjunctival scarring	Usually upper tarsal conjunctiva in remission (as GP resolution)	Higher incidence, frequent lower fornix scarring and epithelial metaplasia
IgE	Specific sensitization to aeroallergens, frequently only to house dust mites Nonspecific hyperreactivity	Multiple allergen sensitization, including food allergens Frequently hyper-IgE Nonspecific hyperreactivity
T cell	Th2. Possible Th17	Th2–Th1. Possible Th17
Inflammation	Mixed inflammatory cells with eosinophilia	Mixed inflammatory cells with prevalence of eosinophils and neutrophils

AKC, atopic keratoconjunctivitis; IgE, immunoglobulin E; VKC, vernal keratoconjunctivitis.

overlaps exist, a child with AD, facial and eyelid involvement should be considered AKC patients with the prognosis of having the disease in the adulthood. In these cases, the treatment of comorbidities may consider the possibility to use specific systemic biologics, for example omalizumab and dupilumab, which are also potentially useful in the management of severe keratoconjunctivitis.

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The remaining authors have no conflicts of interest.

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