

Clinical grading of atopic keratoconjunctivitis

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Purpose of review

Atopic keratoconjunctivitis (AKC), the most severe and chronic form of ocular surface allergy-related disorder, is the ocular surface complication that some atopic dermatitis patients can suffer. Its wide range of severity, from mild and occasional problems to persistent and intense inflammation, makes it difficult to appropriately select uniform patients for clinical studies. This article proposes a new classification system for AKC based on clinical severity.

Recent findings

Recent reports on AKC have contributed to a better understanding of the pathogenesis and clinical manifestations, and are offering new therapeutic candidates for AKC. No reports, however, have been found that address a classification of this disease.

Summary

A new definition and classification for AKC is presented by this review, based on clinical severity, grading the main symptoms and signs. It intends to serve as a first forum of discussion among clinicians and other scientists working in the field of ocular surface inflammation. The final intention is to have a common language helping develop efficient clinical trials leading to successful approval of new therapeutic compounds for this blinding ocular surface condition.

Keywords

AKC, allergy, atopic dermatitis, atopic keratoconjunctivitis

Introduction

AKC is the most severe and chronic form among the four types of ocular surface allergy-related disorders [1–3]. It is the most frequent and severe ophthalmic problem that a patient suffering from atopic dermatitis, usually in adulthood, can suffer [4,5]. In very old reports [reviewed in 5], it has been reported to affect between 25–40% of patients suffering from atopic dermatitis, but as there is no universal agreement about its definition, its real prevalence is unknown.

The wide range of severity of AKC has never been attempted to be graded, probably due to the lack of a uniform definition and nomenclature and a scarcity of reports correlating etiopathogenesis and clinical findings. The logical consequence is a difficulty to recruit patients for clinical trials who have a similar degree of disease and, therefore, to provide evidence of efficacy with new potential therapeutic strategies.

A more accurate definition and a grading system for AKC is offered by this article, based on a score given to the principal symptoms and to the main signs involving three main components of the ocular surface: eyelid margin, conjunctiva, and cornea.

Origins of atopic keratoconjunctivitis

AKC was first described in 1952 by Hogan [6], and almost forgotten to the ophthalmic community until the description in 1990 of a series of 45 patients who had severe ocular surface involvement and a background of atopic dermatitis [5]. This series of patients made the ophthalmic community aware again of the sight-threatening potential capacity of an allergy-related problem. Since then, the number of publications on this disease grew spectacularly. Clinicians described more and more cases [7,8,9[•],10], highlighting different aspects of this disease that, although mentioned earlier, had not been sufficiently emphasized, such as the high prevalence of severe blepharitis, or the increased risk of secondary infections, including bacterial and herpetic keratitis. Scientists, intrigued by what could be the difference between AKC and other milder forms of ocular allergies, have discovered some interesting etiopathogenetic facts [11–16,17[•],18–20,21[•],22]. Finally, it has been possible to prove efficacy of already existent drugs, such as cyclosporin [23–26], and potential therapeutic candidates are being considered [20,27,28,29[•]–31[•]]. Unfortunately, the sequence of pathogenic events giving rise to this severe disease is still unknown. We

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Abbreviations

AKC atopic keratoconjunctivitis
VKC vernal keratoconjunctivitis

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cannot explain why some atopic dermatitis patients have AKC and others do not, or why AKC is mild in some cases and severe in others. This discrepancy may explain the lack of publications attempting to define and grade this disease. This lack of knowledge hampers the correct recruitment of patients for clinical trials. Pharmaceutical companies may be discouraged from developing clinical trials, the logical consequence being the lack of drugs and the difficulties that clinicians encounter to have these patients under adequate control. A possible first step could be the development of a common language, by reaching consensus among the present discrepancies on AKC.

Discrepancies on atopic keratoconjunctivitis

AKC was first described by Hogan as the chronic manifestation of several ocular surface disorders in a context of atopic dermatitis [6]. This definition implies that it is necessary to have or have had atopic dermatitis as a mandatory diagnostic criterion. Although some authors have considered in the past that a small percentage of patients might have AKC not related to atopic dermatitis, this finding is considered debatable at present.

Unless a very careful clinical history is recovered, those patients could have had atopic dermatitis in the past, not be recognized at the time of ocular involvement. In others, the skin involvement can be misdiagnosed [32,33], or patients could have concomitant rosacea-related ocular surface disorders, a condition that can produce damage very similar to AKC and that can actually be associated with AKC [5,34].

Another point of discrepancy is the fact that, sometimes, there are overlapping clinical pictures. For instance, a young patient with a typical vernal keratoconjunctivitis (VKC) picture can also have atopic dermatitis. Does this patient have VKC or AKC? It is our personal experience that these patients should be diagnosed and treated as VKC with a clear prognostic difference: the disease, instead of disappearing during puberty or adulthood, as typical VKC usually does, may have transformed into AKC. These patients usually start having typical signs of AKC when they transform into adults, but most probably conserve giant papillary reaction in their upper tarsal conjunctivas [5,7]. On the contrary, it is possible for a child suffering from atopic dermatitis to actually have AKC and not VKC (based on the absence of typical VKC findings).

Additionally, atopic dermatitis patients may only have seasonal allergic conjunctivitis and not AKC, especially if they only have seasonal typical ocular symptoms and signs and are absolutely normal out of seasons. It is worth remembering that typical AKC patients may have seasonal flare-ups due to sensitization to seasonal allergens,

added to their background ocular disease. Even more difficult would be the correct diagnosis of a patient who has atopic dermatitis, mild chronic ocular surface involvement, and allergy to a perennial allergen such as dust mite. In cases like this, it would be difficult to ascertain whether the diagnosis is mild AKC or perennial allergic conjunctivitis or both.

In any case, clinicians and scientists dealing with allergies need to understand that any disease can have overlapping situations with similar clinical pictures and that this fact does not invalidate a certain definition or classification.

All the above considerations affect the reported prevalence for AKC. This rate is usually reported as between 25–40% of patients affected with atopic dermatitis, extracted by some authors from old dermatologic reports [reviewed in 5]. This wide range suggests that the real prevalence or incidence of AKC is unknown, and it may well be underestimated considering that the prevalence of its dermatologic counterpart, atopic dermatitis, seems to be growing from a reported 3% of the population in the year 2000 [35], to 6–15% in more recent years [36,37,38]. Clinical studies in which atopic dermatitis patients from different parts of the world can be prospectively and carefully evaluated in search of AKC with strict diagnostic criteria are clearly needed to clarify these issues. Before this evaluation can happen, ophthalmologists must better delineate its definition and reach a consensus on severity grading.

Classification based on clinical severity

AKC has been defined as the chronic manifestation of several ocular surface disorders in a context of atopic dermatitis [5,6]. This definition can be still considered appropriate, but the following slightly more elaborated definition is proposed:

AKC is the chronic ocular surface noninfectious inflammatory condition that atopic dermatitis patients may suffer at any time point in the course of their dermatologic disease and independent of its degree of severity.

To understand this definition, the concept of ocular surface, which is posterior to the first definition of AKC, needs to be clear: epithelium, overlying tear film and underlying supporting stroma of conjunctiva, cornea and limbus. Other ocular manifestations involving other tissues in the context of atopic dermatitis (episcleritis, scleritis, uveitis, keratoconus, cataract, retinal detachment) would be excluded and simply named as ophthalmic disorders in the context of atopic dermatitis, but different from AKC.

The above definition implies that the diagnosis of atopic dermatitis is mandatory. This diagnosis, however, may

Table 1 Clinical grades of ocular symptoms and signs for each eye in atopic keratoconjunctivitis

Grading	Symptoms (itching, burning, photophobia) degree/duration	Eyelid margin involvement	Conjunctival involvement (score of 0–4+)	Corneal involvement (score of 0–4+)
Grade 1	Mild/occasional	Anterior blepharitis	Hyperemia/edema/papillae only in tarsal conjunctiva	Superficial punctate keratitis
Grade 2	Mild/persistent or moderate/occasional	Posterior blepharitis (meibomian gland dysfunction)	Same as in grade 1 + hyperemia/edema in bulbar-limbal conjunctiva (ciliary injection)	Epithelial defects (nonpersistent) in clear cornea
Grade 3	Moderate/persistent or severe/occasional	Posterior blepharitis (meibomitis)	Same as grade 1 and 2 + cicatrizing changes: subepithelial fibrosis	Neovascularization, thinning, scarring involving less than 1/2 or persistent epithelial defects lasting less than 1 month
Grade 4	Severe/persistent	Mixed anterior and posterior blepharitis	Same as grade 1, 2, and 3 + cicatrizing changes: fornix foreshortening or symblepharon	Neovascularization, thinning, scarring involving more than 1/2 or persistent epithelial defects lasting more than 1 month

not be clear to the patient at the onset of ocular surface inflammation for two reasons in our experience: (1) atopic dermatitis was diagnosed in childhood and it has been inactive for years. As AKC typically start during adulthood, the patient is not aware of his/her dermatologic problem any more unless actively and specifically questioned; (2) atopic dermatitis has not been diagnosed (i.e. its low grade of severity prevented the patient from seeking a diagnosis) or misdiagnosed (rosacea, acne vulgaris, psoriasis ...), especially if a dermatologist was not consulted. If this is the case, the ophthalmologist must refer the patient again to an expert dermatologist [32]. We then proposed that evidence of atopic dermatitis at any time point and regardless of its severity must be present to make the diagnosis of AKC. It is also crucial to understand that AKC may evolve independently from its dermatologic counterpart [5,39].

Mixed or overlapping forms can be defined as the coincidence of AKC and VKC, or AKC and allergic conjunctivitis, provided that the patient meets the criterion of having, or having had, in the past atopic dermatitis regardless of its duration or severity. Lastly, AKC patient are especially predisposed, because of the immune alterations due to their atopic dermatitis condition [40,41], to infectious complications of the eyelids, conjunctiva or cornea such as bacterial, fungal, and viral (typically herpes simplex keratitis) [5,41]. These complications should be listed as secondary complications of AKC.

Severity of AKC can adopt a wide range. AKC can be mild or very severe; it can affect only eyelids or it can also affect conjunctiva and cornea. Cornea can display only some mild punctate keratitis or severe chronic persistent epithelial defects that easily get infected, eventually leading to scarring and neovascularisation. No prospective studies on the disease can actually clarify its natural course, although some longitudinal reports have been published [7,9]. Is AKC a progressive disease? Do symptoms begin as mild and progress to severe? Can patients have severe forms from the beginning? Do patients who

begin with a mild involvement have a tendency to remain as such? To answer these questions, we first need to know the natural progression of this disease, so that scientists can further investigate the basis of what is seen in the clinical arena.

Based on the degree of involvement of the different tissues of the ocular surface at the moment of clinical examination, the grading system explained in Table 1 is proposed. Several clarifications need to be made regarding this proposed grading system:

- (1) It is proposed that each eye be judged independently, as AKC can be highly asymmetric.
- (2) Only the most relevant signs are considered, in order to simplify the classification.
- (3) Conjunctival injection and edema are considered the key factors to evaluate activation and potential future corneal involvement if not adequately controlled.
- (4) The eyelid involvement due to atopic dermatitis is not considered in this classification.
- (5) Associations (i.e. keratoconus, cataract) or complications (i.e. herpetic keratitis) would be listed separately and would not be considered in the core of this classification.
- (6) If the patient has another disease, either atopy-related (i.e. seasonal allergic conjunctivitis) or not (i.e. rosacea), these should be listed separately.

Conclusion

AKC is the chronic ocular surface noninfectious inflammatory condition that atopic dermatitis patients may suffer at any time point in the course of their dermatologic disease and independent of its degree of severity. Although some progress has been made in terms of its therapeutic management, there is still a scarcity of marketed drugs to control this inflammatory disease. Its wide range of severity, from mild and occasional problems to persistent and intense inflammation eventually leading to loss of corneal transparency and blindness, make it

difficult to appropriately select uniform patients for clinical studies.

A new classification system for AKC severity is proposed, based on the grading of main symptoms and signs. This classification intends to create a forum for debate and further discussions that can eventually lead to a consensus, and can subsequently facilitate the development of clinical trials.

Acknowledgements

CIBER-BBN, Carlos III Institute of Health, Ministry of Health, Spain.

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 456).

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