

Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy

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Abstract

Background The clinical features of allergic ocular diseases (AOD) are characterized by their wide variety. Clinical evaluation criteria are essential not only for objective assessment in clinical trials, but also for clinical studies on etiological aspects of AOD. However, there have been no internationally established criteria for clinical evaluation and classification of the severity of AOD. We established new criteria and applied them to many cases of AOD, and evaluated their usefulness for clinical purposes. We also studied whether each clinical entity of AOD [allergic conjunctivitis (AC), atopic keratoconjunctivitis (AKC), and vernal keratoconjunctivitis (VKC)] can be distinguished by these criteria.

Methods A prospective study was carried out to assess the differential diagnosis of 1079 patients with AOD (439 male and 640 female patients). Differential diagnosis of AC, AKC or VKC was made. These diseases were diagnosed and classified based on local and systemic clinical findings. Ten objective ocular clinical findings of conjunctival,

limbal and corneal lesions were graded on a 4-point scale, and the total score, with a highest value of 30, was used as the clinical score.

Results Among a total of 1079 cases, seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), AKC and VKC accounted for 876 (81.2%), 115 (10.6%), 47 (4.4%) and 41 (3.8%) respectively. The mean age in each disease was 52.9, 56.1, 25.7 and 16.6 years respectively. Total clinical score in SAC, PAC, AKC and VKC was 1.54, 2.13, 3.72 and 12.68 respectively. Both mean age and total clinical score in all combinations of two diseases showed significantly different results.

Conclusions These results suggest that AOD can be classified by our new clinical grading system, and this system is sensitive enough for clinical evaluation of AOD. Re-evaluation of AOD is essential for constructing future strategies for the treatment of AOD, which consists of various categories of ocular disorders.

Keywords Allergic ocular disease · Allergic conjunctivitis · Vernal keratoconjunctivitis · Atopic keratoconjunctivitis · Clinical evaluation criteria · Epidemiology

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Introduction

Allergic ocular diseases (AOD) are ocular disorders based on allergic inflammation of the ocular surface, and include allergic conjunctivitis (AC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and giant papillary conjunctivitis (GPC). The clinical features of AOD are characterized by their wide variety, and the medical treatment of AOD should be based on the clinical characteristics. AC is defined as an allergic conjunctival disease in which the conjunctiva shows no proliferative

change, and is divided into two subcategories, seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), according to the presence of seasonal exacerbation. PAC belongs to a less severe part of AOD, though still uncomfortable for the patient. Signs and symptoms of PAC include itching, hyperemia, and tearing. Mucous discharge is clear and transient. AKC, which also belongs to the allergic ocular diseases, is a bilateral, chronic hypersensitivity disease of the ocular surface seen in association with systemic atopic dermatitis (AD), characterized by lesions of the conjunctiva and cornea that vary in severity. Ocular symptoms include intense itching, photophobia, burning and the sensation of a foreign body. The clinical signs show a wide spectrum, and in the most severe cases conjunctival scarring with subepithelial fibrosis, fornix foreshortening, symblepharon and corneal ulceration and neovascularization may occur. Therefore, it is a sight-threatening condition, emerging in the 2nd through the 5th decade of life [1]. The disease is associated with eczema of the lids or other parts of the body. VKC is a recurrent seasonal disease of childhood, characterized by severe bilateral inflammation of the conjunctiva, and is characterized by giant papillae of the superior tarsal conjunctiva, gelatinous hypertrophy of the limbus, and keratopathy. It is associated with intense itching, photophobia, and mucous discharge, and is most commonly seen in male patients. However, unlike the severe group of AKC, it tends to resolve spontaneously after several years. The incidence of VKC varies markedly with geographic location, with individuals in Italy, Japan, and other warm climates being more likely to have the disease [2, 3].

For the treatment of AOD, several local ocular drugs, such as antihistamines, anti-allergic agents and corticosteroids, have been developed as commercially available eyedrops recently, and many candidate agents are under clinical trial for patients with AOD. Clinical evaluation criteria are essential not only for objective assessment in clinical trials, but also for clinical studies on etiological aspects of AOD. However, there are no internationally established criteria for clinical evaluation and classification of the severity of AOD. Leonardi et al. [4] proposed a scoring system for severity of AOD; in this system, the severity of allergic ocular lesions is classified into mild, moderate and severe. Although these are useful criteria for clinical evaluation of AOD, local findings are classified into only three categories; conjunctival, corneal and limbal lesions. Therefore, it is impossible to assess each finding in more detail, such as conjunctival hyperemia, papillae or edema, and monitoring the change in size of giant papillae is also not possible with this system. Therefore, we consider it is necessary to develop new objective criteria for clinical evaluation and classification of severity of the entire range of AOD.

In this study, we applied the new criteria to many cases of AOD for clinical scoring, and evaluated its usefulness for

clinical purposes. We also studied whether each clinical entity of AOD (SAC, PAC, AKC, and VKC) can be distinguished by these criteria.

Materials and methods

Patients and classification

A prospective study was carried out to assess the differential diagnosis of 1079 patients with AOD who presented to the Department of Ophthalmology, Yokohama City University Medical Center, Yokohama, Japan, between June 2002 and December 2003. There were 439 male and 640 female patients with a mean age of 50.7 ± 21.2 (mean $\pm$ SD) years. Differential diagnosis was made of AC, AKC or VKC. No case of GPC was observed. These diseases were diagnosed and classified clinically according to the recent report [5]. Patients with AC who showed seasonal (SAC) or perennial (PAC) symptoms such as ocular itching and tearing without proliferative lesions had positive serum antigen specific IgE antibody or skin-prick test to one or several allergens including grass pollen. AKC patients had atopic dermatitis (AD) and conjunctival and/or corneal involvement. Corneal complications may vary in severity from punctate keratitis to frank necrosis. The patients with AKC met the diagnostic criteria of AD proposed by Hanifin and Rajka [6]. VKC was diagnosed by typical cobblestone excrescences (giant papillae of the upper palpebral conjunctiva more than 1 mm in size), perilimbal gelatinous change and corneal lesions, such as stromal lipid deposition or pannus formation. Exclusion criteria were bacterial conjunctivitis, viral keratoconjunctivitis or other unclassified conjunctivitis such as phlyctenular or toxic conjunctivitis.

Clinical grading

We have established the criteria for clinical evaluation of allergic ocular findings (Table 1). The ocular findings of slit-lamp examination were recorded on the patients' first visit to our outpatient clinic. Ten objective ocular clinical findings of conjunctival, limbal and corneal lesions were graded on a four-point scale (0=none, 1=mild, 2=moderate, 3=severe; left and right eye separately in each case; See Table 1 for details). The total score of ten findings, with a maximum of 30, taking the score of the more severe side in bilateral cases, was used as the clinical score.

Statistical analysis

Since it has not been established that the clinical score of AOD shows normal distribution, non-parametric analysis

Table 1 Criteria for clinical evaluation of allergic ocular findings

Descriptions			
Palpebral conjunctiva	Hyperemia	Severe	Impossible to distinguish individual blood vessels
		Moderate	Dilatation of many vessels
		Mild	Dilatation of several vessels
		None	No manifestations
	Edema	Severe	Diffuse marked edema
		Moderate	Diffuse mild edema
		Mild	Localized edema
		None	No manifestations
	Follicles	Severe	20 or more follicles
		Moderate	10–19 follicles
		Mild	1–9 follicles
		None	No manifestations
	Papillae	Severe	Diameter ≥ 0.6 mm
		Moderate	Diameter 0.3–0.5 mm
		Mild	Diameter 0.1–0.2 mm
		None	No manifestations
Bulbar conjunctiva	Giant papillae	Severe	Elevated papillae in 1/2 or more of upper palpebral conjunctiva
		Moderate	Elevated papillae in less than 1/2 of upper palpebral conjunctiva
		Mild	Flat giant papillae
		None	No manifestations
	Hyperemia	Severe	Vasodilatation of all vessels
		Moderate	Dilation of many vessels
		Mild	Dilation of several vessels
		None	No manifestations
	Chemosis	Severe	Cyst-like chemosis of entire conjunctiva
		Moderate	Diffuse thin chemosis
		Mild	Partial conjunctival swelling
		None	No manifestations
Limbus	Limbal edema	Severe	In $\geq 2/3$ of circumference
		Moderate	In 1/3 to 2/3 of circumference
		Mild	In less than 1/3 of circumference
		None	No manifestations
	Trantas' dots	Severe	≥ 9 dots
		Moderate	5–8 dots
		Mild	1–4 dots
		None	No manifestations
Cornea	Epithelial lesions	Severe	Shield ulcer or epithelial erosion
		Moderate	Superficial punctate keratitis with filamentary debris
		Mild	Superficial punctate keratitis
		None	No manifestations

In cases having giant papillae, papillae and giant papillae should be graded simultaneously

was conducted in this study. Mann-Whitney test was used to identify differences among patient groups. A level of $P < 0.05$ was accepted as statistically significant.

Results

Distribution of clinical entities and age distribution

Among a total of 1079 cases, SAC, PAC, AKC and VKC accounted for 876 (81.2%), 115 (10.6%), 47 (4.4%) and 41 (3.8%) respectively. The results for each disease were as

follows: 349 (39.8%) male and 527 (60.2%) female patients with SAC with a mean age of 52.9 ± 20.5 (mean $\pm$ standard deviation) years, 31 (27.0%) male and 84 (73.0%) female patients with PAC with a mean age of 56.1 ± 13.7 years, 24 (51.1%) male and 23 (48.9%) female patients with AKC with a mean age of 25.7 ± 15.1 years, and 36 (87.8%) male and five (12.2%) female patients with VKC with a mean age of 16.6 ± 8.9 years. The age distribution of these four diseases is shown in Fig. 1. Comparison of the mean age of AOD between two diseases was carried out for the following: SAC vs PAC, SAC vs AKC, SAC vs VKC, PAC vs AKC,

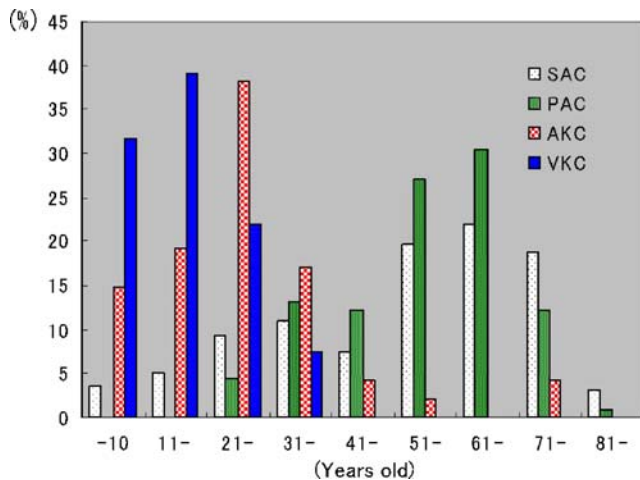


Fig. 1 Age distribution of allergic conjunctival diseases. *SAC*; seasonal allergic conjunctivitis, *PAC*; perennial allergic conjunctivitis, *AKC*; atopic keratoconjunctivitis, *VKC*; vernal keratoconjunctivitis

PAC vs VKC, and AKC vs VKC. All of these differences reached statistical significance ($P < 0.01$).

Comparison of clinical severity of AOD

The mean clinical scores in the four diseases for the ten findings and total score are shown in Table 2. Total clinical score in SAC, PAC, AKC and VKC was 1.54, 2.13, 3.72 and 12.68 respectively. Mean total clinical score in all combinations of two diseases also showed significantly different results ($P < 0.01$).

Discussion

There are numerous classifications for ocular allergy according to the underlying pathophysiology and clinical findings. The different types of allergic disorders in the eye may have similar signs and symptoms, but each has its clinical characteristics, possibly based on its pathognomotic features. It is important to identify the different allergic ocular diseases. This study was planned for several reasons. First, it was intended to evaluate the clinical diagnosis in classifying patients with AOD. The second aim was to better understand the relative percentage of VKC, AKC, SAC and PAC in a particular population. The classification of VKC, AKC, PAC and SAC under the umbrella term of a single entity (i.e., allergic conjunctivitis) is based on the assumption that the classical type I hypersensitivity mechanism is responsible for all clinical forms of AOD. A cellular type IV hypersensitivity reaction has been demonstrated in AKC and VKC, in addition to many other immunological factors [2], and it is evident that AKC and

VKC differ from PAC and SAC in relation to their clinical expression. Therefore, use of the term “allergic conjunctivitis” to describe all ocular allergic disorders has already been discouraged [2]. In particular, it has been accepted that the signs and symptoms in AKC and VKC are more severe than those in SAC and PAC, and the former include severe corneal involvement, which is never present in SAC and PAC [7]. The statistically significant difference in the clinical severity calculated by clinical scores between mild forms of diseases in AOD (PAC and SAC) and severe forms (AKC and VKC) in the present study supports the previous report by Bonini [7].

The serious nature of the severe forms of ocular allergy, AKC and VKC, warrants close attention, although it has been pointed out that AKC and VKC represent just 2% of cases of ocular allergy [3]. Conversely, SAC and PAC are much more commonly seen, comprising of 98% of patients with ocular allergy [3]. However, the percentage of AKC and VKC was 4.4% and 3.8% respectively, in our study, being much higher than that in the previous study. The reason for this high percentage of the severe spectrum of AOD might be as follows; firstly, the warm climate in Japan is a key factor in severe ocular allergy, as reported elsewhere [7], and secondly, our outpatient clinic is a referral center for local ophthalmologists in the Tokyo-Yokohama metropolitan area; therefore, more cases requiring intensive care tend to attend our hospital than other clinics. In another study from a referral clinic of a university hospital in Brazil, VKC and AKC accounted for 46% and 40% respectively, versus 8% for PAC in a consecutive case series [1]. The male-female ratio of VKC was 7:1, and that of AKC was 1:1. This was similar to the results of an epidemiological study reported by Belfort et al. [1], in which the male/female ratio of VKC and AKC was 5:1 and 1:1 respectively. VKC usually starts before 10 years of age and is more common in boys, and it tends to be aggressive for 4 or 5 years and then resolves in the next decade [8]. From a recent study of VKC carried out in a tropical region of Thailand, mean age was 9.6 years and male predominance (81%) was observed [9]. These results are quite close to ours.

Regarding allergic conjunctivitis, it has been pointed out that more than 80% of allergic patients are affected before the 3rd decade of life [5], and all patients with PAC had symptoms before the age of 10 [1]; however, there has been no large-scale epidemiological study of allergic conjunctivitis. Female predominance in AC, with a male/female ratio of 2:3 in SAC and 1:3 in PAC in our study, was supported by a previous report in which far more females than males presented with PAC symptoms, with a male/female ratio of 1:4 [1]. A considerably higher mean age in AC was also observed in our study; 52.9 years for SAC and 56.1 years for PAC. Although the reason for this is unclear, a possible

Table 2 Comparison of mean clinical severity of AOD

		SAC	PAC	AKC	VKC
Palpebral conjunctiva	Hyperemia	0.62	0.62	1.00	1.59
	Edema	0.03	0.11	0.38	0.80
	Follicles	0.10	0.26	0.40	1.00
	Papillae	0.62	0.86	1.23	2.85
	Giant papillae	0	0	0	1.39
Bulbar conjunctiva	Hyperemia	0.16	0.22	0.47	1.83
	Chemosis	0	0.02	0.02	0.27
Limbus	Limbal edema	0	0	0	0.59
	Trantas' dots	0	0	0	0.46
Cornea	Epithelial lesions	0	0.04	0.21	1.90
Total mean clinical score (standard deviation)		1.54 (0.64)	2.13 (1.09)	3.72 (1.60)	12.68 (3.76)

AOD; allergic ocular diseases, AC; seasonal allergic conjunctivitis, PAC; perennial allergic conjunctivitis, AKC; atopic keratoconjunctivitis, VKC; vernal keratoconjunctivitis

reason might be that our hospital was a referral center and elderly patients having other systemic disorders tend to visit the Department of Ophthalmology.

These epidemiological data, while only collected from an ophthalmological clinic but on a large scale, suggest that there are distinct characteristics among different subgroups of AOD including severe ocular allergy. Leonardi et al. proposed a clinical scoring method for the severity of allergic ocular lesions [4]. Although this was a useful system, severity was classified for only three lesions, conjunctival, corneal and limbal; therefore, this was suitable for classifying severe types of AOD, such as VKC and AKC, but was not sensitive to clinical changes in milder diseases, such as SAC or PAC, because of the restricted number of categories. The ability to classify the severity of the disease is also important when designing a clinical trial in AOD [1]. For clinical scoring criteria, a small number of categories is easy to use; however, a large number of categories are necessary to recognize variations over time with changes in the season and patient responsiveness to medication. In severe cases, a number of findings tended to regress simultaneously. However, there is a possibility that, in some cases, palpebral conjunctival findings and bulbar conjunctival findings did not show similar severity. We therefore proposed a new clinical grading system for AOD in this study. In this system, ten objective ocular clinical findings in the conjunctiva (hyperemia, edema, follicles, papillae and giant papillae in the palpebral conjunctiva, hyperemia and chemosis in the bulbar conjunctiva, limbus (limbal edema and Trantas' dots) and cornea) were adopted. Most of these findings were specific for AOD. The results of this study show that AOD can be differentiated clinically, and severe ocular allergy, AKC and VKC in particular can be classified by our new clinical grading system. The fact that the mean total clinical score in all combinations of two diseases showed a significant difference

(SAC 1.54, PAC 2.13, AKC 3.72, and VKC 12.68) suggests that this system is sensitive for the clinical classification of AOD. In the past decade, it has been widely accepted that AOD is classified into several diseases—AC, AKC, VKC etc.—not only by their severity but also by their systemic or local allergological background and pathophysiological differences. It has been reported that the clinical characteristics of PAC are similar to those of SAC in a chronic mode of presentation [8]. However, it was found that the clinical severity was significantly different between PAC and SAC in our study. Although more detailed immunological evaluation is necessary, these results suggest that pathophysiological difference may exist between these two categories of allergic conjunctivitis, and some kind of remodeling might be induced in PAC due to its chronic nature [10]. Owing to its wide spectrum, it seems difficult to characterize clinical features and pathophysiology of AKC. In the present study, it has been demonstrated that clinical severity of AKC was significantly milder than that of VKC. There are several possible reasons for this. Firstly, a lower mean age of patients (25.7 years old) compared with that of the past report [1] means that less cases who had a long-standing history of AD with a variety of ocular complications were included in the study population. Secondly, in the clinical grading system we proposed, common clinical findings in AOD were chosen, but those findings which are especially frequently observed in AKC, such as conjunctival scarring, fornix foreshortening, symblepharon and conjunctival pigmentation, were not included. This might have resulted in lower clinical scores in AKC.

The results of our study suggest that a multicenter or detailed local cohort epidemiological study on AOD is necessary, and re-evaluation of AOD is essential for constructing future strategies for the treatment of AOD which consists of various categories of ocular disorders.

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