A Survey of Seasonal and Perennial Allergic Conjunctivitis in Children in Southwest China: A Case-Control Study

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Research

Keywords: Allergic conjunctivitis, Seasonal allergic conjunctivitis, Perennial allergic conjunctivitis, House dust mites, Allergic diseases, Skin prick test

Posted Date: July 30th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-45303/v1

Abstract

Background Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) were the most usual types of allergic conjunctivitis. House dust mites were the most common sensitization agents for SAC and PAC. This study aimed to explore SAC and PAC risk factors in children.

Methods We recruited 176 children suffering from SAC or PAC and 131 control subjects in southwest China. A questionnaire , several eye exams and the skin prick test (SPT) were performed.The scores of the symptoms/signs were recorded.

Results The percentage of children that had ever been breastfed in the case group was lower than in the control group (P<0.05). The rate of parental allergy history in the case group was higher than for the control group (P<0.01). Compared with the control group, the case group was more likely to have other systemic allergic diseases (P<0.01).The incidence rate of adenoidal hypertrophy (ATH) in case group was higher than control group (P<0.05). The ocular symptoms and signs scores had significant correlation to the course (P<0.05), but no correlation to the SPT results (P>0.05).

Conclusion Allergic conjunctivitis may coexist with a variety of allergic diseases, and SAC and PAC may be a risk factor for ATH. Breastfeeding should be recommended, as it may be an alleviating factor for allergic diseases, especially for children of parents with a history of allergic diseases. The disease severity is closely related to its course. Therefore, to avoid difficulty in treatment caused by the aggravation of symptoms and signs, timely antiallergic treatment was recommended.

Background

Allergic conjunctivitis (AC) is a group of diseases stimulated by allergens to the conjunctiva, associated with type I (IgE-mediated hypersensitivity) and type IV hypersensitivity reactions (non-IgE-mediated hypersensitivity). Although there are several classifications for ocular allergic disorders, based on either clinical signs and symptoms or pathophysiology, the most commonly used classifications are two acute disorders, namely seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), and three chronic diseases, namely vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis(GPC)[1]. Most cases of ocular allergy are SAC and PAC, whereas the severe styles such as AKC and VKC affect a smaller group of patients[2]. In America, PAC accounts for more than 90% of patients with AC [3]. Meanwhile, the AC prevalence is increasing among Asian children [3]. In China, PAC and SAC account for 74% of patients with AC [4]. China lacks epidemiological investigation of AC, especially in children, and the data are badly needed. SAC and PAC are mediated by type I (IgE-mediated hypersensitivity) reactions [4]. PAC is considered to be a variant of SAC that persists throughout the year; 79% of patients who have PAC experience a seasonal exacerbation[5].Although the symptoms of SAC and PAC are mild, they affect the quality of life[6].

There are variations in patients' sensitisations patterns in different geographical areas. House dust mites are the most prevalent allergens in patients with asthma and/or rhinitis in China[7]. SAC and PAC are

always accompanied by symptoms of allergic rhinitis [8]. Dust mites are widely distributed, particularly in the southwest of China, because of the humid climate. Dust mite species include *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*[9]. They are the most common sensitising agents for SAC and PAC[10, 11].

In this study, we administereda survey to the subjects of 307 subjects aged from 4 to 8 years in southwest China; 176 suffered from SAC or PAC, and 131 were normal control subjects. All were studied for more details to explore the risk factors of AC in children and to analyse the related factors affecting the severity of clinical symptoms and signs, with the aim of providing more help for clinical diagnosis and treatment in the future.

Materials And Methods

The study consisted of a disease-specific questionnaire, an ophthalmologic examination and a SPT.

Patients

The study included 176 subjects suffering from SAC or PAC, confirmed by a positive history and positive skin tests, and 131 normal control subjects in the Children's Hospital of Chongqing Medical University (Chongqing, China) from July 2016 to July 2017. Informed consent was obtained from both parents. The diagnosis of ocular allergy was based on clinical history and signs and symptoms, with the support of a positive SPT. All the subjects had not been treated in the previous 4 weeks with topical or systemic H1 receptor antagonists, topical cromolyn or glucocorticosteroids.

The disease-specific questionnaire and ophthalmologic examination

Since the subjects were too young to respond adequately to a questionnaire, all the questionnaires were answered by the children's both parents or their guardians. The questionnaire included questions about the children's basic demographics, breastfeeding history, parental history of allergic disease, the children's experiences of systemic allergic disease, the season of the disease onset and the symptoms. Our ophthalmologists performed eye exams, including a primary ophthalmologic examination, slit lamp observation, corneal fluorescent staining and tear break-up time (BUT). The corneal fluorescein staining scores were modified according to the National Eye Institute grading scale (Table 1) [7].The symptom score and sign score measurements were adapted from Macy M. S. Wu et al. (Table 1) [6, 12].

Table 1
Criteria for scoring symptoms and signs of perennial allergic conjunctivitis.

Item	Scores			
	0	1	2	3
symptoms				
Rubbing eyes	No	mild	moderate	severe
Itching	No	occasional	frequent	constant
Blink	No	occasional	frequent	constant
Redness	No	mild	moderate	severe
signs				
Chemosis	No	one quadrant	two to three quadrants	four quadrants
Tarsal conjunctival papillary hypertrophy	No	mild	moderate, < 1/3 palpebral conjunctival area	severe, appear visualization of the deep tarsal vessels
Bulbar conjunctival hyperemia	No	mild	moderate	severe
Keratitis	No	one quadrant	two quadrants	three or four quadrants
Discoloration	No	mild	moderate	severe
Mucus secretions	No	small amount	moderate amount	eyelid was glued in morning
Limbal hypertrophy	No	one quadrant	two to three quadrants	more than three quadrants

Skin prick test (SPT)

The SPTs were performed using commercial extracts of 13 common inhalation allergen*s:D. farina,D. pteronyssinus*,cockroaches,saccharomycetes, penicillium, dog fur, cat hair,duck feather, birch pollen, artemisia pollen,maize pollen, cotton wooland cigarettes.The negative control solution was a phenolated glycerol-saline solution. The positive control solution was 10 mg/ml histamine hydrochloride (ALK-ABELLO Laboratories,Hrsholm, Denmark). All patients enrolled in the study had discontinued antiallergic drugs for at least 4 weeks prior to the test.The skin reaction was graded 20 minutes later. The skin oedema and erythema that developed were graded from zero to four degrees by comparing the size with positive and negative controls [13].Grade 1 is 25% of the area of histamine-induced wheal, Grade 2 is 50%, Grade 3 is 100% and Grade 4 is 200%. Grades 2, 3, and 4 were considered as positive skin reactions [14].

Statistics

The inter-group indicators of the case and control groups were described and compared. The quantitative data were described as mean ± standard deviation (SD) and compared by the t-test. The rank data were described by the median (quartile spacing), and the rank sum Wilcoxon or Kruskal–Wallis tests were used for inter-group comparisons. Qualitative data were described by frequency (percentage), and the Chi-Square test was used to compare the groups. All hypotheses were tested on both sides of the P value. A P value of 0.05 was set to be statistically significant. The confidence interval was 95%. SPSS software (version 21.0) was used for all statistical calculations (SPSS,Inc.,Chicago, IL, USA).

Results

Clinical features

The mean age at first examination was 5.99 ± 5.98 years. There was no significant difference in age between the case and control group. The AC morbidity was higher in male than in female children (P < 0.01) (Table 2).

Table 2
The clinical features of all the objects.

	-	Control group	Case group	P value
Age	Mean ± SD	5.92 ± 2.51	6.21 ± 2.74	0.336
	M (Q1 - Q3)	6.00 (4.08–8.17)	5.83 (4.00–7.42)	
	Min - Max	1.00–13.08	1.00–15.00	
Sex	Male	70 (53.44%)	46 (26.14%)	< 0.01
	Female	61 (46.56%)	130 (73.86%)	

Season of onset

The subjects were asked about the seasons in which they experienced AC. 26.70% suffered in the spring (from March to May) and 36.36% in the autumn (from September to November), and 89.20% almost abated during the winter (from December to February). PAC occurred in 18.18% of the patients throughout the whole year without remission.

Breastfeeding history

The parents were asked if the children were exclusively breastfed and about its duration. The relationship between breastfeeding and AC outcomes was investigated; a small number of children in the case group were ever breastfed, and the percentage was far lower than in the control group (19.85% vs. 63.64%) ($P < 0.01$). Among those who were ever breastfed, the mean duration of exclusive breastfeeding in the case group was shorter than in the control group ($P < 0.05$) (Table 3). We explored the correlation between duration of exclusive breastfeeding and the age of AC onset, but no positive result was found. We also explored the correlation between the duration of exclusive breastfeeding and the degree of allergic reaction to different house dust allergens found by the SPT, but no positive result was found.

Table 3
Relationship between breast-feeding and allergic conjunctivitis outcomes.

		Control group	Case group	P value
Ever breast-fed	No	26 (19.85%)	112 (63.64%)	< 0.01
	Yes	105 (80.15%)	64 (36.36%)	
Duration of exclusive breast-feeding (months)	Means	9.22 ± 4.74	7.82 ± 3.47	0.014

Parental history of allergic disease

The parents were asked about their history of allergic diseases, such as allergic rhinitis, eczema and urticaria. The rate of parental allergy history in the case group was higher than in the control group ($P < 0.01$, both in the father and the mother) (Table 4). The proportion with allergicrhinitis was the highest at 18.69% (n = 20) in the father and 24.18% (n = 22) in the mother. Eight children in the case group had parents who both had a history of allergic rhinitis.

Table 4
The relationship between parental allergic history and the onset of perennial allergic conjunctivitis

		Control group	Case group	P value
Father	0	127 (96.95%)	107 (60.80%)	< 0.01
	1	4 (3.05%)	69 (39.20%)	
mother	0	129 (98.47%)	97 (55.11%)	< 0.01
	1	2 (1.53%)	79 (44.89%)	
Both	0	131 (100%)	173 (98.30%)	0.26
	1	0 (0%)	3 (1.70%)	
0 means without allergy history				
1 means with allergy history				

Systemic allergic disease and AC

We studied the relationship between systemic allergic diseases and AC in children. In the case group, allergic rhinitis in 85.80% of the group was the most closely related to AC, followed by eczema (76.14%). The third most common allergic disease was asthma (65.34%). Atopicdermatitis and urticaria papulosa were also associated with AC. Compared with the control group, these findings all had significant differences (all $P < 0.01$). Surprisingly, we found some patients had ATH. Meantime, although the proportion was not high at 6.25%, there was a statistical difference between the case group and the control group ($P < 0.05$) (Table 5).

Table 5
The subjects with systemic allergic diseases in two groups.

		Control group	Case group	P value
Allergic rhinitis	without	126 (96.18%)	25 (14.20%)	< 0.01
	with	5 (3.82%)	151 (85.80%)	
Asthma	without	122 (93.13%)	61 (34.66%)	< 0.01
	with	9 (6.87%)	115 (65.34%)	
Atopic dermatitis	without	131 (100.00%)	141 (80.11%)	< 0.01
	with	0 (0.00%)	35 (19.89%)	
Urticaria papulosa	without	122 (92.86%)	97 (55.56%)	< 0.01
	with	9 (7.14%)	79 (44.44%)	
Eczema	without	116 (88.55%)	42 (23.86%)	< 0.01
	with	15 (11.45%)	134 (76.14%)	
Adenoidal hypertrophy	without	129 (98.47%)	165 (93.75%)	0.048
	with	2 (1.53%)	11 (6.25%)	
0 means without this disease.				
1 means with this disease.				

Eye symptoms

The top three symptoms of SAC and PAC were eye rubbing, itching, and blinking. More than half of children in the case group suffered from the top three symptoms.The redness was the forth most common sign which present in 26.7% of the case group, it also could not be ignored as it was hard to distinguish from conjunctivitis.

Ocular signs

The top three clinical signs of SAC and PAC were chemosis, tarsal conjunctival papillary hypertrophy and bulbar conjunctival hyperaemia. However, they all occurred in no more than half of the case group children. Interestingly, discolouration was specific and accounted for 21% (n = 37) of the cases, slightly lower than the top three signs. Limbal hypertrophy was also specific, and the proportion was 13.6% (n = 24), which was lower than discoloration but it still always happened. The keratitis and mucus secretions were uncommon, with a proportion of 8.0% and 9.7%, respectively; as previously reported, corneal

involvement rarely happened[5]Moreover, only 2.84% (n = 5) of the patients had scales and scurf of the eyelid skin, and 2.27% (n = 4) cases had meibomian gland obstruction.

Relationship between the ocular symptom/sign scores and the disease duration

The mean clinical course in the case group was 3.09 ± 2.92 months. We found significant positive correlations between the ocular symptom/sign scores and the disease duration (Table 6).

Table 6
The correlations between scores of ocular symptom/sign and the duration of the disease.

		Clinical course (months)	Mean ± SD
Sign scores	*r*s	0.81	4.91 ± 3.73
	P value	< 0.01	
Symptom scores	*r*s	0.85	7.49 ± 4.66
	P value	< 0.01	

Relationship between the ocular symptom/sign scores and the SPT results for two Dust mite allergens

The SPT results in the control group were all negative. In the case group, the results of the skin reaction to *D. pteronyssinus* were in accord with the *D. farina*results; the goodness of fit was up to 81.25% (n = 143). Grade 3 was the main SPT result for both the dust mite allergens (The results are displayed in supplementary Table.1).There is no correlation between the ocular symptom/sign scores and the grading of the SPT results for the response to these two dust mite allergens(The results are shown in supplementary Table 2).

Discussion

In this study, SAC mostly happened in the spring and the autumn,but seldom in the winter.

The SPT results showed that SAC and PAC patients more frequently and severely displayed allergic reactions to dust mite allergens and mites maybe the most common allergen in children with allergic conjunctivitis. Because dust mites like warm and wet weather, so dust mites bred more in the spring and autumn than in the winter.

No correlation was found between the ocular symptom/sign scores and the SPT grades in response to dust mite allergens. But we found significantly positive correlations between ocular symptom/sign scores and disease duration. The longer the disease lasted, the higher the patients' symptom or sign scores. Lasting moderate or severe allergic reaction to dust mite allergens may be responsible for the ocular symptoms and signs. Therefore, to avoid treatment difficulty and the aggravation of symptoms and signs caused by the delay in diagnosis, timely antiallergic treatment is recommended.

The results showed that the number of children in the case group who had ever been exclusively breastfed was lower than in the control group. The mean duration of exclusive breastfeeding in the case group was shorter than in the control group. These results indicated an association between a history of breastfeeding with a lower rate of allergic eye diseases.We speculate that exclusive breastfeeding may play an important protective role in the AC.As reported by Kull et al. that breastfeeding for four months or more could reduce the risk of eczema and onset of the allergy[15]. In addition, we found that parental allergy history in the case group was significantly higher than in the control group. Allergic rhinitis was most common among their parents. Therefore, prolonged breastfeeding could be a particularly recommended way for infants to reduce the risk of onset of AC, especially with a parental allergy history.

Systemic allergic diseases were closely related with AC. According to our study, allergic rhinitis was the most common, followed by eczema, asthma and urticaria papulosa. Investigatingthe systemic allergic history was necessary in the clinic, especially for children without typical symptoms and signs or children were too young to express themselves. This would help with diagnosis and provide appropriate treatment.

Interestingly, children with ATH were more common in the case group, which suggested thatallergic conjunctivitis may be related to ATH, a result consistent with previous researches [16–18].The conjunctiva are located in the upper extremity of the respiratory system, and the nasolacrimal duct is a drainage system into the nose [19]. Allergens and allergic mediators drain to the nose by this pathway, generating nasal symptoms. The conjunctiva and the nose make up an entire system [1, 2, 5–8]. This can also be explained, allergic rhinitis and conjunctivitis were always co-existent and persistent to repeatedly happen. SAC and PAC were considered to be associated with type I hypersensitivity reactions[20]. Xiaowen Zhang et al. found that the rate of IgE presenting in the adenoids or tonsils was significantly higher than in the serum of childhood ATH, which suggests a role for local atopy [21, 22]. Allergy control may play a role in reducing the rate of adenotonsillectomy in children suffering from allergic reactions caused by ATH [23]. We assumed that in children suffering from PAC combined with ATH, effective PAC control could alleviate the ATH symptoms. Children with ATH would be suggested to have an ophthalmic exam to determine if they are suffering from AC, in order to give more suitable synchronous treatments.

The ocular surface inflammation was usually driven by mast cells, which led to rubbing eyes, itching, blinking and redness in the acute phase [20].The symptoms of SAC and PAC in children were typical, mainly including eye rubbing, itching, blinking and redness. Nearly half the children experienced these symptoms. The top three clinical signs of AC were chemosis, tarsal conjunctival papillary hypertrophy,

and bulbar conjunctival hyperaemia, but they were not specific. Discoloration, limbal hypertrophy, mucus secretions and keratitis were the characteristic signs. Discoloration and limbal hypertrophy always occurred and could make the eye circumference become thickened and opaque. Keratitis and mucus secretions were rare and often happened when eye rubbing was uncontrollable[5].As children are different from adults, they were not be able to express their feelings accurately and have a variety of clinical manifestations. We always have difficulties in clinical diagnosis, so the more we learn about the characteristics of symptoms and signs of SAC and PAC in children, the more professional the decisions we will make concerning diagnosis and treatment.

This study also had some limitations. First, the sample of subjects in this study was small. In the further research, we need to recruit more to verify our positive findings. Second, we used SPT instead of conjunctival provocation test which is an established diagnostic procedure for allergic conjunctivitis. Because the conjunctival provocation test is not usually used in the clinic regarding the relative risks for children [24]. SPT has higher accuracy in the diagnosis compared with serum-specific IgE in vitro[2, 25]. Even so, conjunctival provocation test, serum-specific IgE or SPT can only be considered as a diagnostic tool for evaluation the allergic status of individuals, but not to a diagnosis tool[26]. Third, since our subjects were too young to accomplish such a questionnaire adequately, all the questionnaires were answered by their parents. But even parents can have limited understanding of subjects' routines. Last but not the least, our results showed all subjects in the control group were negative to the SPT test considering dust mite allergen, allergic conjunctivitis patients more frequently displayed allergic reactions to it. It suggested that allergic background made subjects more sensitive to dust mite allergen rather than dust mite causing seasonal and perennial allergic conjunctivitis.

Conclusion

In this study, we explored the risk factors in children with SAC and PAC, and found such as history of breastfeeding, parental history of allergic disease and systemic allergic disease were closely related to the incidence of allergic conjunctivitis. Ophthalmologist need pay more attention to the children's systemic symptoms/signs and family histories, and SPT results to provide a firm diagnosis and timely treatments.

List Of Abbreviations

AC: Allergic Conjunctivitis

AKC: Atopic Keratoconjunctivitis

ATH: Adenoidal Hypertrophy

BUT: Tear Break Time

GPC: Giant Papillary Conjunctivitis

PAC: Perennial Allergic Conjunctivitis

SAC: Seasonal Allergic Conjunctivitis

SPT: Skin Prick Test

VKC: Vernal Keratoconjunctivitis

Declarations

The study followed the Tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University, Chongqing, China (Permit No.004/2016). Written informed consent was obtained from the parents of each subject.

Consent for publication:

Not applicable.

Availability of data and material:

Some or all data generated were used during the study are available from the corresponding author by request.

Competing interests:

The authors declare that they have no competing interests

Funding:

The study and the writing of the manuscript were supported by Chongqing Municipal Health Bureau (ZY201702067). The funding body no financial relations with this research.

Authors' contributions:

XG was a major contributor in writing the manuscript, doing the statistical analysis and editing tables. QX revised the manuscript and helped perform the analysis with constructive discussions. XG, LH and QX completed the acquisition of data, analysis and interpretation of data together. XG made substantial contributions to conception and revised the manuscript, given final approval of the version to be published. All authors read and approved the final manuscript. Each author had participated sufficiently in the work to take public responsibility for appropriate portions of the content, agreed to be accountable

for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements:

The authors thank all patients and their parents enrolled in the present study.

Ethical review

The study followed the Tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University, Chongqing, China (Permit No.004/2016). Written informed consent was obtained from the parents or their guardians.

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