A survey of seasonal and perennial allergic conjunctivitis in children in southwest China: a case-control study

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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 was provided to all the subjects’ parents. Several eye exams were performed, and all the subjects received the skin prick test (SPT). We analyzed the questionnaire data, the scores of the symptoms/signs and the SPT results.

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). Some children in case group had adenoidal hypertrophy (ATH), and incidence rate was different from control group (P<0.05). The ocular symptoms and signs scores had significant correlation to the clinical course (P<0.05), but there was 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 administered a 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.

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 2015 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 H1receptor 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. 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 several 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].

**Skin prick test (SPT)**

The SPTs were performed using commercial extracts of 13 common inhalation allergens: *D. farina*, *D. pteronyssinus*, cockroaches, saccharomycetes, penicillium, dog fur, cat hair, duck feather, birch pollen, artemisia pollen, maize pollen, cotton wool and 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).

Season of onset

The subjects were asked about the seasons in which they experienced AC. A larger percentage suffered in the spring (from March to May) and the autumn (from September to November), and most experienced that it almost abated during the winter (from December to February). PAC occurred in 18.18% of the patients throughout the whole year without remission (Fig. 1).

Bedtime routines

The survey included questions about the children’s bedtime routines. There was no difference between the two groups (P >0.05); the results are displayed in supplementary Table 1.

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 (data not shown).

**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 allergic rhinitis 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.

**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%). Atopic dermatitis 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).
**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 (Fig. 2).

**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] (Fig. 3). 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 (data not shown).

**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).

**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 (Table 7).

We investigated the correlation between the ocular symptom/sign scores and the grading of the SPT results for the response to these two dust mite allergens, but found no correlation. 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. Investigating the 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 that allergic 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.001/2013). Written informed consent was obtained from the parents of each subject. The study was registered in the Chinese Clinical Trial Registry (Registration number ChiCTR-OCC-14004140).

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

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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, XT and QX completed the acquisition of data, analysis and interpretation of data together. QX 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.

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**Tables**

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       | No                            | mild                   | moderate, <1/3 palpebral| severe, appear visualization of conjunctival area |
| hyperpapillary                      | No                            | mild                   | moderate, <1/3 palpebral| severe, appear visualization of conjunctival area |
| 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                | eyelid was glued in morning |
| Limbal hypertrophy                  | No                            | one quadrant           | two to three quadrants  | more than three quadrants |
Table 2: The clinical features of all the objects.

|                | Control group | Case group | P value |
|----------------|---------------|------------|---------|
| Age            | 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%)|

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

| Ever breast-fed | Control group | Case group | P value |
|-----------------|---------------|------------|---------|
| No              | 26 (19.85%)   | 112 (63.64%)| < 0.01  |
| Yes             | 105 (80.15%)  | 64 (36.36%) |         |

| Duration of exclusive breast-feeding (months) | Control group | Case group | P value |
|------------------------------------------------|---------------|------------|---------|
| Means                                          | 9.22 ± 4.74   | 7.82 ± 3.47| 0.014   |

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

Table 5: The subjects with systemic allergic diseases in two groups.
| Diseases                  | Control group | Case group | P value |
|---------------------------|---------------|------------|---------|
| Allergic rhinitis         | 126 (96.18%)  | 25 (14.20%) | < 0.01 |
|                          | 5 (3.82%)     | 151 (85.80%) |        |
| Asthma                    | 122 (93.13%)  | 61 (34.66%) | < 0.01 |
|                          | 9 (6.87%)     | 115 (65.34%) |        |
| Atopic dermatitis         | 131 (100.00%) | 141 (80.11%) | < 0.01 |
|                          | 0 (0.00%)     | 35 (19.89%)  |        |
| Urticaria papulosa        | 122 (92.86%)  | 97 (55.56%)  | < 0.01 |
|                          | 9 (7.14%)     | 79 (44.44%)  |        |
| Eczema                    | 116 (88.55%)  | 42 (23.86%)  | < 0.01 |
|                          | 15 (11.45%)   | 134 (76.14%) |        |
| Adenoidal hypertrophy     | 129 (98.47%)  | 165 (93.75%) | 0.048  |
|                          | 2 (1.53%)     | 11 (6.25%)   |        |

0 means without this disease.  
1 means with this disease.

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

|                         | Clinical course (months) | Mean ± SD |
|-------------------------|--------------------------|-----------|
| Sign scores             | rs 0.81                  | 4.91 ± 3.73 |
|                         | P value < 0.01           |           |
| Symptom scores          | rs 0.85                  | 7.49 ± 4.66 |
|                         | P value < 0.01           |           |

Table 7: Grading of the skin prick testing results in case group.

| Diseases                  | Grading | N   | %       |
|---------------------------|---------|-----|---------|
| Dermatophagoides pteronyssinus | Grade 1 | 34  | 19.32%  |
|                           | Grade 2 | 38  | 21.59%  |
|                           | Grade 3 | 70  | 39.77%  |
|                           | Grade 4 | 34  | 19.32%  |
| Dermatophagoides farinae  | Grade 1 | 42  | 23.86%  |
|                           | Grade 2 | 24  | 13.64%  |
|                           | Grade 3 | 76  | 43.18%  |
|                           | Grade 4 | 34  | 19.32%  |

Grade 1 is 25% of area of histamine-induced wheal, Grade 2 is 50% of this area, Grade 3 is 100% of this area, Grade 4 is 200% of it.

Figures
Figure 1

The percentages of symptoms in case group in the period of the year. 36.4% patients occurred in the autumn (n=64); 26.7% occurred in the spring (n=47); 4.5% occurred in the summer (n=8); 1.1% occurred in the winter (n=2); 5.7% patient occurred in both the spring and autumn (n=10); 3.4% occurred in both the summer and autumn (n=6); 4.0% occurred in both the autumn and winter (n=7); 18.2% patients occurred all the year around (n=32).
The percentages of symptoms in case group including rubbing eyes, itching, blinking and redness. 50.6% patients had symptoms of rubbing eyes (n=89); 40.3% patients had itching (n=71); 46.0% patients had blinking (n=81). 26.7% patients had redness (n=47).
The percentages of clinical signs in case group including chemosis, tarsal conjunctival papillary hypertrophy, bulbar conjunctival hyperemia, keratitis, discoloration, mucus secretions and limbal hypertrophy. 38.1% patients had signs of chemosis (n=67); 29.5% patients had tarsal conjunctival papillary hypertrophy (n=52); 22.2% patients had bulbar conjunctival hyperemia (n=39); 8.0% patients had keratitis (n=14); 21.0% patients had discoloration (n=37); 9.7% patients had mucus secretions (n=17); 13.6% patients had limbal hypertrophy (n=24).

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.
sTable 2.docx
Questionnaire.docx
stable 1.docx