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Original Article

Predisposition of hypersensitivity in patients with exfoliative cheilitis

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Abstract *Background/purpose:* Exfoliative cheilitis (EC) is a chronic and reversible inflammatory disease of the lips without definite etiology. Clinically, different types of allergens can be found in exfoliative cheilitis patients, however, few studies have focused on the relationship between exfoliative cheilitis and hypersensitivity. This research aimed to investigate the prevalence of hypersensitivity in EC patients.

Materials and methods: A prospective study was conducted in 30 patients with exfoliative cheilitis and 30 healthy controls, matched in age and sex. Laboratory tests included serum total IgE, allergen-specific IgE, and food-specific IgG.

Results: Increased serum total IgE level, positive food-specific IgG were seen more frequently in exfoliative cheilitis patients than in healthy control ($P < 0.05$). Special IgE level to FX5 and the degree of food-specific IgG to wheat were seen higher in exfoliative cheilitis patients than in healthy control ($P < 0.05$).

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Conclusion: This study suggests that patients with exfoliative cheilitis may have predisposition of hypersensitivity. The detection of allergens should be strengthened in the future clinical work. © 2021 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Exfoliative cheilitis (EC) is a recurrent and reversible condition affecting upper or lower of lip, presenting as dryness and cracking, desquamation of scales, exudation and incrustation on the lips (see Fig. 1).^{1–3} The etiology of exfoliative cheilitis is still unclear,^{2,4} the known related factors including: psychiatric condition, vitamin deficiency, bacterial/fungal infection, long-term continuous stimulation, such as climate dryness, lip licking, etc.^{1–6}

Owing to the of non-specific inflammation feature, all other subtypes of cheilitis need to be excluded when the patient is diagnosed as exfoliative cheilitis, especially particularly contact cheilitis and actinic cheilitis. Repeated and entire inquiry about allergic exposure and chronic exposure to sunlight should be emphasized.^{3,7}

Type I hypersensitivity reaction is the most common kind of hypersensitivity, mainly mediated by the specific IgE antibody. Elevated IgE levels and positive allergen-specific IgE are commonly associated with allergic diseases, such as atopic dermatitis, allergic rhinitis, allergic asthma.⁸ Food intolerance is a complex hypersensitivity disease (belongs to type III hypersensitivity) mediated by IgG antibodies. It is believed that IgG-mediated food intolerance is caused by increased intestinal permeability, allowing access for food substances to the circulation and triggering food-specific IgG production.⁹ Food particles is regarded as antigen and combined with specific IgG antibody to form antigen–antibody complexes. To evaluate these distinct immunological mechanisms, the enzyme-linked immunosorbent assay (ELISA) is a common method, meanwhile the ImmunoCAP test is reliable and reproducible to measure serum/plasma total and specific IgE in vitro.^{10–12}



Figure 1 Clinical photograph of patient with exfoliative cheilitis.

Some studies have shown that tacrolimus ointment, an immunosuppressant, is effective in exfoliative cheilitis,^{2,13,14} which may imply a relationship between EC and hypersensitivity. Also, in clinical work, patients clinically diagnosed with EC may also be found to have different types or degrees of positive rate of allergen. However, few studies have focused on the relationship between hypersensitivity and exfoliative cheilitis.¹⁵ As the lack of information in the literature on EC and these immunological mechanisms, we sought to investigate the prevalence of hypersensitivity in EC by detecting serum total IgE, allergen-specific IgE, and food-specific IgG.

Materials and methods

Ethical approval

This is a prospective study that has been approved by the Human Research Ethics Committees of the West China Hospital of Stomatology, Sichuan University (WCHSIRB-D-2015-162). Written informed consent was obtained from all subjects before inclusion into the study.

Study participants

30 patients with exfoliative cheilitis and 30 healthy controls were recruited to detect the peripheral blood antigens. All samples included were visitors of West China Hospital of Stomatology from December 2014 to December 2016. There was no significant difference in the median age, gender ratio and cultural hierarchy between the two groups.

To minimize variability in the present study, the diagnosis of EC was determined jointly by the second (postgraduate doctor) and eighth (professor) authors of the article.

Inclusion and exclusion criteria

Inclusion criteria were: (1) prolonged course and reversible outbreak for more than 3 months; (2) clinical manifestations of repeated drying, desquamation, exudation and crusting on vermilion lips; (3) patients' lips were soft texture.

Exclusion criteria were: (1) patients were pregnancy or lactation; (2) patients with systemic diseases such as anemia, diabetes, connective tissue disease, etc.; (3) sex hormones, tricyclic antidepressants, benzodiazepines, antihistamines and glucocorticoid were used within one month; (4) patients with other oral mucosal diseases; (5) patients with a history of contact stomatitis/cheilitis or chronic exposure to sunlight; (6) patients were diagnosed as other cheilitis of specific causes.

Serum total IgE and special IgE

Blood was allowed to coagulate at room temperature for 20–30 min, centrifuged at 3000r for 10 min at 4 °C, separated and stored the sera in aliquots at –80 °C until analysis.

Total and specific IgE levels in patient serum were detected by the UniCAP system (Pharmacia & Upjohn, Upsala, Sweden). Specific IgE was determined for 6 kinds of allergens including: animal fur scraps (ex1), shrimp (f24), house dust mixed (hx2), mixed allergen of food (fx5), mold (mx2) and weed pollen (wx5). All test results will be output to the Information Data Manager software by automatic immunofluorescence analyzer.

Food-specific IgG

Food-specific IgG production was determined in serum using the BIOMERICA Allerquant IgG Food Allergy Screening ELISA Kit (BIOMERICA, INC. 1533 Monrovia Avenue Newport Beach, CA 92663, America). The experiment followed strictly to the instructions of the kit. Standard serum of 50U/ml, 100U/ml, 200U/ml, 400U/ml were prepared respectively. For each specimen and standard control, the Thermo Scientific Varioskan Flash multimode reader was used to measure optical density at 450 nm per pore. The standard curve and working curve were drawn. The IgG concentration of specimens is calculated from the working curve.

Statistical analysis

All the data were analyzed by software SPSS 22.0. Test level $\alpha = 0.05$.

Chi-square test, Mann–Whitney U test, rank sum test was used for non-normally distributed variables. Student's t test was used in statistical analysis of age. Comparison of total serum IgE concentration between the two groups was statistically analyzed by a one-way ANOVA test and Student's t test.

Results

This study included 30 patients with exfoliative cheilitis (age range 16–50 years, mean age 27.1 years) and 30 healthy subjects (age range 18–55 years, mean age 26.6 years). No significant differences were found in

Table 1 Demographic features of the study population.

Group	Gender ^a		Average age	
	Male	Female	Male ^b	Female ^c
Exfoliative cheilitis (n = 30)	12	18	27.75 ± 9.68	26.61 ± 9.25
Control (n = 30)	14	16	26.64 ± 9.23	26.56 ± 9.40

^a $\chi^2 = 0.271, P = 0.602$

^b Comparison between the two groups, $t = 0.298, P = 0.768$

^c Comparison between the two groups, $t = 0.015, P = 0.988$

Table 2 Laboratory findings of IgE in exfoliative cheilitis group and healthy control.

Laboratory findings	Exfoliative cheilitis (n = 30)	Control (n = 30)	P value
Serum total IgE levels (KU/L) ^b	105.01 ± 110.94	54.83 ± 72.42	0.042 ^a
Serum total IgE >80kU/L ^c	13 (43.3%)	6 (20%)	0.052
Serum special IgE>0.35 kU/L ^c	8 (26.67%)	7 (23.33%)	0.766
Special IgE to EX1 ^d	MD:0.03 25th:0.02 75th:0.06	MD:0.03 25th:0.02 75th:0.13	0.989
Special IgE to F24 ^d	MD:0.04 25th:0.01 75th:0.1675	MD:0.02 25th:0.01 75th:0.155	0.604
Special IgE to FX5 ^d	MD:0.05 25th:0.04 75th:0.085	MD:0.04 25th:0.03 75th:0.045	0.034 ^a
Special IgE to HX2 ^d	MD:0.085 25th:0.0275 75th:0.3625	MD:0.11 25th:0.025 75th:1.04	0.790
Special IgE to MX2 ^d	MD:0.065 25th:0.06 75th:0.08	MD:0.08 25th:0.045 75th:0.1	0.705
Special IgE to WX5 ^d	MD:0.02 25th:0.01 75th:0.035	MD:0.01 25th:0.005 75th:0.02	0.181

MD: median values; 25th: 25th percentiles; 75th: 75th percentiles; EX1: animal fur scraps; F24: shrimp; FX5: mixed allergen of food; HX2: house dust mixed; MX2: mold; WX5: weed pollen.

^a $P < 0.05$, the difference is statistically significant.

^b One-way ANOVA test and Student's t test were used.

^c Chi-square test was used.

^d Mann–Whitney U test was used.

demographic features between EC group and healthy subjects ($P > 0.05$, Table 1).

Laboratory findings of IgE in exfoliative cheilitis group and healthy control

The laboratory findings of IgE in exfoliative cheilitis group and healthy control are shown in Table 2. The serum total IgE levels of exfoliative cheilitis group was significantly higher than that in control group (105.01 ± 110.94 vs 54.83 ± 72.42 (KU/L), $P = 0.042 < 0.05$). Then, we analyzed the sIgE levels of 6 kinds of allergens including: animal fur scraps (ex1), shrimp (f24), house dust mixed (hx2), mixed allergen of food (fx5), mold (mx2) and weed pollen (wx5). The special IgE level to FX5 was significantly higher levels in patients with exfoliative cheilitis ($p = 0.034 < 0.05$). Two patients found EX1 positive, while none of normal control showed positive IgE to EX1.

For IgE to HX2, F24, MX2, WX5, EX1, there is no significant differences between healthy subjects and patients with exfoliative cheilitis.

Table 3 Comparison of food intolerance between exfoliative cheilitis group and control group.

	Positive case	Negative case	Total	Positive rate (%)
Exfoliative cheilitis	24	6	30	80.00
Control	16	14	30	43.33
Total	40	20	60	66.67

$$\chi^2 = 4.80, P = 0.028.$$

Laboratory findings of food intolerance of exfoliative cheilitis group and healthy control

The positive rate of total food-specific IgG of exfoliative cheilitis group was significantly higher than that in control group (80.00% vs 43.33%, $P = 0.028 < 0.05$) (Table 3).

Table 4 shows the degree and positive rate of intolerance to each kind of food, including beef, milk, chicken, pork, cod, rice, corn, shrimp, crab, soy, egg, tomato, mushroom, wheat. In exfoliative cheilitis group, the intolerance degree of eggs, milk, wheat, shrimp, chicken, corn, tomatoes, soy were higher than in normal control. The degree of wheat was found significant higher in exfoliative cheilitis group ($P = 0.03 < 0.05$). Among exfoliative cheilitis group, egg was the food with the highest positive rate with frequency 16 (53.33% of individuals with exfoliative cheilitis were diagnosed with an intolerance to egg) and then follows the milk with 9 (30%) and wheat with 6 (20%).

Discussion

We investigated the relationship between exfoliative cheilitis and hypersensitivity by detecting serum total IgE, allergen-specific IgE, and food-specific IgG using ELISA and UniCAP system. In our study, we found serum total IgE level was significantly elevated in exfoliative cheilitis group.

Also, we found high IgE level to FX5 in exfoliative cheilitis group than normal control with significance. As for IgG, we also found positive total food-specific IgG was more prevalent in exfoliative cheilitis patients than in control group (80.00% vs 43.33%, $P = 0.028 < 0.05$). The intolerance degree of eggs, milk, wheat, shrimp, chicken, corn, tomatoes, soy were higher in exfoliative cheilitis patients than normal control, significant difference was found in wheat.

According to a study of 907 allergy patients, the average age of first allergic reaction was 31, and 68% of first allergic reactions occurred in the 18–50 age range.¹⁶ Also, exfoliative cheilitis is most prevalent in young women.¹⁷ Similarly, in our study, the mean age of the exfoliative cheilitis group was 27.1 years old, and the sex ratio (male/female) of the exfoliative cheilitis group was 2/3. Both allergic reaction and exfoliative cheilitis occur in young people, thus, we assumed that hypersensitivity might be important in the development of EC.

High levels of serum total IgE often indicate the possibility of hypersensitivity and are related to the degree of hypersensitivity frequently.¹⁸ Some allergens have been reported to be associated with cheilitis.¹⁹ In a study of 396 atopic dermatitis patients, patients with positive serum total IgE showed more positive clinical features of cheilitis.²⁰ The relationship between food intolerance and oral mucosal disease has been reported in many literatures.²¹ One case of cheilitis associated with vitamin B12 has been reported in the literature, the symptoms were relieved with withdrawal of vitamin B12.²² Food intolerance is becoming more and more common with an incidence rate of 20%–45%.²³ IgG-mediated food intolerance is associated with a wide range of specific and nonspecific symptoms, for example, the most common nonspecific symptoms such as chronic fatigue and hair loss.²⁴ These symptoms start slowly and insidiously days even months after eating, presents with slow progression. Because of its insidious onset, and the non-specific

Table 4 Distribution of detected food-specific IgG in study and control groups.

Allergen	Exfoliative cheilitis group				Control group				χ^2	P
	Concentration of IgG			Positive number	Concentration of IgG			Positive number		
	+	++	+++		+	++	+++			
Egg	9	5	2	16	6	2	2	10	2.44	0.12
Milk	3	3	3	9	3	0	1	4	1.57	0.21
Wheat	5	1	0	6	0	0	0	0	4.63	0.03 ^a
Cod	5	0	0	5	3	1	0	4	0.13	1.00
Shrimp	4	1	0	5	2	1	0	3	0.14	0.70
Chicken	3	1	0	4	1	0	0	1	0.87	0.35
Corn	4	0	0	4	1	0	0	1	0.87	0.35
Tomato	4	0	0	4	0	0	0	0	2.41	0.12
Rice	2	1	0	3	2	0	0	2	0.00	1.00
Crab	1	0	0	1	3	0	0	3	0.27	0.61
Soy	0	0	1	1	0	0	0	0	0.00	1.00
Mushroom	1	0	0	1	0	3	0	3	0.27	0.61
Beef	0	0	0	0	0	0	0	0	0.00	1.00
Pork	0	0	0	0	0	0	0	0	0.00	1.00

Concentration of IgG: +, 50–100 U/ml; ++, 100–200U/ml, +++, >200 U/ml.

^a $P < 0.05$, Chi-square test was used

symptoms, it may lead to long-term chronic damage to the body. Exfoliative cheilitis is a recurrent and chronic subtype of cheilitis without clear etiology and histopathology, whether food intolerance is the cause of exfoliative cheilitis needs to be further explored.

Contact/eczematous cheilitis is a subtype of reversible cheilitis caused by partial contact with special irritating or allergic substances, which also manifests as dryness, scaling, erythema or fissuring.²⁵ Exposure to local materials in contact cheilitis, such as toothpaste and metal materials, has been reported in many literatures.^{14,26,27} The patch test is an important way to identify these allergens that cause contact cheilitis locally.²⁸ O'Gorman et al. used patch test in recalcitrant non-actinic cheilitis subjects, 45% patients had a final diagnosis of allergic contact cheilitis.²⁷ Interestingly, patients clinically diagnosed with exfoliative cheilitis after eliminating local contact allergen were detected varying degrees of positive peripheral blood antigens in our study.

There are no previous investigations of peripheral blood antigens to allergens in exfoliative cheilitis subjects in the current literature. Therefore, this was the first study that investigated peripheral blood antigens to detect the relationship between EC and allergy. Total IgE level and positive total food-specific IgG rate was higher in EC subjects. Possibly due to the limitation of numbers of detected cases and allergens, IgE level to EX1/HX2/F25/MX2/WX5 did not find statistically significant differences. Another limitation of our study is that no clinical follow-up conducted to correlate testing results with clinical outcomes.

In summary, we have demonstrated the possible link between exfoliative cheilitis and hypersensitivity. In clinical diagnosis and treatment, allergen detection should be performed to check whether allergen is the cause of lip inflammation. Allergen detection, especially detection of serum IgE level in vitro by ImmunoCAP test, is effective way to avoid missed diagnosis of allergic cheilitis. Expanding sample size and clinical follow-up need to conduct to confirm the relationship between exfoliative cheilitis and hypersensitivity.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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