Inhaled steroid inhibits development of total and mite IgE

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\begin{abstract}
Serum levels of total immunoglobulin E (IgE) and allergen-specific IgE are related to asthma severity and risk factors for persistent asthma in childhood wheezing. Inhaled corticosteroids (ICS) have been the most effective therapy in children with asthma, as well as in adults. The serum levels of total and mite specific IgE in children with asthma and the effects on IgE levels of beclomethasone dipropionate (BDP) treatment on IgE levels in asthmatic children were investigated. First, a cross-sectional study of 255 children with asthma was carried out to measure IgE levels. Children under three years of age with asthma who were negative for Df-specific IgE were then treated with BDP or disodium cromoglycate (DSCG) as controls for one year. Serum IgE levels, numbers of eosinophils in peripheral blood and clinical variables were determined before and after treatment. After one-year DSCG treatment, the total IgE levels increased significantly, whereas the levels remained the same during BDP treatment. Five of 22 (23\%) patients in the DSCG-treated group became positive for Df-specific IgE; however, only one of 13 (8\%) in the BDP-treated group became positive. Taken together, ICS therapy may modulate the levels of total IgE and allergen-specific IgE.
\end{abstract}

1. Introduction

Inhaled corticosteroids (ICS) are recognized as the most effective anti-inflammatory treatment in bronchial asthma, since the pathogenesis of this disease is related to chronic airway inflammation [1]. It has been reported that early intervention with ICS therapy can improve the prognosis in children with asthma, as well as in adults [2,3]. Disodium cromoglycate (DSCG) is thought to have some anti-inflammatory action through inhibition of histamine release from mast cells [4]. Treatment of children with asthma requires attention to the effects of medications on mental and physical growth [5]. For example, the fact that many children with asthma (wheezing) show natural remission during adolescence [6] should be considered during treatment. Therefore, many pediatricians still prefer to use DSCG, which has few adverse effects and some preventive effects in exercise-induced bronchoconstriction [7]. However, the long-term efficacy of DSCG has not been investigated as extensively as that of ICS therapy [8]. On the other hand, the precise mechanism of action of ICS therapy in asthmatic patients has not been well clarified and this may lead physicians to hesitate in choosing ICS as a first-line therapy.

It is well known that disease severity in asthmatics is closely related to serum levels of total and allergen-specific IgE [9,10]. Such levels may be the outcome of the frequency of antigen exposure and may also increase naturally from infancy through school age [11]. \textit{Dermatophagoides farinae} (Df) is a mite for which specific IgE is found in more than 80\% of school age children with asthma in Japan [12]. To study when children with asthma develop allergen-specific IgE and if anti-inflammatory medication affects IgE levels in cases of childhood asthma (wheezing) is of interest in devising optimal therapies.

In this study, background levels of total and positive rates of Df-specific IgE were first determined in children with asthma (wheezing). Both total IgE and Df-specific IgE levels seemed to increase between 0 and three years of age. Changes in serum levels of total and Df-specific IgE were then compared in groups of children with asthma (wheezing) following beclomethasone dipropionate (BDP) or DSCG treatment.

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2. Methods and materials

2.1. Patients

All data were gathered from children with asthma who attended or were admitted to the Department of Pediatrics, Osaka Prefectural Medical Center for Respiratory and Allergy Diseases. Data from April 1994 to June 1999 were analyzed retrospectively. All the asthmatic children were trained to record daily symptoms, values of peak flow (more than six years old) and compliance checks. A total of 255 asthmatic patients were continuously followed from June 1999 with clinical examinations for more than six months. Df-negative children with asthma (wheezing) who were selected from this population were 0–3 years old and were given either BDP or DSCG from 1994 to 1998. They were continuously followed every 1–4 weeks for more than one year.

2.2. Cross-sectional study of serum levels of total IgE and Df-specific IgE in children with asthma

To determine the changes in serum levels of total and Df-specific IgE under natural conditions, 255 asthma patients were investigated. Patients were diagnosed with asthma according to the following criteria: recurrent wheezing, family history of asthma, existence or history of atopic disease and a lab test result such as eosinophilia, higher levels of IgE or a positive skin test to allergens. Children were divided into eight groups by age as follows: 0–1, 2–3, 4–5, 6–7, 8–9, 10–11, 12–13 and ≥14 years old. To measure levels of IgE, 3–5 ml of blood were collected and the serum was separated.

2.3. Changes of serum levels of total and mite Df-specific IgE, eosinophil numbers in peripheral blood and clinical symptoms with BDP and DSCG treatment

Since serum IgE levels in asthmatic children began to increase at 1–3 years of age, only children with asthma (wheezing; <3 years of age) were recruited. When initial DSCG treatment failed to control the wheezing or severe cough, which was defined as four days or more in a week with usage of a β2-stimulant, the medication was changed to BDP treatment. After disease stabilization with either of the treatments, BDP ($n=13$) or DSCG ($n=22$), patients were followed for up to one year to avoid bias from seasonal changes and clinical conditions. All children with asthma were first given additional DSCG inhalation treatment. When patients were resistant to initial DSCG or DSCG added to theophylline treatment, BDP treatment was started as second-line therapy. Both treatments were maintained for up to one year during the study if the patient’s disease
conditions were stable. When patients were not well controlled and additional medication was added or there was step up to other medications during this study, they were excluded from this study. The serum levels of total IgE, Df-specific IgE and eosinophil numbers in peripheral blood were measured before and after one year of therapy. The dose of BDP in this study was 300–600 μg/day (average 430 μg/day). Before BDP therapy started, all patients were trained with their parents to use spacer devices. DSCG was also administered as an aerosol (20 mg, three times a day) by nebulizer compressor. The degree or severity of the asthma in the two groups was compared by summation of the symptom scores, the numbers of days with usage of rescue medicine, either bronchodilator (β₂-antagonists) or systemic corticosteroid administration and the numbers of admissions for acute asthma exacerbation for one month before and after the study. Symptom scores for wheezing were compared, with dyspnea-free, mild, moderate and severe exacerbations taken as levels 1, 2, 3 and 4, respectively.

Total and allergen-specific IgE levels in serum were determined and expressed as described above. The numbers of total blood cells and percentages of eosinophils in peripheral blood were determined by automatic hemocytometer (ADVIA120 Hematology System, Bayer Diagnostics, New York, NY) and then values were calculated and expressed as eosinophil numbers per ml.

2.4. Statistical analysis

The data were analyzed by the paired t-test, unpaired t-test and the chi-squared test, as appropriate. p values of less than .05 were considered significant.

3. Results and discussion

3.1. Results

3.1.1. Serum levels of total IgE and positive rates of Df-specific IgE at different ages in children with asthma

As shown in Figure 1, levels of total IgE were significantly lower in 0–3 year-old asthmatic children than in those more than six or eight years old. The positive rates of Df-specific IgE were also significantly lower in asthmatic children less than three years old than in those more than four or six years old.

3.1.2. Effect of one-year treatment with BDP or DSCG on serum IgE levels and other clinical variables

As shown in Table 1, baseline characteristics of subjects before treatment showed no significant difference in sex, age, total IgE in serum and numbers of eosinophils in peripheral blood between the BDP and DSCG groups. Almost all subjects in both groups had some atopic factors, although subjects with atopic dermatitis and an atopic family history in their close blood relatives having asthma, atopic dermatitis, allergic conjunctivitis or allergic rhinitis were higher in the BDP group than in the DSCG group.
The BDP group had more allergic factors than the DSCG group.

As shown in Figure 2, the numbers of eosinophils in peripheral blood from the respective treatment groups showed a significant decrease after one-year BDP treatment (from 601 to 321/ml; \( p < .05 \) paired t-test), while significant changes were not found in the DSCG group. As shown in Figure 3, baseline levels of total IgE in the BDP and DSCG group were comparable (1.71 and 1.32 log10IU/ml). After one-year therapy, total IgE levels in the BDP group were significantly decreased (1.32 to 1.05 log10IU/ml). On the other hand, in the DSCG group, total IgE levels remained stable (1.71 to 1.64 log10IU/ml). The BDP group had more allergic factors than the DSCG group.

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Figure 3. Changes in serum total IgE levels before and after each therapy. DSCG: disodium cromoglicate; BDP: beclomethasone dipropionate. Paired t-test. \( \ast p < .05 \).

4. Discussion

Serum levels of total and allergen-specific IgE have been thought to be a hallmark of atopic asthma and is closely related to disease severity. In childhood asthma (wheezing) serum total IgE, allergen-specific IgE, peripheral eosinophil, allergic family history and past other allergic diseases are recognized as risk factors for persistent asthma (GINA guideline).

In the present study, total and Df-specific IgE levels were examined in children with asthma. Total levels of serum IgE were lower in preschool age asthmatic children than in school age children, as described in previous studies [11,12]. The Df-specific IgE-positive rates were lower in the infancy period than in the school age period. Similar findings were shown in a study of atopic dermatitis patients [13]. Thus, total serum and allergen-specific IgE likely develop during infancy (under three years of age) in asthma. Detailed mechanisms of how asthmatic children develop allergen-specific IgE have not been well understood. There may be genetic as well as environmental factorsthat contribute to the development of IgE [14].

In the present study, IgE levels were 1.71 log10IU/ml in the BDP-treated group and 1.32 log10IU/ml in the DSCG group and both levels were high compared to normal subjects. Most of the patients in both groups had allergic aspects, such as atopic dermatitis and a family history of allergic disease. Taking these into account, the patients in both groups had more prominent atopic symptoms and higher levels of serum IgE than those of normal subjects and the difference between the two groups became more prominent at the age of 4–6 years.

The BDP group, which had significantly more prominent atopic symptoms and higher levels of total IgE (not significantly) compared to the DSCG group at the study entry point and would develop higher total and Df-specific IgE levels in serum than the DSCG group over time. BDP treatment significantly reduced the number of eosinophils in peripheral blood, while the levels of the DSCG group were

| Table 2. Df-specific IgE of the two treatment groups after one year. |
|-----------------|-----------------|-----------------|-----------------|
|                | BDP             | DSCG            |                |
| **Before**     | **After**       | **Before**      | **After**      |
| Df-specific IgE positive (number) | 0 | 1 | 0 | 5 |
| Df-specific IgE class (number)   |   |   |   |   |
| Class 0         | 13             | 12             | 22             | 17          |
| Class 1         | 0              | 0              | 0              | 0           |
| Class 2         | 0              | 1              | 0              | 0           |
| Class 3         | 0              | 0              | 0              | 3           |
| Class 4         | 0              | 0              | 0              | 1           |
| Class 5         | 0              | 0              | 0              | 0           |
| Class 6         | 0              | 0              | 0              | 1           |
| **Mean (SD)**   | 0 (0.0)        | 0.6 (0.2)      | 0 (0.0)        | 1.7 (0.4)   |

Df: Dermatophagoides farinae; DSCG: disodium cromoglycate; BDP: beclomethasone dipropionate; \( \ast \) Chi-square test (Positive/Negative) and paired t-test (Class).
sustained. Whereas the initial levels of eosinophils were different between the two groups, BDP treatment likely had a more potent anti-inflammatory effect. BDP as ICS therapy has been thought to have the most efficient anti-inflammatory and anti-allergic actions in allergic airway disease [8]. Furthermore, the present study showed that BDP treatment might reduce the development of Df-specific IgE in children with asthma.

Loh et al. [16] reported that DSCG may inhibit IgE production from B cells in vitro; however, there was no inhibitory effect on the development of IgE in vivo in the present study. As Jones et al. [17] reported, DSCG prevents and improves exercise-induced bronchoconstriction by reducing allergic airway inflammation. Thus, DSCG may act as a bronchodilator in children with asthma. It may improve symptoms, but it may not be sufficient to suppress allergic airway inflammation, as found in the present study. Therefore, in the treatment of children with asthma, ICS therapy may be considered instead of DSCG alone, because of its established long-term efficacy [9] with anti-inflammatory effects and relative safety [18].

The mechanism by which ICS treatment inhibits the development of allergen-specific IgE and how long this inhibiting effect is maintained are unknown [19]. Ohrui et al. [10] reported that ICS treatment reduced serum IgE levels in adults with asthma by three months, which is a brief period compared to the present study. In contrast, Kerstjens et al. [20] showed no effect with ICS treatment on IgE levels in adults with asthma, but their dose of BDP was relatively low (200 μg/day). Zieg et al. [21] reported that systemic corticosteroid therapy enhanced IgE production in serum, as well as in in vitro cultured cells from asthmatic patients. Their corticosteroid administration route was different from that of the present study. Moreover, adults with asthma may already be sensitized and could have developed specific IgE to allergens, unlike children; therefore, they may react differently to corticosteroid therapy. It is likely that inhaled corticosteroids prevent immunoglobulin isotype switching in B-lymphocytes by interruption of antigen-presenting cells to prime T cell activation when allergens reach the airway. Recently, anti-IgE therapy showed efficacy for asthmatic patients, even in childhood asthma [22], whereas anti-eosinophil (anti-IL-5) therapy did not show a sufficient effect [23]. These results suggest that allergen-specific IgE plays a critical role in the pathogenesis of asthma and may also contribute to disease prognosis.

The NIH reported in 2007 [24] that asthma was defined by: (1) parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens or (2) evidence of sensitization to foods, ≥ 4% peripheral blood

Figure 4. Asthmatic status of the two groups before and after therapy. The one-month period clinical symptom score (0–4) (A) Frequency of β2-agonists as rescue medication, (B) frequency of admissions due to acute asthma exacerbation and (C) frequency of systemic corticosteroid administration (D) are shown. DSCG: disodium cromoglicate; BDP: beclomethasone dipropionate. Paired t-test (A and B) and chi-squared (C and D) test results *p < .05, **p < .01 and ***p < .001.
eosinophilia or wheezing apart from colds. In the GINA guideline 2014 [25], a family or past allergic history was also taken as a feature suggesting asthma in children <5 years old.

5. Conclusion

Children with asthma develop IgE in infancy. Early intervention with inhaled corticosteroid therapy in children with asthma may be beneficial not only for its anti-inflammatory effect, but also for preventing the development of allergen-specific IgE as risk factors for persistent asthma. For further investigations to address this issue, a randomized, controlled study is needed.

Disclosure statement

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References

[1] Busse WW. Inflammation in asthma: the cornerstone of the disease and target of therapy. J Allergy Clin Immunol. 1998;102:S17–S22.
[2] Spahn JD, Szeffler SJ. Childhood asthma: new insights into management. J Allergy Clin Immunol. 2002;109:3–13.
[3] Martinez FD. Present and future treatment of asthma in infants and young children. J Allergy Clin Immunol. 1999;104:169–174.
[4] Haddad ZH, Gillman SA. Disodium cromoglycate and human reagin (IgE)-mediated reactions. Effect on wheal and flare skin reactions and histamine release from rat mast cells in vitro. Int Arch Allergy Appl Immunol. 1973;45:439–446.
[5] Graham LM. Balancing safety and efficacy in the treatment of pediatric asthma. J Allergy Clin Immunol. 2002;109:S560–S566.
[6] Phelan PD, Robertson CF, Olinsky A, et al. The Melbourne Asthma Study: 1964–1999. J Allergy Clin Immunol. 2002;109:189–194.
[7] Kelly KD, Spooner CH, Rowe BH, et al. Nedocromil sodium versus sodium cromoglycate in treatment of exercise-induced bronchoconstriction: a systematic review. Eur Respir J. 2001;17:39–45.
[8] LeFlein JG, Szeffler SJ, Murphy KR, et al. Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: results of a randomized outcomes trial. Pediatrics. 2002;109:866–872.
[9] Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995;332:133–138.
[10] Ohru T, Funayama T, Sekizawa K, et al. Effects of inhaled beclometason dipropionate on serum IgE levels and clinical symptoms in atopic asthma. Clin Exp Allergy. 1999;29:357–361.
[11] Orgel HA, Kemp JP, Melzter EO, et al. Atopy and IgE in a pediatric allergy practice. Ann Allergy. 1977;39:161–168.
[12] Tang RB, Tsai LC, Hwang HM, et al. The prevalence of allergic disease and IgE antibodies to house dust mite in schoolchildren in Taiwan. Clin Exp Allergy. 1990;20:33–38.
[13] Miyakawa K. Analysis of clinical factors and IgE-RAST of Dermatophagoides farinae and rice in atopic dermatitis by multiple factor analysis of quantification theory type II Arerugi. Arerugi. 1991;40:1500–1510.
[14] Busse WW, Rosenwasser LJ. Mechanisms of asthma. J Allergy Clin Immunol. 2003;111:S799–S804.
[15] Shimazu S, Enomoto T. Serum IgE levels in healthy children. J Investig Allergol Clin Immunol. 1995;2:62–67.
[16] Loh RK. Disodium cromoglycate inhibits S mu-->S epsilon deletional switch recombination and IgE synthesis in human B cells. J Exp Med. 1994;180:663–671.
[17] Jones RM, Horn CR, Lee DV, et al. Bronchodilator effects of disodium cromoglycate in exercise-induced bronchoconstriction. Br J Dis Chest. 1983;77:362–369.
[18] Inoue T, Doi S, Takamatsu I, et al. Effect of long-term treatment with inhaled beclometasone dipropionate on growth of asthmatic children. J Asthma. 1999;36:159–164.
[19] Corne J. Do inhaled corticosteroids reduce serum IgE levels? The answer is maybe but how relevant is the question? Clin Exp Allergy. 1999;29:294–297.
[20] Kerstjens HA, Kauffman HF, Postma DS, et al. Corticosteroids and IgE. Dutch CNSLD Study Group. J Allergy Clin Immunol. 1996;97:138.
[21] Zieg G, Lack G, Harbeck RJ, et al. In vivo effects of glucocorticoids on IgE production. J Allergy Clin Immunol. 1999;94:222–230.
[22] Hamelmann E, Takeda K, Oshiba A, et al. Role of IgE in the development of allergic airway inflammation and airway hyperresponsiveness—a murine model. Allergy. 1999;54:297–305.
[23] Barnes PJ. Cytokine-directed therapies for asthma. J Allergy Clin Immunol. 2001;108:S72–S76.
[24] NIH. Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma. Full Report Section 2, p. 25.
[25] Features suggesting asthma in children, Global Initiative For Asthma (Gina) 2014, Box6–2.