ELSEVIER

High Level of Fc Epsilon Receptor I-Bindable Immunoglobulin E in the Tear Fluid and Increased Immunoglobulin E-saturated Cells in the Giant Papillae of Vernal Keratoconjunctivitis Patients

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Purpose: To investigate the concentrations of Fc epsilon receptor I (FcεRI)-bindable immunoglobulin E (IgE) in the tear fluid and the proportion of IgE-saturated cells among FcεRI-positive cells in giant papillae from vernal keratoconjunctivitis (VKC) patients.

Methods: The tear fluids and giant papillae were obtained from 8 VKC patients with their informed consent. To detect the quantitative difference between FcεRI-bindable IgE and total IgE in the tear fluid, we used a new enzyme-linked immunosorbent assay system we have developed. Next, to estimate the proportion of IgE-saturated cells among FcεRI-positive cells, we used two distinct monoclonal antibodies for FcεRI for the immunohistochemistry. One antibody recognizes all FcεRI regardless of whether it is with or without receptor-bound IgE. The other does not recognize IgE-bound FcεRI.

Results: The quantitative difference between FcεRI-bindable IgE and total IgE were detected in the tear fluid of VKC patients. FcεRI-positive cells were significantly increased in the giant papillae of VKC compared with normal conjunctivae. The proportion of IgE-saturated cells among FcεRI-positive cells in giant papillae was higher than that in normal conjunctivae.

Conclusion: These results suggest that FcεRI-bindable IgE may be a critical factor to estimate the severity of VKC. **Jpn J Ophthalmol 2002;46:357–363** © 2002 Japanese Ophthalmological Society

Key Words: Fc epsilon receptor I, immunoglobulin E, vernal keratoconjunctivitis.

Introduction

Cross-linking of allergen-specific immunoglobulin E (IgE) bound to Fc epsilon receptor I (FcεRI) on the surface of mast cells with multivalent allergens results in the release of both preformed and newly generated mediators, and in the manifestation of allergic symptoms. FcεRI is expressed not only on mast cells and basophils but also on eosinophils, Langerhans cells, and monocytes.[1–4] Concerning its function, it was reported that FcεRI cross-linking induced peroxidase release from eosinophils and prostaglandin E_2 secretion from monocytes.[1,5] Recently, several groups revealed that human professional antigen-presenting cells (APC), such as peripheral blood dendritic cells and epidermal Langerhans cells, expressed FcεRI.[2,3,6] APC expressing FcεRI are able to capture allergens via specific IgE, leading to receptor-mediated endocytosis, and to loading of allergens onto major histocompatibility complex (MHC) class II molecules. This makes the APC efficient antigen presentation to T cells possible.[6,7] Therefore, FcεRI-expressing cells and IgE play a crucial role in the development of allergic diseases.

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Vernal keratoconjunctivitis (VKC) is an allergic chronic inflammatory disease in youth, characterized by recurrent symptoms of severe itching, photophobia, pain, lacrimination, and discharge.[8] VKC shows a florid condition characterized by giant papillae found in the upper tarsal conjunctiva. The etiology of VKC is unknown, but there seems to be a strong but not absolute association with IgE. Increased levels of histamine, tryptase, and specific IgE in tears, as well as the increase of mast cells in both epithelium and substantia propria, suggest that VKC is related to type I hypersensitivity.[9–13] It is well known that there is not necessarily a good correlation between disease activity and IgE levels. For example, atopic dermatitis patients frequently have greatly elevated serum IgE, but do not always suffer from severe dermatitis.[14] Several studies thus showed that IgE molecules may be heterogeneous with respect to cell-binding via FcεRI, and that all IgE molecules may not always bind to FcεRI on the cell surface and may not always evoke allergic reaction.[15–18] Taking these reports into consideration, FcεRI-bindable IgE may be an important factor in affecting the severity of allergic disease. Therefore, in this study first we estimated FcεRI-bindable IgE in the tear fluid, using a novel enzyme-linked immunosorbent assay (ELISA) developed in the Allergy Research Center of Juntendo University School of Medicine.[19] We discussed the relationship between the level of FcεRI-bindable IgE in the tear fluid and the severity of VKC. Next, we investigated the proportion of IgE-saturated cells among FcεRI-positive cells in the giant papillae from VKC patients by immunohistochemical analysis, using two distinct anti FcεRI-α chain monoclonal antibodies (mAbs). One antibody recognizes all FcεRI-α chains regardless of whether with or without receptor-bound IgE; the other does not recognize the FcεRI-α chain when IgE binds to the receptor, that is, it is competitive with IgE.

Materials and Methods

Patients, Tissue Processing, and Tear Collection

By slit-lamp microscopy examination, papillae with a diameter larger than 1 mm were designated as giant papillae. We scored superficial punctate keratopathy (score of 0–3), pseudo-exfoliative change of corneal epithelium (score 4), shield ulcer (score 4), corneal plaque (score 4), swelling and redness of limbus (score 0–3), and mucus production (score of 0–3) before sample collection. The scoring was simplified to 0: not observed, 1: minimum, 2: moderate, 3: severe, 4: very severe. Total clinical score was evaluated as follows: minimum (0≦, <4), moderate (4≦, <7), severe (7≦, <9), and very severe (9≦). Of 8 VKC patients (nos. 1–8), 2 patients (nos. 3,5) were estimated as minimum, 2 patients (nos. 1,4) as moderate, 2 patients (nos. 7,8) as severe, and the other 2 (nos. 2,6) were very severe. Patients 2, 3, 4, 6, and 7 suffered from atopic dermatitis. Giant papillae were obtained from these 8 VKC patients after securing informed consent. Tissue samples from the normal upper tarsal conjunctiva were obtained from 6 patients during ptosis surgery after obtaining informed consent. The specimens were embedded in OCT Compound® (Miles, Elkhart, IN, USA), and snap-frozen by liquid nitrogen. Cryostat sections (5 μm) were fixed by 100% cold acetone for 10 minutes, and dried. Tear fluid samples were obtained from the same 8 VKC patients and 8 healthy volunteers. At least 5 μL of unstimulated tear fluid was collected from each eye of all subjects by placing a 20-μL capillary tube in the inferior cul-de-sac.

Monoclonal Antibodies

Two distinct anti FcεRI-α chain mAbs (AER37 and AER24) were established by the Allergy Research Center, Juntendo University School of Medicine. AER37 is able to recognize the FcεRI-α chain regardless of whether it is with or without receptor-bound IgE, but AER24 is not able to recognize the FcεRI-α chain when IgE binds to the receptor, that is, when AER24 is competitive with IgE.

Immunohistochemical Analysis

Immunohistochemical staining was carried out using a labeled streptavidin biotin technique (LSAB kit®, DAKO, Tokyo) following the supplier's instructions. Samples were incubated with primary antibodies at 4°C for 24 hours. Mouse IgG_1 was used as isotype-matched control. The chromogen AEC (3-amino-9 ethylcarbazole) was used for staining of the FcεRI-α chain. The sections were counterstained with hematoxylin.

The Proportion of IgE-saturated Cells

The AER24 mAb-positive cell count was compared with the AER37 mAb-positive cell count in adjacent sections. For each specimen, three sequential sections of three different regions were examined.

The percentage of IgE-saturated cells among FcεRI-positive cells was determined by the following equation:

IgE-saturated cells among FcεRI positive cells =

$$\frac{A - B}{A} \times 100\%$$

where *A* is the number of AER37 mAb-positive cells and *B* is the number of AER24 mAb-positive cells.

Measurement of IgE

The concentrations of FcεRI-bindable IgE in the tear fluid were determined by our new ELISA method mentioned previously.[19] Briefly, 96-well microtiter plates were coated with soluble FcεRI-α chain (a recombinant soluble form of the ectodomain of the human FcεRI-α subunit) in coating buffer (90 ng/100 μL · per well) at 4°C overnight. The wells were washed, blocked with blocking buffer at 37°C for 1 hour and washed again with the washing buffer. The serially diluted IgE standard (100 μL/well) or diluted tear samples in dilution buffer were added to the wells and were incubated at 37°C for 3 hours. Wells were washed and were then incubated with horseradish-peroxidase-labeled goat anti-human IgE polyclonal antibody at 37°C for 1 hour. After washing, the substrate solution (100 μL/well) was added and incubated at room temperature for 10 minutes. After stopping the reaction, optical absorbance of the samples was measured at a wavelength of 450 nm using a Bio-Rad microplate reader (model 450; Bio-Rad Laboratories, Richmond, CA, USA) with a 450-nm filter. The sensitivity of the soluble FcεRI-α chain-ELISA was 300 pg/mL–1600 ng/mL.

On the other hand, to determine the level of total IgE in the tear fluid, conventional sandwich-ELISA was performed using an ELISA®-IgE kit (International Reagents, Kobe) following the manufacturer's instructions. The sensitivity of the sandwich-ELISA was 1.5 ng/mL–35000 ng/mL.

Statistical Analysis

The data (Table 2) were statistically analyzed by the Student *t*-test. A probability of 5% or less was considered statistically significant.

Results

High Concentrations of FcεRI-bindable IgE in the Tear Fluid of VKC Patients

Table 1 shows the concentrations of FcεRI-bindable IgE and total IgE in the tear fluids. In all 8 VKC patients high concentrations of total IgE were detected by a conventional sandwich ELISA. These concentrations were higher than those of FcεRI-bindable IgE measured by the ELISA developed in the Juntendo Allergy Research Center. Especially the concentrations of total IgE of patients no. 2, no. 6, no. 7, and no. 8 were very high. The data on the FcεRI-bindable IgE of these patients also were comparably high, because these patients were suffering from severe manifestations of VKC. On the other hand, patients no. 3 and no. 5, who had high concentrations of total IgE in tear fluid, were not suffering from severe manifestations of VKC. The concentrations of FcεRI-bindable IgE in these patients were much lower than the concentrations of total IgE. These results demonstrate that FcεRI-bindable IgE may play a critical role in the development of severe VKC. There was no correlation in the levels of total

Table 1. Fc Epsilon Receptor I (FCεRI)-bindable Immunoglobulin E (IgE) and Total IgE in the Tear Fluid

Patient No.	FcεRI-bindable IgE in Tear Fluid (ng/mL)	Total IgE in Tear Fluid (ngmL)	FcεRI-bindable IgE/Total IgE (%)	Clinical Score of VKC* Patients
1	140	200	70.0	Moderate
2	470	1200	39.2	Very severe
3	80	820	9.8	Minimum
4	100	140	71.4	Moderate
5	60	780	7.7	Minimum
6	680	2200	31.9	Very severe
7	320	720	44.4	Severe
8	280	640	43.8	Severe
Normal volunteers (n = 6)	under 1	under 10		

*VKC: vernal keratoconjunctivitis.

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Table 2. Immunoglobulin E (IgE)-saturated Cells Among Fc Epsilon Receptor I (FcεRI)-Positive Cells

Type of Cell*	VKC Patients†	Normal Control‡	*P* Value
FcεRI-positive cells (AER37 mAb-positive cells)	108.3 ± 14.3 cells/field (n = 8)	12.8 ± 3.4 cells/field (n = 6)	<.05
FcεRI-positive cells (AER24 mAb-positive cells)	23.7 ± 12.8 cells/field (n = 8)	11.2 ± 2.3 cells/field (n = 6)	NS§
Mean percentage of IgE saturating cells among FcεRI-positive cells	78.7 ± 14.3 (n = 8)	12.5 ± 3.8 (n = 6)	<.05

*mAb: monoclonal antibody.
†VKC: vernal keratoconjunctivitis. Data are mean ± SD.
‡Data are mean ± SD.
§NS: not significant.

IgE and FcεRI-bindable IgE between patients with or without atopic dermatitis.

Proportion of IgE-saturated Cells Among FcεRI-positive Cells

FcεRI-positive cells were detected in normal conjunctivae without allergic ocular diseases. As shown in (Figure 1), dendritic-shaped cells in the epithelium and round cells in the substantia propria of normal conjunctivae were stained by AER24 mAb. These dendritic cells may be Langerhans cells and the round cells may be mast cells. In the normal conjunctivae, FcεRI-positive cells were not saturated with IgE because the number of AER24 mAb-positive cells was nearly equal to the number of AER37 mAb-positive cells (Table 2). On the other hand, the number of FcεRI-positive cells (AER37 mAb-positive cells) was significantly increased in the giant papillae from VKC patients compared with the number in the normal conjunctivae (Table 2). However, in giant papillae, the number of AER24 mAb-positive cells was much lower than the number of AER37 mAb-positive cells (Table 2). For example, Figures 2A and B show adjacent sections of giant papillae ob-

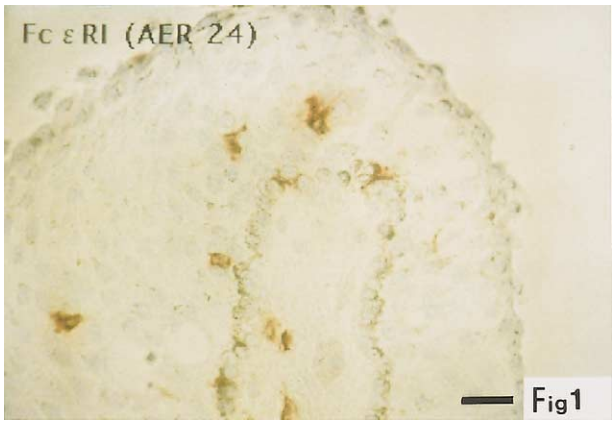

Figure 1. Fc epsilon receptor I (FcεRI)-positive cells (AER24 monoclonal antibody-positive cells) in normal conjunctivae. Bar = 20 μm.

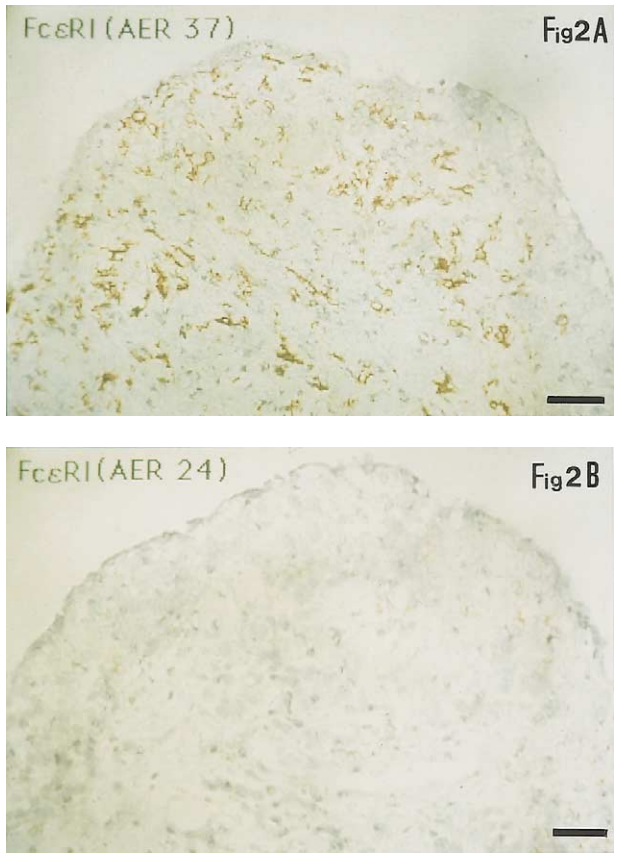

Figure 2. Immunostaining of giant papillae with two distinct monoclonal antibodies to Fc epsilon receptor I (FcεRI)-α chain; AER37 (**A**) and AER24 (**B**). Bar = 100 μm.

tained from a very severe VKC patient (no. 6), and AER37-positive cells were significantly increased in number (Figure 2A). Few AER24-positive cells were observed (Figure 2B). AER37 mAb is able to recognize all FcεRI-α chains whether with or without IgE. However, AER24 mAb is not able to recognize the FcεRI-α chain when IgE binds to FcεRI, meaning it is competitive with IgE. These results reveal that more FcεRI-positive cells are saturated with IgE in VKC eyes than in normal conjunctivae (Table 2). By observation at high magnification, many AER37 mAb-positive cells in giant papillae could be seen to have a dendritic shape (Figure 3).

Discussion

FcεRI-positive cells were significantly increased in giant papillae from VKC patients (Table 2, Figures 2,3). Furthermore, FcεRI receptors of these cells were fully saturated with IgE (Table 2), because anti-FcεRI-α chain mAb (AER37) recognized many FcεRI-positive cells in giant papillae, but AER24 mAb recognized only a few (Figure 2). AER24 mAb is competitive with IgE for binding to the FcεRI. As displayed in (Figure 3) most of the FcεRI-positive cells are of dendritic shape. It is well known that Langerhans cells and dendritic cells efficiently capture and internalize allergens via FcεRI-bound IgE, and strongly present allergens with MHC class II molecules to T cells, and these cells expressing a large amount of FcεRI are also activated upon receptor ligation via IgE, to secrete various cytokines.[7,20,21] Therefore, FcεRI-positive dendritic cells in giant papillae may play a crucial role in the pathogenesis of VKC. It is well known that dendritic cells exist in normal conjunctivae and increase in the papillae of VKC.[22] Bieber et al reported that FcεRI is not constitutively expressed on human epidermal Langerhans cells and dendritic cells, but displays a large variation of expression density on the cell surface.[21,23,24] Most interestingly, remarkable upregulation of FcεRI expression is observed on Langerhans cells and dendritic cells in the lesional skin of patients with atopic dermatitis, and correlates with serum IgE levels.[23–25]

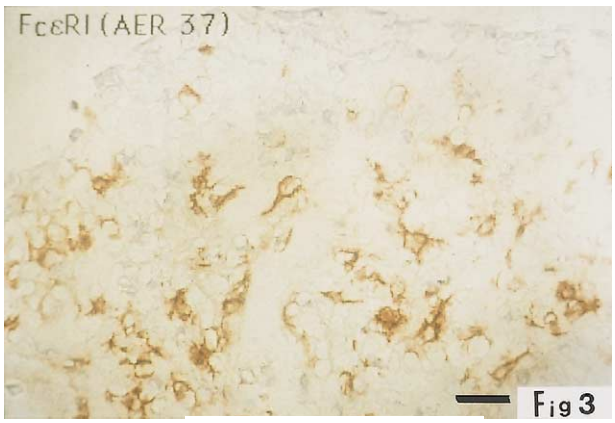

Figure 3. Immunostaining of giant papillae with AER37 monoclonal antibodies. At high magnification, many Fc epsilon receptor I (FcεRI)-positive cells show dendritic shape. Bar = 20 μm.

Yoshida et al demonstrated an increased number of IgE-bearing Langerhans cells in the conjunctiva of atopic dermatitis patients with hyper IgE serum.[26] Recently, Yamaguchi et al reported that exposure to IgE results in striking upregulation of the surface expression of FcεRI on mouse mast cells in vitro and in vivo.[27] Therefore, the strong expression of FcεRI on dendritic shape cells in giant papillae may depend on a large amount of FcεRI-bindable IgE in the microenvironment, like the tear fluid. It is well known that FcεRI is expressed on mast cells and basophils and that these cells increase in the papillae of VKC. However, FcεRI-positive dendritic shape cells were detected more than round shape cells in this study. This phenomenon may be explained by the fact that FcεRI on the surface of the degranulated mast cell is internalized and is difficult to detect by immunostaining.

FcεRI consists of α, β, and γ chains.[28,29] In these three chains, the α chain is the key molecule for binding IgE because mice genetically engineered to lack expression of the FcεRI-α chain (FcεRI-α chain KO mice) did not suffer from experimentally induced type I allergy.[30] The binding between FcεRI-α chain and IgE is essential for type I allergic reaction. Twenty years ago, one report documented that the number of cell-bindable IgE molecules did not always correlate with serum IgE levels in atopic individuals.[15] Some reports showed that serum IgE molecules may be heterogeneous with respect to cell-binding and histamine release of mast cells.[16–18] Wada et al estimated the levels of FcεRI-bindable serum IgE in normal volunteers and in patients with atopic dermatitis and bronchial asthma by the same method employed in this study. They revealed that the levels of FcεRI-bindable IgE are lower than those of total IgE measured by a conventional sandwich-ELISA.[19] Furthermore, Matsumoto et al reported the differences in the proportion of the FcεRI-bindable IgE in the serum (FcεRI-bindable IgE/total IgE) between atopic keratoconjunctivitis and seasonal allergic conjunctivitis patients.[31] Also, for a better understanding of the pathogenesis of VKC, it would be useful to estimate the tear fluid IgE that is able to bind to FcεRI.

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In this study, we evaluated the concentrations of FcεRI-bindable IgE using the new ELISA system and compared them with those of total IgE measured by a conventional sandwich-ELISA. High concentrations of FcεRI-bindable IgE in the tear fluid of VKC patients were detected and the levels were reflected in the severity of VKC. In all tear fluids, the concentrations of FcεRI-bindable IgE were substantially lower than those of total IgE. For instance, patients no. 3 and no. 5 were not suffering from severe VKC despite the high concentrations of total IgE in tear fluid. On the other hand, the concentrations of FcεRI-bindable IgE were much lower than total IgE in these patients. These results indicated that FcεRI-bindable IgE might be an important factor contributing to the severity of VKC, suggesting that there may be some factors in the tear fluid, such as anti-IgE or anti-FcεRI autoantibodies that block IgE binding to FcεRI. Anti-IgE autoantibodies have been reported to significantly increase in the serum of patients with bronchial asthma and atopic dermatitis, and to occur as immune complexes with IgE in these sera.[32–34] Hayashi et al revealed that anti-IgE autoantibody was detected in the sera of atopic dermatitis patients, and that some of these autoantibodies exhibited inhibitory activity for IgE-FcεRI binding.[35]

In contrast, anti-FcεRI-α chain autoantibodies had been detected in the sera of chronic urticaria and atopic dermatitis patients.[35–38] Some reports showed that anti-FcεRI-α chain autoantibodies had histamine-releasing activity for peripheral blood leukocytes.[35,36] However, if anti-FcεRI-α chain autoantibodies recognize the binding site for IgE, they will block IgE binding to the receptor. Furthermore, if soluble forms of the FcεRI-α chain occur in the tear fluid, they may also contribute to the blocking of IgE binding to FcεRI.[39,40] In this study, we did not investigate the levels of anti-IgE, anti-FcεRI-α chain autoantibodies, or the soluble form of the FcεRI-α chain. Further analyses at the molecular level are required to determine what factors affect IgE binding.

In conclusion, high concentrations of total IgE were detected in the tear fluid of VKC patients, and these levels were much higher than those of FcεRI-bindable IgE. There was a positive relationship between the levels of FcεRI-bindable IgE and the severity of VKC. FcεRI-positive cells significantly increased in giant papillae obtained from VKC patients. Most of the FcεRI-positive cells showed dendritic shape and these FcεRI cells were saturated with IgE. Considering all these findings, FcεRI-bindable IgE may be an important factor affecting the severity of VKC.

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