

Assessing the onset of allergic rhinitis by nasal cytology and immunoglobulin E antibody levels in children

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ABSTRACT

Background: It is difficult to identify the onset of allergic rhinitis in infants because making a conclusive diagnosis can be challenging.

Objective: We used a combination of cell differentials in nasal swabs and immunoglobulin E (sIgE) antibody values to food and inhalant allergens to make the diagnosis and identify relevant allergens for investigation of the onset of allergic rhinitis.

Methods: We studied 302 children, 2 to 120 months old, who visited our clinic for rhinorrhea. Nasal swabs were taken from all children, and neutrophils (N), eosinophils (Eo), and mast cells (Mc) were identified by nasal cytology and their numbers were estimated. Levels of sIgE antibodies to various food and inhalant allergens were determined in patients with nasal Eo and Mc.

Results: Percentages of participants with Eo-Mc and Eo-Mc-N at 2–14 ($n = 84$), 15–24 ($n = 57$), 25–60 ($n = 73$), and 61–120 months of age ($n = 88$) were 20, 23, 58, and 65%, respectively. There were no significant differences between the 2–14 and 15–24, and 25–60 and 61–120 months age groups, but there was a significant difference between the 15–24 and 25–60 months age groups ($p = 0.00013$). The percentages of participants with sIgE antibodies to food and inhalant allergens as solitary or main allergen were 12%/0% at 2–14 months old, 10.5%/7% at 15–24 months old, 1.3%/42.4% at 25–60 months old, and 0%/56.8% at 61–120 months old, respectively with a significant difference between 15–24 and 25–60 months old groups ($p = 0.00025$) for inhalant allergens.

Conclusion: Allergic rhinitis associated with inhalant allergens in infants <15 months of age is rare, but it is tempting to postulate that symptoms of rhinitis in these infants may be associated with sIgE antibodies to food allergens. Transition of sIgE responses from food to inhalant allergens occurred after 15 months of age, and sIgE antibodies to inhalant allergens were predominant after 25 months.

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Pediatricians and otolaryngologists often face the challenge of infants with rhinorrhea, for whom, before treatment, it is important to distinguish between an infectious cause and allergic rhinitis. Reports of the prevalence of allergic rhinitis in infants vary from 0 to 48%.^{1–5} This variation is the result of several factors, including different methods used to diagnose allergic rhinitis and geographic differences. Identifying allergic rhinitis can be difficult because infants and young children are susceptible to upper airway infections that can be misdiagnosed as allergic rhinitis. To diagnose allergic rhinitis, the guidelines on Allergic Rhinitis and Its Impact on Asthma (ARIA)⁶ require a positive immunoglobulin E (sIgE) antibody response for inhaled allergens and typical symptoms.

As reported on a parent questionnaire, nasal symptoms can be caused by infection, and, although results of a serum sIgE antibody test can be positive, which identifies sensitization, the cause of the symptoms may not be allergy. Therefore, the Japanese Guidelines for Allergic Rhinitis⁷ requires the presence of eosinophils (Eo) in nasal swabs in addition to the ARIA guidelines.⁶ Elevated numbers of mast cells (Mc) in nasal swabs are also reported to be important in the diagnosis of allergy rhinitis.⁸ We used a unique protocol to make a conclusive diagnosis of allergic rhinitis in infants and young children. Participants with Eo and/or Mc in nasal swabs were selected from children with rhinorrhea and were examined for specific sIgE antibodies to foods and aeroallergens. Those participants who were symptomatic, who had nasal swabs with

test results positive for Eo and/or Mc, and with sIgE antibodies to foods and/or aeroallergens were diagnosed with allergic rhinitis. The time of onset of allergic rhinitis in infants and children was determined by using these criteria.

METHODS

Participants

A total of 302 participants from 2 to 120 months old (161 boys, 141 girls) were examined between January 2013 and December 2015. All the participants visited our clinic for treatment of rhinorrhea that had a duration of at least 1 week. Participants with purulent rhinorrhea, the common cold, systemic infectious disease, or eosinophilia syndrome were excluded. The ethics committee of Nippon Medical School approved the study, and the parents of all the participants provided informed consent.

Analysis of Cell Types in Nasal Swabs

Nasal swabs were taken by using a cotton applicator (applicator tip, 2 × 10 mm) and transferred onto glass slides, dried, and fixed in 99% methanol for 3 minutes. They were stained by using Hansel solution (Torii Co., Tokyo, Japan) for 1 minute.⁹ Neutrophils (N) and Eo were mainly observed in the mucous compartment of the swabs, whereas Mc were observed among epithelial cells. A trained observer (H.O.)¹⁰ assessed the numbers of N, Eo, and Mc in nasal swabs, and, based on the abundance of cell types, the participants were classified as having Eo, Eo-Mc, Mc, Eo-N, Eo-Mc-N, Mc-N, and N (Table 1). For data presentation, the participant categories of Eo, Eo-Mc, or Mc were collectively called the Eo-Mc group; categories Eo-N, Eo-Mc-N, or Mc-N were collectively called the Eo-Mc-N group; and the swabs from the N group contained only N.

Immunoassay for Specific sIgE Antibodies

After obtaining permission from the parents, sera from the infants and children which were in Eo-Mc and Eo-Mc-N were analyzed by using fluorescence enzyme immunoassay for specific sIgE antibodies

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Table 1 Cell types in nasal swabs*#

Eo	Eo + to 3+
Eo-Mc	Eo + to 3+, and Mc + to 3+
Mc	Mc + to 3+
Eo-N	Eo + to 3+, and N + to 3+
Eo-Mc-N	Eo + to 3+, Mc + to 3+, and N + to 3+
Mc-N	Mc + to 3+, and N + to 3+
N	N + to 3+

Eo = Eosinophil; Mc = mast cell; N = neutrophil.

*Subject categories of Eo, Eo-Mc, or Mc were the Eo-Mc group; categories Eo-N, Eo-Mc-N, or Mc-N were the Eo-Mc-N group; the swabs from the N group contained only N.

#Grading the abundance of each cell type was by examination with the aid of a microscope and at $\times 200$ magnification.

For Mc: Mc + few cells; 2 + 1–5 cells and 3+ ≥ 6 cells among the epithelial cells.

None; $\pm$: few scattered cells; +: found cells easily; 2+: between + and 3+; 3+: abundant cells, often in clumps (for neutrophil and eosinophil).

(ImmunoCap assay; Phadia Co., Uppsala, Sweden) for mite, Japanese cedar pollen (JCP), orchard grass, ragweed, *Alternaria*, dog, cat, egg white, and milk as well as other food allergens suspected from questionnaire of episodes of other food allergy. A positive test result was defined by an sIgE antibody level of class 1 or higher (≥ 0.35 UA/mL).¹¹

Statistical Analyses

For comparison of the proportion of the participants with positive test results for Eo and/or Mc, and the percentage of positive results for Specific IgE antibodies (sIgE) to inhalant allergens among the various age groups, Mann-Whitney U tests were used; $p < 0.05$ was considered statistically significant.

RESULTS

Four age groups of participants, 2–14 months ($n = 84$), 15–24 months ($n = 57$), 25–60 months ($n = 73$), and 61–120 months ($n = 88$), were assessed for the proportions with Eo and Mc in nasal swabs and sIgE antibodies to food and inhalant allergens.

Nasal Cytology

Nasal cytology results are presented in Fig. 1. The percentages of participants number categorized in the Eo and Eo-Mc-N groups per total numbers of participant were 20% (17/84) at 2–14 months old, 23% (13/57) at 15–24 months old, 58% (42/73) at 25–61 months old, and 65% (57/88) at 61–120 months old. By contrast, the percentages of patients numbers categorized as being in the N group at ages 2–14 months, 15–24 months, 25–60 months, and 61–120 months were 80, 77, 42, and 35%, respectively. Percentages of the Eo-Mc and Eo-Mc-N groups in the 25–60 months old and 61–120 month old groups were significantly higher than in the 2–14 months old ($p = 0.00007$ and $p = 0.00000028$) and the 15–24 months old age groups ($p = 0.00013$ and $p = 0.000013$).

sIgE Antibodies in Participants Categorized as Nasal Eo-Mc and Eo-Mc-N

The relationship among cell type groups and the number of participants with sIgE antibodies to food or inhalant allergens at each age are shown in Table 2 and Fig. 2. The levels (classes 1–6) of serum sIgE antibodies and the corresponding allergens in the age groups are shown in Table 3.

2–14 Months. Thirteen of 17 participants in the Eo-Mc and Eo-Mc-N groups were tested for sIgE. Nine participants had sIgE solely to

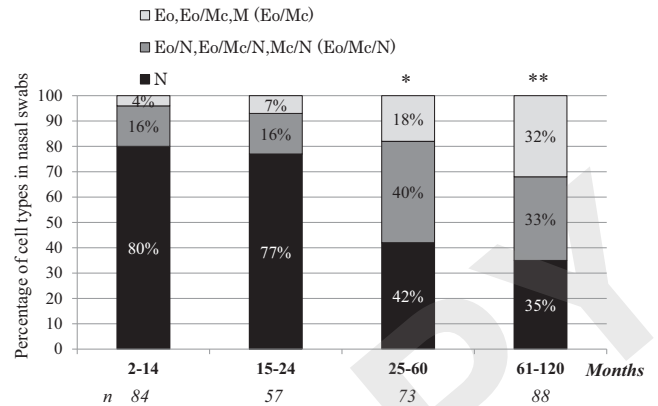


Figure 1. Subpopulations and percentages of Eo-Mc, Eo-Mc-N and N groups in nasal swabs among each age group (months) of children. *The proportion of Eo-Mc and Eo-Mc-N at 25–60 months of age was significantly higher than in 2–14 months ($p = 0.00007$) and 15–24 months of age ($p = 0.00013$). **The proportion of Eo-Mc and Eo-Mc-N in 61–120 months of age was significantly higher than in 2–14 months ($p = 0.00000028$) and 15–24 months of age ($p = 0.000013$). There were no significant differences in the proportion of Eo-Mc and Eo-Mc-N between 0–14 and 15–24 months ($p = 0.78$) and between 25–60 and 61–120 months ($p = 0.95$).

food allergens and one had sIgE to both food and inhalant allergens (egg and dog). Nine of 10 participants with sIgE to food allergens had atopic dermatitis and episodes of food allergy, such as wheezing and/or redness of skin after eating. Three infants negative for sIgE antibody levels had no atopic dermatitis, no episodes of food allergy, who had nasal Mc+ or Eo+, and N3+, but the presence of small numbers of Mc and Eo was not confirmed at repeated cytology. Four of nine participants with food allergic had Mc or Mc-N in nasal swabs.

15–24 Months. sIgE antibodies were assessed in all 13 participants in the Eo-Mc and the Eo-Mc-N groups. Eleven of 13 were positive for sIgE and two had no sIgE. Six of these 11 participants with sIgE were only responsive to food allergens and had atopic dermatitis or episodes of food allergy. Three participants had sIgE to only inhalant allergens, and two had sIgE to both food and inhalant allergens. Two participants who were negative for sIgE had no atopic dermatitis and no episodes of food allergy who had Mc+ or Eo+, and N3+, but the Mc and Eo were not found at repeated cytology. The youngest child with positive sIgE solely to inhalant allergens (mite) was 15 months old.

25–60 Months. Thirty-three of 42 participants in the Eo-Mc and Eo-Mc-N groups were tested for sIgE. One participant had sIgE solely to food allergens, whereas 18 participants and 13 participants had positive sIgE to inhalant allergens only and to both food and inhalant allergens, respectively. In participants with positive sIgE to both food and inhalant antigens, the predominant sIgE responses were to inhalant allergens (Table 3).

61–120 Months. Fifty-one of 57 participants in the Eo-Mc or the Eo-Mc-N groups were tested for sIgE. Forty-three participants had positive sIgE to only inhalant allergens, and seven had positive sIgE to both food and inhalant allergens. In these seven participants, the predominant allergens were inhalant (Table 3).

The Predominant (class score) Allergens in the sIgE Responses

The predominant (class score) allergens in the sIgE responses are presented in Table 3. In children ≤ 14 months old, 9 of 10 with sIgE were solely responsive to food (egg) allergens, and one was responsive predominantly to food allergens (mixed with dog). Among children 15–24 months old, 6 of 11 with sIgE were responsive solely to

Table 2 The number of subjects in each nasal cell type group and serum sIgE antibody responses in age groups (months) of children with rhinorrhea

Age Groups	A N	B						Total B
		Eo	Eo-Mc	Mc	Eo-N	Eo-Mc-N	Mc-N	
2–14 Months (<i>n</i> = 84)	67	0	1	2	2	5	7	17
sIgE tested (13)		0	1	1	1	5	5	
Food allergen +ve (9)			1	1		4	3	
Inhal allergen +ve (0)								
Both allergens +ve (1)						1		
Both allergens –ve (3)					1		2	
ND (4)				1	1		2	
15–24 Months (<i>n</i> = 57)	44		3	1	2	2	5	13
sIgE tested (13)			3	1	2	2	5	
Food allergen +ve (6)				1	1	1	3	
Inhal allergen +ve (3)			2				1	
Both allergens +ve (2)			1			1		
Both allergens –ve (2)					1		1	
ND (0)								
25–60 Months (<i>n</i> = 73)	31	4	9		7	16	6	42
sIgE tested (33)		4	8		3	13	5	
Food allergen +ve (1)						1		
Inhal allergen +ve (18)		1	6		1	7	3	
Both allergens +ve (13)		3	2		1	5	2	
Both allergens –ve (1)					1			
ND (9)			1		4	3	1	
61–120 Months (<i>n</i> = 88)	31	3	22	3	13	14	2	57
sIgE tested (51)		2	19	3	11	14	2	
Food allergen +ve (0)								
Inhal allergen +ve (43)		2	17	2	8	13	1	
Both allergens +ve (7)			2		3	1	1	
Both allergens –ve (1)				1				
ND (6)		1	3		2			

A = N group contained only N; B = Eo-Mc group and Eo-Mc-N group (refer Table 1); N = neutrophil; Eo = eosinophil; Mc = mast cell; sIgE = immunoglobulin E; +ve = positive sIgE; inhal = inhalant; –ve = negative sIgE; ND = not done.

food allergens and one was responsive predominantly to food allergens (mixed with JCP), whereas three were responsive solely to inhalant allergens, and one was predominantly responsive to inhalant allergens.

Among those participants 25–60 months old, 18 of 32 with sIgE were solely responsive to inhalant allergens, 13 were responsive to both inhalant and food allergens, and the predominant allergens were inhalant. One participant had sIgE to only food allergens. Among children 61–120 months old, 43 of 51 with sIgE were responsive solely to inhalant allergens, seven were responsive to both inhalant and food allergens but predominantly to inhalant allergens. The youngest child with sIgE antibodies to JCP was a 26-month-old boy. After this age, the numbers of participants with sIgE to JCP and mite increased. The number of children with sIgE to ragweed or orchard grass was small, even when they were 10 years old.

Percentage of Participants with sIgE Responses to Inhalant and Food Allergens

The percentages of participants with sIgE responses to inhalant and food allergens are presented in Fig. 3. The percentages of participants with sIgE to inhalant allergens (solitary and predominant) per total participants at 2–14, 15–24, 25–60, and 61–120 months old were 0% (0/84), 7% (4/57), 42.4% (31/73), 56.8% (50/88), respectively. The percentages of participants with sIgE to food allergens were 12% (10/84) at 2–14, 10.5% (6/57) at 15–24, 1.3% (1/73) at 25–60, and 0% (0/88) at 61–120 months old. The proportion of participants with sIgE to inhalant allergens in children

25–60 and 61–120 months were significantly higher than in the 2–14 and 15–24 months of age groups.

DISCUSSION

Infections frequently cause nasal symptoms, particularly rhinorrhea, in infants. Malmberg¹² reported neutrophilia in nasal secretions in 97% of infants, 79% of schoolchildren, and 47% of university students with symptoms of allergic rhinitis. We showed that the percentages of children with rhinorrhea and only N in nasal swabs (likely caused by infections) were 80% at 2–14 months of age, 77% at 15–24 months of age, 42% at 25–60 months of age, and 35% at 61–120 months of age. By contrast, the proportions of children with rhinorrhea and positive for Eo and/or Mc in nasal swabs were 20% at 2–14 months old, 23% at 15–24 months old, 58% at 25–60 months old, and 65% at 61–120 months old. In children with nasal Eo or Mc, the proportions with N were 82% at 2–14 months old, 69% at 15–24 months old, 69% at 25–60 months old, and 51% at 61–120 months old. Given the presence of N, infection may be involved in symptoms of nasal allergy in children with Eo and Mc in nasal swabs and sIgE antibodies to allergens. Interestingly, the proportion of children with Eo and Mc who also had N was greatest at 2–14 months of age, when few had sIgE.

These observations question what defines the onset of allergic rhinitis in infants and children, and whether their nasal symptoms are caused by infection or allergic reactions or by a combination of these. To diagnose allergic rhinitis, ARIA guidelines⁶ require positive sIgE antibody responses to inhaled allergens and typical

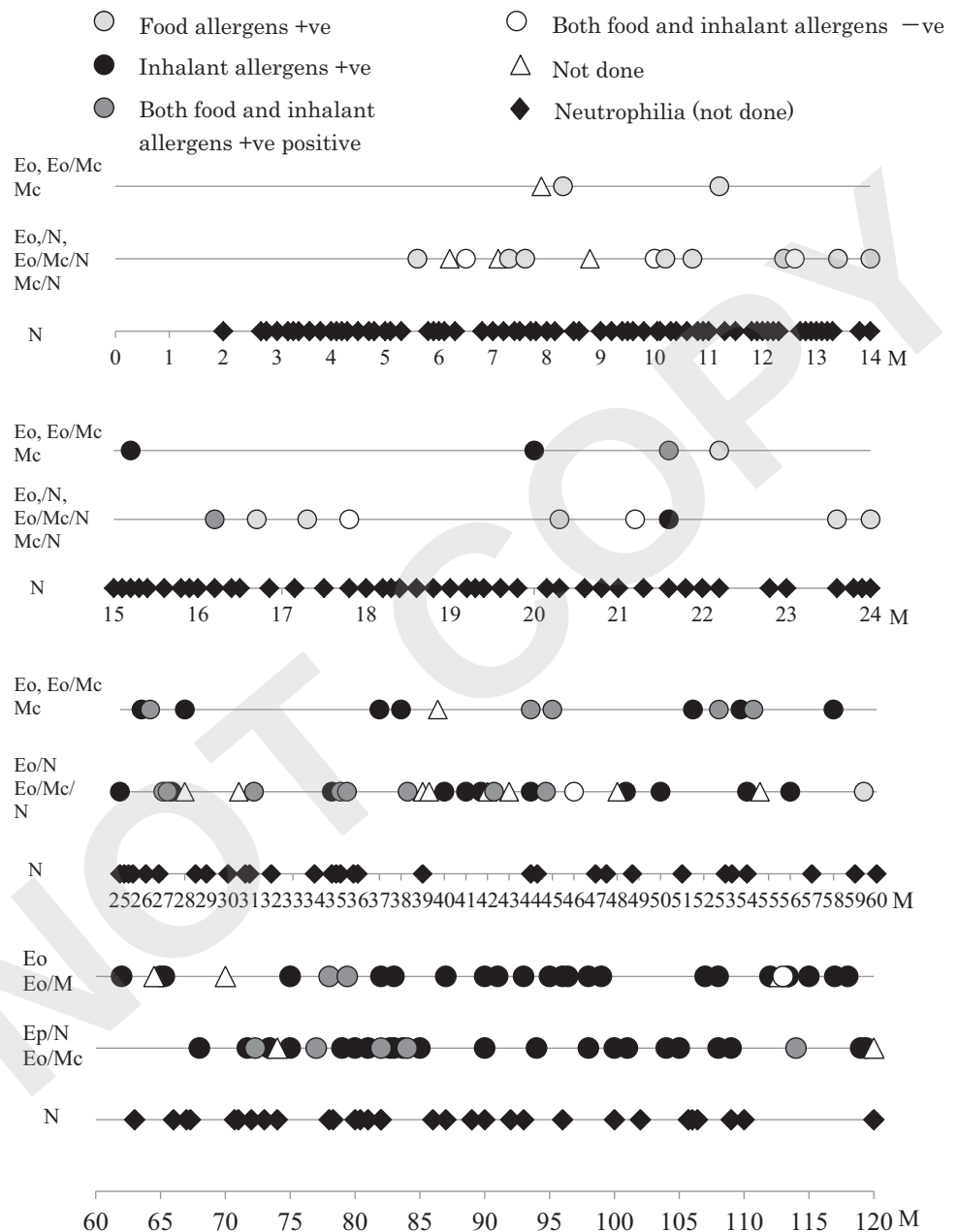


Figure 2. Relationship among immunoglobulin E (sIgE) responses, nasal cell type categories, and age (months).

symptoms. For example, Kulig *et al.*⁵ reported seasonal symptoms of allergy identified by questionnaire in 3% of children at age 1 year and 13% at age 3 years. However, none of these infants at 1 year and only 4% at 3 years were diagnosed by using a combination of assessing typical symptoms and sIgE sensitization.⁵ For the diagnosis of allergic rhinitis, the Japanese Guidelines⁷ also require the presence of Eo in nasal swabs, in addition to the ARIA criteria.⁶ Osawa *et al.*⁴ identified a 2% prevalence of allergic rhinitis diagnosed by nasal Eo and sIgE antibodies in 408 children, 18 months old, who underwent a free health check but did not discuss the timing of the onset of allergic rhinitis.

Recently, Yenigun *et al.*¹³ used the blood Eo counts and Eo-to-lymphocyte ratio to aid in characterizing patients with allergic rhinitis (5–15 years of age) in comparison with nonsensitized or sensitized (sIgE antibodies) patients who were asymptomatic. The Eo counts and ratio to lymphocytes were higher in patients who were sensitized than in participants who were not sensitized but

were unable to distinguish symptomatic and asymptomatic, sensitized participants. Our study focused on the diagnosis of allergic rhinitis and its onset in infants and children with rhinorrhea by assessing N, Eo, and Mc numbers in nasal swabs and selected participants with nasal Eo and/or Mc to measure specific sIgE antibodies.

Seventeen of 21 participants of <24 months of age with nasal Eo and/or Mc were positive for sIgE antibodies solely or predominantly to food allergens (Tables 2 and 3). Only Mc or Mc with N but without Eo were detected in nasal swabs in eight of these participants. Kajosaari¹⁴ also observed Mc in nasal swabs of patients <3 years old and with food allergy. Mc numbers in nasal swabs were increased by 36 hours after oral allergen provocation in participants with food allergy,¹⁵ which supported our suggestion that food allergens can cause symptoms of allergic rhinitis in some patients.

Fifteen of our 17 participants who were ≤24 months old with sIgE to food allergens had atopic dermatitis or at least one episode

Table 3 Levels (classes 1–6) of serum sIgE antibodies and allergen reactivity in patients of different ages*

Gender	Age, mo	Mite	JCP	Ragweed	Orchard Grass	Dog	Cat	Egg	Milk	Others
M	5	—	—	—	—	—	—	3#	2	
M	7	—	—	—	—	2	—	4#	—	
M	8	—	—	—	—	—	—	3#	—	
M	8	—	—	—	—	—	—	3#	—	
F	10	—	—	—	—	—	—	4#	—	
M	11	—	—	—	—	—	—	3#	—	
M	11	—	—	—	—	—	—	3#	—	Soybean1
F	12	—	—	—	—	—	—	3#	—	Soybean1
M	13	—	—	—	—	—	—	3#	—	
M	14	—	—	—	—	—	—	2#	—	
M	15	4#	—	—	—	—	—	—	—	
M	16	—	2	—	—	—	—	—	3#	Soybean3 Wheat2
F	17	—	—	—	—	—	—	3#	—	
M	17	—	—	—	—	—	—	2#	—	
M	20	3#	—	—	—	—	—	—	—	
F	20	—	—	—	—	—	—	2#	—	Salmon roe1
M	22	3#	—	—	—	—	—	—	—	
M	22	4#	—	—	—	—	—	3	—	
M	22	—	—	—	—	—	—	2#	—	Salmon roe4
F	24	—	—	—	—	—	—	2#	—	
F	24	—	—	—	—	—	—	2#	—	
F	25	5#	—	—	—	—	—	—	—	
M	26	1	3#	—	—	2	—	—	—	
F	26	3#	—	—	—	—	—	2	—	Wheat1
F	27	6#	—	—	—	—	3	2	—	Shrimp2
M	27	4#	—	—	—	—	—	2	1	Soybean2
M	27	—	4#	—	—	—	—	—	—	
M	28	—	4#	—	—	—	—	—	—	
M	31	4#	—	—	—	—	—	2	2	
M	35	4#	—	—	—	—	—	—	—	
M	35	2	4#	—	1	—	—	2	1	Wheat1
M	36	5#	2	—	—	3	—	2	—	
M	37	6#	—	1	—	—	—	—	—	
F	38	3#	—	—	—	—	—	—	—	
M	38	2	4#	—	—	—	—	3	—	
M	40	—	2#	—	—	—	—	—	—	
M	41	3#	—	—	—	—	—	—	—	
M	42	5#	4#	—	—	—	—	—	—	
F	42	6#	2	—	—	—	—	—	3	Salmon roe3
F	44	5#	—	—	—	—	—	—	—	
M	44	6#	—	—	—	—	—	2	—	Sesame2
M	45	2#	—	—	—	—	—	2	—	
M	45	5#	3	—	—	3	—	2	—	
M	48	2#	2#	—	—	—	—	—	—	
M	50	3#	—	—	—	—	—	—	—	
M	53	—	5#	—	—	—	—	—	—	
M	53	2	4#	—	—	2	—	2	1	
M	54	5#	1	—	—	2	—	—	—	
F	54	3#	—	—	—	—	—	—	—	
M	54	4#	—	—	—	—	—	2	—	
M	56	4#	—	—	—	—	—	—	—	
F	58	—	4#	2	2	—	—	—	—	
M	59	—	—	—	—	—	—	2	1	Wheat1
F	62	—	2#	2#	—	—	—	—	—	
M	65	5#	—	—	—	2	—	—	—	
F	65	—	6#	—	—	—	—	—	—	
M	68	4	5#	2	—	2	3	—	—	
F	72	6#	2	—	—	—	2	—	—	
F	72	3	4#	—	—	4#	4#	1	—	
M	73	3	4#	—	—	—	—	—	—	

Table 3 Continued.

Gender	Age, mo	Mite	JCP	Ragweed	Orchard Grass	Dog	Cat	Egg	Milk	Others
M	75	3#	3#	—	—	—	—	—	—	
F	75	—	5#	2	2	—	—	—	—	
F	77	6#	3	—	—	3	3	—	—	Soba3
M	78	6#	3	—	—	2	—	—	—	Peanut3
M	79	6#	6#	—	—	—	—	—	—	
M	79	6#	2	2	2	—	—	—	1	
M	80	4#	—	—	—	—	—	—	—	
M	81	4#	3	—	—	—	—	—	—	
F	82	6#	5	—	—	3	2	—	2	Salmon roe3
M	82	2	4#	1	2	—	—	—	—	
M	83	4#	2	—	—	—	—	—	—	
M	83	6#	2	—	—	—	—	—	—	
M	83	6#	3	1	—	—	—	—	—	
F	84	5#	2	—	—	2	2	—	—	
F	84	—	3#	—	—	—	—	1	2	
F	85	6#	3	—	—	—	—	—	—	
M	87	6#	—	—	—	—	—	—	—	
M	90	4#	—	—	—	—	—	—	—	
F	91	4#	3	—	2	—	—	—	—	
F	91	6#	5	4	4	—	—	—	—	
F	93	—	2#	—	—	—	—	—	—	
F	94	4#	—	—	—	—	—	—	—	
F	95	6#	1	—	—	—	2	—	—	
M	96	2	4#	1	2	—	—	—	—	
F	98	—	3#	—	—	—	—	—	—	
M	98	4#	2	—	—	—	—	—	—	
F	99	—	3#	—	—	—	—	—	2	
F	100	—	2#	—	—	—	—	—	2	
M	101	4#	3	—	—	—	—	—	—	
M	104	3#	2	—	—	—	—	—	—	
F	105	—	3#	—	—	—	—	—	—	
M	107	4#	3	—	—	—	—	—	—	
F	108	2#	2#	1	1	—	—	—	—	
M	108	4#	2	—	—	—	—	—	—	
M	109	4#	1	—	2	—	—	—	—	
F	112	4#	5#	—	1	—	—	—	—	
F	113	3	5#	1	1	—	—	—	—	
F	114	3#	3#	—	—	—	—	2	—	Salmon roe3
M	115	3#	—	—	—	—	—	—	—	
F	117	6#	2	—	—	—	—	—	—	
M	118	6#	5#	—	—	—	—	—	—	
M	119	2#	3#	—	—	—	—	—	—	
M	120	6#	—	—	—	1	2	—	—	

sIgE = Immunoglobulin E; JCP = Japanese cedar pollen. Others = positive IgE antibodies to other food allergens.

*Data represent a secondary allergen unless otherwise noted.

Solitary or main allergen (determined by the sIgE class score).

of food allergy. Five of 26 participants who were ≤ 24 months old tested for sIgE, were negative for such antibodies. These participants had a small number of Mc or Eo but an abundance of N in nasal swabs at their first visit; however, the Mc and/or Eo disappeared at the follow-up cytology, which supported the lack of allergic responses. For children ≥ 25 months old and with sIgE antibodies, the sole or predominant allergens were inhalants in 49 of 50 children. One child, a 59-month-old boy, had sIgE antibodies only to food. These observations indicated that sensitizations to food allergens appeared in Japanese infants < 14 months and that sIgE responses to inhalant allergens become predominant in children ≥ 25 months of age.

Baatenburg de Jong *et al.*¹⁶ identified sIgE antibodies to food allergens in 18% of Dutch infants at 0–1 years, 22% at 1–2 years, and 26% at age 2–3 years, whereas the percentages with sIgE antibodies to

inhaled allergens at the same ages were 2, 5.8, and 15%, respectively. Although we did not follow the evolution of allergic disease in infants with food allergy, Yonekura *et al.*¹⁷ reported that 20 of 48 children with atopic dermatitis but who did not have allergic rhinitis or asthma at the beginning of the study developed allergic rhinitis associated with sIgE antibody to house-dust mite. In our studies, the youngest children with sIgE antibody responses to house-dust mite and JCP were 15- and 26-month-old boys. Allergic rhinitis to mite and JCP become prominent after 25 months of age, whereas, in our study, sensitizations for ragweed and orchard weed were infrequent in participants < 10 years old.

Grabenherrich *et al.*¹⁸ identified that 11.8% of children 2–3 years old had sneezing or a runny or blocked nose, and, at 2 years of age, 15.2% had sIgE antibodies to inhalant allergens. They concluded that allergic rhinitis could start in the first 2 years of life.¹⁸ Kulig *et al.*¹⁹ also

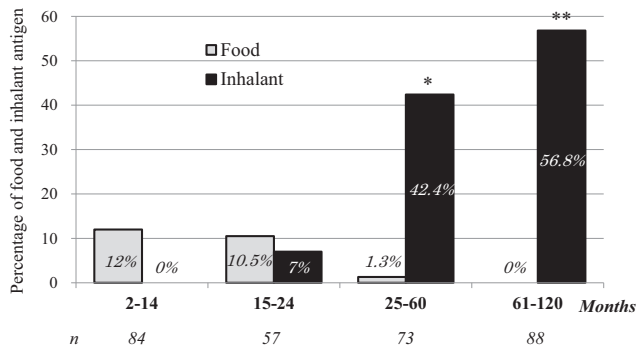


Figure 3. Proportions of patients with immunoglobulin E (sIgE) responses to food and inhalant allergens among each age group (months). *Significantly higher than in 2–14 months ($p = 0.0000025$) and 15–24 months ($p = 0.00025$) groups. **Significantly higher than in 2–14 months ($p = 0.00000000071$) and 15–24 months ($p = 0.00000021$). There were no significant differences between 2–14 and 15–24 months ($p = 0.28$) and the 25–60 and 61–120 months groups ($p = 0.11$).

indicated that seasonal allergic rhinitis shows a marked increase in prevalence and incidence after the second year of life. By using retrospective parent questionnaires, Masuda *et al.*²⁰ identified the onset of asthma as early as 2.8 years and that of allergic rhinitis as early as 2.9 years.

CONCLUSION

With our augmented methods, we found that there was no infant <15 months with symptoms of allergic rhinitis who also had sIgE antibodies to inhalant allergens. However, symptoms of allergic rhinitis were present in some younger infants who also had sIgE antibodies to food allergens. The transition of sIgE responses from food to inhalant allergens occurred at ages >15 months and responses to inhaled allergens increased markedly after 25 months of age.

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