

ORIGINAL ARTICLE

WILEY

Development of allergic rhinitis in early life: A prospective cohort study in high-risk infants

Sawako Masuda¹ | Mizuho Nagao² | Satoko Usui¹ | Kazutaka Nogami² | Yuji Tohda³ | Takao Fujisawa²  | Investigators of Kinki Hokuriku Airway Disease Conference (KiHAC)

¹Department of Otorhinolaryngology and Allergy Center, National Hospital Organization Mie National Hospital, Tsu, Japan

²Department of Pediatrics and Allergy Center, National Hospital Organization Mie National Hospital, Tsu, Japan

³Department of Respiratory Medicine and Allergology, Kindai University, Faculty of Medicine, Osaka-Sayama, Japan

Correspondence

Takao Fujisawa, National Hospital Organization Mie National Hospital, 357 Osato-Kubota, Tsu, Mie 514-0125, Japan.
Email: eosinophilosophy@gmail.com

Funding information

This research was supported in part by an unconditional grant-in-aid from Kyorin Pharmaceutical Co., Ltd.

Editor: Ömer Kalayci

Abstract

Background: Allergic rhinitis (AR) is the most common allergic disease in children. The development process of AR in early childhood, however, is not well understood. We prospectively investigated the process in regard to not only the nasal symptoms and sensitization but also the nasal cytology, in relation to recurrent wheeze in a high-risk cohort.

Methods: Infants under 2 years of age with atopic dermatitis (AD) and/or food allergy (FA) symptoms were recruited and followed prospectively for 2 years. The phenotype of perennial AR was classified based on the presence/absence of (1) persistent nasal symptoms, (2) nasal eosinophils, and (3) HDM sensitization, the most common allergen for perennial AR in Japan. AR-like phenotypes were defined as positive for at least two of those three categories. High-risk recurrent wheezer was diagnosed based on the Japanese guidelines and Global Initiative for Asthma. Cox proportional hazards regression analyses for high-risk recurrent wheeze and the AR-like phenotype, adjusting for known covariate risk factors for asthma.

Results: A total of 299 children were enrolled, and 237 subjects (78%) completed the 2-year observation. The prevalence of eosinophilia in nasal secretions increased from 18.5% to 69.9%, while HDM-specific IgE ≥ 0.35 kU_A/L increased from 30.6% to 74.8%. AR-like phenotypes increased from 18.4% to 65.0%. The AR-like phenotype at 2 years was associated with development of high-risk recurrent wheezer (HR 2.062; 95% CI 1.005–4.796).

Conclusions: The prevalence of an HDM-related AR-like phenotype was markedly increased during infancy in infants with AD/FA and was associated with high-risk recurrent wheezer.

KEYWORDS

allergic, asthma, cell count, child, eosinophils, infant, perennial, rhinitis

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; FA, food allergy; GINA, Global Initiative for Asthma; HDM, house dust mite.

© 2022 EAACI and John Wiley and Sons A/S. Published by John Wiley and Sons Ltd.

1 | INTRODUCTION

Allergic rhinitis (AR) is a common allergic disease in childhood, and its prevalence is increasing worldwide.^{1–3} AR significantly impacts the quality of life by causing various problems, such as sleep disturbance, emotional stress, and impairment of school activities.⁴ The International Study of Asthma and Allergies in Childhood (ISAAC) employed standardized methodology and showed clearly that the prevalence of AR increased during childhood, that is, from 6–7 y.o. to 13–14 y.o.⁵ Recent cohort studies suggest that childhood AR is heterogenous in its development.^{6,7} Although classical hypothesis stated that AR is a risk factor for asthma in atopic march,⁷ complete manifestation of the march was found only in a small population.⁶

Precise process of the onset of AR in children is still to be studied because most of the epidemiological studies relied on questionnaire in the absence of definitive diagnostic criteria. We previously reported that, in school children with asthma, AR started even before 3 years of age.⁸ In the PARIS birth cohort study, the prevalence of AR-like symptoms was 9.1% at 18 months of age.⁹ However, in the above studies, diagnosis of AR was based only on the parents' recall in the former and a symptom questionnaire in the latter. In addition, those reports did not provide a good description of the development process.

With the aim of improving our understanding of the onset of AR, we designed and carried out a high-risk infant cohort study, the Impact of Allergic Rhinitis on Atopic March (IRAM) in children. Infants less than 2 years of age who had food allergy or atopic dermatitis were recruited into the study. We prospectively followed up not only their nasal symptoms but also their nasal cytology and allergic sensitization for 2 years. The ARIA guidelines classify AR as intermittent or persistent, not seasonal or perennial.¹⁰ However, Japan is characterized by sole high morbidity of seasonal AR due to Japanese cedar pollen and a high prevalence of perennial AR due to house dust mite (HDM). Accordingly, the Japanese guidelines include classifications for seasonal AR and perennial AR.¹¹ Here, in light of the relatively late development of pollen sensitization in young children,¹² we focused on development of HDM-sensitized perennial AR in infancy.

2 | METHODS

2.1 | Study design and subjects

This is a multicenter observational prospective cohort study named IRAM (Impact of Rhinitis on Atopic March; UMIN000004157). Children aged 6–23 months with atopic dermatitis (AD) food allergy (FA) and/or AR were recruited from 30 sites in the central region of Japan in 2011 by investigators of the IRAM study group in Kinki Hokuriku Airway Disease Conference (KiHAC).¹³ Inclusion criteria for this study were described elsewhere.¹² In brief, the diagnoses of AD and FA were made by the study physicians. AD was diagnosed based on the criteria by Hanifin and Rajka.¹⁴ Suspicion of FA was based on

Key Message

Allergic rhinitis (AR) starts early in childhood. However, the precise course of AR's development has remained unclear. We investigated AR development in a cohort of high-risk infants with atopic dermatitis and/or food allergy symptoms by prospectively observing them for nasal symptoms and sensitization and also their nasal cytology. We found that the prevalence of AR increased markedly between 1 and 3 years of age and was associated with high-risk recurrent wheezers.

clinical history of food-induced symptoms and corresponding sensitization to the food. Oral food challenges were performed to confirm the diagnosis.¹⁵ As oral food challenges were not done in all children, the term "FA symptom" will be used instead of "FA" throughout this study combining the groups of children with confirmed food allergy and of children with suspicion of food allergy, respectively. The IRAM study aimed to delineate atopic march in high-risk infants, focusing especially on development of AR and asthma. Children who had been diagnosed with asthma were not enrolled. In the on-going follow-up of the IRAM cohort, the first part consisted of 5 visits—at 6-month intervals—in the first 2 years.¹² At enrollment, the following background factors were surveyed: the family history of allergic diseases, history of wheezing not diagnosed as asthma, history of lower respiratory infections, number of siblings, environmental factors such as pets and passive smoking at home, and other medical information. Every 6 months, the study physicians diagnosed asthma when a child had more than three episodes of wheeze lasting more than 24 h in the previous year that responded to beta2 agonists and/or asthma controller medications including inhaled corticosteroids.¹⁶ Although definitive diagnosis of asthma in preschool age is not possible, due to practical needs to control bothersome recurrent wheeze in young children, the Japanese guidelines¹⁶ and the Global Initiative for Asthma (GINA)¹⁷ define asthma in children 5 years and younger. Thus, the term "high-risk recurrent wheezer" as "probable" asthma will be used for those who fulfilled the above definition based on the guidelines.^{16,17} Blood and nasal secretion samples were collected at enrollment, 1 year and 2 years.

The study was approved by the Ethics Committee of Mie National Hospital, (#21-9). The parents/guardians of all participants gave written informed consent.

2.2 | Assessment of respiratory symptoms

A questionnaire regarding respiratory symptoms was developed by making minor modifications of the questionnaire of the International Study of Asthma and Allergies in Childhood.¹⁸ The parents/guardians completed the questionnaire at 6-month intervals. For perennial AR, the following question was used: "In the past 6 months, has your child consistently had any of following symptoms, (1) sneezing, (2) a runny

TABLE 1 Classification of rhinitis in preschool children

Phenotypes	Nasal symptoms	Nasal eosinophilia	HDM sensitization
AR-like phenotypes			
Classical AR	+	+	+
Eosinophilic rhinitis	+	+	-
AR without nasal eosinophilia	+	-	+
Subclinical AR	-	+	+
Non-AR phenotypes			
Non-allergic rhinitis	+	-	-
Local eosinophilia	-	+	-
HDM-sensitization	-	-	+
No rhinitis ^a	-	-	-

^aAbsence of rhinitis symptoms in all three categories of "non-AR phenotypes."

(3) blocked nose, even when he/she DID NOT have a cold or flu?" If the answer was "yes," the parents further indicated frequency of each symptom, that is, sneezing, runny nose, and/or blocked nose.

2.3 | Examination of nasal secretions

Cytological examination of nasal secretions was performed when children had no signs of an acute respiratory infection. Nasal secretions were sampled by swabbing the bilateral inferior turbinates with cotton swabs. The samples were spread onto a slide glass, air-dried, fixed, and stained with Hansel solution (Eosinostein®; Torii Pharmaceutical). The specimens were examined by light microscopy for eosinophils, neutrophils, and bacteria by a single well-trained laboratory technician, who was blinded to symptoms of the subjects and specific IgE results. The entire slide was examined, and the cells were enumerated at ×400 magnification. Nasal eosinophilia was defined as the presence of eosinophils that were found easily in the whole field,¹⁹ when five or more cells were seen. The percentage of eosinophils compared with neutrophils was also determined, and >10% was defined as significant nasal eosinophilia.²⁰

2.4 | Sensitization to common allergens

Serum samples were analyzed for total IgE and specific IgE antibodies using the ImmunoCAP® system according to the manufacturer's guidelines (Phadia AB). The tested allergens were as reported elsewhere.¹² In this study, we focused on house dust mite (HDM) sensitization (positive = HDM-sIgE ≥ 0.35 kU_A/L).

2.5 | Classification of HDM-sensitized perennial AR in young children

Allergic rhinitis is IgE-mediated inflammation of the nasal mucosa. It is diagnosed based on the presence of typical allergic

symptoms and nasal eosinophilia and identification of the causative allergen(s).^{21,22} AR in children, however, is often undiagnosed, or misdiagnosed because of the multitude of causes for rhinitis.²¹ Thus, we tentatively classified the phenotypes of the nasal condition in young children in relation to HDM-sensitized perennial AR based on 3 clinical criteria: persistent nasal symptoms, nasal eosinophilia, and HDM sensitization. IgE for JCP, which represents the most common seasonal allergen in Japan, was also measured and found positive in several children, but the lack of any seasonal rhinitis symptoms at study entry led to the decision only to consider perennial rhinitis in this study. The various combinations of those 3 criteria make up eight phenotypes, as shown in Table 1. We defined the subtype that was positive for all 3 criteria as "classical AR," and the subtypes that were positive for 2 of the 3 criteria as "eosinophilic rhinitis," "AR without nasal eosinophilia," and "subclinical AR," respectively. We classified those four subtypes as "AR-like phenotypes" (Table 1). Four subtypes that met only one, or none, of the 3 criteria were classified as "non-AR phenotypes" (Table 1). A Sankey diagram was produced by using The Sankey Diagram Generator (<http://sankey-diagram-generator.acquireprocure.com/>) to depict the prevalence of these subtypes over time.

2.6 | Statistical analysis

The chi-square test for trend was used to compare the distribution of the prevalence of various factors at each of the yearly visits. We performed Cox proportional hazards regression analyses for the time of enrollment to the diagnosis of high-risk recurrent wheezer to evaluate the impact of AR-like phenotypes. Specifically, we calculated hazard ratios (HR) for AR-like phenotypes and known risk factors of asthma, namely, history of lower respiratory tract infection, parental asthma, daycare use, pet at home, and passive smoking with the diagnosis of "probable" asthma. All reported *p* values are 2-tailed, with a *p* value of <.05 considered to be statistically significant. Statistical analyses were performed with GraphPad Prism 9.3 (GraphPad Software) and SPSS (version 26; SPSS).

3 | RESULTS

3.1 | Study population

A total of 304 children were screened, and 299 were enrolled in the study. Of them, 269 (90%) were retained at the 1st year, and 237 (79%) were retained at the 2nd year (Figure S1). Table 2 presents the characteristics of the study population. The mean age in months was 13.3, and 51% of the children were less than 12 months. Figure S2 shows the age distribution. More boys (64.5%) than girls were enrolled. Most (86.3%) of the children had food allergy symptom, including to egg (77%), milk (43%), wheat (25%), and other foods (17%). Those rates correspond with the reported prevalence of food allergies in Japan.^{15,23} Atopic dermatitis was diagnosed in 70.2% of the children. A history of wheezing that was not diagnosed as asthma was found in 17.3%, and a history of lower respiratory infection was found in 10.0%. Table 2 also shows the prevalence of various environmental factors such as pet keeping, presence of

siblings, daycare use and passive smoking, and a parental history of asthma and allergic rhinitis.

3.2 | Prevalence of persistent nasal symptoms

Table 3 summarizes the changes in the prevalence of the nasal symptoms, nasal cytology findings, and HDM sensitization during the 2-year observation period. The prevalence of each of sneezing, runny nose, nasal eosinophils, and positive HDM-specific IgE increased significantly from enrollment to the 2nd-year visit. Although the high initial prevalence of neutrophils in the nasal secretions increased even further over the 2 years, the eosinophil/neutrophil ratio also increased, indicating that nasal eosinophilia became progressively prevalent in early childhood.

3.3 | Prevalence of phenotypes related to perennial AR

Figure 1 shows the changes in the prevalence of the 8 phenotypes related to early AR. The prevalence of "classical AR" that met all 3 criteria was 2.9% at enrollment, 17.1% at the 1st-year visit, and 29.5% at the 2nd-year visit. The prevalence of "subclinical AR"—in which nasal eosinophilia and HDM sensitization were present even when there were no nasal symptoms—also increased from 3.3% at entry to 11.7% and 26.6%, respectively, at the 2 later time points. In contrast, the prevalence of the "no rhinitis" phenotype, which met none of the 3 criteria, decreased from 33.1% to 15.2% and 8.4%, respectively (Figure 1).

Since the presence/absence of each criterion had the potential to have changed at each visit, a positive finding did not always persist throughout the study. Figure 2 shows the actual numbers of subjects classified as 3+ criteria and 2+ criteria (AR-like phenotypes), HDM-sensitization-only, and other non-AR-like phenotypes at each visit. Overall, it can be seen that the AR-like phenotypes increased during the observation period, whereas the HDM-sensitization-only phenotype population remained small, and the other non-AR phenotypes decreased markedly (Figure 2).

3.4 | Association of AR-like phenotypes with high-risk recurrent wheezer during the study

Table 4 shows the results of Cox proportional hazard regression analyses for the development of high-risk recurrent wheezer and the six possible risk factors for asthma, including AR-like phenotype. Parental asthma, history of lower respiratory tract infection, and day case use were significant risk factors for development of high-risk recurrent wheezer as expected. AR-like phenotype at 2 years was also a risk factor (HR 0.2086; 95%CI 1.016–4.852). However, AR-like phenotype at entry or at 1 year were included in the model, the corresponding HRs were not statistically significant (data not shown).

TABLE 2 Baseline characteristics of the participants

	N (%)
Age in months at entry	13.3 ± 5.4 (5–23) ^a
Gender (M/F)	193/106
Gestational age (weeks)	39.0 ± 1.4 (29–42)
Birth weight (g)	3093 ± 363 (1178–4122)
Allergic diseases	
Food allergy symptom	258 (86.3%)
Atopic dermatitis	210 (70.2%)
Allergic rhinitis	0
History of wheezing	52 (17.4%)
History of lower respiratory infection(s)	30 (10.0%)
Pet at home	39 (13.0%)
Siblings	149 (49.8%)
Daycare	60 (19.8%)
Passive smoking	
Father	108 (36.1%)
Mother	11 (3.6%)
Parental history of asthma	
Father	59 (19.7%)
Mother	45 (15.0%)
Parental history of allergic rhinitis	
Perennial allergic rhinitis	
Father	89 (29.8%)
Mother	96 (32.1%)
Seasonal allergic rhinitis	
Father	135 (45.2%)
Mother	116 (38.8%)

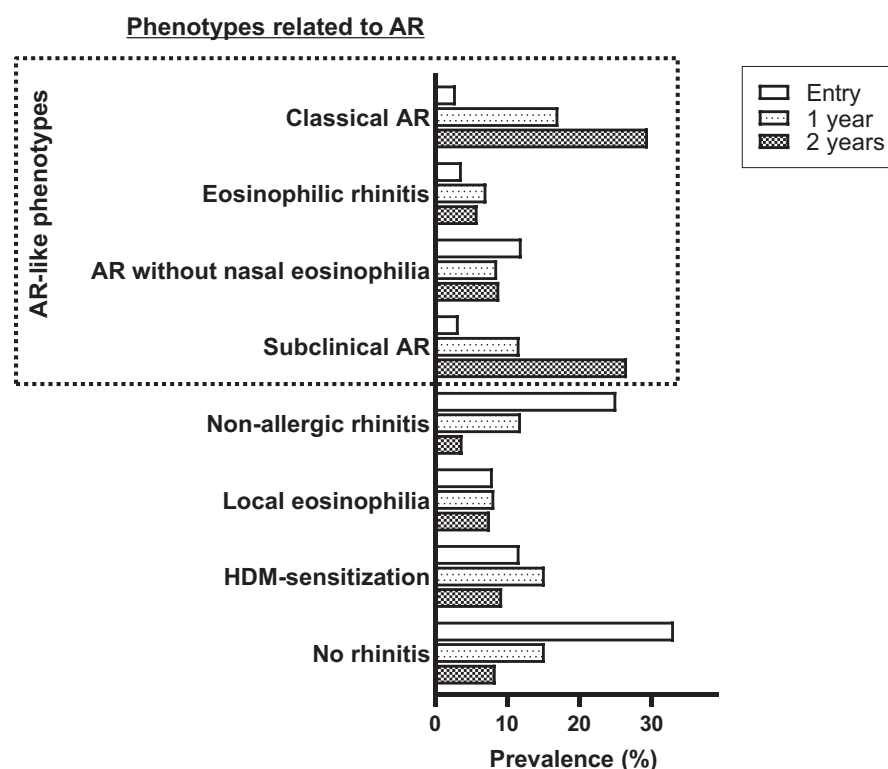
^aMean ± SD (range).

TABLE 3 Changes in prevalence of perennial nasal symptoms, inflammatory cells and bacteria in nasal secretion and positive HDM-specific IgE during 2 years

	Entry (n = 299)	1 year (n = 269)	2 years (n = 237)	p value ^a
Perennial nasal symptoms				
Sneezing	30.1%	35.9%	45.5%	.0010
Runny nose	37.2%	44.0%	50.0%	.0071
Stuffy nose	23.4%	27.4%	28.2%	.2419
Cytology of nasal secretion				
Positive eosinophils	18.5%	49.3%	69.9%	<.0001
Positive neutrophils	97.0%	98.9%	100.0%	.0038
Eosinophil/neutrophil ratio ≥10%	5.6%	17.9%	24.3%	<.0001
Positive bacteria	94.0%	99.3%	100.0%	<.0001
HDM-specific IgE				
>0.35 kU _A /ml	30.6%	57.8%	74.8%	<.0001

^aChi-square test for trend.

FIGURE 1 Prevalence of eight rhinitis-related phenotypes (Table 1) classified based on the three features of allergic rhinitis (AR), that is, nasal symptoms, nasal eosinophilia and HDM-sensitization at entry (open bar), 1 year (dot-shaded bar) and 2 years (cross-shaded bar)



4 | DISCUSSION

This study aimed to elucidate and characterize the development of allergic rhinitis (AR) in young children below 2 y.o. who had atopic dermatitis and/or food allergy symptom. Those children are regarded as a high-risk population for atopic march leading to respiratory allergies, including asthma and AR, in later life. Since there are no definitive diagnostic criteria for AR in young children, we tentatively defined eight subgroups based on three major clinical features of HDM-related AR, which is the most prevalent type of AR in Japanese children below the age of 6 years.¹¹ We found that the prevalence of AR-like phenotypes, which meet two or more of the 3 clinical criteria (i.e., persistent nasal symptoms, nasal eosinophilia,

and HDM sensitization), increased significantly during the 2-year follow-up and was associated with high-risk recurrent wheezer in preschool age.

Several papers have reported on the prevalence of AR in infants and young children. The PARIS birth cohort study found that 9.1% of infants at age 18 months had AR-like symptoms (runny nose, blocked nose, sneezing; apart from a cold).⁹ Positive associations of AR-like symptoms with inhalant allergen sensitization, HDM sensitization and a blood eosinophil count $\geq 400/\text{ml}$ were described, with adjusted odds ratios of 2.2, 2.9, and 1.5, respectively. Osawa et al.²⁴ reported that general health examinations at age 18 months found that 8 (2%) of 408 infants had both inhalant allergen sensitization and nasal eosinophils, and 6 (1.5%) infants also had rhinorrhea.

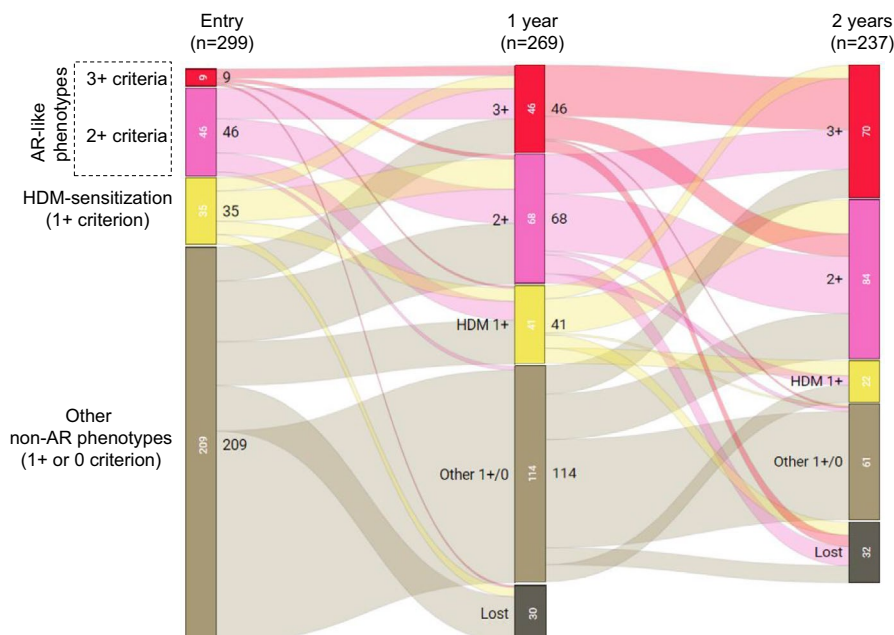


FIGURE 2 Sankey diagram of phenotype changes, demonstrating the proportion of subjects with each category of allergic rhinitis over time: at entry, 1 year, and 2 years of follow-up. Th phenotype changes were dynamic in early childhood but generally many of the subjects developed AR-like phenotypes. 3+; satisfied all 3 criteria: persistent nasal symptoms, nasal eosinophilia, and HDM sensitization, 2+; satisfied 2 of the 3 criteria, HDM 1+; only HDM sensitization was positive among the 3 criteria, other 1+/0; satisfied 1 or none of the 3 criteria, Lost; lost to follow-up

Variables	HR	95% CI (profile likelihood)
AR-phenotype at 2 years	2.086	1.016–4.852
Parental asthma	1.828	1.046–3.184
History of lower respiratory infection	2.457	1.206–4.662
Daycare use	2.316	1.201–4.919
Older siblings	1.337	0.7679–2.353
Pet at home	0.9731	0.4573–1.880
Passive smoking	0.9221	0.5280–1.604

TABLE 4 Multivariate Cox regression analysis for the diagnosis of probable asthma and possible risk factors for asthma

Zeiger et al.²⁵ investigated nasal basophilic cells and eosinophils in a cohort of high-risk infants with atopic parents who participated in an intervention study of maternal allergenic food avoidance for allergy prevention. They found that the prevalence of nasal eosinophils increased from 0.7% at age 4 months to 38.2% at 48 months, and the prevalence was higher in infants with an allergic disease such as FA. In the MAS birth cohort, the prevalence of AR (based on the ISAAC questionnaire) was investigated from age 3 years to 13 years.²⁶ The prevalence of symptom-based AR increased from 6% at age 3 to 24% at age 13 in children with no parental history of allergy and from 13% to 44% in those with parental allergy. Sensitization to aeroallergens was a significant risk for AR, with an odds ratio of 18.9. Collectively, AR starts in infancy and becomes more common as children grow older, especially in those with a genetic predisposition to allergy and/or aeroallergen sensitization.

Our present results from a high-risk cohort of infants with AD and/or FA symptom were in accord with those earlier findings. An added strength of our study is that we prospectively investigated AR development in regard to not only the nasal symptoms but also nasal eosinophilia and sensitization during a critical 2-year period of infancy (up to 37.3 months of age).

Allergic rhinitis is a Th2-type inflammatory disease of the upper airways.^{27,28} It is diagnosed on the basis of the pathogenesis, that is, IgE antibody to an aeroallergen, IgE-mediated mast cell activation leading to mucosal symptoms such as rhinorrhea, nose itching, sneezing, blocked nose, and eosinophilic inflammation of the nasal mucosa leading to nasal hyper-reactivity. Positive findings for the “triad” of AR criteria, i.e., (1) “allergic” nasal symptoms, (2) aeroallergen sensitization, and (3) nasal eosinophilia, can establish the diagnosis. However, in the early stage of AR development, the triad may not be present due to the non-specific nature of symptoms and variable nasal mucosal pathology. Moreover, in preschool children, viral upper respiratory infections are common and symptom recognition relies on a mother's observation, not the perception or complaints of the child him/herself. To circumvent those problems, we employed a classification system of AR-like phenotypes that allows for fluctuation of AR manifestations in children. We found that our classifications corresponded well with previous observations in several birth cohort studies and, importantly, correlated positively with development of high-risk recurrent wheezer in this age group.

Nasal eosinophilia has been variously defined. In adults, more than 10%²⁰ or 20%²⁹ eosinophils in inflammatory cells were

regarded to be eosinophilia. In 11- to 15-year-old children, more than 10 eosinophils per high-power field was defined as nasal eosinophilia, with a diagnostic specificity of 96% and a sensitivity of 62% for AR.³⁰ We defined nasal eosinophilia in young children as when eosinophils were present and easily visible in the whole field, which may be a lower cut-off level for nasal eosinophilia compared with those in adults and older children. Because the number of eosinophils in nasal smears was reported to be much lower in young children with rhinorrhea and no signs of acute infection,³¹ we employed our above definition. Yet, we found that a higher cut-off of $\geq 10\%$ for the eosinophil/neutrophil ratio yielded similar results, although the prevalence of eosinophilia with this definition was lower than that with the former definition. Overall, we believe that our definition of positive nasal eosinophilia may be optimal due to its higher sensitivity.

Multimorbidity is a characteristic feature of allergies in children.²⁸ The MeDALL (mechanisms of the development of ALLergy) study, involving 12 cohort studies, reported that coexistence of asthma, rhinitis, and eczema in the same child was more prevalent than would be expected by chance.³² An important aspect of multimorbidity is development of asthma, because it places the largest burden on children. We previously reported that 78% of children younger than 10 years old with asthma had AR, and onset of AR preceded asthma onset in one-third of them.⁸ In a German MAS birth cohort, AR at 2 years and 5 years of age predicted later presence of wheeze.³³ Our present study, in which we focused on "multimorbid" infants with AD and/or FA, confirmed those earlier findings.

This study has several limitations. First, the number of subjects was relatively small compared with large birth cohort studies. In addition, since we intended to recruit subjects not only from hospitals but primary care clinics to balance the population, some of the clinics registered only small number of subjects. However, prospective investigation of the development of AR relied on not only the nasal symptoms but also HDM sensitization and nasal eosinophilia, which we believe enhanced the reliability of our findings. Second, definitive diagnosis of asthma in preschool age is not possible. However, because of practical need for the treatment of recurrent wheeze, GINA and other guidelines define high-risk recurrent wheezer in children 5 years and younger based on symptom patterns such as frequent wheezing, minor respiratory symptoms between episodes and comorbid allergic diseases^{16,17} and we employed the diagnostic criteria. Since the symptom pattern may change as they grow old, we continue to follow the subjects for development of school-age asthma and will confirm our results by using more objective findings, such as lung function. Third, our cohort was high-risk infants with AD/FA, and we may not be able to extrapolate the findings to natural history in the general population. However, because of the focused population, we were able to describe the clinical course of early AR in our relatively small number of subjects. In addition, they are the population whose parents likely concern about future development of respiratory allergies under common concept of atopic march and information obtained

in this study may be of worth. Fourth, the ISAAC questionnaire we employed in this study for nasal symptoms is designed to assess symptoms in school aged children and may limit the interpretation of the results.

In conclusion, we described the early phase of AR development in a high-risk cohort of children and proposed practical diagnostic criteria for AR in young children. Our findings show that AR increased markedly during 1 to 3 years of age and that the presence of AR at 2 years was positively associated with high-risk recurrent wheezer in preschool age. Additional studies will be needed to clarify the natural history of AR in children.

ACKNOWLEDGMENTS

The authors would like to thank Mr. Yoshiki Segawa at the Institute for Clinical Research, Mie National Hospital, for his excellent technical assistance. The authors would also like to thank the IRAM study investigators who actively participated in the study: Dr. Ogura Kanae (Department of Pediatrics, Kyoto Yawata Hospital); Drs. Yutaka Suehiro, Yukiko Hiraguchi, Yuko Ebishima and Saeko Shimodera (Department of Pediatrics, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases); Drs. Makoto Kameda, Yuri Takaoka, Tomoki Nishikido, Hiroko Yajima and Mineko Ikeoka (Department of Pediatrics, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases); Drs. Hideo Ogura and Yukiko Ogura (Department of Pediatrics, Kochi National Hospital); Dr. Gyokei Murakami (Murakami Pediatric & Allergy Clinic); Drs. Toshimi Nakamura and Yoko Yamashita (Department of Pediatrics, Kanazawa Medical University Hospital); Dr. Yoko Kawasaki (Hotarugawa Clinic); Drs. Taku Oishi, Hiroaki Hisakawa, Akihiko Hisakawa and Hiroshi Wakiguchi (Department of Pediatrics, Kochi University); Dr. Hiroyasu Okahata (Department of Pediatrics, Kure Kyousai Hospital); Drs. Ikuo Okafuji and Shigeta Shimizu (Kobe City Medical Center General Hospital); Drs. Naomi Kondo, Eiko Matsui and Kazuo Kubota (Department of Pediatrics, Gifu University Hospital); Dr. Yutaka Morisawa (Kera Child & Allergy Clinic); Dr. Mitsuhiro Nambu (Department of Pediatrics, Tenri Hospital); Dr. Miki Takao (Department of Pediatrics, Takashige Memorial Hospital); Dr. Yoshinori Matsuaki (Department of Otorhinolaryngology, Ota General Hospital); Drs. Yuichi Adachi and Toshiko Itazawa (Department of Pediatrics, Toyama University); Dr. Youichi Onoue (Onoue Pediatric Clinic); Dr. Osamu Higuchi (Department of Pediatrics, Kurobe City Hospital); Dr. Yoko Adachi (Department of Pediatrics, Takaoka Minami Hospital); Dr. Akihiko Terada (Terada Kid's Allergy & Asthma Clinic); Dr. Yoko Osawa (Department of Otorhinolaryngology, Tannan Regional Medical Center); Dr. Rentaro Abumi (Abumi Clinic); Drs. Tatsuya Fuchizawa and Junko Yamamoto (Saiseikai Takaoka Hospital); Drs. Motokazu Nakabayashi and Masaharu Kasei (Department of Pediatrics, Kouseiren Takaoka Hospital); Drs. Takanori Abe and Mayumi Sugimoto (Department of Pediatrics, Japanese Red Cross Kochi Hospital); Dr. Hisashi Kondo (Kondo Pediatrics Clinic); and Drs. Akiko Toga and Nobuyuki Doichi (Department of Pediatrics, Fukui-ken Saiseikai Hospital).

CONFLICT OF INTEREST

SM has received research grants from Torii Pharmaceutical Co., Ltd. TF has received lecture fees from Maruho Co., Ltd., and Torii Pharmaceutical Co., Ltd. All other authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

Sawako Masuda: Data curation (equal); Formal analysis (equal); Investigation (equal); Writing – original draft (equal). **Mizuho Nagao:** Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal). **Satoko Usui:** Investigation (equal). **Kazutaka Nogami:** Investigation (equal). **Yuji Tohda:** Funding acquisition (equal); Supervision (equal). **Takao Fujisawa:** Conceptualization (lead); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (lead); Supervision (lead); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (lead).

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13733>.

ORCID

Takao Fujisawa  <https://orcid.org/0000-0002-9196-9436>

REFERENCES

- Moyes CD, Clayton T, Pearce N, et al. Time trends and risk factors for rhinoconjunctivitis in New Zealand children: an International Study of Asthma and Allergies in Childhood (ISAAC) survey. *J Paediatr Child Health*. 2012;48(10):913-920.
- Björkstén B, Clayton T, Ellwood P, Stewart A, Strachan D, ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol*. 2008;19(2):110-124.
- Sasaki M, Morikawa E, Yoshida K, Adachi Y, Odajima H, Akasawa A. The change in the prevalence of wheeze, eczema and rhinoconjunctivitis among Japanese children: findings from 3 nationwide cross-sectional surveys between 2005 and 2015. *Allergy*. 2019;74(8):1572-1575.
- Sih T, Mion O. Allergic rhinitis in the child and associated comorbidities. *Pediatr Allergy Immunol*. 2010;21(1 Pt 2):e107-e113.
- Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multi-country cross-sectional surveys. *Lancet*. 2006;368(9537):733-743.
- Belgrave DC, Granell R, Simpson A, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. *PLoS Medicine*. 2014;11(10):e1001748.
- Loo EXL, Liew TM, Yap GC, et al. Trajectories of early-onset rhinitis in the Singapore GUSTO mother-offspring cohort. *Clin Exp Allergy*. 2021;51(3):419-429.
- Masuda S, Fujisawa T, Katsumata H, Atsuta J, Iguchi K. High prevalence and young onset of allergic rhinitis in children with bronchial asthma. *Pediatr Allergy Immunol*. 2008;19:517-522.
- Herr M, Clarisse B, Nikasinovic L, et al. Does allergic rhinitis exist in infancy? Findings from the PARIS birth cohort. *Allergy*. 2011;66(2):214-221.
- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8-160.
- Okubo K, Kurono Y, Ichimura K, et al. Japanese guidelines for allergic rhinitis 2020. *Allergol Int*. 2020;69(3):331-345.
- Nagao M, Borres MP, Sugimoto M, et al. Sensitization to secretoglobins and lipocalins in a group of young children with risk of developing respiratory allergy. *Clin Mol Allergy*. 2017;15:4.
- Iwanaga T, Tohda Y. Importance of clinical epidemiology research in studies on respiratory diseases. *Respir Investig*. 2013;51(4):217-223.
- Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol*. 1980;92:44-47.
- Ebisawa M, Ito K, Fujisawa T. Committee for Japanese Pediatric Guideline for Food Allergy TJSOPA, Clinical I, Japanese Society of A. Japanese guidelines for food allergy 2020. *Allergol Int*. 2020;69(3):370-386.
- Arakawa H, Adachi Y, Ebisawa M, et al. Japanese guidelines for childhood asthma 2020. *Allergol Int*. 2020;69(3):314-330.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021. Accessed January 28, 2022. www.ginasthma.com
- Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8(3):483-491.
- Otsuka H, Otsuka K, Matsune S, Okubo K. Nasal symptoms reduction and decreased neutrophilia in Japanese cedar pollinosis with prophylactic treatment with a combination of montelukast, fexofenadine, and fluticasone nasal spray. *Am J Rhinol Allergy*. 2019;33(4):369-377.
- Lee HS, Majima Y, Sakakura Y, Shinogi J, Kawaguchi S, Kim BW. Quantitative cytology of nasal secretions under various conditions. *Laryngoscope*. 1993;103(5):533-537.
- Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001;108(1 Suppl):S2-8.
- Okubo K, Kurono Y, Ichimura K, et al. Japanese guidelines for allergic rhinitis 2017. *Allergol Int*. 2017;66(2):205-219.
- Ebisawa M, Ito K, Fujisawa T. Japanese guidelines for food allergy 2017. *Allergol Int*. 2017;66(2):248-264.
- Osawa Y, Suzuki D, Ito Y, et al. Prevalence of inhaled antigen sensitization and nasal eosinophils in Japanese children under two years old. *Int J Pediatr Otorhinolaryngol*. 2012;76(2):189-193.
- Zeiger RS, Heller S. Development of nasal basophilic cells and nasal eosinophils from age 4 months through 4 years in children of atopic parents. *J Allergy Clin Immunol*. 1993;91(3):723-734.
- Keil T, Bockelbrink A, Reich A, et al. The natural history of allergic rhinitis in childhood. *Pediatr Allergy Immunol*. 2010;21(6):962-969.
- Ciprandi G, Tosca MA. House dust mites-driven allergic rhinitis: could its natural history be modified? *Expert Rev Clin Immunol*. 2021;17(2):109-114.
- Papadopoulos NG, Aggelides X, Stamataki S, Prokopoulos E, Katotomichelakis M, Xepapadaki P. New concepts in pediatric rhinitis. *Pediatr Allergy Immunol*. 2021;32(4):635-646.
- Jankowski R, Persoons M, Foliguet B, Coffinet L, Thomas C, Verient-Montaut B. Eosinophil count in nasal secretions of subjects with and without nasal symptoms. *Rhinology*. 2000;38(1):23-32.
- Miri S, Farid R, Akbari H, Amin R. Prevalence of allergic rhinitis and nasal smear eosinophilia in 11- to 15 yr-old children in Shiraz. *Pediatr Allergy Immunol*. 2006;17(7):519-523.
- Otsuka H, Otsuka K, Matsune S, Okubo K. Assessing the onset of allergic rhinitis by nasal cytology and immunoglobulin E antibody levels in children. *Am J Rhinol Allergy*. 2018;32(1):16-22.
- Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitized and non-IgE-sensitized

children in MeDALL: a population-based cohort study. *Lancet Respir Med*. 2014;2(2):131-140.

33. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol*. 2010;126(6):1170-1175 e1172.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Masuda S, Nagao M, Usui S, Nogami K, Tohda Y, Fujisawa T; Investigators of Kinki Hokuriku Airway Disease Conference (KiHAC). Development of allergic rhinitis in early life: A prospective cohort study in high-risk infants. *Pediatr Allergy Immunol*. 2022;33:e13733.
doi:[10.1111/pai.13733](https://doi.org/10.1111/pai.13733)