Asia Pacific **allergy**

Original Article

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Phenotypes of atopic dermatitis up to 36 months of age by latent class analysis and associated factors in Japan

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ABSTRACT

Background: Atopic dermatitis (AD) in early childhood is the first allergic manifestation in the atopic march. Recently, latent class analysis (LCA) has revealed the presence of AD subgroups in childhood.

Objective: This study aimed to elucidate different AD phenotypes up to 36 months of age and identify factors associated with a particular AD phenotype in early childhood.

Methods: Pediatric allergists or dermatologists examined children who visited local public health centers in Chiba or Yokohama city at 4, 18, and 36 months of age for regular health checkups between 2003 and 2005. LCA was used to identify AD subtypes on the basis of the course of skin symptoms and comorbidity of other allergic diseases. After LCA, the association between genetic and environmental factors and AD phenotypes was assessed.

Results: A total of 1,378 children who underwent the 3 checkups were included. Complete data were available for 515 children up to 36 months of age. Of 515 children, 183 were diagnosed with AD at least at one out of the 3 time points. The LCA model of these children with AD separated 4 AD phenotypes: early-persistent (EP), early-transient (ET), late-onset (LO), and variable (V). Antibiotic use by 4 months of age was significantly higher in EP group than in other 3 groups. Mother's allergy was significantly higher in EP and LO groups than in other 2 groups. Passive smoking at 18 months of age was higher in LO group than in other groups. Furthermore, >80% of V group was born in spring–summer.

Conclusion: We identified 4 AD phenotypes using LCA on the basis of the onset/course of AD and comorbidity of other allergic diseases and also identified several factors related to the particular phenotypes, which may be useful markers for the prediction of prognosis of AD in early childhood.

Keywords: Cohort study; Dermatitis, Atopic; Latent class analysis; Child; Phenotype

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INTRODUCTION

Atopic dermatitis (AD) is a common skin disease with an estimated prevalence of more than 20% in childhood [1]. It is considered the first manifestation in the allergic march, which describes the typical progression of clinical symptoms of allergic diseases during childhood. Several researchers have attempted to prevent an allergic march via vigorous treatment or prevention of AD [2]. It is thought that early-onset AD—the development of AD before 2 years of age—is a risk factor for allergic march and the development of airway allergies [3]. Nevertheless, the clinical course of AD in early childhood is not uniform and heterogeneous [4]. Additionally, most of the birth cohorts to elucidate AD trajectories have been conducted in Western countries, and a few studies were reported from Asian countries where factors related to AD phenotypes may be different from those in Western countries. Therefore, it is important to define different AD phenotypes in early childhood and find the genetic and environmental factors related to AD with other comorbid allergic diseases to identify and treat AD subtypes to prevent allergic march in Asia.

In Japan, it was common in the early 2000s to take regular health checkups for infants at 4, 18, and 36 months of age at the local health centers. We took advantage of this system to study the natural course of AD in early childhood and set up a cohort to prospectively investigate whether different AD phenotypes could be identified during early childhood regarding allergic march. In this study, we used the latent class analysis (LCA) to define different AD phenotypes on the basis of AD course and comorbid allergic diseases. Moreover, we examined whether AD subtypes are differently associated with genetic and environmental factors.

MATERIALS AND METHODS

Study design and cohort
Infants and their parents who visited local public health and welfare centers in Chiba or Yokohama city for regular health checkups from 2003 to 2005 (3 consecutive time points: 4, 18, and 36 months of age) were invited to participate in this observational follow-up study. Written consent for participation in this study was provided by parents. The questionnaire was distributed to the parents 2 weeks before a visit to the center, completed by the parents, and collected at the survey. The questionnaire included sex, concomitant allergic diseases, parental allergic history, smoking, number of siblings, antibiotic exposure, daycare attendance, and nutrition. Also, it included whether the child had been diagnosed with AD, food allergy, allergic rhinitis, and asthma in a clinic or hospital and whether the symptoms experienced by the children who had been diagnosed with the disease were still present. On the examination day, without reference to the questionnaires, pediatric allergists or dermatologists examined the children and diagnosed whether the child had AD or not. The study protocol was approved by the Ethics Committee of Chiba University Graduate School of Medicine (No. 426).

Diagnostic definition of AD
AD was diagnosed by experienced pediatric allergists or dermatologists on the basis of the Japanese Dermatological Association criteria [5], which is similar to that of Hanifin and Rajka [6].

LCA and statistics
The LCA was performed to identify phenotype subgroups in infants with AD on the basis of the following items: AD at 3 time points (4, 18, and 36 months) and comorbidity of other

allergic diseases. Using model selection criteria, Akaike information criterion (AIC) values, a multiple-group latent class model [7] with the optimal number of computer-derived subgroups (latent classes) was determined. After choosing the number of classes, individuals were assigned to the class with the highest posterior probability of membership. The chi-square test was used to assess the association between genetic and environmental factors and AD phenotypes in early childhood. LCA was performed using the PROC LCA (ver. 1.3.2) [8]. The remaining analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA); $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the study population

A total of 2,433 infants at 4 months of age were recruited at health checkups. The flowchart of participants in this study is shown in **Fig. 1**. Among them, 1,378 infants completed 3 consecutive health checkups. Of these children, the complete dataset of 515 children was available. Of the 515 children, 183 were diagnosed with AD at least at 1 time point (cumulative prevalence 35.5%). The point prevalence of AD was 19.4% at 4 months, 14.8% at 18 months, and 17.9% at 36 months. At 18- and 36-month medical examinations, about half of the infants with AD in the previous medical examinations had no AD, and nearly the same number was newly diagnosed with AD.

LCA with AD and comorbidity of other allergic diseases

LCA was used to define different AD phenotypes on the basis of the course at 3 time points (4, 18, and 36 months) and comorbidity of other allergic diseases. Using AIC, 4 classes were identified as the best fitting model, with the smallest value representing the most optimal model (with 2 classes, AIC = 132.4; with 3 classes, AIC = 88.1; with 4 classes, AIC = 55.9; with 5 classes, AIC = 62.1; and with 6 classes, AIC = 73.4). Therefore, we could define 4 different
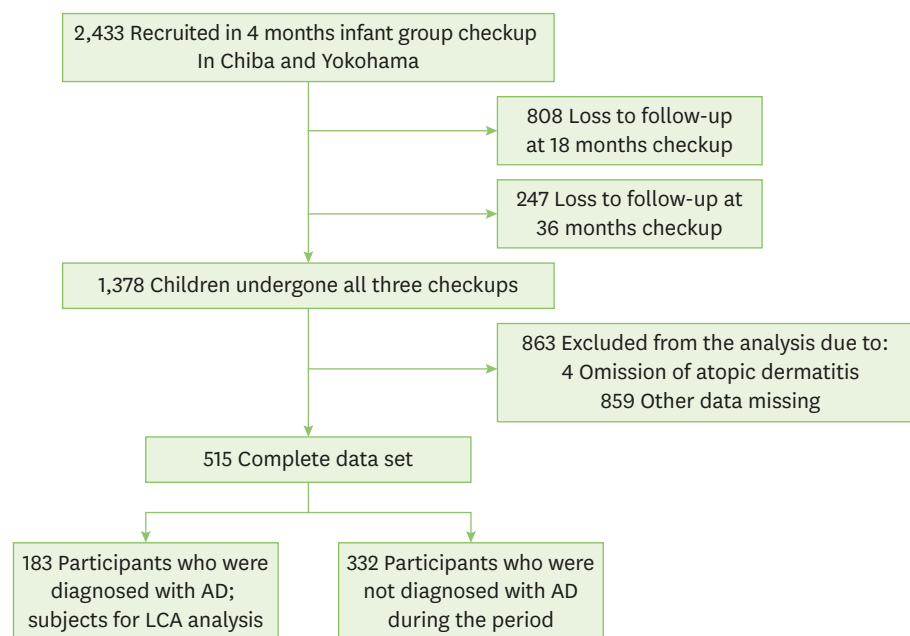

Fig. 1. Flow chart of participants in the present study. AD, atopic dermatitis; LCA, latent class analysis.
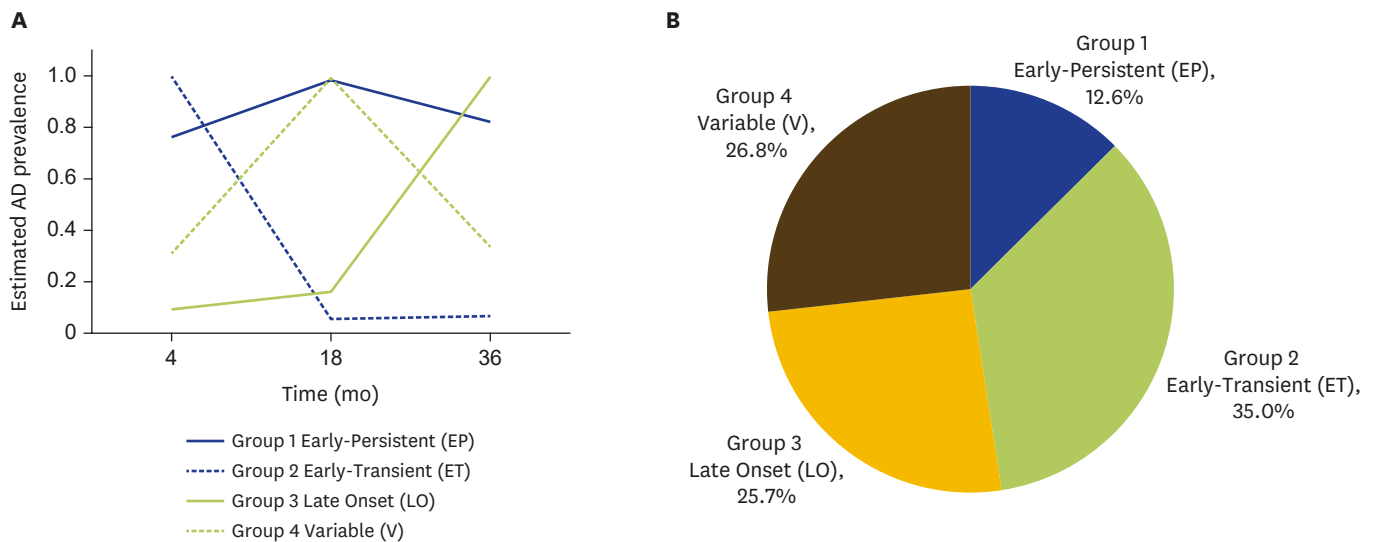
Fig. 2. Four AD phenotypes identified by LCA. (A) Estimated prevalence of AD at 3 time points (4, 18, and 36 months) for each phenotype. (B) Percentage of AD participants belonging to each phenotype. AD, atopic dermatitis; LCA, latent class analysis

AD phenotypes: the early-persistent (EP) phenotype (onset before 4 months and lasting up to 36 months) (n = 23, 12.6%); the early-transient (ET) phenotype (onset before 4 months and resolved before 18 months) (n = 64, 35.0%); the late-onset (LO) phenotype (onset after 18 months) (n = 47, 25.7%); and the variable (V) phenotype (n = 49, 26.8%) (**Fig. 2**).

Association between genetic and environmental factors and AD phenotypes in early childhood

Table 1 shows the prevalence of comorbid allergic diseases, such as food allergy, allergic rhinitis and asthma, and the association between genetic and environmental factors and AD phenotypes up to 36 months. Among the 4 groups, the EP group had the highest rate of food allergy and asthma but the ET group had the same low rate as the LO and V groups. At 36 months, the LO group had the second most common rate of asthma, following the EP group. Among the 4 groups, there were no differences in sex, presence of older children, daycare attendance, presence of pets, father's history of allergies, and nutrition. Antibiotic use at 4 months was approximately 40% in the EP group, which was higher than that in the other groups (chi-square test, $p = 0.0306$). Passive smoking at 18 months was over 60% in the LO group, which was higher than that in the other groups ($p = 0.0316$). Regarding the season of birth, more than 80% of the V group was born in spring–summer ($p = 0.0005$). More than 90% of mothers in the EP and LO groups had a history of allergy ($p < 0.0001$).

DISCUSSION

The course of AD in infancy is not uniform. Clinically, it is well known that there are groups in which AD disappears early, even if it develops in infancy [4]. This study supported the heterogeneity of AD in early childhood and identified 4 AD phenotypes in early childhood by LCA, in the perspective of allergic march. Among the 4 groups, only the EP group was highly associated with food allergy and asthma. This indicates that the EP phenotype is really a group presenting "allergic march." Among the phenotypes reported to date based on the course of AD, early phenotype (onset before 2 years of age) has been shown to have a high complication rate of food allergies and airway allergies [9]. In this study, a large difference was observed

Table 1. Association between genetical and environmental factors and atopic dermatitis (AD) phenotypes

	Group 1 (n = 23)	Group 2 (n = 64)	Group 3 (n = 47)	Group 4 (n = 49)	p value
Comorbid allergy diseases					
Food allergy					
4 Months	13.0	1.6	0	0	-
18 Months	56.5	6.3	6.4	6.1	-
36 Months	47.8	3.1	6.4	8.2	-
Asthma					
18 Months	17.4	0	6.4	0	-
36 Months	34.8	6.3	12.8	0	-
Allergic rhinitis					
18 Months	0	0	0	0	-
36 Months	0	1.6	4.4	0	-
Genetical and environmental factor					
Male sex	60.9	57.8	48.9	57.1	0.7344
Antibiotics use					
4 Months	39.1	10.9	19.2	18.4	0.0306*
Elder siblings					0.7387
0	52.2	51.6	44.7	46.9	
1	34.8	37.5	48.9	42.9	
2	8.7	10.9	6.4	8.2	
3 or more	4.4	0	0	2.0	
Daycare attendance					
4 Months	4.4	1.6	0	2.0	0.5975
18 Months	13.0	17.2	19.2	28.6	0.3545
36 Months	47.8	28.1	29.8	30.6	0.3551
Passive smoking (ETS)					
4 Months	34.8	40.6	53.2	42.9	0.4361
18 Months	39.1	37.5	63.8	40.8	0.0316*
36 Months	39.1	35.9	61.7	44.9	0.0521
Pet ownership					
4 Months	13.0	12.5	0	12.2	0.0901
18 Months	8.7	12.5	0	12.2	0.0942
36 Months	4.4	9.4	0	10.2	0.1464
Season of birth					0.0005*
Spring–Summer	47.8	43.7	61.7	81.6	
Autumn–Winter	52.2	56.3	38.3	18.4	
Parental history of allergic diseases					
Father	69.6	67.2	68.1	63.3	0.9418
Mother	91.3	54.7	91.5	59.2	<0.0001*
Breast milk feeding	87.0	81.3	74.5	91.8	0.1359

Values are presented as percentage of each category of AD phenotype.
Group 1, early-persistent; group 2, early-transient; group 3, late-onset; group 4, variable; ETS, environmental tobacco smoke.
*p<0.05, by chi-square test.

in the rate of food allergy and asthma between 2 early phenotypes, EP and ET. Furthermore, the discrepancy may be due to the classification of AD. Early phenotypes indicate that AD developing before 4 months of age in ET phenotype remits before 18 months of age, whereas AD lasted until 36 months of age in EP phenotype in our study. Shoda et al. [10] reported that AD of which the onset was before 4 months is a risk factor for food allergy at 36 months. Our data suggest that even if AD develops very early in infancy, there is a low risk of developing food allergy and airway allergies if the child resolves AD by 18 months of age.

This study presented several environmental and genetic factors associated with AD phenotypes in early childhood. Antibiotic use before 4 months of age was strongly associated with EP phenotype. Furthermore, antibiotic use during infancy was reported to increase the incidence of AD in infants [11-13]. Interestingly, antibiotic use in early infancy is related only to EP but not ET phenotype. Furthermore, the relationship between environmental tobacco smoke

at 18 months and LO phenotype was found. Although there was no statistically significant difference, the frequency of ETS was the highest among the 4 phenotypes at both 4 and 36 months. Johansson et al. [14] reported that ETS at birth is associated with prolonged AD in infants. Although there is no information on ETS during pregnancy and childbirth in this study, ETS in infancy may be associated with the development of AD and affect its course. Moreover, the season of birth may influence the development of AD in early childhood, although there is a discrepancy among studies [15]. We found that most of the children in the V group were born in spring–summer, which suggests that in some populations, the climate is a major important factor of AD in early childhood. In this study, maternal allergies, but not paternal allergies, were strongly associated with ET and LO phenotypes, that is, AD at 36 months. Furthermore, there was no big difference in terms of risk of AD development in Asian countries between the maternal and paternal history of allergic diseases [16]. Hence, to explore the influence of the maternal history of allergic diseases on AD in early childhood, future studies are needed.

The strengths of this study are that (1) it is a follow-up study of the general population by use of the medical examination system in Japan and (2) the diagnosis of AD was made by a doctor but not by questionnaire. Also, there are several limitations to this study including (1) high dropout rate through the follow-up period, (2) no long-term AD course and complications of other allergic diseases, (3) no evaluation of AD severity, and (4) no information regarding sensitization by skin prick test or blood sampling. In the sensitivity analysis, we performed the same analysis after missing data on items were handled by the expectation=maximization algorithm in the LCA, and similar results were obtained. We believe this study adds valuable information on AD phenotypes and the genetic and environmental risk factors for AD-related allergic march in early childhood.

In conclusion, we identified 4 AD phenotypes using LCA on the basis of the onset/course of AD and comorbidity of other allergic diseases. We also found several environmental and genetic factors related to the particular phenotypes, which may be a useful marker in the prediction of the prognosis of AD in early childhood. These findings may be important for the prevention of allergic march from early childhood AD.

ACKNOWLEDGEMENTS

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