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Original Article

Using family atopy scores to identify the risk of atopic dermatitis in infants

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Abstract

Background Atopic dermatitis is the first manifestation of allergic disease in early life. Early interventions may prevent the development of allergy disease. Allergy trace cards have been used to identify the level of allergic risk, based on family atopy scores. Because environmental factors may also influence the development of atopic dermatitis, the usefulness of the allergy trace card needs to be reevaluated.

Objective To compare the incidence of atopic dermatitis in infants aged 0-4 months with total family atopy scores of > 0 to those with scores of 0.

Methods We conducted this cohort study from June 1, 2012 to December 31, 2012 at Sanglah Hospital, Denpasar. Family atopy score was tabulated from all pregnant woman in the Obstetric Outpatient Clinic and the Maternity Room. Subjects were divided into two groups based on their total family atopy score: those with scores > 0 and those with scores of 0. The appearance of atopic dermatitis symptoms in the infants were evaluated until they reached 4 months of age. The incidence of atopic dermatitis in two groups was compared using Chi-square test.

Results The incidence of atopic dermatitis in this study was 10.9%. The group with total family atopy scores of 0 had a significantly higher incidence of atopic dermatitis than the group with scores > 0 (adjusted RR 22.5; 95%CI 8.8 to 57.0; P = 0.001).

Conclusion The incidence of atopic dermatitis is higher in infants with total family atopy score > 0 and this group has a 22.5 times higher risk of atopic dermatitis compared to infants with total family atopy score of 0. Allergy trace cards are relevant in differentiating the risk of atopy with regards to development of atopic dermatitis. We suggest that family atopy scores be evaluated during antenatal care in order to limit the development of atopic dermatitis in infants. **[Paediatr Indones. 2014;54:330-7.]**

Keywords: *atopic dermatitis, allergy trace card, family atopy score*

Allergic disease has its own natural history and may manifest at different stages of childhood in the form of atopic dermatitis, allergic rhinitis, wheezing, urticaria, or asthma.[1] Atopic dermatitis is a chronic, inflammatory skin disease that occurs with peak onset in infancy, and a large majority of cases present in the first few years of life.[2-3] Atopic dermatitis in the first few months of life can cause significant family stress, interfere with infant sleep and feeding, lead to physician visits, and increased health care expenditures. It also may be a risk factor for aeroallergen sensitization, asthma, allergic rhinitis, and urticaria later in childhood.[4-5] The risk of atopy may begin very early in life, even before birth. Both genetic and environmental factors may predispose a child to allergic disease. In utero exposure may be modulated by postnatal factors to predispose the developing fetal immune system to atopy.[1]

Allergic manifestations can be prevented with early detection, such as identification of a high risk population based on family atopy history.[6]

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Allergy trace cards used by the *Indonesian Pediatric Society* (IPS) and the *Indonesian Society of Obstetrics & Gynecology* (ISOG) help to identify high risk populations by family atopy score.[6] The influence of environmental factors on the development of atopy has led us to question the usefulness of the allergy trace card. We aimed to reevaluate the use of the allergy trace card by comparing the incidence of atopic dermatitis in infancy based on family atopy scores in monthly evaluations of the infants for their first 4 months of life.

Methods

We performed a cohort study on all pregnant women and their infants up to 4 months of age in Sanglah Hospital, Denpasar from June to December, 2012. Inclusion criteria were subjects living in Bali, not planning to leave Bali for 4 months after birth, as well as parents able to be contacted by phone and providing written proxy consent. We excluded mothers with immunologic disorders, autoimmune disorders, and those who received long-term corticosteroid therapy. Subjects were considered to have dropped out if they were stillborn, had multiple congenital anomalies, or were lost to follow-up. Subjects were considered to be lost to follow-up if the parents could not be contacted by phone or subjects died before a diagnosis of atopic dermatitis was established.

Sample size was calculated based on Z score for α =0.05 of 1.96 and power 80%, P1 32%, P2 5%, and 10% for lost to follow-up, yielding a minimum sample size of 72, with 36 infants in each group.[8] Infants were selected by consecutive sampling, then allocated into two groups based on their family atopy scores of either > 0 or 0. Family atopy scores were assessed using allergy trace cards by IPS and ISOG.[6]

The main objective of our study was to compare the incidence of atopic dermatitis between the two groups: those with family atopy score of > 0, and those with scores of 0. Diagnoses of atopic dermatitis were confirmed by the Hanifin and Rajka criteria.[9]

We assessed total family atopy scores of parents and siblings. Subjects received a score of 2 if parents and/or siblings had allergic disease diagnosed by a doctor, a score of 1 if they had suspected allergic disease or symptoms, and a score of 0 if they had no allergic disease or symptoms. Exposure to cigarette smoke was defined as a history of maternal smoking during pregnancy or after birth, and/or any family member who smoked in the house or near the subjects. Exposure to pets (dogs and cats) was obtained by a history of pets in the house. Immunization status was considered to be complete according to the IPS 2011 immunization schedule. Mode of delivery was defined as caesarian section or vaginal delivery. A history of neonatal infection was obtained by medical records that confirmed infection had occurred at <1 month of age. Number of siblings was defined as the number of siblings at home and categorized as < 3 or $\geq$ 3. Early solid feeding was defined as feeding solid food at < 6 months of age. Exclusive breastfeeding was defined as subjects' consumption of breast milk only. Exposure to cow's milk was defined as any history of exposure of cow's milk from birth to the age of 4 months.

Pregnant women who visited the Obstetrics and Gynecology Outpatient Clinic and gave birth at Sanglah Hospital were given information about this study and asked to participate. We collected data by questionnaire and recorded phone numbers to prevent subjects being lost to follow up. We assessed paternal history of allergies either directly, or by phone for fathers who did not visit the hospital. All histories of allergy in fathers, mothers and siblings were converted into family atopy scores in the IPS-ISOG allergy trace cards. Total scores were divided into 3 groups: total score of 0, total score of 1-3, and total score of 4-6. Subjects with total score of 1-3 and total score of 4-6 were included in the group with total atopy score > 0. Subjects were followed up monthly for 4 months or until a diagnosis of atopic dermatitis was confirmed. Subjects who did not visit the Pediatric Outpatient Clinic every month were contacted by phone or short messages service (SMS). We asked about symptoms of atopic dermatitis every month. If we suspected symptoms of atopic dermatitis such as redness on cheeks or itchy extremities, the researcher would visit the home or advise subjects to seek further examination in Sanglah Hospital. Subjects with suspected atopic dermatitis were reevaluated in the Pediatric Outpatient Clinic by the chief resident using the Hanifin Rajka criteria[9] and treated. If a diagnosis of atopic dermatitis was confirmed, that subject was considered to have fulfilled the study outcome and was not further followed up. Inter-rater reliability

among the pediatricians and chief residents was good, with a Kappa value of 72.2%. Subjects with atopic dermatitis were treated according to standard medical care. The time when diagnosis of atopic dermatitis was confirmed were recorded. Chief residents who established diagnoses of atopic dermatitis were blinded to family atopy scores.

We calculated the mean, median and range to describe the basic characteristics of the study subjects. Differences in incidence of atopic dermatitis between the groups were compared and analyzed with Chi-square test. The onset of atopic dermatitis evaluated by Kaplan-Meier curve. Statistical analyses were performed with *SPSS version 16*.

This study was approved by the Research Ethics Committee at Udayana University Medical School, Sanglah Hospital, Denpasar.

Results

During the study period, a total of 280 subjects who met the inclusion criteria were chosen by consecutive sampling. Study subjects were divided into two groups. In the group with family atopy score of 0, 3 subjects died and 11 were lost to follow up during the 4-month period, leaving 218 subjects. In the group with a family atopy score of > 0, 1 subject died and 1 was

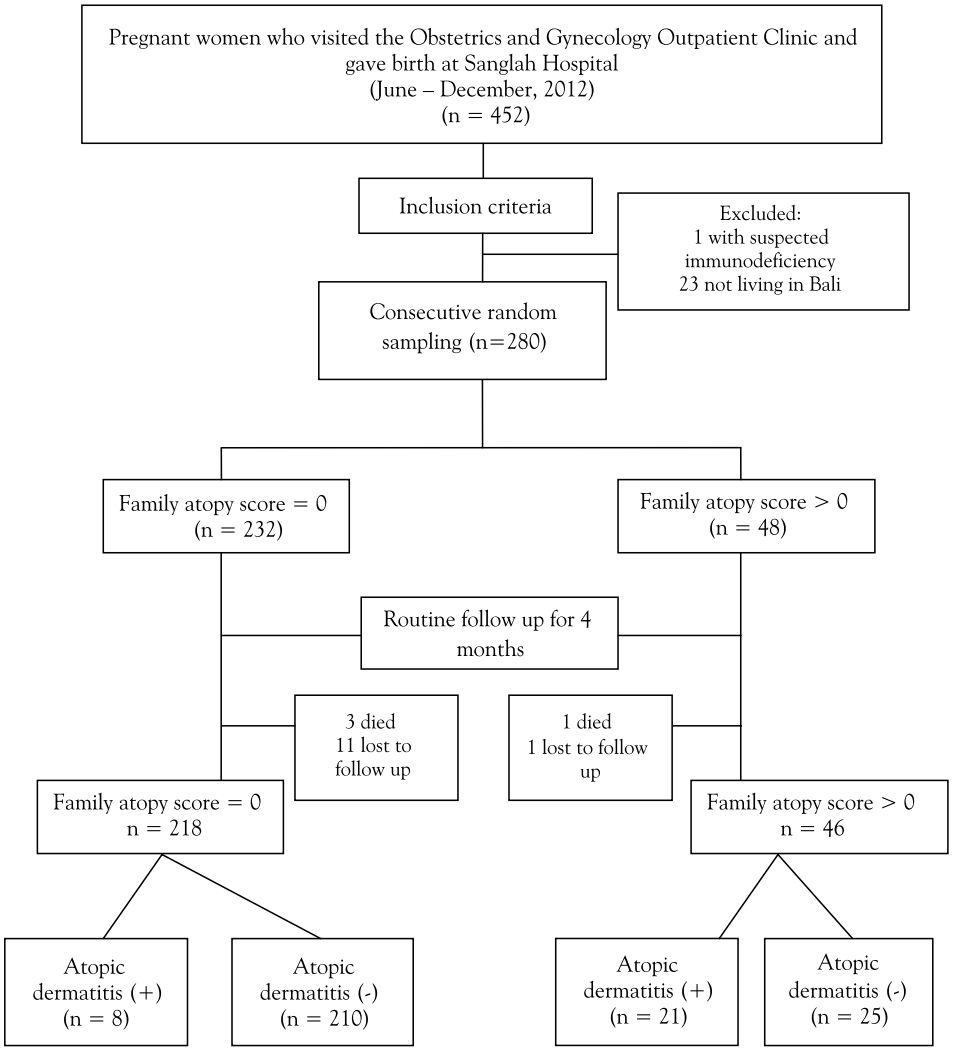

Figure 1. Study flowchart

lost to follow up, leaving 46 subjects (**Figure 1).** The causes of death of the 4 study subjects were meconium aspiration syndrome (1 child), hyaline membrane disease (2 children), and severe asphyxia (1 child). Baseline characteristics of subjects are presented in **Table 1**.

We conducted Kolmogorov-Smirnov normality testing on the baseline characteristics of subjects and found no significant differences between the two groups with regards to gender, birth weight, mode of delivery, gestational age, exclusive breastfeeding, exposure to cow's milk, pets, history of infection, and the number of siblings (all P>0.05), with the exception of cigarette smoke exposure. None of our subjects in both groups got complete immunization based on 2011 IPS immunization schedule or early solid feeding.

As much as 14% of subjects who had been exposed to cigarette smoke developed atopic dermatitis, while 86% did not. Chi-square test revealed a statistically significant difference in cigarette smoke exposure between the group with atopic dermatitis and the group without atopic dermatitis (RR= 3.2; 95%CI 1.1 to 9.7; P=0.02).

The incidence of atopic dermatitis in our study population was 10.9%. To clarify the role of family atopy on the risk of allergies, we also calculated the incidence of atopic dermatitis in the group with atopy scores > 0, and found it to be 45.6%. However, the incidence of atopic dermatitis in the group with atopy score of 0 was significantly lower at 3.6%. From Chi-square testing we found a significant difference in the occurrence of atopic dermatitis (RR= 12.4; 95%CI 5.8 to 26.3; P=0.001) (**Table 2**).

Table 1. Baseline characteristics of subjects

Characteristics	Family atopy score	
	> 0 (n=46)	0 (n=218)
Male gender, n (%)	23 (50)	119 (54)
Median maternal age, years (min-max)	25 (19-37)	25.5 (19-37)
Median paternal age, years (min-max)	26 (21-38)	27 (20-40)
Gestational age, n (%)		
< 37 weeks	6 (13)	26 (12)
≥ 37 weeks	40 (87)	192 (88)
Mean birth weight (SD), g	3.0 (6.3)	3 (5.4)
< 2500 g, n (%)	8 (17.4)	25 (11.5)
≥ 2500 g, n (%)	38 (82.6)	193 (88.5)
Mode of delivery, n (%)		
Vaginal	29 (63)	64 (70.6)
Caesarian section	17 (37)	154 (29.4)
Number of siblings, n (%)		
<3	44 (96)	200 (91.7)
≥3	2 (4)	18 (8.2)
Exposed to cigarette smoke, n (%)	38 (83)	141 (64.6)
Pet(s) in the house, n (%)	2 (4.3)	13 (5.9)
Exclusively breastfed, n (%)	28 (61)	141 (64.7)
Exposed to cow's milk, n (%)	18 (39.1)	77 (35.3)
History of neonatal infection, n (%)	2 (4.3)	4 (1.8)

Table 2. Comparison between family atopy score and incidence of atopic dermatitis

Family atopy score	Atopic dermatitis		RR	95% CI	P value
	Yes (n= 29)	No (n= 235)			
>0	21	25	12.4	5.8 to 26.3	0.001*
0	8	210			

*Chi-square test

To reduce bias on the results of this study, we performed multivariate analysis by logistic regression testing on the influence of cigarette smoke exposure on the occurrence of atopic dermatitis. Statistical analysis revealed an adjusted relative risk of 3.5 and 95%CI 1.0 to 11.5 (P=0.04) for those exposed to cigarette smoke and an adjusted relative risk of 22.5 and 95%CI 8.8 to 57.0 (P=0.001) for those with family atopy score > 0 for the development of atopic dermatitis (**Table 3**).

We divided the group with family atopy scores of > 0 further into two groups: those with atopy scores of 1-3 and those with atopy scores of 4-6. Chi-square test revealed a significantly higher occurrence of atopic dermatitis in the group with atopy scores of 4-6, compared to the group with scores of 1-3 (RR= 5.5; 95%CI 2.2 to 13.8; P=0.001).

The time to develop atopic dermatitis in the original two family atopy score groups is presented in the Kaplan-Meier curves (**Figure 2**). In these curves, it is apparent that the development of atopic dermatitis started at the age of 1 month in the group with atopy scores > 0. The average time of the event occurring was at 2.5 months of age (standard error 0.189; 95%CI 3.1 to 3.8) in the group with atopy scores > 0. In the group with atopy scores of 0, the average time of occurrence was 3.5 months (standard error 0.203; 95%CI 2.1 to 2.9). Hence, the time to develop atopic dermatitis was significantly less in the group with family atopy scores > 0 (P=0.01).

Table 3. Multivariate analysis*

Variables	adjusted RR	95% CI	P value
Cigarette smoke exposure	3.5	1.0 to 11.5	0.04
Family atopy score	22.5	8.8 to 57.0	0.001

*Regression logistic test

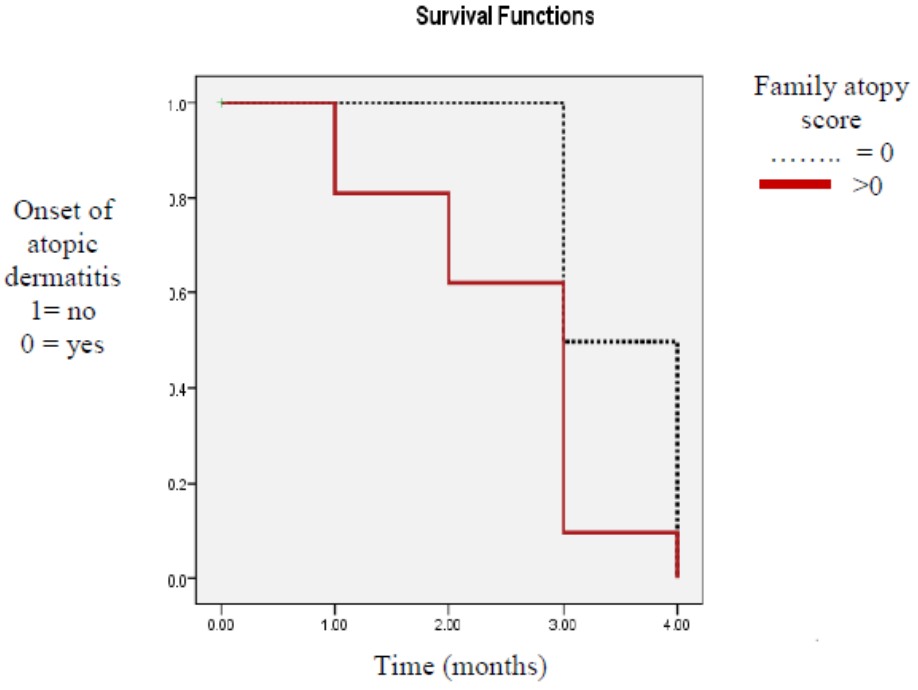

Figure 2. Kaplan-Meier curves show the onset of atopic dermatitis in each group

Discussion

In our study, we found that atopic dermatitis developed within the first 4 months of life in 10.9% of

subjects. Previous studies found incidences of atopic dermatitis to be 17.1% at 6 months of age,[1] and 36.4% at 12 months of age.[10] A cohort study reported a cumulative incidence of atopic dermatitis to be 31% among 1-year-olds, 41% at 2-years old, and 44% at 3-years old.[8] The incidence of atopic dermatitis in our study was lower compared to previous studies, because of our smaller sample size and shorter period of observation.

Atopic dermatitis is an early manifestation of atopic disease with the highest incidence during the first 3 months of life, and reaching the highest prevalence during the first 3 years of life.[11] The *Copenhagen Prospective Study on Asthma in Childhood* (COPSAC) reported the earliest occurrence of atopic dermatitis at the age of 1 month, increasing in frequency with age and reaching a peak at 2.5 years of age.[8] The Kaplan-Meier curve of our study also shows the earliest onset starting at 1 month of age, with an average of 2.5 months in the group with atopy scores > 0.

Atopic dermatitis develops due to an interaction between genetics, heredity (history of atopy), environment, and lifestyle, including diet and hygiene. Genetic factors alone cannot explain the increase in atopic dermatitis during the past two decades. Environment and lifestyle play important roles in the occurrence of these changes. The development of allergic disease begins in utero, at the gestation age of 11 weeks, when IgE starts to be produced.[8] The influence of various factors on the occurrence of atopic dermatitis during the first few months of infant life has been controlled for in this study, including for delivery method, birth weight, exposure to cigarette smoke, pets, exposure to cow's milk, immunization status, number of siblings, history of infection during the neonatal period, and history of early solid feeding (at < 4 months of age). Bivariate analysis (Chi-square test) did not reveal a significant influence of these factors in our study on the development of atopic dermatitis, with the exception of exposure to cigarette smoke.

Exposure to cigarette smoke influenced the occurrence of atopic dermatitis among infants aged 0-4 months in our study (P=0.02). Similarly, Yi *et al.* in Korea studied the influence of cigarette exposure on subjects with actively smoking mothers during pregnancy and/or during the first year of life, and found a 2.06 times increased risk for developing atopic dermatitis compared to subjects from mothers who did not smoke during pregnancy or during the first year of life.[12] Shinohara *et al.* also observed that the prevalence of atopic dermatitis increased significantly among infants exposed to cigarette smoke during the third trimester (OR 6.1; 95%CI 1.2 to 29.4), compared to those not exposed to cigarette smoke.[13] Wang *et al.* found an association between the concentration of cotinine (a metabolite of nicotine in blood) from umbilical cord blood and maternal blood and the occurrence of atopic dermatitis.[14] This may be caused by the general, irritating effect of air pollutants on skin and mucosa, enabling potential allergen penetration into the body, leading to symptoms of atopic dermatitis and increased risk of sensitization. Furthermore, maternal exposure to cigarette smoke during gestation may have a long term effect on the intestinal immune response of infants and play a role in allergic sensitization.[12] Major issues in preventing allergic disease are the unpredictability of allergic manifestations that may develop, the method for preventing the occurrence of allergic disease, and prevention of sensitization to allergens during the fetal or infantile periods to prevent the development of allergic disease. The main targets for primary prevention of allergic disease are fetuses, infants, pregnant mothers, and their environment.[15]

The COPSAC study reported that a maternal history of atopic dermatitis (OR 0.33; 95%CI 0.22 to 0.50; P<0.0001), history of asthma (OR 0.50; 95%CI 0.27 to 0.92; P=0.02), history of allergic rhinitis (OR 0.50; 95%CI 0.33 to 0.78; P=0.002), history of allergy to aeroallergens (OR 0.49; 95%CI 0.32 to 0.76; P=0.001), and a paternal history of type IV hypersensitivity (OR 2.58; 95%CI 1.09 to 6.11; P=0.03) are risk factors significantly related to atopic dermatitis in 3-year-old children.[8] Another cohort study revealed that family history of atopy was related to an increased risk of atopic dermatitis in 1,005 infants during the first 6 months of life. A maternal history of dermatitis was the strongest variable associated with an increased risk for atopic dermatitis (adjusted OR 2.67; 95%CI 1.74 to 4.10). A maternal history of asthma, hay fever, and other atopic conditions was also related to an increased risk for atopic dermatitis (adjusted OR 1.58; 95%CI 1.01

to 2.47; adjusted OR 1.3; 95%CI 0.9 to 3.2; adjusted OR 1.9; 95%CI 1.4 to 3.2, respectively). In addition, a paternal history of atopic dermatitis was related to an increased risk for atopic dermatitis (adjusted OR 1.73; 95%CI 0.9 to 3.2). A history of other paternal atopic conditions were not related to an increased risk for atopic dermatitis.[2]

In our study we found an increase in the occurrence of atopic dermatitis in the group with a positive family history for atopy (family atopy score >0) with adjusted relative risk of 22.5 and 95%CI 8.8 to 57.0 (P=0.001) The increase in the total family atopy score, comparing the group with scores of 1-3 to the group with scores of 4-6 also revealed a significant relationship with an increased risk for atopic dermatitis in the higher scoring group (RR= 5.5; 95%CI 2.2 to 13.8; P=0.001).Our results were similar to those of prior studies, which reported an increased risk for atopic dermatitis in infants born to parents with a positive history for atopy.[2,3] Another study reported that of 54 children aged 3 months to 12 years with atopic dermatitis, 64.8% were found to have a positive family history for atopy (P <0.05).[16] The results of this study are also similar to the results from classification with the allergy trace card, with an increased risk of 20-60% in the group with atopy score > 0, compared to the group with a score of 0.[7]

A limitation of our study was the brief observation period, preventing us from studying the development of allergic disease further along in the subjects' lives. In our study, we directly measured family atopy scores based on allergy trace card results. Atopic dermatitis occurring early in life is the result of interactions between genetic factors, hereditary factors, and the environment. In our study, we did not evaluate the prenatal environment, such as the mother's diet during pregnancy, maternal history of infection during pregnancy, exposure to cigarette smoke during pregnancy, history of antibiotics use during pregnancy, or folic acid intake during pregnancy.

The family atopy score as stated in the allergy trace card is capable of predicting the occurrence of atopic dermatitis prenatally, and should, therefore, be used routinely as a screening tool before birth. The allergy trace card is an easy and cost-effective method to identify a population at high risk for allergies. The allergy trace card can be used at various levels of health care, even in settings with limited resources.

Conflict of interest

None declared

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