Genetic and Environmental Predictors for Pediatric Atopic Dermatitis

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Background: *The purpose of this study was to evaluate the influence of genetic and various environmental factors for atopic dermatitis (AD) occurring in the first 18 months of life.*

Methods: *We used the multistage stratified systematic sampling to recruit 2,048 mother-child pairs from the Taiwan National Birth Registry in 2003. Information on family history of atopy and environmental risk factors for AD of children were gathered by questionnaires at 18 months of age. Multiple logistic regressions were performed to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for risk factors of the AD after adjusting for potential confounders.*

Results: *AD was noted in 147/1618 (9.08 %) of the children. We found maternal history of AD, maternal grandparents' history of AD, higher family income, and higher maternal education level increased the risk of pediatric AD. The adjusted ORs and their 95% CIs were 4.10 (1.27-13.25), 4.56 (1.39-15.00), 1.66 (1.00-2.77), and 1.71 (1.56-6.97), respectively. However, duration of breast feeding did not alter the risk estimates of AD.*

Conclusions: *AD may be inherited preferentially through the maternal line. Prevention of special environmental exposures is urgently needed for children with maternal history of AD. (Acta Paediatr Tw 2006; 47:238-42)*

Key words: atopic dermatitis, family history, environmental factors

INTRODUCTION

The frequency of atopic dermatitis (AD) appears to have increased over the past decades.[1,2] The development and phenotypic expression of AD depends on a complex interaction between genetic factors, perinatal environmental exposure to allergens, and non-specific adjuvant factors, such as pollution, infections, and climates.[3] Attempts to identify parameters predictive of the development of AD have been made by many investigators during the last decades. However, there are few large prospective studies of the early-life presentation of AD, especially in Taiwan.

The purpose of this study was to investigate genetic and environmental factors of pediatric AD in Taiwan. We assessed AD in the first 18 months of life, a period during which the condition causes considerable morbidity, in terms of sleep and feeding disruption, family stress, physician visits, health care expenditures, and later asthma, allergic rhinitis, and urticaria.[4] These children with early AD may suffer from severe or long-lasting symptoms and thus are very influential for further studies. In addition, clarification of genetic and early environmental impacts for prenatal allergy sensitization and postnatal development of AD will provide better strategies to predict and prevent AD early.

MATERIALS AND METHODS

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Study population and sampling strategy

Multistage stratified systematic sampling design was used to collect a representative samples from the national birth registration data in 2003. A total of 2,048 mother and child pairs were recruited. Written consents were obtained from the mothers, and the study was approved by the Medical Ethics Committee and Data Protection Board in Taiwan.

Data collection and case definition

We conducted a home interview of mothers 18 months after their deliveries using a questionnaire. Finally, 1618 postpartum women completed the interview, making the interviewed rate 79%. Cases of AD were defined as children whose mothers reported that the child had AD diagnosed by a doctor.[5] Exclusion criteria included multiple gestation (twins, triplets, etc) and inability to answer questions in Chinese.

Variables

Questions about potential confounders and risk factors were asked, including family income and education, paternal and maternal family history of atopy, older siblings, pet raising, cockroaches, carpets at home, residence, etc. From the records of the cooperating hospitals, we collected neonate health data at birth, such as gender, weeks of gestation, birth body weight, and vaccination history.

Statistical analysis

The odds ratio (ORs) with 95% confidence intervals (95% CIs) were calculated using multiple logistic regressions, adjusting for potential confounders of infant gender, gestational age, and birth weight. All hypothesis testing was two-sided at the significance level of 0.05 and performed with SAS software version 8.2.

RESULTS

Firstly, we compared the information between 1,618 responders and 430 non-responders. There were no significant differences of the characteristics between the non-responders and the responders, including maternal age, family history of atopy, birth weight, gender, and preterm delivery of newborns. During the study period, a diagnosis of a maternal report of doctor-diagnosed AD was made in 147/1618 (9.08 %) of children by the age of 18 months. About 970/1618 (59.95 %) infants were male and 125/1618 (7.73%) infants were premature (Table 1).

The results of genetic influence on AD are shown in Table 2. After simultaneous control for infant gender and gestational age, we found maternal history of AD and maternal grandparents' history of AD significantly increased the risk of pediatric AD. The adjusted ORs and their 95% CIs were 4.10 (1.27-13.25) and 4.56 (1.39-15.00), respectively.

Table 1. Demographic Characteristics

Variable	No. of subjects	Rate (%)
Sex		
Male	970	59.95
Female	648	40.05
Gestational age		
< 36	125	7.73
≥ 36	1493	92.27
Birth body weight		
< 2500 gm	116	7.17
2500–3500 gm	1247	77.07
> 3500gm	255	15.76
Body weight at 18 months old		
< 10 kg	1441	89.06
≥ 10 kg	177	10.94
Small for gestational age		
Yes	1200	74.17
No	418	25.83
Residence*		
Rural area	703	43.86
Urban area	844	52.65
Suburban area	56	3.49
Family income		
< 400,000 NT$	354	22.32
400,000–1000,000 NT$	912	57.50
> 1000,000 NT$	320	20.18
Maternal education		
≤ Junior high school	235	14.82
Senior high school	689	43.44
≥ University	662	41.74

Abbreviations: NT$: new Taiwan dollars.
* Participants living in rural area were those living in the countryside, mountains, or on the seashore. Participants living in suburban area were those living in the county, a little bit away from the city. Participants living in urban area were those living in the city.

As to environmental exposures, duration of breast feeding, older siblings, vaccination, cockroaches at home, indoor smoking, and residence were not associated with AD (Table 3). Carpets at home might increase the risk of AD, while raising pets might have protective effect against AD, though not statistically significant. Higher family income and higher maternal education level enhanced the risk of AD. The adjusted ORs and their 95% CIs were 1.66 (1.00-2.77) and 1.71 (1.56-6.97), respectively.

DISCUSSION

Among several genetic and environmental factors, we did find that maternal history of AD, maternal

Table 2. Genetic Predictors of Pediatric AD

Variable	No. of subjects	No. of AD	AD Rate (%)	aOR	95% CI
Family history of asthma					
Yes	121	8	6.61	0.69	0.33-1.45
No	1457	135	9.27	1.00	(referent)
Paternal grandparents' history of asthma					
Yes	40	3	7.50	1.00	(referent)
No	1538	140	9.10	1.24	0.38-4.06
Paternal history of asthma					
Yes	23	1	4.35	1.00	(referent)
No	1555	142	9.13	2.21	0.30-16.52
Maternal grandparents' history of asthma					
Yes	27	3	11.11	1.26	0.38-4.24
No	1551	140	9.03	1.00	(referent)
Maternal history of asthma					
Yes	33	1	3.03	1.00	(referent)
No	1545	142	9.19	3.24	0.44-23.88
Family history of allergic rhinitis					
Yes	169	19	11.24	1.31	0.79-2.19
No	1409	124	8.80	1.00	(referent)
Paternal grandparents' history of allergic rhinitis					
Yes	47	7	14.89	1.80	0.79-4.08
No	1531	136	8.88	1.00	(referent)
Paternal history of allergic rhinitis					
Yes	40	3	7.50	1.00	(referent)
No	1538	140	9.10	1.24	0.38-4.06
Maternal grandparents' history of allergic rhinitis					
Yes	45	5	11.11	1.26	0.49-3.26
No	1533	138	9.00	1.00	(referent)
Maternal history of allergic rhinitis					
Yes	51	6	11.76	1.35	0.57-3.23
No	1527	137	8.97	1.00	(referent)
Family history of atopic dermatitis					
Yes	59	12	20.34	2.71	1.40-5.23*
No	1519	131	8.62	1.00	(referent)
Paternal grandparents' history of atopic dermatitis					
Yes	19	3	15.79	1.90	0.55-6.60
No	1559	140	8.98	1.00	(referent)
Paternal history of atopic dermatitis					
Yes	15	2	13.33	1.55	0.35-6.95
No	1563	141	9.02	1.00	(referent)
Maternal grandparents' history of atopic dermatitis					
Yes	13	4	30.77	4.56	1.39-15.00*
No	1565	139	8.88	1.00	(referent)
Maternal history of atopic dermatitis					
Yes	14	4	25.87	4.10	1.27-13.25*
No	1564	139	8.89	1.00	(referent)

* $P < 0.05$
Abbreviations: aOR: adjusted odd ratio; CI: confidence interval

grandparents' history of AD, higher family income, and higher maternal education level significantly increased the risk of pediatric AD. Our data are consistent with previous reports that children are likely to develop atopic diseases similar to those of their parents and that maternal history predicts greater risk for childhood eczema than does paternal history.[6] Atopy may be inherited preferentially through the maternal line, or mothers may carry relatively more of the predisposing genes.[7] Transplacental transfer of antigens, maternal antibodies, and maternally-derived cytokines may shape early atopy,[8] and intense sharing of postnatal environmental factors through a shared home environment may also play a role.[9]

The inverse relationship between the incidence of AD and frequency of respiratory tract infections led to the "hygiene hypothesis", which suggested that diminished exposure to childhood infections and increased immunization in modern society has led to decreased TH1-type responses and the development of atopic diseases.[10] We found that higher family income

Table 3. Predictors of Environmental Exposures and Social-economic Status for Pediatric AD

Variable	No. of subjects	No. of AD	AD Rate (%)	aOR	95% CI
Duration of breast feeding					
No	388	30	7.73	1.00	(referent)
< 4 month	610	61	10.00	1.29	0.92-1.90
4–6 month	552	50	9.06	1.17	0.68-2.01
> 6 month	68	6	8.82	1.16	0.46-2.90
Older siblings					
Yes	1191	106	8.90	1.00	(referent)
No	412	39	9.47	1.07	0.73-1.57
Pets at home					
Yes	31	2	6.45	1.00	(referent)
No	1587	145	9.14	1.42	0.66-1.73
Carpets at home					
Yes	1510	139	9.21	1.47	0.63-3.42
No	93	6	6.45	1.00	(referent)
Cockroaches at home					
Yes	272	30	11.03	1.30	0.85-1.99
No	1323	115	8.69	1.00	(referent)
Having received Influenza vaccine					
Yes	1126	95	8.44	1.00	(referent)
No	492	52	10.57	1.29	0.90-1.85
Having received Varicella vaccine					
Yes	1374	128	9.32	1.22	0.74-2.01
No	244	19	7.79	1.00	(referent)
Having received HAV vaccine					
Yes	62	7	11.29	1.29	0.58-2.88
No	1556	140	9.00	1.00	(referent)
Indoor exposure to tobacco smoke					
Everyday	88	10	11.36	1.40	0.69-2.82
Sometimes	832	70	8.41	1.00	(referent)
No	683	65	9.52	1.15	0.80-1.63
Residence					
Rural area	703	55	7.82	1.00	(referent)
Urban area	844	84	9.95	1.30	0.91-1.86
Suburban area	56	6	10.71	1.41	0.58-3.44
Family income					
< 400,000 NT$	354	28	7.91	1.00	(referent)
400,000–1000,000 NT$	912	77	8.44	1.07	0.68-1.69
> 1000,000 NT$	320	40	12.50	1.66	1.00-2.77*
Maternal education					
≤ Junior high school	235	15	6.38	1.00	(referent)
Senior high school	689	58	8.42	1.32	0.96-5.34
≥ University	662	72	10.88	1.71	1.56-6.97*

* $P < 0.05$

Abbreviations: aOR: adjusted odd ratio; CI: confidence interval; NT$: new Taiwan dollars.

and maternal education level had effects on the promotion of AD, which was consistent with the "hygiene hypothesis". However, vaccination did not show this impact. This might be due to divergent effects of different vaccines.[11] Also, we chose selective immunization vaccines such as Influenza vaccine, Varicella vaccine, and HAV vaccine instead of regular immunization vaccines such as BCG vaccine, HBV vaccine, and DTP vaccine because we couldn't obtain a control group of children without immunization from children who received regular vaccines.

Although there was no significant difference in the frequency of AD in our study, pet raising suggests a potential protection. Previous findings on the role of pets have been inconsistent.[12] This may be due to the fact that people avoid exposing their child to something that they believe is a risk factor for allergies. The distribution of pet-keeping in the population is largely explained by avoidance behavior, meaning that those who have pets mainly are those who can stand them, indicating a "healthy pet-keeping effect", and not "hygiene hypothesis". Further followed-up of this cohort might give us an answer.

Carpets at home suggest a potential enhancement

of AD risk. This might be because there were high loads of house mites in bedroom carpets. Furthermore, house dust mite allergens might induce and maintain AD.[13] Simple mite allergen avoidance measures should be recommended to families with children affected by extrinsic AD in order to control the clinical manifestations and prevent mite sensitization.[14]

The strengths of our study include the large sample size and the population-based cohort design, and because of the large sample size we were able to control for numerous potential confounders. The multistage stratified systematic sampling including both urban, suburban, and rural population could enhance generality. Our study was limited by the use of maternal report of doctor-diagnosed AD as the outcome variable, which might not be so specific as the standard diagnostic criteria of AD. However, maternal report of doctor-diagnosed AD has been previously validated versus clinical examination in the United States.[15]

In conclusion, we observed that AD may be inherited preferentially through the maternal line, or mothers may carry relatively more of the predisposing genes. Children born by mother with family history of AD are worth paying more attention to for early primary prevention of special environmental exposures.

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