Determinants of allergic signs and symptoms in 24-48-month-old Turkish children

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SUMMARY: Özmert EN, Kale-Çekinmez E, Yurdakök K, Şekerel BE. Determinants of allergic signs and symptoms in 24-48-month-old Turkish children. Turk J Pediatr 2009; 51: 103-109.

The expression of asthma and allergic diseases depends upon an interaction of genetic and environmental factors and thus may differ between populations. This study was performed to document the factors determining allergic signs and symptoms in early childhood in a group of Turkish children. Children followed at the Well-Baby Clinic who were 2 to 4 years were invited and re-evaluated. In addition to face-to-face questionnaire for allergic signs and symptoms and review of files, skin prick test was performed. The associations between risk factors and different aspects of atopy were analyzed. One hundred and nine patients (mean age: 31.6±3.5 months) were included in the study. All had been breast-fed with mean exclusive and total breastfeeding durations of 3.3±2.7 and 13.3±7.2 months, respectively. Eight children had physician-diagnosed allergic diseases (4 atopic eczema, 3 bronchial asthma and 1 food allergy) and the overall prevalence of sensitization was 13%. Introduction of cow's milk before 12 months appeared to be a significant risk factor for atopy. Smoking during lactation and having an older sibling showed a trend towards an increase while regular yoghurt consumption showed a trend to decrease the risk for atopy. No significant risk factor could be defined for ever wheezing.

It was concluded that in young Turkish children, early introduction of cow's milk, passive smoking and having an older sibling may predict atopy whereas regular yoghurt consumption may decrease the risk of atopy. These results also support the concept that variability may exist between populations.

Key words: allergy, atopy, young children, predictive factors, wheezing.

In recent years, a consistent increase in the prevalence of asthma and other allergic diseases has been reported from various regions of the world. Concomitantly, the social and economic impact of allergic diseases is also increasing, indicating a need to formulate strategies leading to a reduction in morbidity and mortality[1,2].

According to our current understanding, the expression of asthma and allergic diseases depends upon an interaction of genetic and environmental factors. These factors might increase or decrease the risk of allergy development, and some might be amenable to manipulation[1,2]. Although a number of risk factors during the early years of life have been identified, such as early introduction of supplementary food, diet, infections, allergens, pollutants, and tobacco smoke, they differ between various populations[2], and there is a clear need to document risk factors in different populations, especially in developing and underdeveloped societies, as most of the data in the medical literature comes from developed countries.

Turkey has distinctive characteristics from the western world in terms of lifestyle, dietary habits and culture. Though a number of studies have been performed in Turkish schoolchildren to investigate potential risk factors for allergic diseases[3-4], there is no study in young children. This study was performed to determine risk factors for allergic diseases in preschool children.

Material and Methods

Study Population

The study was conducted in Hacettepe University İhsan Doğramacı Children's Hospital, Department of Social Pediatrics, Well-Baby Clinic, in Ankara, Turkey, where children are followed at 2, 4, 6, 9, 12, 15 and 18 months of age routinely. Children who were between 24-48 months of age and had regular follow-up at the clinic (at least 5 out of 7 scheduled visits) were invited for a final visit. Children were excluded if any chronic respiratory diseases like bronchopulmonary dysplasia, cystic fibrosis, primary ciliary dyskinesia, tuberculosis, or other seriously interfering disease was present. All parents provided informed consent to participate in the trial, which was approved by the Hacettepe University Ethics Committee.

Study Design

A detailed entry questionnaire was completed, which included demographics, pre- and perinatal history, family history of chronic diseases including atopic diseases, personal history of atopic disease and wheezing episodes, pets, duration of breastfeeding, and beginning of weaning period. The file records of the subjects were reviewed, and data obtained from the questionnaire and file records were merged. All children included in the study had a complete physical examination and skin prick test (SPT) was performed. Data on current demographics, symptom frequencies, any medications, number of wheezing attacks if present, and emergency admittances and hospitalizations experienced during the past 12 months were also recorded.

Questionnaire and Interviews

The questionnaire was prepared by the investigators and based on the information available in the International Study of Asthma and Allergies in Childhood (ISAAC) phase II questionnaire, for which a Turkish translation was validated and used previously[5]. All the information was also checked for consistency by using patients' files and in case of inconsistency, the investigator decided which to use. Face-to-face interviews lasted approximately 25 minutes and were conducted by a single investigator (EK).

Skin Prick Tests

Skin prick tests (SPT) with common allergens, including house dust mites (D. pteronyssinus and D. farinae), mixed weeds (Artemisia vulgaris, Chenopodium, Salsola kali), mixed grasses (Phleum pratensa, Poa pratensis, Dactylis glomerata, Lolium perennae, Avena eliator, Festuca pratensis), mixed trees (Betula verrucosa, Olea europoa, Coryllus avellena), molds (Alternaria, Cladosporium), cat, dog, and foods (cow's milk, egg, peanut, wheat, and soy) were performed on the back side of the chest with commercially available extracts (ALK, Allergologisk Laboratorum A/S; Hørsholm, Denmark), saline solution and histamine control (10 mg/ml) using Stallergen lancets (Stallergen, France). Before the SPT, patients had to discontinue their antihistamines for at least five days. A positive SPT response was defined as a wheal 3 mm larger than the wheal of a negative control[6]. Cases were considered atopic if they had at least one positive skin reaction to common allergens[7].

Statistics

Results were expressed as either mean ± SEM (standard error of the mean) or percentages of the responses to each question. The distributions of the variables were checked for normality by Kolmogorov-Smirnov test, and were log transformed to obtain normal distribution if required. Atopy and ever wheezing were the primary study outcomes. Chi-square and t-test were used for univariate analysis. The interactions between factors were analyzed by multivariate logistic regression. Variables that were associated with the outcomes in the univariate analysis at a p value of less than 0.20 and those that were shown to be an important risk factor previously were included in the multivariate logistic regression model, where a backward reduction modeling strategy was used. The size of the effect of each of the risk factors was measured by using the odds ratios (ORs) and 95% confidence intervals (CIs).

For all hypothesis tests, two-sided p values less than 0.05 were regarded as statistically significant; all analyses were performed using the SPSS software version 11.0 (SPSS, Inc, Chicago, IL, USA).

Results

Patient Characteristics

The study was conducted between April and June 2004. According to our database, a total of 1,125 children were seen in the clinic between 2000-2002. Of these, 628 patients fulfilled the exclusion-inclusion criteria. Of these 628, 264

could be reached by repetitive telephone call or regular mail and 109 families accepted to participate in the study (109 children, male/female: 53/56). All of the families completed the questionnaire, but 10 refused SPT for the child because of their concerns for pain. The characteristics of the cases are summarized in Table I. Their ages during the final visit ranged between 24 and 48 months (mean age: 31.6±3.5 months). All children in the study group had been breastfed and the mean exclusive breastfeeding duration was 3.3±2.7 months, with a total breastfeeding duration of 13.3±7.2 months. When the environmental factors were evaluated, 66% of the children were exposed to environmental tobacco smoke (ETS) and 15% of the mothers smoked during pregnancy and lactation. Only 6 families kept pets at home; 71% (77) reported use of wool-made pillow, mattress and/or cushion. Only 8 children were attending a day care center.

Table I. Demographic Characteristics of the Study Group

Characteristic	n=109
Age (mean±SEM) (months)	31.6±3.5
Gender (male/female)	53/56
Gestational age	
<37 weeks	8 (7%)
≥37 weeks	101 (93%)
Birth weight	
<2500 g	10 (9%)
≥2500 g	99 (91%)
Maternal education	
<8 years	21 (19%)
≥8 years	88 (81%)
Paternal education	
<8 years	2 (2%)
≥8 years	107 (98%)
Family history of allergic disease	23 (21%)
Older siblings	63 (58%)
Physician-diagnosed atopic diseases	8 (7%)

Eight children had physician-diagnosed allergic diseases: 4 atopic eczema, 3 bronchial asthma and 1 food allergy. According to the questionnaire, 5 (4.6%) children reported eczema (recurrent eczema with pruritus) and 25 ever wheezing (23%). SPT was found to be positive in 14 children (14.1%) (4 food, 7 aeroallergen and 3 food and aeroallergen).

Risk Factors

Characteristics of atopic vs. non-atopic cases and ever vs. never wheezers are summarized in Tables II and III, respectively. More mothers in the atopic group reported smoking during lactation and early introduction of cow's milk ($p<0.05$), whereas regular yoghurt consumption defined as at least three cups a week was more common among non-atopic cases. More children in the never wheezing group compared to ever wheezers had wall to wall carpeting in the bedroom.

Multivariate logistic regression analysis was performed to determine the risk factors for atopy and ever wheezing, and results are displayed in Tables IV and V. Introduction of cow's milk before 12 months appeared as a significant risk factor for atopy. However, smoking during lactation seemed to increase the risk for atopy with borderline significance (Table IV). Having an older sibling at home seemed to increase and regular yoghurt consumption seemed to decrease the risk of atopy, with a significance of only $p=0.08$. No significant risk factor could be defined for ever wheezing (Table V). When atopy and ever wheezing were considered as dependent variables in multivariate logistic regression, no interaction between cases with ever wheezing and atopy was detected.

Discussion

This study showed that in a group of young Turkish children, ever wheezing, sensitization and physician-diagnosed atopic disease prevalences were 23, 14 and 7%, respectively. Besides the striking differences in terms of indoor exposures (less pet keeping and frequent exposure to tobacco smoke) when compared to the western world, we observed that early introduction of cow's milk increased the probability of sensitization in the study group. Moreover, there was a trend towards an increase in sensitization with smoking during lactation and having an older sibling, whereas regular yoghurt consumption appeared to lead to a trend of decrease.

The complex and multifactorial nature of asthma and allergies makes it obligatory to observe real-life scenarios and, in this respect, there is a need for a significant contribution of epidemiology especially from the developing world, as most of the data in the medical literature comes from developed countries. This is the first study

Table II. Comparison of the Risk Factors in Atopic and Non-Atopic Children

Characteristics	Atopic children n=14 [n(%)]	Non-atopic children n=85 [n(%)]
Gender (male/female)	5/9	41/44
Gestational age <37 weeks	1 (7)	5 (6)
Birth weight <2500 g	0 (0)	8 (9)
Paternal education <8 years	0 (0)	1 (1)
Maternal education <8 years	3 (21)	15 (18)
Exclusive breastfeeding (<4 months)	12 (86)	57 (67)
Total duration of breastfeeding (<12 months)	6 (43)	39 (46)
Introduction of cow's milk (<12 months)	9 (64)	22 (26)*
Regular yoghurt consumption	8 (67)	78 (92)*
Regular cow's milk consumption	10 (83)	80 (94)
Formula or other food in newborn period	5 (38)	29 (39)
Environmental tobacco smoke exposure	10 (71)	57 (67)
Smoking during lactation	5 (36)	9 (11)*
Smoking during pregnancy	3 (21)	12 (14)
Wall to wall carpeting	2 (14)	26 (31)
Wool-made mattress, cushion and/or pillow	10 (71)	60 (71)
Humidity and mold	1 (7)	20 (24)
Animal at home	2 (14)	4 (5)
Attendance at daycare	1 (7)	7 (8)
Older sibling	11 (79)	49 (58)
Lifelong URTI >15	1 (7)	4 (5)
Lifelong otitis >3	0 (0)	6 (7)
Family history of allergic disease	3 (21)	20 (24)

URTI: Upper respiratory tract infection.
*: $p<0.05$.

Table III. Comparison of Risk Factors in "Ever Wheezing" and "Never Wheezing" Children

Characteristics	Ever Wheezer n=25 [n(%)]	Never Wheezer n=84 [n(%)]
Gender (male/female)	13/12	40/44
Gestational age <37 weeks	2 (8)	6 (7)
Birth weight <2500 g	2 (8)	8 (9)
Paternal education <8 years	1 (4)	0 (0)
Maternal education <8 years	6 (24)	14 (17)
Exclusive breastfeeding (<4 months)	8 (32)	24 (29)
Total duration of breastfeeding (<12 months)	13 (52)	36 (43)
Introduction of cow's milk (<12 months)	12 (48)	26 (31)
Regular yoghurt consumption	2 (8)	10 (12)
Regular cow's milk consumption	24 (84)	75 (91)
Formula or other food in newborn period	7 (28)	31 (37)
Environmental tobacco smoke exposure	20 (80)	52 (62)
Smoking during lactation	5 (20)	11 (13)
Smoking during pregnancy	5 (20)	11 (13)
Wall to wall carpeting in bedroom	3 (12)	28 (33)*
Wool-made mattress, cushion and/or pillow	16 (64)	61 (73)
Humidity and mold	6 (24)	16 (19)
Animal at home	2 (8)	4 (5)
Attendance at daycare	4 (16)	4 (5)
Older sibling at home	15 (60)	48 (57)
Lifelong URTI >15	3 (12)	2 (2)
Lifelong otitis >3	2 (8)	4 (5)
Family history of allergic disease	3 (12)	21 (25)

URTI: Upper respiratory tract infection.
*: $p<0.05$.

Table IV. Multivariate Logistic Regression of Risk Factors in Atopic Children

Risk Factor	OR	95% CI	p
Exclusive breastfeeding (<4 months)	0.71	0.07-6.94	0.31
Total duration of breastfeeding (<12 months)	0.46	0.07-3.18	0.43
Introduction of cow's milk (<12 months)	5.59	1.12-27.78	0.04
Regular yoghurt consumption	0.15	0.02-1.25	0.08
Environmental tobacco smoke exposure	1.62	0.21-12.35	0.64
Smoking during lactation	55.56	1.10->1000	0.05
Smoking during pregnancy	0.12	0.00-5.35	0.27
Older sibling at home	8.33	0.80-86.96	0.08
Wall to wall carpeting	0.45	0.04-4.85	0.51
Humidity and mold	0.17	0.01-2.07	0.16
Animal at home	1.88	0.12-28.57	0.65
Family history of allergic disease	0.31	0.03-3.43	0.34

OR: Odds ratio. CI: Confidence interval.

Table V. Multivariate Logistic Regression of Risk Factors for Ever Wheezing

Risk Factor	OR	95% CI	p
Exclusive breastfeeding (<4 months)	1.77	0.49-6.45	0.38
Total duration of breastfeeding (<12 months)	0.81	0.26-2.50	0.72
Introduction of cow's milk (<12 months)	2.39	0.74-7.63	0.14
Environmental tobacco smoke exposure	2.34	0.63-8.69	0.20
Smoking during lactation	0.81	0.09-6.99	0.85
Smoking during pregnancy	1.27	0.16-10.10	0.82
Attendance at daycare	3.45	0.59-20.41	0.17
Wall to wall carpeting	0.22	0.05-1.03	0.06
Paternal education	0.72	0.31-1.67	0.45
Lifelong URTI >15	6.83	0.62-75.33	0.12
Family history of allergic disease	0.63	0.15-2.75	0.54

URTI: Upper respiratory tract infection. OR: Odds ratio. CI: Confidence interval.

to describe early childhood factors predictive for wheezing and atopy in Turkey as well as in this region. As in most of the developing countries, a westernized lifestyle predominates in most central urban districts. Nevertheless, many neighborhoods within the central urban districts may include a significant number of people of low socioeconomic class with a predominantly oriental lifestyle like that seen in the rural areas.

Besides cultural and lifestyle differences from western countries, we documented that young Turkish children are very frequently exposed to tobacco smoke. These are by far the highest smoking rates reported in any cross-sectional survey to date[8]. Smoking during lactation appeared to cause a trend towards increased risk of atopy. Though it had borderline significance, considering the relatively low number of cases and very high rates of passive smoking, we believe that this result should not be ignored (type I statistical error). Kulig et al.[9] demonstrated that pre-natal and post-natal exposure to cigarette smoke increases the risk of positive SPT to food allergens without an increase in aeroallergens at three years of age, which is suggested to be due to the adjuvant effect of ETS with the food allergens. In a comprehensive meta-analysis, Cook and Strachan[10] concluded that the balance of evidence did not support a positive association between allergic sensitization and pre- and post-natal parental smoking. It is suggested that pre- and post-natal exposure to tobacco smoke may have an adjuvant effect for atopic sensitization in the context of a genetic risk, more specifically a maternal atopic disease.

Another striking difference from western countries is the infrequent maintenance of pets at home, which is mostly due to religious and cultural habits. However, whether it really reflects low exposure to animal products remains obscure, since use of wool-made pillows is very common.

Fortunately, all children in the study group had been breastfed and the durations were similar with the country results[11]. The role of breastfeeding in the prevention of allergic diseases is still disputed. Some studies showed that prolonged (6 months to 1 year) breastfeeding was associated with a lower risk of eczema[12] and mite sensitization[13]. On the other hand, the MAS-90 study[14] showed that each additional month of breastfeeding increased the risk of atopic eczema in high-risk children. However, breastfeeding practices should be promoted, as it not only provides a safe, cheap and appropriate food for the baby but also helps to create an emotional bond between the baby and the mother. In our study, no effect of exclusive breastfeeding could be demonstrated on either atopy or ever wheezing since we did not have a non-breastfed group.

While discussing the protective effect of breast-feeding on allergic diseases, the other point put forward is the avoidance of "high dose" of cow's milk protein consumption. The results of our study are in accordance with this hypothesis, showing an increased risk of atopy in children who were given cow's milk before 12 months of age. It is highly recommended not to use cow's milk before 4-6 months of age. In fact, in our study, the mean age of introduction of cow's milk among early users was 9.5±5.3 months. Although this was related with an increased risk of atopy, there was no cow's milk SPT-positive case. However, it is known that the first allergic stimulants are mostly food, but they may resolve in months to years just leaving the subjects more susceptible to aeroallergens.

An interesting finding of our study is that regular yoghurt consumption appeared to lead to a tendency towards a decrease in atopy. Yoghurt is a conventional weaning food in Turkey and is usually introduced at six months, preferably as the first solid food during the weaning period. Like breast-milk, yoghurt may facilitate the development of favored gastrointestinal flora and this is very critical for the development of the immune system. The World Health Organization also recommends the consumption of fermented milk compounds to decrease the risk of microbiologic contamination in infants. In the medical literature, the studies with yoghurt mostly involve adults. These studies have revealed different results, with some showing an impact on allergic disease and some not[15,16]. Only the study by Kalliomaki et al.[17] administered probiotics to the mother during the last months of pregnancy and during the first six months of life, and they found a protective effect in terms of atopic dermatitis.

Another interesting factor that appeared to cause a tendency towards an increase in atopy was having an older sibling at home. Contrary to this finding, consistent documentations of the protective effects of having siblings at home and early introduction to daycare were the first two findings leading to the "hygiene hypothesis"[18]. This hypothesis is the most likely mechanism by far to explain the development of allergic sensitization. However, there are a number of studies showing that the contrary may also be true[19,20]. The underlying reasons for the relationship between having an older sibling and atopic sensitization are not clear. However, it can be hypothesized that different mechanisms may operate in children with different environmental exposures.

In conclusion, in a limited number of children who were all breastfed, introduction of cow's milk before 12 months of age was found to be the only factor significantly related with increased risk of atopy. Breastfeeding and avoidance of ETS are recommended, just as cited in the literature. However, for infant feeding, yoghurt is suggested to be an appropriate weaning food that could be recommended lifelong.

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