

Follow-up of children with rhinitis and cough associated with milk allergy

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Young children sensitized with foods may develop early respiratory symptoms including nasal symptoms and cough, but not clinical manifestations in the skin or gastrointestinal tract. The long-term outcome of these patients is largely unknown. We studied 36 children sensitized with cow's milk and three different age-matched control groups. The patients were followed from 12 to 18 months of age for at least 5 yr with repeat skin testing and oral food challenge. After 2½ yr, 63.9% ($n = 23$) of those in the mild allergy group lost sensitivity to foods; after 5 yr, the number was 86.1% ($n = 31$). However, during the study period of 5 yr, 69.4% ($n = 25$) simultaneously developed a sensitivity to common indoor airborne allergens. A similar trend was found only in the egg allergy control group. A positive family history and a history of parental smoking significantly increased the relative risk (RR) of sustaining nasal allergy symptoms (RR = 3.33 and 1.79, respectively). We concluded that allergy march from food sensitivity to sensitivity to airborne allergens may occur in a subset of children before 4 yr of age. Genetics and environmental factors might independently contribute to the continuation of these respiratory symptoms.

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Epidemiological data indicate that the incidence of food allergy in younger children is increasing (1, 2), and this has become a common diagnostic and management challenge for pediatricians (3). It is estimated that 6–8% of children younger than 3 yr experience allergic reactions to food (1, 2). Most of the clinical manifestations of food allergy in children are gastrointestinal symptoms (vomiting, abdominal cramps, diarrhea), skin manifestations (erythema, urticaria, atopic dermatitis), or both (1, 4). Although a few patients also present with respiratory symptoms such as bronchial asthma and/or rhinitis (5), reports of isolated nasal symptoms or cough without wheezing associated with food sensitivity are very rare. Thus, the long-term outcome of these children is

largely unknown. In this study, we report the clinical outcome of children with cow's milk allergy and respiratory symptoms for 5 yr after the onset of symptoms.

Methods

After obtaining parental consent, 36 children initially referred to our allergy clinic for evaluation of nasal symptoms were enrolled in the study.

Inclusion criteria

- 1 Age at the time of enrollment of 12–18 months.
- 2 A history of repeated parental observation of the presence of clear nasal discharge, sneezing spells, watery eyes, or nasal congestion within 2 h after feeding of cow's milk formula or whole milk (all of the children were on soy or on hypoallergenic formula within 1 month).

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- 3 Presence of additional respiratory symptoms including frequent cough but not wheezing for more than 3 months.
- 4 No skin or gastrointestinal symptoms.
- 5 Positive skin test against cow's milk protein with prick test at the initial visit.
- 6 Negative skin test against common airborne indoor allergens (molds, house dust mites, cat antigens, dog dander, kapok, and cockroaches) at the initial evaluation.
- 7 Confirmation of emerging respiratory symptoms using an open oral challenge performed at the clinic on the first visit.

Controls

In addition to the study group (milk allergy patients), three control groups were recruited and enrolled during the study period to compare with the study group. Control group 1 consisted of 18 age-matched children who only had egg allergy; control group 2 consisted of 32 age-matched children who had respiratory allergy symptoms without known food allergy; control group 3 consisted of 40 age-matched controls who were on cow's milk formula and without respiratory symptoms.

Study design

The skin test and oral challenge with cow's milk was repeated when the children returned for a visit after 2½ and 5 yr. The relative risk of family history of allergy and any history of parental smoking were recorded at the end of the study. All patients and controls who had active symptoms of rhinitis or cough were advised to use oral antihistamines (prescribed or over-the-counter) on an as-needed basis. Once the diagnosis of milk allergy was established, parents were not allowed to offer milk or dairy products (milk contained in processed foods such as cakes, cookies, candies, or pasta) during the study period. Parents were advised of exercising precaution when dining out with the children. Either soy milk or hypoallergenic formula (Nutramigen® LIPIL®; Mead Johnson, Evansville, IN, USA) was given as a supplement to those children who had to avoid cow's milk formula. Those children with known egg allergy were placed on an egg-free diet.

Skin testing

A skin-prick test (Multi-Test; Lincoln Diagnostics, Inc., Decatur, IL, USA) was used on the

backs of the patients. After 15 min, if the reaction was an area of induration > 3 mm or an erythema > 5 mm (greater than the reactions of the negative controls with normal saline), the test was considered to be positive.

Oral challenge

Parents were instructed to feed milk as follows: start with 2.5 ml (half a teaspoonful); if no symptoms occurred, the volume was increased to 5.0, then 7.5, and then 10 ml at 20-min intervals. The final cumulated volume was to be 25 ml (five teaspoons). The oral challenge was discontinued if the children began to exhibit clinical symptoms, including respiratory, skin, or gastrointestinal effects. The oral challenges were closely supervised by clinicians. The patients were observed for two more hours before being released from the clinic.

Those children with egg allergy were fed home-made scrambled eggs. They were started with half a teaspoon of egg at first. If no reaction occurred, the same amount was given every 20 min. The final amount was three teaspoonfuls of eggs in 2 h. The patients were observed for two more hours before being discharged from the clinic.

Statistical analysis

The chi-squared test was performed to compare the risk of respiratory allergy between the children in study group and those in the control group. Relative risk was calculated for family history of allergy and exposure to secondhand tobacco smoke. Both the chi-square and relative risk were analyzed using GraphPad Prism software (version 3.0; San Diego, CA, USA).

Results

The results of skin test and oral challenge showed chronological changes in the prevalence of cow's milk allergy, egg allergy, and airborne allergen sensitivity between the study group and the three control groups (Table 1).

Trends of decreasing prevalence of sensitivity to foods and increasing sensitivity to respiratory allergens were found to be very similar between the study group and the egg allergy group, although the latter group had a smaller number of patients. The difference between the two groups was not statistically significant ($p = 0.09\text{--}0.919$).

The most dramatic differences were seen between the study group and control group 4 – children who did not show milk sensitivity at the

Table 1. Comparison of chronological prevalence of allergy between study group and control groups

Group	Time of measurement		
	Enrollment %	2 yr* %	5 yr* %
Study group (milk allergy) (n = 36)			
Cow's milk allergy	100 (n = 36)	36.1 (n = 13)	13.9 (n = 5)
Respiratory allergy	0 (n = 0)	33.3 (n = 12)	72.2 (n = 26)
Control group 1 (egg allergy) (n = 18)			
Egg allergy	100 (n = 18)	30 (n = 6)	11.1 (n = 2)
Respiratory allergy	0 (n = 0)	22.2 (n = 4)	44.4 (n = 8)
Control group 2 (respiratory allergy) (n = 32)			
Egg and milk allergy	0 (n = 0)	0 (n = 0)	0 (n = 0)
Respiratory allergy	100 (n = 32)	84 (n = 27)	78 (n = 25)
Control group 3 (non-allergy) (n = 40)			
Cow's milk allergy	0 (n = 40)	0 (n = 0)	0 (n = 0)
Respiratory allergy	0 (n = 0)	0 (n = 0)	7.5 (n = 3)

*Yate's continuity chi-square ($p < 0.0001$) between the study group and the non-allergy group on prevalence of cow's milk and respiratory sensitivity at 2 and 5 yr after the study began. The difference between the group with milk allergy and egg allergy was not significant ($p = 0.09$ – 0.919).

time of enrollment. In the latter group, no milk allergy developed in the 5 yr of follow-up, while only 3 out of 40 (7.5%) developed respiratory allergy. The difference in the prevalence of milk sensitivity between the study group and control group 3 was statistically significant at 2½ and 5 yr ($p < 0.0001$).

All patients in control group 2 had respiratory allergy at the time of enrollment. The prevalence of respiratory allergy decreased slightly to 84% and 78% at 2½ and 5 yr, respectively. However, none of these patients developed food allergy during the 5 yr of the study.

In the study group (milk allergy), the skin test remained positive to cow's milk in five children (13.9%), but only 1 out of 35 children (2.9%) showed a positive reaction to oral challenge at 5 yr. That patient presented with increased clear nasal discharge and nasal congestion within 2 h after challenge with cow's milk. He showed no skin or gastrointestinal symptoms after the oral challenge. Only 3 out of 40 (7.5%) patients in the non-allergy group developed respiratory symptoms at 5 yr.

In 26 out of 36 patients in the study group, one or both parents had a history of allergic rhinitis that required medication more than 2 wk out of a month. Among the 26, 20 (76.9%) had clearly established allergic rhinitis 5 yr later. The relative risk of family history to allergic rhinitis in this milk allergy group was 2.564 (0.9719–6.765; 95% confidence interval). Also among these 26, at least one parent smoked cigarettes and 17 (65.3%) developed allergic rhinitis 5 yr after the study. The relative risk was 1.518 (0.6714–3.431; 95% confidence interval). Patients in the egg

allergy group were not investigated as to family history because the number was too small for statistical analysis.

Discussion

Cow's milk is a major source of nutrition for young children worldwide. Therefore, the development of sensitivity to cow's milk protein remains a major challenge for parents and pediatricians. In the latest prospective study of 6209 unselected, healthy, full-term infants in Finland, it was estimated that the cumulative cow's milk sensitivity rate was 2.4% (5). Curiously, it even occurred in 1.7% of infants who were fed pasteurized human milk (5) in an 18- to 34-month follow-up.

Like other food allergies, the prevalence of cow's milk allergy in young children has been increasing worldwide. Most of the studies about cow's milk allergy report clinical manifestations in two ways. In many studies, a conglomeration such as the gastrointestinal tract symptoms of vomiting, cramps, and diarrhea or skin reactions such as erythema, urticaria, and atopic dermatitis and asthma (5–7) are reported. In others, the development of major symptoms such as eczema, gastrointestinal symptoms, or asthma, are emphasized separately (8–10). Compared with skin or gastrointestinal manifestations, respiratory symptoms are reported less often. Isolated rhinitis symptoms are rarely cited in children with food allergy, including children with cow's milk allergy. This is contrary to what we saw in our study population.

Prior to the study, many parents believed that cow's milk might have contributed to the runny eyes and nasal symptoms exhibited by their children. A review of four recent studies of children with cow's milk allergy indicated that the respiratory symptoms most cited were asthma and/or rhinitis (8), asthma or allergic croup (9), bronchitis (9), asthma and rhinitis (9), or rhinitis and cutaneous or gastrointestinal manifestations (11). Our study may therefore be the first to focus on the subset of children with cow's milk allergy manifested only as rhinitis symptoms appearing before the age of 5.

It was interesting that in this group of children with cow's milk-related rhinitis, the majority outgrew their milk sensitivity, as judged from the results of skin prick and oral challenge tests later. When followed up, the respiratory symptoms had often temporarily diminished in some but persisted in many others. When the results of skin test were compared against foods and airborne allergens 2½ and 5 yr after the study

began (Table 1), there was a gradual but noticeable shift in sensitivity. While milk sensitivity decreased, there was a steady rise of airborne allergy in a span of 5 yr. This observation of transition of sensitivity helps to explain why the respiratory symptoms either only temporarily diminished or persisted in these children.

Although the number of enrollees was smaller in patients who had egg allergy, the same trend that occurred in milk allergy group was also apparent, suggesting that allergy march may be seen in other food allergy patients as well. No such trends were seen in patients who had early onset of respiratory allergy without food allergy or in non-allergic children (control group 3).

The results of our study raise the question of how such a marching of sensitivity from cow's milk to airborne allergens occurs. One previous study, which was conducted to explain the cause of asthma after food challenge, suggested that the process may be the result of sensitization through inhalation (12), meaning that children may inhale food particles through the airway. Another suggestion is that some airborne allergens may share homologous proteins with food. However, this possibility needs to be studied further, as the only available data so far were reported in a study of a few fruit proteins that might cross-react with that of pollens (13) and another study of immunoglobulin-E (IgE) to soy cross-reacting with pollen allergens (14). Benlounne et al. (15), in their study of the time course of cow's milk allergy in children, analyzed the clinical phenotypes between groups of children with either skin manifestations or gastrointestinal symptoms. It was concluded that the kinetics of tumor necrosis factor- α (TNF- α) secretion in response to cow's milk protein may be able to predict the clinical course of these patients. Two peaks of TNF- α secretion were seen in children with digestive symptoms, compared with only one in those with skin manifestations (15). However, it is unclear if TNF- α was equally involved in children with isolated respiratory symptoms. Hidvegi et al. (16) suggested that perhaps IgE, IgA, and IgG to different cow's milk proteins may affect prognosis and clinical manifestation.

It is also possible that the initial sensitization from food to later development of sensitivity to airborne allergens might occur insidiously in the immune system, meaning that the sensitization of lymphocytes occurs chronologically, from those in Peyer's patches in the gastrointestinal system to those in the lymphoid tissues near the airway. This would suggest that hereditary factors, early immunological responses, environmental factors,

and allergen exposure all join in concert to promote the marching of allergy symptoms. In that regard, the results of our study suggest that there are at least two clearly identifiable risk factors that help to predict the development of respiratory allergy from food allergy. First, family history – especially parental history – is very important, with a relative risk of 2.56 in the milk allergy group. This supports the earlier observation that heredity always plays a role in the onset of allergy in siblings (17). Second, it further bolsters the view that exposure to secondhand parental smoking contributes to the continuation of allergy symptoms in children (17). A relative risk of 1.51 was found in the present study.

In that context, it is generally assumed that the first challenging allergens for younger children are the proteins in foods such as cow's milk protein or egg protein, followed by the indoor allergens to which they are likely to be exposed at a young age. As the tolerance to sensitized foods develops (18), respiratory allergy would manifest. Results from a meta-analysis on the early onset of atopic diseases in children (19) and a study of TH2 dominance in infants (20) support the view that heredity, immune response, and environmental factors form the driving force that drives allergic march. More studies are needed to answer these questions, especially regarding developmental immunology in young children.

A question that cannot be answered satisfactorily from the results of the present study is whether the open oral challenge test that was used would predict cow's milk allergy as well as a double-blind, placebo-controlled oral challenge, currently considered the gold standard of diagnosing food allergy (21). However, it is obvious that such a trial would be impractical to enforce in an outpatient setting, which is where most allergy patients are seen. First of all, the cost is prohibitive. Further, in young children, who are not sophisticated enough to distinguish an adverse effect from a placebo effect, an open challenge test may be unnecessary. Close observation during an open oral challenge remains a practical and convenient way of making the diagnosis of food allergy in the outpatient setting. However, in cases where there is a potential for anaphylaxis, the oral challenge test should only be conducted in an environment in which emergency equipment is readily available.

Finally, this study further emphasizes the importance of identifying symptoms of subtle food allergy by parents, pediatricians, and family physicians. The symptoms that can cause mouth

breathing, increasing the chance of upper respiratory infection and affecting significantly the quality of sleep, should be a matter of concern. In the group of children studied here, it became apparent that even minor modifications to the diet may help to minimize the early occurrence of rhinitis, which can affect the quality of life in affected children and their parents. Many cases of cow's milk allergy, egg allergy, or other food allergy may go undetected or be casually regarded as early signs of airborne allergy. Therefore, food-related rhinitis (ICD code 477.1) reported in this study may be more common than previously thought.

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References

1. SAMPSON HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999; 103: 717–28.
2. SICHERER SH, NOONE SA, MUNOZ-FURLONG A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol* 2001; 87: 461–4.
3. SAMPSON HA, ANDERSON JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J Pediatr Gastroenterol Nutr* 2000; 30: S87–94.
4. GUSTAFSSON D, SJÖBERG O, FOUCARD T. Sensitization to food and airborne allergens in children with atopic dermatitis followed up to 7 years of age. *Pediatr Allergy Immunol* 2003; 14: 448–52.
5. SAARINEN KM, JUNTUNEN-BACKMAN K, JÄRVENPÄÄ A-L, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. *J Allergy Clin Immunol* 1999; 104: 457–61.
6. HILL DJ, FIRER MA, SHELTON MJ, et al. Manifestation of mild allergy in infancy: clinical and immunologic findings. *J Pediatr* 1986; 109: 270–6.
7. JAMES JM. Food allergy: what link to respiratory symptoms? *J Respir Dis* 1997; 8: 379–92.
8. BUISSERT PD. Common manifestations of cow's milk allergy in children. *Lancet* 1978; II: 304–5.
9. HYDE DW, GUYER BM. Clinical manifestations of allergy related to breast- and cow's milk-feeding. *Pediatrics* 1985; 76: 973–5.
10. SAMPSON HA. IgE-mediated food intolerance. *J Allergy Clin Immunol* 1988; 81: 495–504.
11. JAMES JM. Respiratory manifestations of food allergy. *Pediatrics* 2003; 111: 1625–30.
12. JAMES JM, BERNHISEL-BROADBENT J, SAMPSON HA. Respiratory reactions provoked by double-blind food challenges in children. *Am J Respir Crit Care Med* 1994; 149: 59–64.
13. SICHERER SH. Is food allergy causing your patient's asthma symptoms? *J Respir Dis* 2000; 21: 127–36.
14. KLEMOLA T, KALIMO K, POUSSA T, et al. Feeding a soy formula to children with cow's milk allergy: the development of immunoglobulin E-mediated allergy to soy and peanuts. *Pediatr Allergy Immunol* 2005; 16: 641–6.
15. BENLOUNEE N, CANDALH C, MATARAZZO P, et al. The time-course of milk antigen-induced TNF- α secretion differs according to the clinical symptoms in children with cow's milk allergy. *J Allergy Clin Immunol* 1999; 104: 863–9.
16. HIDVEGI E, CSERHATI E, KERKEI E, et al. Serum immunoglobulin E, IgA, and IgG antibodies to different cow's milk proteins in children with cow's milk allergy: Association with prognosis and clinical manifestations. *Pediatr Allergy Immunol* 2002; 13: 255–61.
17. WOOD RA. The natural history of food allergy. *Pediatrics* 2003; 111: 1631–7.
18. KANNY G, MONERET-VAUTRIN DA, FLABBEE J, et al. Population study of food allergy in France. *J Allergy Clin Immunol* 2000; 108: 133–40.
19. CANTANI A. The growing genetic links and the early onset of atopic diseases in children stress the unique role of the atopic march: a meta-analysis. *J Investig Allergol Clin Immunol* 1999; 9: 314–20.
20. WAHN U. Review Series VI: The immunology of fetuses and infants. What drives the allergic march? *Allergy* 2000; 55: 591–9.
21. BOCK SA. *A Health Professional's Guide to Food Challenges*. Fairfax, VA: Food Allergy and Anaphylaxis Network, 2004.