

Short communication

Nasal metachromatic cells in infancy in relation to the appearance of atopic disease during the first 6 years of life

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**M. P. Borres¹, K. Irander²,
B. Björkstén¹**

Departments of ¹Pediatrics and
²Otorhinolaryngology, University Hospital,
Faculty of Health Sciences, Linköping
University, Linköping, Sweden

The relationship between the appearance of nasal metachromatic cells (basophils and mast cells) during the first 18 months of life and the development of respiratory and other allergic diseases up to 6 years of age was studied prospectively in 67 children. Follow-up was done at 3, 6, 9, and 18 months and 6 years. Of the 31 children who had detectable metachromatic cells in the nasal mucosa during infancy, 18 had atopic manifestations at 6 years (58%), two were probably atopic (6%), and 11 (36%) were nonatopic. The corresponding numbers for the 33 children without detectable metachromatic cells during infancy were 10 atopic (30%), two probably atopic (6%), and 21 nonatopic (64%) at 6 years ($P < 0.05$). Children having detectable nasal metachromatic cells at every examination were more often allergic than children with no detectable cells at any time during the 6-year follow-up period ($P < 0.05$). In contrast, nasal metachromatic cells were equally commonly demonstrated at 6 years in children with and without current atopic manifestations. We conclude that metachromatic cells appear at an earlier age in the nasal mucosa of atopic than nonatopic infants. The observation further supports the existence of a primary immunologic abnormality in atopic patients as related to allergic inflammatory responses. The diagnostic efficacy of this marker was too low, however, to be clinically useful as a predictor of allergy.

Key words: allergy prediction; infancy; metachromatic cells; nasal mucosa.

Dr Magnus P. Borres
Department of Pediatrics
University Hospital
Faculty of Health Sciences
Linköping University
S-581 85 Linköping
Sweden

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The nasal cellular inflammatory reaction is part of the atopic response in allergic rhinitis. Primary effector cells in this response include basophil leukocytes mainly on the mucosal surface and two types of mast cells, mainly in the epithelium and in the deep lamina propria, respectively (1). The numbers of metachromatically staining cells are increased in allergic disorders and, to some extent, correlate with the severity of allergic rhinitis during seasonal exposure and with the outcome of nasal allergen challenge (2-4).

The appearance of metachromatic cells in the nasal mucosa of infants has been less extensively studied (5-7). Therefore, it is not known whether the presence of metachromatic cells in the nasal mucosa of infants should be regarded as normal, as a sign of atopic disease, or as a predictive marker of atopic propensity. Beginning in 1985, we initiated

a prospective study, enrolling 67 mothers-to-be from families with ($n=46$) and without ($n=21$) history of atopy. The development of allergic disease in their children was monitored at 3, 6, 9, and 18 months, and nasal metachromatic cells were assessed at each visit through nasal scrapings (8).

Most (20/30; 67%) of the children who developed atopic disease during the first 18 months of life had detectable nasal metachromatic cells on at least one occasion. No cells were found in any of the infants who had neither a family history of atopy nor atopic disease (8).

Atopic dermatitis was the most common manifestation of atopy at 18 months. Since allergic disorders, such as rhinoconjunctivitis and asthma, often develop later in life, a second evaluation of the children was performed when they were 6 years

old. This study reports the relationship between allergic manifestations at 6 years of age and the appearance of nasal metachromatic cells during infancy.

Material and methods

The study group comprised 67 children born between October 1985 and April 1988. They underwent physical examination and venous blood sampling at 3, 6, 9, and 18 months, as described previously (8). On these occasions, nasal smears for cytology were taken (8). A follow-up was done between January 1993 and March 1994, i.e., when the children were between 5 and 7 years old (range: 5.5–7.3 years). This included a questionnaire, physical examination, skin prick and lung function tests, nasal smear, and venous blood sampling. The questionnaires were completed by parents of all the 67 children, while 63 children underwent physical examination and 61 skin prick testing. Nasal smears were obtained from 60 children.

Skin prick tests (SPT) were performed in duplicate at 6 years of age with the same criteria for positivity and same allergens as in the first evaluation (8), with one exception. ALK (Hørsholm, Denmark) provided the inhalation allergens at the second evaluation. A physical examination and interview were conducted for all children by the same pediatrician as during infancy (M.P.B.). In addition, the parents completed a questionnaire about signs and symptoms of food intolerance, eczema, rhinoconjunctivitis, and asthma in their children and whether they had received medication for allergic disease.

Atopic dermatitis, allergic rhinoconjunctivitis (ARC), and urticaria were defined as in the first evaluation (8). Asthma was defined as a history of recurrent bronchial obstruction, verified at least once by a physician, in combination with a $\geq 15\%$ reduction in forced expiratory volume at 1 s (FEV_1) after a simple running exercise test (9). This test was performed for 6 min, and the reduction was measured with a dry wedge spirometer. The best of three measurements was used for analysis. Children who reported airway obstructive symptoms in conjunction with respiratory infection or history of recurrent wheezing but who failed to demonstrate a significant fall of FEV_1 were classified as probably asthmatic.

The classification of 63 children as allergic, probably allergic, and nonallergic at the age of 6 years was based on the case history, physical examination, and results of a running test. Results of the SPT were not included in the diagnosis. In children fulfilling some, but not all the diagnostic criteria

for a disease, probable atopic dermatitis, asthma, ARC, and urticaria, respectively, were indicated.

A gentle scraping-cyocentrifugation method for collection of mucosal specimens, suitable for infants, was used for nasal cytology (2, 8, 10). The method was similar at 6 years and performed by the same rhinologist (K.I.). At 6 years, however, the cells were obtained through gentle rubbing of the inferior concha with a commercially available 5.5-mm diameter nylon brush (11) (Doft AB, Östhammar, Sweden) instead of a wooden rod. However, the preparation of slides, staining procedure, and scoring of cells were unchanged. Slides from 6/60 children could not be assessed because of too few cells. Another five slides with scarce material were found to contain metachromatic cells, but were not included when scoring the material. Thus, 54 samples were analyzed and evaluated when comparing results from subjects with or without detectable metachromatic cells. In 64 children, we could evaluate metachromatic cells during infancy (8). The Mann-Whitney U-test and chi-square analysis with Yates' correction were used as statistical methods, and the study was ethically approved.

Results

Twenty-nine children (43%) of the original group of 67 children were diagnosed as allergic at the age of 6 years (Fig. 1). Sixteen of them had a single diagnosis and 13 had more than one atopic diagnosis. Atopic dermatitis ($n=19$) was the most common diagnosis, followed by rhinoconjunctivitis ($n=16$), asthma ($n=11$), and urticaria ($n=5$). Five children were regarded as probably atopic and 33 as nonatopic. Most children who were classified as atopic or nonatopic during infancy had the same classification at 6 years of age ($n=42$). However, six children had recovered, and seven had become allergic.

Of 31 infants who had metachromatic cells on at least one occasion during the first 12 months of life, 18 were atopic at 6 years of age, two were regarded as probably atopic, and 11 had no atopic symptoms (Table 1). The corresponding figures for the 33 children without nasal metachromatic cells during infancy were 10 atopic, two probably atopic, and 21 nonatopic. Thus, the allergic children at 6 years of age had significantly more often metachromatic cells in their nasal mucosa during infancy than the nonallergic children ($P<0.05$). Nasal metachromatic cells were detected at 6 years in 40/54 children in whom the cytology could be assessed. Nineteen of them were atopic, four probably atopic, and 17 nonatopic. Of the 14 children without detectable nasal metachromatic cells at 6 years,

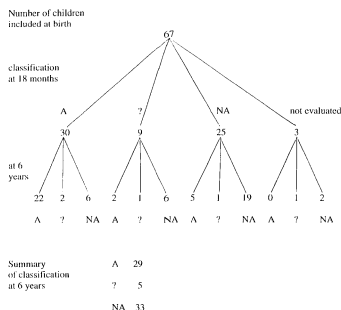


Fig. 1. Classification into atopic (A), probably atopic (?), and nonatopic (NA) at 18 months and 6 years of age. Three children could not be classified at 18 months of age but could be at 6 years.

five were classified as atopic, one as probably atopic, and eight as nonatopic (NS). Nineteen children had metachromatic cells both during infancy and at 6 years, while 13 children never had detectable metachromatic cells. Atopic manifestations were more common in the former group ($P<0.05$).

Twelve of the 16 atopic children with metachromatic cells (67%) had asthma and/or ARC as compared with 6/10 atopic children without nasal metachromatic cells during infancy (Table 1) (NS).

There was no relationship between cell scores at either infancy or at 6 years of age and atopic manifestation. Thus, 13/20 children with metachromatic cell scores ≥ 2 during infancy were classified as atopic (65%), two as probably atopic (10%), and five as nonatopic (25%) at 6 years. The corresponding figures for the 34 children with lower cell scores at 6 years were 15 atopic (44%), three probably atopic (9%), and 16 nonatopic (47%).

Metachromatic cells were detected at 6 years in 15/23 children with both a positive family history

of allergy and current atopic disease (65%). Eight of the nine children with a negative family history never had detectable cells during the 6-year follow-up period. The only child with a negative family history in whom metachromatic cells were demonstrated at 6 months of age had asthma during infancy but was healthy at 6 years.

Eighteen children (62%) had positive SPT at 6 years, and 16 of them were classified as allergic, one as probably allergic, and one as nonatopic. Of the 18 SPT-positive children, 15 had metachromatic cells at 6 years and 12 during infancy. Twenty-three of the 42 SPT-negative children had metachromatic cells at 6 years.

Discussion

Children with detectable metachromatic cells in nasal smears during infancy developed atopic disease more often than children without detectable cells ($P<0.05$). This was particularly obvious if a positive SPT was required for a diagnosis of allergy in addition to the presence of convincing clinical

Table 1. Allergic manifestations at 6 years of age in relation to presence of nasal metachromatic cells during infancy. Table shows number and percentage (in parentheses) of children in each group.

Nasal cells detected	n	Allergy at 6 years			Atopic manifestation		
		Yes	Probable	No	Skin	Respiratory	Both
Present	31	18 (58%) ^a	2 (6%)	11 (36%) ^a	6	8	4
Not present	33	10 (30%) ^a	2 (6%)	21 (64%) ^a	4	5	1

^a Significant difference between groups, $P<0.05$.

symptoms. These cell findings are of limited value for the prediction of allergy in individual infants, however, as both the sensitivity and specificity were too low to allow early identification of atopic infants.

The findings are interesting in the light of several recent studies indicating that T-cell responses and the expression of cytokines differ between non-atopic infants and those with a genetic propensity to atopic disease (12–15). There are now strong indications of the existence of similar subsets of T-helper cells in man and rodents (16, 17). The major cytokine of the TH1 phenotype is interferon- γ , while cells of the TH2 phenotype associated with excessive IgE antibody formation release cytokines such as interleukin (IL)-3 and IL-4 (18). We have observed elevated serum levels of IL-4 in infants who developed allergic manifestations during the first 18 months of life (12).

The early appearance of metachromatic cells in the nasal mucosa of atopic infants could be explained by an early TH2-type immune response. If the difference in primary immune responses to inhaled allergens between atopic and nonatopic children is not absolute but a difference in the kinetics, then the lack of relationship between clinical symptoms and the presence of nasal metachromatic cells at 6 years would not be surprising.

The appearance of nasal metachromatic cells during infancy coincides with a period in early life during which primary exposure to allergens occurs and sensitization may take place (16, 19). The presence of these cells appeared to be more associated with the development of atopic disease, however, than with the presence of atopic disease at the time of the investigation. This is contrary to the findings by Zeiger & Heller (7), who demonstrated a correlation between nasal metachromatic cells and atopic disease. On the other hand, they did not find a relationship between atopic propensity and the presence of metachromatic cells, as the nonatopic children had no or few cells, even though all the participants had a family history of atopic disease. This difference might be explained by the use of different techniques.

A study of resident inflammatory cells in the human adult nasal mucosa observed that mast cells are widely distributed in the nasal mucosa even under normal conditions, suggesting a homeostatic role for them (20). However, our data suggest that metachromatic cells are more indicative of an atopic propensity, as they tend to appear at an earlier age in infants who will develop atopic manifestations.

In conclusion, the appearance of metachromatic cells in the mucosa early in life is more common in children who develop allergic disease, particularly

manifestations from the respiratory tract. Both the sensitivity and specificity are too low for the findings to be used as a means of allergy prediction. However, the findings do indicate that the appearance of mast cells may be part of the early sensitization process that may lead to later allergic manifestations.

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