

EDITORIAL

Pediatric Allergy Research – are we on the right track?

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To cite this article: Björkstén B. Pediatric Allergy Research – are we on the right track?. *Pediatr Allergy Immunol* 2014; **25**: 4–6.

DOI:10.1111/pai.12184

Asthma, allergy, and other conditions characterized by hypersensitivity represent rapidly growing health problems in industrialized countries, and today in many countries, they affect over 30% of the population under 30 yr of age (1). While symptomatic treatment has improved considerably over the past 40 yr, efforts to prevent allergic manifestations have failed. Major discoveries in basic science, regarding the relationship between asthma and allergy and IgE, chemokines, leukotrienes, and NO levels in exhaled air have provided us with a much better understanding of the pathophysiological mechanisms underlying these conditions and resulted in significant improvement in diagnostic procedures and symptomatic treatment. The introduction of inhaled corticosteroids, long-acting beta-agonists, effective antihistamines with mostly minor side effects, leukotriene inhibitors, and improved specific allergy vaccinations have enabled most allergic children to live a normal life. At the same time, numerous suggestions to prevent the onset of allergic disease have been disappointing. Over the past 30 yr, several suggestions have been suggested. Unfortunately, the suggestions are not supported by appropriate studies. The word ‘prevention’ is here used for measures taken to avoid the development of IgE-mediated allergic manifestations. Sometimes the terms ‘primary’, ‘secondary’, and ‘tertiary’ prevention are used. The term ‘primary’ prevention denotes that sensitization, that is, the appearance of IgE antibodies against defined antigens would not appear. Secondary prevention would mean that clinical symptoms of an allergic reaction is avoided, for example, by excluding exposure to an allergen that would elicit clinical symptoms in an individual, while tertiary prevention indicates that remodeling is prevented in patients suffering from allergic disease. The terms are unfortunate, as transient appearance of IgE antibodies does not prove disease, but may appear in healthy individuals with no present, previous, or subsequent allergy (2). Similarly, it is obvious that a cat allergic individual should not be exposed to cats, as they trigger symptoms. This is analogous with treatment of other diseases. For example, if a child with diabetes is encouraged to keep a certain diet and to be

physically active, this is usually not regarded as secondary prevention, but part of the treatment. Avoiding keeping cats if it would cause an attack of asthma is therefore ‘treatment’ rather than ‘prevention’.

Ethical aspects

Measures for prevention should meet certain criteria. They should not be harmful, and they must respect the autonomy of the individual, that is, the right to decide. Fairness must be present, including non-discrimination and fair distribution of available resources. Any preventive measures should be effective. If not all these conditions are met, a prevention program is not ethically acceptable. Preventive measures may interfere with the life of the individual, and self-determination should be fully respected. It is therefore reasonable to request that preventive measures should be equally well documented as required for a new drug or treatment.

Protection of young children against the development of allergic disease is by no means an old concept, and it was not until the 1980s that such suggestions started to become common. Not until the tenth edition of Nelson's Textbook of Pediatrics published in 1975, prevention is discussed under a separate heading (3). It is recommended that the baby should be protected against potential allergens, to avoid exposure to wheat, egg and chocolate and to avoid feather and animal fur ‘whenever feasible in a simple way’. The advice was not supported by any studies.

The interest for allergy prevention has mainly been limited to possible preventive measures in infancy. Originally, it was thought that by preventing allergies in an infant, notably eczema, one would block a subsequent ‘allergic march’ that would later lead to asthma and hay fever. The expectations of these hopes have not been met.

Breast-feeding

The first prospective publication suggesting that breast-fed babies were less likely to develop eczema appeared already in

1936 (4). At the time, allergy was not regarded as a major public health concern, however. Since the 1970s, scores of publications have reported either that breast-fed babies are less likely to develop allergic disease, that breast-feeding does not have any appreciable effect, or that it might even increase the risk. It has also been argued that all babies should be subject to exclusive breast-feeding, alternatively that any effects would be limited to babies with a family history of allergy. To some extent, this discussion may still continue, despite the fact that there is little support from many studies for any major protective effect against IgE-mediated allergy (5). Although breast-feeding is encouraged for its multiple benefits on child health, most recent studies do not confirm the 'conventional wisdom' that breast-feeding is protective against allergy and asthma. Early reduction in childhood wheezing may reflect protection from viral infections, but allergies and asthma at later ages may possibly even be increased.

There is no global support for any significant impact of breast-feeding in industrialized countries. Swedish infants are breast-fed, and this is still the case in 70% of the babies at 3 months (6). These figures are not mirrored by any lower prevalence of allergies as compared with other industrialized countries with a much lower rate of breast-feeding (7). It is also noteworthy that the rapid increase in the rate of breast-feeding in Sweden in the 1970s was not accompanied by any slowing of the increasing incidence of allergies.

It is generally accepted that breast-fed babies are to some extent protected against infection. This is particularly true for gastrointestinal infections, but also the incidence of respiratory tract infections is reduced. In developing countries with poor hygienic standard, this may be a matter of life and death. As it is well established that lack of adequate amounts of breast milk is associated with a substantially increased infant mortality.

The situation is different in industrialized counties with high hygienic standard, though. There is little evidence that formula-fed infants have a higher rate of gastrointestinal infections, as compared with exclusively breast-fed infants and any effects are modest. In conclusion, while breast-feeding remains the normal way to feed an infant, with economic and practical advantages, allergy prevention is not a valid reason.

Diet

Extensively and partially hydrolyzed infant formulae have been recommended in several studies. While there seems to be a slightly lower incidence of eczema, particularly to cow's milk in such babies as compared with regular formula feeding, there is no evidence that it would protect against allergy in general, notably not against the development of respiratory allergy.

It has been suggested that long-chain polyunsaturated fatty acids (PUFAs) could protect against allergy. Although PUFAs do affect some metabolites in the leukotriene cascade, clinical studies have been negative. The only exception reported so far is that administration to pregnant mother might have an effect

(8). More studies are required, however, before any recommendations could be given.

Inhalant allergens

Several studies, notably review articles, suggest that exposure to inhalant allergens early in life would be a risk of developing allergy. The suggestions were based on a seemingly logical concept. Exposure to an allergen is a prerequisite for antibody formation, and total avoidance of exposure would then prevent the appearance of IgE antibodies against that allergen. At the same time, it is well established that many severely allergic children may be sensitized and have allergic manifestations early in life. It was never shown, however, that avoidance of exposure would protect against allergy. On the contrary, in 1998, we showed that children who had a dog or cat at home during the first year of life were less likely to be allergic at the age of 12 yr (9). It is now more or less generally accepted that avoidance of exposure to allergens early in life does not reduce subsequent allergy.

Tobacco smoke and pollution

It is well established that exposure to tobacco smoke, 'passive smoking', irritates the airways and that it may trigger asthma in sensitized individuals. Thirty years ago, higher levels of IgE were also shown in rats exposed to tobacco smoke (10). Smoking in the homes of infants and young children used to be common even in countries with a high hygienic standard. In the Scandinavian countries, this practice is uncommon and currently only 2–7% of Swedish mother smoke at home (6). Despite the much lower rate of tobacco smoke exposure, there has been no decline in the incidence of allergic diseases. A comprehensive analysis has concluded that passive smoking is associated with wheezing (11), but significant effects on allergy have not been confirmed. Furthermore, smoking was common in many of the formerly socialistic countries in Eastern Europe, yet the prevalence of allergies was low (12).

Several studies have reported that various pollutants may trigger allergy. Thus, traffic, poorly ventilated houses, indoor painting, etc., have all been suggested as risk factors. Again, these studies suggest a relationship between exposure and airways irritation, but not with allergy. There are no intervention studies to confirm an effect. Clearly, such studies are almost impossible to perform, yet the evidence for a significant impact is poor.

Microbial exposure

Several studies have demonstrated differences in the composition of gut microbiota in allergic and non-allergic infants and young children. Consequently, several strains of probiotic bacteria have been employed as possible tools for allergy prevention. The conclusion of these studies is that they may slightly reduce the incidence of infantile eczema, but not respiratory allergies (13, 14). So far, however, only single or a few strains of bacteria have been tested. Much research, probably

including a broader modulation of the gut microbiota is required before this potential has been explored.

Concluding remarks

There are currently no preventive measures that would be useful to prevent the pronounced increase in allergic diseases. Although breast-feeding, avoidance of tobacco smoke, and air pollution are all reasonable from a general health perspective, it is ethically doubtful to claim that they are significantly related to the development of allergic diseases. They do not even nearly explain the pronounced increase over the past 40- to 50-yr public health recommendations should meet high standards as they affect the life of the individual. Meaningful

allergy preventive measures have not been documented and current advice raises ethical questions as it may interfere with self-determination. While traditional research approaches have been very successful regarding treatment, it has become increasingly obvious that many problems are complex by nature and they require broad collaboration in order to be identified and solved. Currently, modulation of the gut microbiota early in life remains the only suggested strategy that has not yet been properly explored. Future studies should be directed toward a full understanding of the processes by which immune regulation develops, as there are indications that modern lifestyle is associated with a delayed development.

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