Epidemiology And Prevention Of Allergy In Children

ProfessorArnaldo Cantani

Department of Pediatrics, Division of Pediatric Allergy and Immunology, University of Roma "La Sapienza", Roma, Italy

ABSTRACT

In this paper we present 94 children affected with atopic dermatitis (AD), aggravated by respiratory allergy, asthma and/or allergic rhinitis (AR). AD is a common disorder, frequently complicated by asthma-like symptoms, we debate either disorder and conclude that both AR and asthma can afflict most babies with AD, especially when both parents smoke. We confirm our previous statistics, according to which little children not fed breast milk may react to smallest doses of allergens

INTRODUCTION

Several reports indicate an ongoing increase in the incidence, prevalence and severity of atopic diseases both in industrialized and developing countries (1). The prevalence of atopic disorders is steadily increasing especially in the last 20 years (2). Babies of atopic parents are particularly prone to develop atopic diseases, and for this reason they are called "high risk babies" (3-15). During the last decade, great interest has been devoted to testing different measures to prevent the development of allergy and atopic disease in previously healthy subjects (primary prevention). Several studies shown that dietary and environmental measures, such as prolonged breast-feeding, delayed weaning and elimination of the house-dust mite exert a prophylactic effect on the development of atopic disease in this group of babies at high risk (4-9). In addition, it has been shown that the avoidance of the most common offending foods (cow milk-CM, and peanuts) in the nursing mother's diet during the first three months of lactation induces a significantly lower prevalence of atopic dermatitis at the age of six months (9). However, there is no general agreement on the most suitable formula when breast milk (BM) is not available. Some investigators have had encouraging results with soy protein formulas when BM was not available (4-6), while others had such using cow's milk protein hydrolysate formulas (10,11).

ENVIRONMENTAL FACTORS

It has been long known that a series of prenatal, neonatal and environmental factors such as season birth, home exposure to pets and tobacco smoking, viral infections, and dietary factors can be important in the phenotypic expression of atopy. The first weeks of life are extremely important for the expression of the allergic phenotype, because the mucosal and immune systems of newborns and young infants may be particularly susceptible to a variety of environmental influences that should be avoided.

1) PRENATAL FACTORS

Several studies have suggested that infections during pregnancy and drugs administered to pregnant women are likely to lead to an increased risk of developing atopic allergy in babies. Michel et al (16) reported that IgE concentration was higher in cord blood if the pregnant mothers had been administered progesterone. However, these elevated levels were not associated with an increased development of atopic disease in the infants (16). Bjorksten et al (17) found that the B-blocking agent metoprolol, intake during pregnancy, significantly increased the appearance of elevated neonatal IgE concentrations and the development of atopic symptoms before 18 months of age.

Antibodies to cow's milk and soy proteins have been detected in both the amniotic fluid and cord

blood. Since the mothers had no antibodies to these allergens, it follows that the antibodies had been synthetized by the fetus (18,19). In addition, it was also demonstrated that the fetus is capable of producing specific IgE antibodies to food allergens that were ingested by the mother during pregnancy (20). However a randomised study performed in a large series of pregnant women showed that a strict CM and egg free diet during the last 3 months of pregnancy, had no effect on the development of atopy in the babies (21).

2) PERINATAL FACTORS

Instrumental delivery and use of drugs during delivery are factors over-represented in the history of children with atopic disease (22). Perinatal stress and early operation were suggested to increase the likelihood of subsequent atopic disease (23).

A massive first pollen season seems to imply higher risk for subsequent allergy than a normal pollen season (24). The season of birth seems to be a predisposing factor in atopy sensitization. Subsequently a significantly higher incidence of sensitization to pollens in children born in March-May and to mites in children born in September-October has been shown by several investigators (25,26).

3) HOUSEHOLD EXPOSURE TO ALLERGENS

The house-dust mite appears to be the most common offending allergen in asthma, and an early exposure to this allergen is associated with a significant increase of the risk of asthma at the age of 11 (27). Sporik et al concluded that "increased exposure to dust mites and other indoor allergen may be a factor contributing to the recent increases in the morbidity and mortality associated with asthma" (27). Wickman et al (28) found that the exposure during the 2 first year of life to environmental tobacco smoke and home dampness was more frequently found among the house dust-mite sensitized children than among the controls. Arshad et al (29) demonstrated in a prospective study on 1167 infants that some environmental factors such as maternal smoking,

lower social classes, was interdependent and had a profound effect on the prevalence of asthma but not on other allergic disorders.

4) INFECTIONS

Viral infections frequently trigger asthmatic attacks in children. Their cytopathic effect on respiratory mucosal membranes might favor antigen penetration. Many studies have reported that several of these viruses, including respiratory syncytial virus, parainflenza (types 1-3), coronavirus, adenovirus, and cytomegalovirus may contribute to the development of allergic sensitization in the predisposed children. They could depress T-suppressor cells, which in turn allow increased IgE synthesis (30).

5) CIGARETTE SMOKING

Amog the environmental factors favoring the development of atopic disease, cigarette smoke plays the primary role. Not only is tobacco smoke an irritant, but an increasing body of evidence also indicates that it predisposes to an increased susceptibility to respiratory viral infections (31,32). Since these affections are asthmogenic, a vicious circle is started, especially in winter months in which a greater virus transmission is facilitated: parents' smoking---viral respiratory infections---asthma in the child. As a result, only a drastic inhibition of smoking can interrupt this circle. Several authors studying relationship between cigarette smoking and serum IgE levels reported higher IgE levels in adult smokers (33) and in infants of smoking atopic parents (34). Smoking during pregnancy both seem to increase cord blood IgE concentrations and also the prevalence of atopic symptoms in infants (16,35).

DIETARY FACTORS

Mother's milk has been for millions of years the only source of feeding newborn babies and infants in the first years of life. Since the beginning of this century cow milk formulas have become a widely used breast milk (BM) substitute and solid food has been given to babies at a very early age. This dramatic change in early feeding habit has

been thought to have played a role in increasing the prevalence of food allergy. IgE antibodies to foods (CM, egg, wheat, peanut, etc) are present in a large proportion of children with atopic dermatitis (36), and positive challenge test to foods are positive in at least 50% of children with this disorder (37,38). CM is the most common offending food both in gastrointestinal and in cutaneous manifestations. It has been recently estimated that 2% of children suffer from CM allergy (39).

The phenotypic expression and the natural history of food allergy varies widely according to patient's age, disease presentation and type of the offending food. In many children, the clinical course of the disease may be trivial, or mild, severe and frustrating in others, but even lifethreatening in some.A quite large proportion of children outgrow food allergy by the age of 2-3 years, however in many of them food allergy persists for life (40).

1) TYPE OF FEEDING IN EARLY LIFE AND FOOD ALLEGY Since the pioneering study by Grulee and Sandford which showed that atopic dermatitis was 7 times more frequent in bottle fed babies, than in breast fed ones (41), and the early studies by Glaser and Johnstone (42) and by Johnstone and Dutton (4) on the use of soy formulas for the prevention of atopic disease, a large debate in the literature occurred on the influence of early infant feeding and the development of food allergy in children. Forty years after the study by Grulee and Sandford (41), Matthew et al (5) conducted a prospective study of the development of eczema in infants of atopic parents, who were either subjected to an allergen-avoidance regimen from birth to six months or managed conventionally. The dietary measures included: breast feeding for 6 months, soy-bean formula when BM was not sufficient and selected weanings were only permitted between three and six months. The group on the allergen-avoidance regimen had less eczema at six months and one year than did the control group (p=0.017) (5). According to several studies, the preventive effect of human milk seems to be confined to atopic prone babies and to those who were breast fed for six months or more (6). With a similar

protocol by Matthew et al (5) we have evaluated the prophilactic effect of dietary (mainly prolonged breast-feeding with soy formula supplements) and environmental measures on the development of atopic disease in newborns of atopic parents when they had a median age of 3 years and 8 months (8). Only 14.5% of the study group compared to the 38.5% of the control group developed atopic manifestations (p<0.001). More recently, we confirmed a prevalence of 10% of atopic disease in 174 high risk babies followed up to 52 months with the same preventive program (43). At the last follow-up (52 months), only 1 child (O.5%) had atopic dermatitis, and 2 (1%) had symptoms due to food allergy. These two children had urticaria due to CM allergy since both had IgE to CM and positive double blind placebo controlled food challenge to CM. The prevalence of CM allergy, in this highly atopic prone babies, was thus only 1% (43). In a multicenter study, which comprises 2.270 high risk babies we have shown that babies breast and/or soy-milk fed had at two years of age a significant lower prevalence of atopic diseases (12%) in comparison with CM fed babies (34%) (p < 0.01) (44).

2) DIETARY MANIPULATION DURING PREGNANCY According to several observations, antenatal sensitization to food antigens may occur (18,19,45). Recent randomized studies did not show any preventive effect of dietary manipulation during pregnancy (21,46).

3) DIETARY MANIPULATION DURING LACTATION Since the beginning of this century Stuart (47) demonstrated that food antigens ingested by the mothers might pass into the BM, thus sensitizing the babies. More recently it has been shown that human milk contains as a mean 4.2 ng/ml of Beta-lactoglobulin which is 60.000-100.000 times lower than those of CM formulas (48). The supplements of CM formulas occasionally given to full term healthy neonates in nurseries may sensitize predisposed babies, and the minute amount of CM proteins of human milk may subsequently act as a booster dose, triggering allergic reactions. The results of several studies support this hypotesis: CM allergy

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was significantly more common in babies who received supplements of CM formulas early in life in comparison to babies fully breast fed (48,49).

The efficacy of a restrict diet during lactation has been shown by recent studies (9,50). A prospective, randomized study showed that the exclusion of CM, egg, and fish during the first 3 months of lactation, was associated with a statistically significant reduction in both the prevalence and the severity of atopic dermatitis at the age of 3 and 6 months and a significantly lower cumulative prevalence of atopic disease at the age of 4 years (9).

4) TYPE OF WEANING AND FOOD ALLERGY

Kajosaari and Saarinen (51,52) showed that total solid food elimination for the first six months of life, in addition to exclusive breast feeding, is prophylactic for atopic disease in children who are at hereditary risk. It has been shown by Fergusson et al (53) that rates of eczema increased in almost direct proportion to the number of different types of solid food given to the child in the first 4 months of life: children given five or more different solid foods had over twice the risk of eczema when compared with children given no solid food (53).

5) COW MILK SUBSTITUTES

There is no agreement on the most suitable formula if the mother cannot breast feed (54-57). Soy-bean formulas have been employed for many years for the prevention of food allergy, in high risk babies, when BM is not available with controversery results (5,8,43,58). More recently Bardare et al (58) studied a high number of children and demonstrated that the infants at risk of atopy whose parents complied whit the prescribed diet (prolonged breast-feeding with soy formula supplements, etc.) were found to have a lower incidence of atopy during the first year of life (13.3%) than infants whose parents had ignored the prescribed diet (54.7%) or infants whose parents were offered no dietary recommendation (28.9%) (58). Soy proteins are

immunogenic, but according to experimental and clinical studies they are less immunogenic and allergenic than CM proteins (36,59-63). Soy protein formulas are nutritionally adequate, the taste is well accepted by most infants, and the formulas are less expensive than extensively hydrolyzed formulas.

In the last few years, several studies have been published on the use of hydrolysate formulas (HFs) for the prevention of CM allergy, in high risk babies, when BM is not available (64,65,50,10). These products widely vary in the degree of hydrolysis: the highly casein HFs contain peptides with molecular weight (m.w.) below 1.500 K.D., whereas the whey partially HFs contain a significant amount of peptides with m.w. more than 4.000 daltons and 5% of the peptides has m.w. even more than 15.000 daltons (66). Due to the significant amount of immune reactive epitopes and intact CM proteins, partially HFs may be not only allergenic but even immunogenic in a predisposed host (55,67,68).In two studies highly casein HFs have been employed (11,69), in others a whey partially HF (64,65) and in one an ultrafiltrate whey HF (70). Chandra et al (64) showed that the feeding of a whey proteins-partially HF to infants with a positive family history of atopy significantly decreased the prevalence of atopic disease in these babies compared with that found in soy or cow milk fed infants. However in this study there was no evidence that CM allergy was prevented. Of the five HF fed infants who developed atopic symptoms, four had a positive skin test to CM proteins thus suggesting that sensitization to milk proteins may occur in infants receiving this formula (64). In another study by Vandenplas (65) performed in high risk babies fed either a whey partially HF or a CM formula, the prevalence of CM allergy at six months of age was 15,6% in the HF fed group and 40% in the CM formula fed group. The 40% prevalence of CM allergy, reported in the CM fed babies, is unusually high and it is not in agreement with other studies (3,8,43,45). Therefore serious doubt arises on the diagnostic criteria employed by these Aa for the diagnosis of CM allergy and the 15,6% prevalence of CM allergy, found in the partially whey HF fed

babies, confirms that this product can be immunogenic. More recently, we have described several cases of anaphylaxis, which occurred following the first feed with a partial HF in breast fed babies, who have been given the same product in the nursery (68).These data strongly suggest that partial HFs can be immunogenic when given in the first days of life. In a randomised study, an extensivily soya-based protein HF was given in association with several environmental measures (71). At the age of 12 months atopic diseases had developed in 40% of the infants in the control group and in 14% of the infants in prophylaxis. Asthma and eczema were present rispectevely in 19% and 7% of the babies of the control group and in 7% and 7% of the infants in prophylaxis. Only one baby of the prophylactic group had CM allergy (71).

In conclusion,several studies indicate that it is possible to prevent the onset of atopic dermatitis, CM allergy and food allergy with some dietary manipulations, however further studies are necessary to investigate the role of partially HFs for the prevention of CM allergy in atopic prone neonates.

ARNALDO CANTANI

Professor of Pediatric Allergy and Immunology Allergy and Clinical Immunology Division, Department of Pediatrics, University of Roma "La Sapienza" Medical School

EPIDEMIOLOGY OF ASTHMA IN 94 CHILDREN WITH ATOPIC DERMATITIS

SUMMARY

In this paper we present 94 children affected with atopic dermatitis (AD), aggravated by respiratory allergy, asthma and/or allergic rhinitis (AR). AD is a common disorder, frequently complicated by asthma-like symptoms, we debate either disorder and conclude that both AR and asthma can afflict most babies with AD, especially when both parents smoke. We confirm our previous statistics, according to which little children not fed breast milk may react to smallest doses of allergens.

INTRODUCTION

Atopic dermatitis (AD) has a clinical pattern which often manifests itself in association with a personal and/or family history of atopic respiratory disorders such as asthma or allergic rhinitis. AD is characterized by a clinical pattern dominated by eczematic skin lesion and itching, which provokes an unremitting scracthing, aggravating the lesions and is frequently associated with asthma and/or AR (1-5).

MATERIALS AND METHODS

Among 855 children extracted from the card-file of AD by chance (with the aleatory numbers) we selected 94 babies of either sex aged 3-6 years affected with both AD and asthma and/or AR, all children less two were fed maternal milk for 1- 6 months (median 4,5), after which they were weaned cow's milk (CM) diluted with water. The first CM weaning precipitated the symptoms, such as vomiting and diarrhea and the babies were mostly fed soy milk.

Appropriate emergency equipment and medications were available on site. All possible drugs were stopped at least 2 weeks before the application of the SPTs. Ninety three healthy babies of the same age and sex with the permission of their parents were the controls. SPTs were done at baseline by the prick method on the volar surface of the forearm by myself with the co-operation of a qualified nurse. The skin was marked with a ballpoint pen for the allergens to be tested. The babies were then tested with: histamine hydrochloride (1 mg/ml) as a positive control and isotonic saline as a negative control. We continued with a battery of food allergens, including whole CM protein, beta-lactoglobulin, casein, lactalbumin and a battery of inhalant allergens, including house dust mite pollen, dust, dust mite, mold, animal dander (Lofarma). The diagnostic extract of each individual allergen was placed on the volar surface of the forearm as drops through which the skin was superficially pricked with a straight pin for one second. A new pin was used for each SPT and then discarded, and the

drop of the extract was then wiped off about one minute after the prick.

SPT reading

SPTs were read 20 minutes after the test was finished and considered positive as follows:

+ when the wheal was the half of the histamine wheal;

++ when the wheal was equal to the histamine wheal;

+++ when the wheal was two-fold the histamine wheal;

++++ when the wheal was more than two-fold the histamine wheal.

We took for positive only children with a +++ or ++++ reaction, that is a wheal = 3 mm with an area = 7 mm2 (cut-off).

So we considered as positive only the children with a mean wheal diameter of 3 mm or larger than the negative (saline) control. A positive (histamine) control was performed to ensure the absence of any antihistamine drug interference.

Statistical analysis

The statistical analysis was performed using the X2 test. Results with a p < 0,05 were considered as statistically significant.

At the CM reintroduction, for diagnostic purposes, all babies presented again with diarrhea, one with a short state of shock, promptly regressed after immediate parenteral treatment.

The 94 healthy controls, similar for sex and age had no clinical reactions by eating whatever food

RESULTS

All 94 babies suffered from either respiratory or food allergy. Among them 23 (24,9%) were affected by both AD and respiratory allergy. Of these 23, 13 children, 7 males and 6 females, aged between 2 and 6 years, median 3, showed a positive food provocation test (FPT) and in the

remaining 10 negative, 6 males and 4 females aged between 2 and 9 years, median 5,5 the test was negative. We stress that some children reacted to very small doses of allergens:14 asthmatic children fed foods reacted with wheezing. Therefore, I recommend that in FPTs, medical doctors with a resuscitation equipment are present on the scene since the first moment. It is of note that the statistical analysis had a highly significant difference with SPTs (p = 0,013). Hovever, 80/94 children (85, 1%) had SPTs done and only 46 the RAST.

DISCUSSION

An important result is suggested by this study: Allergic sensitization to any food allergen was associated with late introduction of potatoes (4 months), oats (5.5 months), rye (7 months), meat (5.5 months), fish (8.2 months), and eggs (10.5 months) who studied 994 children. The median duration of exclusive breastfeeding in the whole study population was 1.8 months (range: 0.0 –10.0 months). In this study breastfeending was continued for 1- 6 months however we have calculated the median 4,5), which gives a high duration of breastfeeding. We suggest that a longer duration of breast feeding, as in the present study may have protected the children by Nwaru et al. AD complicated by asthma and or AR is a severe disease, which poses in the first place the house dust controls. The children in this study were protected from cigarette smoke since beginning since their mothers failed to smoke only during pregnancy and the children must be prevented from wheezing, a severe disease (7, 8).

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