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A study on 300 asthmatic children, 300 controls and their parents confirms the genetic transmission of allergy and asthma

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Abstract. – *Background:* **Several studies have shown the role of genetic factors in allergies, and ascertained that atopic diseases are transmitted by parents, especially by mothers.**

Materials and Methods: **In order to explore the genetic risk of a child with a family history (FH) of allergy, we have enrolled into this prospective study 300 children, 173 males and 127 females, aged 3.5 to 7.5 years (median age 4.4 years), that included: family (FH) and personal history skin prick tests (SPTs) and specific IgE (RAST), who attended the Pediatric Allergy and Immunology Division of Rome University because affected with respiratory allergy We have studied the FH of these children asking whether their parents and brothers/sisters had atopic diseases, and detailing whether such diseases were respiratory or food allergies (FA). The parents of all children gave their informed consent. We analyzed data using the X^2 method.**

Results: **One hundred and twentyseven parents were atopic (42.3%), in addition to 20 brothers/sisters. In detail 90.2% of fathers, 84% of mothers and 65% of brothers/sisters had asthma or allergic rhinitis (AR). Very less parents had urticaria, especially the mothers and brothers/sisters suffered with atopic dermatitis (AD), and some mothers with FA. In 23 children from these parents most had AD and respiratory allergy. In 300 children comparable for age and sex with no respiratory illness recruited from our out-patient clinic 40 parents, 14 mothers and 26 fathers and 9 brothers/sisters had asthma or AR (p = 0.0001), some fathers had also urticaria and two brothers AD.**

Conclusion: **A relevant part of respiratory allergy is not transmitted by mothers. Our prospective study stresses that 42.3% of parents are atopic, and FH of their children was positive for respiratory allergy in 82-92% of cases. Thus respiratory allergy can have an autosomal dominant mode of inheritance, but considering the other atopic diseases, the transmission can be polygenic. The impact of genetic factors in these children is emphasized by the high part of asthmatic brothers/sisters.**

Key Words:

Children, Young age, Family history, Atopic dermatitis, Allergic rhinitis, Urticaria, Food allergy, Genetic factors.

Introduction

Asthma is a complex genetic disorder in which the mode of inheritance is not known. Many segregation studies suggest that a major gene could be involved in asthma, but until now different genetic models have been obtained. Family studies may involve twins, helpful in differentiating genetic and environmental factors. Additional studies on the genetic basis of atopy have found a decisive genetic effect on total serum IgE levels in twins: the total serum IgE level variation is significantly lower in pollen sensitive monozygotic (MZ) than in dizygotic (DZ) twins (0.15 vs 0.51)[1] and the inheritability index (the part variability attributed to genetic factors) is estimated to be 59% in adults and 79% in children[2]. The concordance of atopic dermatitis (AD) and asthma was higher in genetically identical MZ twins[3]. MZ twins have a concordance ratio greater for atopy[1,4], while in DZ twins bronchial hyperreactivity (BHR) and total and specific IgE[1] prevail. Thus, the most reliable approach seems to be the concordance between MZ and DZ twins[5]. Twin studies have also revealed substantial evidence for environmental influences, in which non shared environmental influences appeared to be important[6]. Most published studies in this area have shown that anywhere between 40% and 70% of the determinants of asthma is attributable to genetic factors[7].

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Finally, several studies on the genetics of asthma have been confirmed by various genome-wide searches, that have identified the linkage between asthma and genetic markers on 13 chromosome regions including chromosomes 5q31-33 (the gene cluster of several interleukins), 6p21.3, 11q13 and 12q14.3-24.1[6,8-15].

In this prospective paper on 300 children we have evaluated the genetics of asthma, by studying the FH of atopy of their respective family, including parents and brothers and/or sisters.

Materials and Methods

In order to explore the genetic risk of a child with a family history (FH) of allergy, we have enrolled in this prospectic study 300 children, 173 males and 127 females of Italian ethnicity, aged between 3.5 and 6.5 years (median age 4.4 years), In particular we have studied the personal and FH of both parents and children.

Study Children

We assessed whether the babies were "at risk" of atopic disease because of a positive FH of atopy since one or both parents and/or their siblings suffered from asthma, or AD, or allergic rhinitis (AR). The diagnosis of atopic diseases in the children was done according the following criteria: clinical history, physical examination and positive skin tests and/or RAST to the most common inhalant and/or food allergens. Three hundred healthy children, and their parents recruited during the same period from our outpatient clinic with no history of atopy of comparable age, sex, and Italian ethnicity were matched with the study group.

Informed consent was obtained from parents of each child.

Skin Prick Test (SPT)

Appropriate emergency equipment and medications were available on site. Antihistamine drugs and topical steroids were stopped at least 2 weeks before the application of the SPTs. Skin testing was done at baseline by the prick method on the volar surface of the forearm by a trained in allergy doctor 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 and inhalant allergens, including whole Cow's milk (CM) protein, casein, lactalbumin, egg, fish, wheat, soy, *Dermatophagoides pteronyssinus, Alternaria alternata, Lolium perenne, Olea europea and Parietaria officinalis* (SARM, Roma, Italy). 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[22].

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[16].

We took for positive only children with a +++ or ++++ reaction, that is a wheal ≥3 mm with an area ª 7 mm^2 (cut-off) So we considered as positive only the children with a mean wheal diameter of ≥3 mm than the negative (saline) control. A positive (histamine) control was performed to ensure the absence of any antihistamine drug interference[23].

Total IgE

The determination of the total serum IgE level was done by paper radioimmunosorbent test (PRIST, Pharmacia Diagnostics AB, Sweden), and results were expressed in International Units per ml.

Specific IgE antibodies and determination of specific IgE levels by radioallergosorbent test (Phadezym RAST, Pharmacia Diagnostics, AB, Sweden).

RAST results are expressed in »RAST Units« (PRU = Phadebas Rast Unit) as follows:

1^{st} class = IgE levels < 0.35 IU/ml,
2^{nd} class = IgE levels > 0.35 IU/ml and lesser than 0.7 IU/ml,
3^{rd} class = IgE levels between 0,7 IU/ml and 17 IU/ml,
4^{th} class = IgE levels higher than 17 IU/ml.
Only RAST results > 0.35 IU/ml were considered positive.

The diagnosis of AD was made according to Hanifin and Rajka criteria[24]. The severity score of AD was evaluated according to the SCORAD index[25].

For the diagnosis of asthma, 3 episodes of wheezing without fever were required. Provocation tests with inhalant allergens were not feasible due to the young age of the children studied.

For the diagnosis of rhinitis, nasal discharge and/or blockage occurring continuously for at least 4 weeks plus the typical pale aspect of allergic mucosa on rhinoscopy, without any sign of infective rhinitis in other relatives was required.

Statistical Analysis

The statistical calculations were performed using the X_2 test. Results with $p < 0.05$ were considered statistically significant.

Results

As demonstrated by FH, SPTs and RAST, 127 parents of the study children were affected with atopic disease (42.3%), in particular 51 fathers and 76 mothers, in addition to 25 brothers and/or sisters. These parents all tested positive for inhalant allergens (both SPTs and RAST), with the exception of 3 mothers positive to cow's milk (CM) allergens and two children with allergic migraine. We stress that 90.2% of fathers, 81.6% of mothers and 91.7% of brothers/sisters suffered from respiratory allergy. In detail, 41.2% of fathers, 40.8% of mothers and 72.2% of brothers/sisters were asthmatic. In addition 49%, 40.8% and 19.4%, respectively, were affected with AR. Moreover 9.8% of fathers and 6.6% of mothers had urticaria, 2.9% of mothers and 10.5% of brothers/sisters had AD, and 4% of mothers had CMA (Table I).

Twenty-five children were allergic, with a high proportion of cases of AD (52%), however the respiratory allergy affects 30.4% of these children (Table II) who appear to have multiple sensitizations in 34.8% of cases (Table III). Thirteen of these children had SPTs and RAST positive for food allergens (mostly CM and egg) and 10 for inhalant allergens.

In the control group 61 parents were allergic, and 40 were affected with respiratory allergy. In detail, 14.7% of fathers and mothers and l8.2% of brothers/sisters had asthma. 6.6%, 13.1% and 4,9%, respectively had AR and 6,6% of fathers and mothers ed 3.3% of brothers/sisters allergic oculorhinitis Further, 6.6% of fathers 13.1% of mothers and 1.6% of brothers had urticaria, 11.5% of mothers and 1,6% of fathers and brothers AD, in addition to 3.3% of fathers, 11.5% of mothers and 8.2% of brothers/sisters with FA.

In the control group, 11 children were sensitized who in 15.5% of cases had respiratory allergy Study children vs controls ($p = 0.0161$).

We have ascertained that a high number of parents of the study and control children were active smokers (Table IV). The statistical analysis revealed high statistically differences between fathers and mothers of the study group versus the parents of the controls, $p = 0.0196$ and $p = 0.0387$, respectively.

The statistical analysis has demonstrated highly significant differences between the two samples ($p = 0.0001$).

Discussion

The results do not allow us to confirm that a significant proportions of respiratory allergy is transmitted by mothers. We underline that 42.3% of parents are atopic, with a FH positive for res-

Table I. Parents of children affected with atopic disease.

Atopic disease	No. (%)	F	M	(B/S)
Asthma	52 (40.9)	21	31	6
Allergic rhinitis	57 (44.8)	25	32	4
Atopic dermatitis	2 (1.6)	0	2	3
Urticaria	10 (7.8)	5	5	3
Oculorhinitis	3 (2.5)	1	2	1
Food allergy	3 (2.5	0	3	2
	127	52	75	19

F = Fathers, M = Mothers.

Table II. Children affected with atopic disease.

Atopic disease	No. (%)
Atopic dermatitis	12 (52.2)
Asthma	5 (21.7)
Urticaria	4 (17.3)
Allergic migraine	2 (8.6)
Oculorhinitis	1 (4.3)
Allergic rhinitis	1 (4.3)
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piratory allergy in 82-92% of cases In the study sample 147 parents and brothers were affected with respiratory allergy (45.94%) versus 10.3% of controls who in 65.5% of cases had respiratory allergy.

Therefore, asthma is a genetic disease, at least in 42.3% of cases. Respiratory allergy can have an autosomal dominant mode of inheritance, but considering the whole atopic whole, the transmission can be polygenic. The high impact of the genetic factors in these children is stressed by the high proportion (85%) of asthmatic brothers/sisters.

As regards the smoking parents it is very significant the number of couples smoking together. The low number of other relatives probably depends by the smaller apartments prevailing in Italy.

What our study evidently stresses is that a high number of parents, atopic parents, yet they themselves asthmatic, as we have ascertained, are smoking parents of asthmatic sons and daughters. Such data demonstrates in an unequivocal manner that cigarette smoke should be considered as a triggering factor of respiratory allergy. Therefore in babies at risk of atopy cigarette smoke should be regarded as an additional genetic factor, since asthma is more easily transmitted if an atopic parent smokes (even more if both parents smoke). However cigarette smoke is able to provoke asthma even in children of nonatopic parents, especially if the smokers are pregnant women: their children frequently suffer with Der p-induced asthma[16].

Allergic asthma and rhinitis, AD, urticaria and FA are genetic diseases of infants and children. Several investigators have provided evidence for a genetic localization for atopy. Babies of atopic parents are at high risk of developing atopic diseases, however the phenotypic expression of such diseases varies widely, being very mild in some infants and children, severe and frustrating in many, even life-threatening in others, being also common, disabilitating, and chronic[17]. In particular we can now understand how strictly the genetic factors are linked with atopy: several cytokine genes are associated in the gene cluster of chromosome 5q23-q31, such as IL-3, IL-4, IL-5, IL-9, IL-12b, IL-13, and GM-CSF, together with the genes for the β2-adrenergic receptor[18]. It is likely that plural loci in the chromosome 5q31-q33 region are synergistically related to asthma susceptibility.

We have frequently spoken of respiratory allergy. However, a large number of cross-sectional studies have reported that asthma and AR commonly occur in children and adolescents[19-21]. Studies have demonstrated that AR occurs in 28-78% of older children and adolescents[19-21], versus approximately 5-20% of the general population[22]. Conversely, asthma has also been shown to affect up to 38% of AR patients[19,21], a data significantly

Table III. Degree of sensitization of the 23 children.

Degree of sensitization	No. (%)
Single sensitization	15 (65.2)
Multiple sensitization	8 (34.8)

Table IV. Number of people smoking in the home of 300 children and 300 controls.

	Children in study		Controls	
Relative	Number	%	Number	%
Fathers	175	60.6	153	51
Mothers	109	37.7	89	29.7
Others	15	5.2	25	8.3
Fathers and mothers	93	32.2	73	24.3

Fathers vs mothers $p = 0.0036$.

higher than the 3-5% prevalence noted in the general population[22]. In an unpublished study on 411 children aged 7-13 years, asthma had an incidence of 31.5% and AR of 25.8%.

Asthma and AR can have an early onset. The asthma affair is a little more intricate: the onset within the first year is certain in 34.5%[23-26]-56.2%[24,27] of babies, but a higher level (82.4%) is evident between the 4th and the 7th year[24,27-29]. That within the 8th year the asthma onset is manifest in 90% of children[28] is confirmed by the 92% proportion reached in patients less than 20 years of age[31]. As regards AR, the onset may be in the first year in 35% of children and in 59% of those aged 2-5 years[24], who in other studies are affected in 13-19% of cases[23,30].

Once atopy develops, it is now possible to prevent the clinical manifestations in a great proportion of cases (secondary prevention) by the use of pharmacological agents such as cromones and ketotifen[32]. In addition as demonstrated by the ETAC study we can prevent the onset of respiratory allergy in 50% of babies with AD following an 18-month administration of cetirizine[33]. Since the commitment to the Th2 phenotype in atopics appears to occur at any time between the ages of 2 and 5 years[34], the net implication is that within the first years of life there is a window open for immunoprophylaxis[35].

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