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A Great Discovery Allergy and Asthma are fully Genetic in Children

Abstract

Background: Allergic asthma and rhinitis, atopic dermatitis, urticaria and food allergy 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, disabling, and chronic.

Methods: A meta-analysis was done of all available studies on the age of onset of the atopic march, without attempting at being comprehensive in this meta-analysis, but instead selecting what appeared the most relevant articles in the literature.

Results: In the first year of life, there is the onset of atopic dermatitis in 79,8% [60,2% to 100%], of cow's milk allergy in 72,7%, egg allergy in 71%, and fish allergy in 51,3% of babies. Asthma starts in the first year of life in 41,8%, in the 2nd in 49,3%, and within the 8th year in 92,5% of children. Allergic rhinitis begins in 35% of babies in the 1st year of life, and in 59% or 13-19% in those aged 2-5 years. It seems therefore that the role of pediatric allergy and immunology has been hitherto somewhat obscured, as shown by the atopic march.

Conclusion: It follows that this role is instead substantial, unmatched, focusing on the early and often very early onset of the atopic march, which needs strategic interventions in the very first months of life or even before birth. As the main goal of modern medicine is prevention of chronic and severe diseases, the possibility of preventing such disorders in predisposed children has stimulated the investigators' imagination since the beginning of the century, when atopic diseases were not as common as now.

Introduction

Few diseases like atopic dermatitis, although not being lethal, are causes of invaluable physical and emotional suffering either for children or their parents. Needless to say, there are also growing numbers of wheezing infants at an early age. There appears to be a belief that asthma in children is increasing. Given the fact that the morbidity of asthma has not decreased despite many advances in pharmacologic treatment, it is clear that attempting at reduce exposure should come at an early stage of life [1]. Actually, several data are explaining why atopic diseases are increasing in prevalence in Western countries: "Before birth" is the key, the suggestive site where the origin of atopy was recently unveiled [2-7]. Therefore allergic and immunologic disorders, before being diagnosed in adult patients, start in the fetus, in the neonate, in the infant, that are the youngest pediatric populations. So very soon severe atopic disorders confront doctors with one of the most demanding challenges.

Strongly associated is a positive family history [8], especially maternal in case of asthma [9], although several environmental determinants have been reported [10]. Several scientific advances have shed light in the past few years on the cell interactions that are pivotal in orchestrating the inflammation underlying atopy. In particular we can now understand how strictly are linked with atopy the genetic factors: 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 β 2-adrenergic receptor

[11]. There is a significant linkage between total IgE levels and several of these markers, particularly IL-4R [12] and IL-9 [13]. A linkage of chromosome markers with bronchial hyperreactivity (BHR) and total IgE concentrations has been reported [14]. Two genes account for 78% of the genetic predisposition to high IgE levels [15]. However this linkage has not been confirmed by others, either for total serum IgE or for BHR [16,17]. The genes for the β subunit of the high affinity immunoglobulin E receptor (Fc ϵ RI- β) are located on 11q13 [18], and are associated, but without a complete unanimity of researchers, with one or more genes coding for atopy [11]. The initial study showing a dominant gene on this chromosome [19] has been confirmed [20-24] or not [25-30], while an association between high serum IgE levels and D11S97 on chromosome 11q has been found in Japanese subjects [31]. There is no association of atopic dermatitis with chromosome 11q [32], but with the Fc ϵ RI- β [33]. Other genes located on 14q23, 14q32, and 14q11.2 may contain loci predisposing to high IgE levels, while those on 12q15 and 12q24 are associated with IFN-g concentrations [11] and show linkage with asthma and total serum IgE [34].

Overall, a more suggestive link is an early sensitization within the first-third years of life mediated by indoor allergen exposure [35,36].

Personal Studies

In the following [37-58] we have meta-analyzed the results of several epidemiological studies, which enable me to present here a

state-of-the-art report on the onset of the atopic march, focusing on the early and also very early onset in several cases.

When it is well known that atopic dermatitis [37-42] and food allergy [43-49] have their onset within the first year of life in 70-100% of infants [37-42], and in the second in 69-96% of cases [43,44], it may not be clear that allergy to a panel of foods begins before the first year of age in a wide proportion of babies [45-49]. For example allergy to cow milk evidently begins in at least 72%, and to egg in 71% of infants [45-47]. However the percentages of 52,3% for fish, and of 62% for cereals can be unexpected, and even more the rates of legumes, fruits, and nuts [45-47]. The case of peanuts depends on the country where the study was done [48,49], whereas chocolate has been absolved [45].

The asthma affair is a little more intricate: the onset within the first year is certain in 34,5% [37,38,51,52]-56,2% [38,54] of babies, but a higher level [82,4%] is evident between the 4th and the 7th year [38,54-56]. That within the 8th year the asthma onset is manifest in 90% of children [55] is confirmed by the 92% proportion reached in children less than 20 years of age [57]. The sex difference may be 1,65: 1 at 0-1 years, but it is inversely or practically abrogated within the 8th year [38].

As regards allergic rhinitis, the onset may be in the first year in 35% of children and in 59% of those aged 2-5 years [38], who in other studies are affected in 13-19% of cases [28,37]. The sex difference is high between 4-10 years for males (2,3 : 1), but in older children it seems to disappear [37].

Discussion

This meta-analysis was facilitated by the selection of only one factor, the age, though a cause of variability can be the wide range of disease definitions, especially for asthma. However only in preschool children a definite diagnosis of asthma may be difficult to establish since many wheezing infants lose their symptoms in the first years of life [59]. On the other side, lack of information on the development of the atopic march early in life may confound the interpretation of early changes. Therefore the role of pediatric allergists is also to be highlighted in view of the early onset of atopic disease, which stresses the pivotal and crucial place held by such specialists in the early diagnosis and treatment of young children.

The early onset of the atopic march is favored in the first place by cow milk allergy [45-47], a peculiar form of allergic disease in which IgE antibodies are directed to introduced daily proteins [4]. The reduction of specific CD8 response could play a crucial role in the dysregulation of IL4 production in at risk babies, and probably in the breakthrough of oral tolerance towards cow milk proteins [4]. Sensitization to foods occurs more commonly early in life, however occasionally it may even occur prenatally. Cow milk appears to be the most common offending food both in gastrointestinal (vomiting, diarrhea, etc.), and in cutaneous manifestations (urticaria and atopic dermatitis). Specific IgE to foods and positive challenge test to a number of food allergens are frequently present in children with such disorders. Food allergy and atopic dermatitis may negatively interfere with the child's life and his physical and physiological development. Prevention should be therefore the early mainstay of each

intervention. According to previous and recent studies, prevention of atopic diseases in genetically predisposed newborn babies, is not only worthwhile [60] but also necessary. The family should have clear advice on the prevention of atopy [61]. We have stressed the negative effects of the maternity wards. To avoid the possible risks it should be clearly stated that giving any formula in the first few days of life is strictly forbidden unless prescribed by a pediatrician or demanded by a mother who is unwilling or incapable to breastfeed her baby [62]. It may also happen that 12/65 (18.5%) mothers included in a preventive program mistakenly eat cow milk and/or fish [63], or offspring's from bilateral atopic parents eat egg at the insistence of the grandmother [62].

A general improvement of the pediatric atopic population seems an unrealistic goal at the moment, however their management should be in the hands of well-trained pediatricians and pediatric allergists, and not in the hands of the various "alternative" practitioners using methods such as homeopathy, bioresonance, auriculo-acupressure, and the like [64], with serious and even dangerous results [65]. We know that postponing the atopy development leads to a lessening of the severity of the clinical manifestations, and even to atopy avoidance forever [66]. 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 cromons and ketotifen [66]. In addition as demonstrated by the ETAC study it is possible to prevent the onset of respiratory allergy in 50% of babies with atopic dermatitis following an 18-month administration of cetirizine [67]. Since the commitment to the Th2 phenotype in atopics appears to occur at any time between the ages of 2 and 5 years [68], the net implication is that within the first years of life there is a window open for immunoprophylaxis [69]. Moreover, dietary prevention is not sufficient if it is not accompanied by strict environmental measures. Possible obstacles confront any allergy prevention program [35,36,70], that should instead balance the contributing factors to the increase of indoor allergens [70]. In the environment we find aeroallergens to be prevented, among which the leaders, such as house dust mite, pets, pollens, molds, cigarette smoke, and the indoor and outdoor air pollution [71-73].

"An ounce of prevention is worth a pound of cure". If we cannot change the atopic inheritance after birth, we can start early and effective preventive measures also before birth. This issue appears to lay in a realm almost to be described as a "no-man's land". Mother Nature teaches that in the neonatal immature gut the first line of defense is formed by some specialized factors. It may be that this first line should be moved forward [74]. I would like to stress, according to the Latin wisdom that stands on the portal of our Clinic "in puero homo", which means "In infant is the seed of the future man", that the goal is not only to reduce morbidity and mortality, but mainly to insure the best quality of life both to infants and adults.

References

1. Cantani A (1990) [Epidemiologia e prevenzione dell'allergia respiratoria nel bambino]. *Eur Rev Med Pharmacol Sci* 12: 147-157.
2. Jones AC, Miles EA, Warner JA, Warner JO (1995) IFN γ production and proliferative responses from fetal leukocytes during 2nd and 3rd trimester of pregnancy. *J Allergy Clin Immunol* 95: 380A.

3. Jones AC, Miles EA, Warner JO, Colwell BM, Bryant TN, et al. (1996) Fetal peripheral blood mononuclear cell proliferative responses to mitogenic and allergenic stimuli during gestation. *Pediatr Allergy Immunol* 7: 109-116.
4. Parronchi P, Sampognaro S, Giannarini L, Ruffilli A, Chersi A, et al. (1996) T-cell response to milk proteins in atopic and nonatopic donors. *Monogr Allergy* 32: 121-129.
5. Piastra M, Stabile A, Fioravanti G, Castagnola M, Pani G, et al. (1994) Cord blood mononuclear cell responsiveness to β -lactoglobulin: T-cell activity in "atopy-prone" and "non-atopy-prone" newborns. *Int Arch Allergy Immunol* 104: 358-365.
6. Szépfalusi Z, Nentwich I, Gerstmayr M, Jost E, Todoran L, et al. (1997) Prenatal allergen contact with milk proteins. *Clin Exp Allergy* 27: 28-35.
7. Piccinni M-P, Mecacci F, Sampognaro F, Manetti R, Parronchi P, et al. (1993) Aeroallergen sensitisation can occur during fetal life. *Int Arch Allergy Immunol* 102: 301-303.
8. Dold S, Wjst M, von Mutius E, Reitmer P, Stieper E (1992) Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child* 67: 1018-1022.
9. Moffatt MF, Cookson WOCM (1998) Maternal effects in atopic disease. *Clin Exp Allergy* 28: 56-61.
10. Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA (1996) Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child* 75: 392-398.
11. Anderson GG, Morrison JFJ (1998) Molecular biology and genetics of allergy and asthma. *Arch Dis Child* 78: 488-496.
12. Marsh DG, Neely JD, Breazeale DR, Ghosh B, Freidhoff LR, et al. (1994) Linkage analysis of IL-4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. *Science* 264: 1152-1156.
13. Meyers DA, Postma DS, Panhuysen CIM, Xu J, Amelung PJ, et al. (1994) Evidence for a locus regulating total serum IgE level mapping to chromosome 5. *Genomics* 23: 464-470.
14. Postma DS, Bleecker ER, Amelung PJ, Holroyd KJ, Xu J, et al. (1995) Genetic susceptibility to asthma - bronchial hyper responsiveness co inherited with a major gene for atopy. *N Engl J Med* 333: 894-900.
15. Xu J, Levitt RC, Panhuysen CMI, Postma DS, Taylor EW, et al. (1995) Evidence for two unlinked loci regulating total serum IgE levels. *Am J Hum Genet* 57: 425-430.
16. Sandford A, Daniels SE, James AL, LeSouëf PN, Musk AW, et al. (1995) Chromosome 5 markers, total IgE and bronchial responsiveness in a random population. *Am J Respir Crit Care Med* 151: 354A.
17. Walley AJ, Cookson WOCM (1997) Linkage and allelic association of chromosome 5 microsatellite markers with atopic asthma phenotype in a general population sample. *Am J Respir Crit Care Med* 155: 257A.
18. Sandford A, Weir T, Paré P (1996) The genetics of asthma. *Am J Respir Crit Care Med* 153: 1749-1765.
19. Cookson WOCM, Hopkin JM (1988) Dominant inheritance of atopic immunoglobulin E responsiveness. *Lancet* 1: 86-88.
20. Cookson WOCM, Faux JA, Sharp PA, Hopkin JM (1989) Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1: 1292-1295.
21. Amelung PJ, Panhuysen CIM, Postma DS, Levitt RC, Koeter GH, et al. (1992) Atopy and bronchial hyper responsiveness: exclusion of linkage to markers on chromosome 11q and 6p. *Clin Exp Allergy* 22: 1077-1084.
22. Collée JM, ten Kate LP, de Vries HG, Kliphuis JW, Bouman K, et al. (1993) Allele sharing on chromosome 11q13 in sibs with asthma and atopy [letter]. *Lancet* 342: 936.
23. Shirakawa T, Mao X-Q, Sasaki S, Enomoto T, Kawai M, et al. (1996) Association between atopic asthma and a coding variant of the FcεRIβ in a Japanese population. *Hum Mol Genet* 5: 1129-1130.
24. Young RP, Sharp PA, Lynch JR, Faux JA, Hopkin JM (1992) Confirmation of genetic linkage between atopic IgE response and chromosome 11q13. *J Med Genet* 29: 236-238.
25. Lympany P, Welsch K, McCockrane G, Kemeny DM, Lee TH (1992) Genetic analysis using DNA polymorphism of the linkage between chromosome 11q13 and atopy and bronchial responsiveness to metacholine. *J Allergy Clin Immunol* 89: 619-628.
26. Lympany P, Welsch K, McCockrane G, Kemeny DM, Lee TH (1992) Genetic analysis of the linkage between chromosome 11q13 and atopy. *Clin Exp Allergy* 22: 1085-1092.
27. Hizawa N, Yamaguchi E, Ohe M, Itoh M, Furuya K, et al. (1992) Lack of linkage between atopy and locus 11q13. *Clin Exp Allergy* 22: 1065-1069.
28. Rich SS, Roitman-Johnson B, Greenberg B, Roberts S, Blumenthal MN (1992) Genetic analysis of atopy in three large kindreds: no evidence of linkage to D11S97. *Clin Exp Allergy* 22: 1070-1076.
29. Brereton HM, Ruffin RE, Thompson PJ, Turner DR (1994) Familial atopy in Australian pedigrees: adventitious linkage to chromosome 8 is not confirmed nor is there evidence of linkage to the high affinity IgE receptor. *Clin Exp Allergy* 24: 868-877.
30. Amelung PJ, Postma DS, Xu J, Meyers DA, Bleecker ER (1998) Exclusion of chromosome 11q and the FcεRI-β gene as etiological factors in allergy and asthma in a population of Dutch asthmatic families. *Clin Exp Allergy* 28: 397-403.
31. Hizawa N, Yamaguchi E, Furuya K, Ohnuma N, Kodama N, et al. (1995) Association between high serum IgE levels and D11S97 on chromosome 11q in Japanese subjects. *J Med Genet* 32: 363-369.
32. Coleman R, Trembath R, Harper JI (1993) Chromosome 11q13 and atopy underlying atopic eczema. *Lancet* 341: 1121-1122.
33. Cox HE, Moffatt MF, Faux JA, Walley AJ, Coleman R, et al. (1998) Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 138: 182-187.
34. Barnes KC, Neely JD, Duffy DL, Freidhoff LR, Breazeale DR, et al. (1996) Linkage of asthma and total serum IgE concentration to markers on chromosome 12q: evidence for Afro-Caribbean and Caucasian populations. *Genomics* 37: 41-50.
35. Björkstén F (1986) Early allergen contacts. *J Allergy Clin Immunol* 86: 1010-1012.
36. Wahn U, Kulig M, Lau S, Kulig M, Forster J, et al. (1997) Indoor allergen exposure is a risk factor for early sensitization during the first three years of life. *J Allergy Clin Immunol* 99: 763-769.
37. Blair H (1974) The incidence of asthma, hay fever and infantile eczema in an East London group practice of 9145 patients. *Clin Allergy* 4: 389-399.
38. Koivikko A (1974) Childhood asthma in Finland. *Acta Allergol* 29: 30-72.
39. Queille-Roussel C, Raynaud F, Saurat J-H (1985) A prospective computerized study of 500 cases of atopic dermatitis in childhood. *Acta Derm Venereol* 114: 87-92.
40. Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG (1994) The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 30: 35-39.
41. Musgrove K, Morgan JK (1976) Infantile eczema. A long-term follow-up study. *Br J Dermatol* 95: 365-372.
42. Guillet G, Guillet M-H (1992) Natural history of sensitizations in atopic dermatitis. *Arch Dermatol* 128: 187-192.
43. Crespo JF, Pascual C, Burks AW, Helm RM, Esteban MM (1995) Frequency of food allergy in a pediatric population from Spain. *Pediatr Allergy Immunol* 6: 39-43.
44. Bock SA (1987) A prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 79: 683-688.

45. Quiros AB, Villares ES (1988) Pathogenic basis of food allergy treatment. Nestlé Nutr Workshop Ser 17: 265-270.
46. Martin Esteban M, Pascual C, Diaz Pena JM, Ojeda JA (1992) Basi patogenetiche per la profilassi ed il trattamento dell'allergia alle proteine del latte di vacca. In: Allergie alimentari. Roma: Fisons Italmici SpA 105-117.
47. Bardare M, Zani G, Magnolfi C (1992) Evoluzione della dermatite atopica ad insorgenza nei primi anni di vita. In: Allergie alimentari. Roma: Fisons Italmici SpA 157-165.
48. Ewan PW (1996) Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *BMJ* 312: 1074-1078.
49. Zeiger RS, Heller S, Mellon M, Forsythe A, O'Connor R, et al. (1989) Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 84: 72-89.
50. Croner S, Kjellman N-IM (1990) Development of atopic disease in relation to family history and cord blood IgE levels. *Pediatr Allergy Immunol* 1: 14-20.
51. Croner S, Kjellman N-IM (1992) Natural history of bronchial asthma in childhood. A prospective study from birth up to 12-14 years of age. *Allergy* 47: 150-157.
52. Businco L, Falconieri P, Zannino L (1993) Presentazione dei risultati di uno studio policentrico epidemiologico delle malattie allergiche in età evolutiva in Italia. *Notiz Allergol* 12: 275-278.
53. Silverstein MD, Reed CE, O'Connell EJ, Melton LJ, O'Fallon WM, et al. (1994) Long-term survival of a cohort of community residents with asthma. *N Engl J Med* 331: 1537-1541.
54. Gergen PJ, Turkeltaub PC, Kramer RA (1992) Age of onset in childhood asthma: data from a national cohort. *Ann Allergy* 68: 507-514.
55. Bergmann RL, Bergmann KE, Lau-Schadendorf S, Luck W, Dannemann A, et al. (1994) Atopic disease in infancy. The German multicenter atopy study (MAS-90). *Pediatr Allergy Immunol* 5: 19-25.
56. Linna O, Kokkonen J, Lahtela P, Tammela O (1992) A 10-year prognosis for generalized infantile eczema. *Acta Pædiatr* 81: 1013-1016.
57. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, et al. (1994) Factors in childhood as predictors of asthma in adult life. *BMJ* 309: 90-93.
58. Wüthrich B (1989) Epidemiology in the allergic diseases: are they really on the increase? *Int Arch Allergy Appl Immunol* 90: 3-10.
59. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, et al. (1995) Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 332: 133-138.
60. Kjellman M (1982) Prediction and prevention of atopic allergy. *Allergy* 37: 463-473.
61. Kjellman N-IM (1992) Prevention of allergy - myth or reality? In Godard Ph, Bousquet J, Michel FB, eds. *Advances in allergology and clinical immunology*. Lancs: The Parthenon Publishing Group 401-414.
62. Hamburger RN, Hellers S, Mellon MH, O'Connor R, Zeiger RS (1983) Current status of the clinical and immunologic consequences of a prototype allergic disease prevention program. *Ann Allergy* 51: 281-290.
63. Hattevig G, Kjellman B, Sigurs N, Björkstén B, Kjellman N-IM (1989) The effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 19: 27-32.
64. Wüthrich B (1996) Epidemiology and natural history of atopic dermatitis. *ACI Intern* 8: 77-82.
65. Spiegelblatt L, Lainé-Ammara G, Pless IB, Guyer A (1994) The use of alternative medicine by children. *Pediatrics* 94: 811-814.
66. Cantani A, Businco L (1991) Prevention of atopic disease in at risk newborns. *Allergie Immunol* 23: 387-390.
67. ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blinded, randomised, placebo-controlled trial: First results of ETAC. *Pediatr Allergy Immunol* [in press]
68. Yabuhara A, Macaubas C, Prescott SL, Venaille TJ, Holt BJ, et al. (1997) Th2-polarized immunological memory to inhalant allergens in atopics is established during infancy and early childhood. *Clin Exp Allergy* 27: 1261-1269.
69. Holt PG (1994) A potential vaccine strategy for asthma and allied atopic diseases during early childhood. *Lancet* 344: 456-458.
70. Björkstén B (1994) Risk factors in early childhood for the development of atopic diseases. *Allergy* 49: 400-407.
71. Chandra RK (1987) Environmental engineering in the prevention of atopic disease: how early is early enough? In Chandra RK, ed. *Food Allergy*. St John's: Nutrition Research Education Foundation 373-387.
72. Pauli G, Bessot JC, Dietemann A, de Blay F (1992) Prevention of mite asthma. In Godard Ph, Bousquet J, Michel FB, eds. *Advances in allergology and clinical immunology*. Lancs: The Parthenon Publishing Group 415-425.
73. Warner JO (1993) Environmental changes and asthma control in paediatrics. *Paediatr Respir Med* 1: 9-13.
74. Cantani A (1992) Phénomènes immunitaires locaux du tube digestif chez l'enfant et allergie alimentaire. *Allergol Immunol* 24: 199-205.