Allergol Immunopathol (Madr).2009;**37(6)**:279–280

Allergologia et immunopathologia

www.elsevier.es/ai

EDITORIAL

Early infections and later allergic diseases

In earlier studies, infection was presented as a risk factor for the enhancement of allergic diseases. In that sense, virus, mainly *Rhinovirus*, were identified as triggering factors of asthmatic crisis.[1] Other microorganisms, such as *Bordetella pertussis*,[2,3] and more frequently, *Respiratory syncytial virus* were considered to be a possible cause of allergy in individuals with genetic predisposition.[4] The infection by *Staphylococcus* of injured skin in atopic eczema is a frequent and well-known issue.[5] This overinfection may be the consequence of a local immunodeficiency, but its role in the chronification of eczematous lesions is also accepted. Some authors have speculated about the possibility that an episode of acute gastrointestinal infection could trigger food allergy. The increase of intestinal permeability during the infection or a more complex disturbance of the local balance of cytokines found in inflammation could be the mechanism.

The relationship between infection and allergy was discussed in an empiric way, based on single subjective experiences. The scientific basis for this relationship was introduced with the Th1/Th2 paradigm and then with the hygiene hypothesis.[6] Based on these advances, attempts have been made to explain the role of infection on allergy development. The Th1/Th2 paradigm establishes that a Th1 lymphocyte mediated response protects from the risk of allergy, whereas a Th2-mediated response provides a supplementary risk, at least in genetically predisposed children.[7] Extracellular pathogens stimulate Th2 cells, and intracellular microorganisms, mainly virus and parasites, have a similar effect on cells producing a Th1 profile of cytokines. Theoretically, infections by this type of pathogens may be protective in allergic disease.[8]

The hygiene hypothesis proposed that a general decrease in the infectious burden during early life and variations in the gastrointestinal flora are responsible for the worldwide increase of allergic diseases.[9] Another cornerstone of the hygiene hypothesis depends on the immature pattern of the immune response in children.[10,11] Foetal and cord blood cells tend to respond with Th2-type cytokines (IL-4, IL-5, IL-3), whereas the response of Th1-type cytokines (IL-12, INFg) is lower, and newborns have to change to the adult pattern in the following months, and the rate of maturation is thought to be slower in allergic children.[9] The allergenic stimulation in early childhood, by way of generating Th2 memory cells, may be definitive for the appearance of allergy sensitisation.[12] On the other hand, neonatal infections caused by certain microorganisms are supposed to accelerate the Th1 maturation in children and to protect against later allergic disease.

In this issue of Allergologia et Immumopathologia, Diego Peroni et al.[13] studied 36 newborns with sepsis, and show that the frequency of clinical allergic disturbs or abnormal biological parameters at 5–6 years of age were similar to controls. They were unable to demonstrate that suffering from a severe infection during the neonatal period was neither a protective, nor detrimental factor for asthma or allergy in later stages of life. Peroni's hypothesis was very attractive; although whether the severity of the infection is an additional risk factor remains unknown. Until now, recurrent or persistent infections seem to have a stronger influence than an isolated episode, even when very severe. An interesting aspect to consider is the age of children, newborns, since a lot of studies suggest that immunisations received during the early weeks of life influence definitively in the immunological memory and the later response.

Not all microorganisms cause similar Th1 or Th2 response; for this reason the influence of neonatal sepsis on allergic diseases might be studied by using very homogeneous groups, with similar pathogens, something that is not easy to achieve due to the limited figures of positive blood cultures in neonatal sepsis.

More studies did not confirm that to suffer early infections or bacterial colonisation was a protective factor against developing allergic diseases later.[14] Bremmer et al.[15] followed up 3549 cases and controls, from birth to the appearance of hay fever, evaluating 30 different types of infection diseases. They concluded that none of them were protective against hay fever, except bronchiolitis and only for a subgroup of cases, probably by chance. Previously, Koop MV et al.[16] in 2005, studied 140 newborns with sepsis but did not find a lower frequency of allergic diseases in the patients compared to a group of 696 controls.

0301-0546/$ - see front matter
doi:10.1016/j.aller.2009.10.002

A confounding factor when the importance of infection in allergic prevalence is evaluated, is the use of antibiotic treatment, which is mandatory in severe sepsis. Marra F et al.[17] followed up a cohort of 251,817 newborns from 1997 to 2003, studying the role of antibiotic treatment before 12 months of age on the appearance of asthma after 24 months of age. They found a slight association, which increased after adjusting for other variants like infections. The results supported that antibiotics role is independent of infection; moreover it was a dose-dependent effect. Wickens et al.[18] followed up a cohort of 1011 newborns until 15 months of age and 986 until 4 years. The association antibiotics and asthma was confusing and the causality remained unclear since asthmatic patients might need more antibiotic treatment. However, the authors suggested that antibiotics have a direct role because an association with atopic eczema was also found. Other authors have published less conclusive results,[19,20] so although the use of antibiotics in early life might have a protective effect on allergic disease, further research is needed.

In summary, allergic disease is the result of an important genetic component, which remains largely unknown, interplaying with additional environmental factors, at a critical time when the immune system is still immature. Although infection is likely an important factor in the development of allergy, the number of candidate factors and the diversity of allergic phenotypes are so large, that assessing the weight of an isolated factor, such as neonatal sepsis, represents an enormous task which may be only fulfilled when a vast number of samples are available, and collected following clear and homogeneous criteria.

References

1. Papadopoulos NG, Kalobatsou A. Respiratory viruses in childhood asthma. Curr Opin Allergy Clin Immunol. 2007;7:91–5.
2. Egger M, Zwahlen M, Kuehni CE. Routine vaccination against pertussis and the risk of childhood asthma: A population-based cohort study. Pediatrics. 2009;123:944–50.
3. Kendirli SG, Yilmaz M, Bayram I, Altintas DU, Inal A, Karakoc G. Potential association between allergic diseases and pertussis infection in schoolchildren: Results of two cross-sectional studies seven years apart. Allergol Immunopathol. 2009;37:21–5.
4. Tourdot S, Mathie S, Hussell T, Edwards L, Wang H, Openshaw PJM, et al. Respiratory syncytial virus infection provokes airway remodeling in allergen-exposed mice in absence of prior allergen sensitization. Clin Exp Allergy. 2008;38:1016–24.
5. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358:1483–94.
6. Braun-Fahrlander C, Gassner M, Grize L, Nen U, Sennhauser FH, Varonier HS, et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. Clin Exp Allergy. 1999;29:28–34.
7. Romagnani S. Human Th1 and Th2 subsets: doubt no more. Immunol Today. 1991;12:256–7.
8. Holt PG, Sly PD, Bjorksten B. Atopy versus infectious disease in childhood: a question of balance. Pediatr Allergy Immunol. 1997;8:53–8.
9. Martinez FD, Holt PG. Role of microbial burden in aetiology of allergy and asthma. Lancet. 1999;354:12–5.
10. Schaub B, Liu J, Schleich I, Hoppler S, Sattler C, von Mutius E. Impairment of T helper and T regulatory cell responses at birth. Allergy. 2008;63:1438–47.
11. Tanaka J, Watanabe N, Kido M, Saga K, Akamatsu T, Nishio A, et al. Human TSLP and TLR3 ligands promote differentiation of the Th17 cells with a central memory phenotype under Th2-polarizing conditions. Clin Exp Allergy. 2009;39:89–100.
12. Folkerts G, Walzl G, Openshaw JM. Do common childhood infections "teach" the immune system not to be allergic? Immunol Today. 2000;21:118–20.
13. Peroni D, Pescollderungg L, Piacentini GL, Pollini F, de Luca G, Boner AL. Neonatal sepsis and later development of atopy. Allergol Immunopathol. 2009; this issue: doi:10.1016/j.aller.2009.05.007.
14. Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnelykke K, et al. Cjildhood asthma after bacterial colonization of the airway in neonates. N Engl J Med. 2007;357:1487–95.
15. Bremner SA, Carey IM, DeWilde S, Richards N, Maier WC, Hilton SR, et al. Infections presenting for clinical care in early life and later risk of hay fever in two UK birth cohorts. Allergy. 2008;63:274–83.
16. Kopp MV, Semmler S, Ihorst G, Berner R, Forster J. Hospital admission with neonatal sepsis and development of atopic disease: Is there a link? Pediatr Allergy Immunol. 2005;16:630–6.
17. Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A, et al. Antibiotic use in children is associated with increased risk of asthma. Pediatrics. 2009;123:1003–10.
18. Wickens K, Ingham T, Epton M, Pattemore P, Town I, Fishwick D, et al. the New Zealand Asthma and Allergy Cohort Study Group. The association of early life exposure to antibiotics and the development of asthma, eczema and atopy in a birth cohort: confounding or casualty? Clin Exp Allergy. 2008;38:1318–24.
19. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, Frischer M, et al. Early exposure to infections and antibiotics and the incidence of allergic disease: A birth cohort study with the West Midlands General Practice Research Database. J Allergy Clin Immunol. 2002;109:43–50.
20. Kusel MMH, de Klerk N, Holt PG, Sly PD. Antibiotic use in the first year of life and risk of atopic disease in early childhood. Clin Exp Allergy. 2008;38:1921–8.

A. Blanco Quirós
Pediatrics and Instituto de Biología y Genética Molecular (IBGM), University of Valladolid, Spain
E-mail address: ablanco@ped.uva.es

E. Arranz Sanz
Immunology and Instituto de Biología y Genética Molecular (IBGM), University of Valladolid, Spain