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. Other microorganisms, such as Bordetella pertussis, and more frequently, Respiratory syncytial virus were considered to be a possible cause of allergy in individuals with genetic predisposition. The infection by Staphylococcus of injured skin in atopic eczema is a frequent and well-known issue. 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 an 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. 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. 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.

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. Another cornerstone of the hygiene hypothesis depends on the immature pattern of the immune response in children. 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, INFγ) 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. The allergenic stimulation in early childhood, by way of generating Th2 memory cells, may be definitive for the appearance of allergy sensitisation. 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 Immunopathologia, Diego Peroni et al. 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. Bremmer et al. 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. 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.
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. 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. 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, 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, playing 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