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EDITORIAL

The influence of microorganisms in allergic diseases

In 1819, and for the first time in history, John Bostock presented the Royal London Medical Society with a ''case of a periodical affection of the eyes and chest'', describing the seasonal allergic rhinoconjunctival symptoms of a patient called ''J.B.'' (himself, in fact).[1] Following those observations, towards the end of the XIXth century, allergy was regarded as a ''disease of the aristocracy'', after Bostock concluded that it mainly affected the accommodated classes. Theories linking atopic diseases and lifestyle have been proposed ever since then.

One hundred and seventy years later, in 1989, Strachan proposed a formal theory based on studies about the relationship between hay fever and microbial infections in early childhood and adolescence in the United Kingdom.[2] In a certain way, allergy would be the price to pay in exchange for reducing morbidity-mortality, especially in children, through the reduction or elimination of infections such as measles, tuberculosis or hepatitis A. This author observed that atopy predominates among first-born and single-born children – a circumstance believed to possibly result from a lack of stimulation of the immune system by certain bacterial substances.[2] The so-called ''hygiene hypothesis'' holds that improved hygiene in early life reduces microbial exposure, counteracting the protective role of microorganisms that prime the immune responses, which are important for preventing atopic disorders. The word ''hygiene'' should not be confused with cleaning, but should be taken to indicate less exposure to microbes due to the increasingly widespread use of vaccines, antibiotics, pesticides, pasteurization and processing of food, cesarean delivery, and less exposure to bacterial lipopolysaccharides from farm cattle or pets, among other factors.

In 2002, Bach reviewed the mechanisms underlying the dual role of infectious diseases in autoimmune and allergic disorders. On one hand, infectious diseases can induce autoimmune disorders by promoting autoantibodies, while on the other hand they could reduce allergic and autoimmune syndromes.[3] In fact, Okada et al. applied the hygiene hypothesis to cover asthma and also autoimmune diseases.[4]

Infection by *Helicobacter pylori* is the most common human infection worldwide: approximately 50% of the world population is infected, with a higher risk of primary infection during early childhood; great differences between developed and developing countries; and the existence of a North-to-South gradient.[5] It has been hypothesized that in the same way as other microorganisms, *H. pylori* could protect against allergic diseases, especially when infections are acquired in early childhood, reducing the risk and severity of asthma in childhood.[6] The incidence and prevalence of *H. pylori* infection has been rapidly decreasing in developed countries, especially after World War II,[7] correlated to the increased prevalence of allergic diseases.[8]

The mechanism whereby this gramnegative bacterium protects against allergic diseases is not clear. *Helicobacter pylori* promotes the release of proinflammatory cytokines and the recruitment of both local and systemic regulatory T cells (Treg) towards the gastric mucosa, with both local and systemic effects - shifting immunity towards the Th1 phenotype and inhibiting the Th2 response, which is the most important T cell response related to allergy.[9] In addition, contact between *H. pylori* and the dendritic cells turns the latter into tolerogenic cells that secrete IL-18, a cytokine with an important role in the conversion of naïve T cells into Treg, inhibiting mast cell activation and the production of Th2 cytokines.[10] However, the protective role of *H. pylori* remains controversial. Wang et al. found weak evidence for an inverse association between asthma and *H. pylori* infection,[11] while Karimi et al. concluded that *H. pylori* infection plays no role in asthma.[12]

Several virulence markers have been identified from *H. pylori*, such as vacuolating cytotoxin A (VacA), γ-glutamyl transpeptidase (GGT), and *H. pylori* neutrophil-activating protein (HP-NAP). They efficiently induce stronger Treg and Th1 responses characterized by high levels of IFN-γ and TNF-α production, helping to prevent allergic asthma.[13,14] In the present number of *Allergologia et Immunopathologia*, Karakullukcu et al. describes the results of a cross-sectional study examining the protective role of HP-NAP among children in the prevention of asthma. The study included 92 asthmatic children (mean age 5.67 years, males 58.6%, family history of asthma 60.87%) and 88 matched healthy controls (mean age 5.43 years, males 59%, family history of asthma 35.22%). The authors quantified *H. pylori* bacteria in the stool samples of asthmatic children and in healthy con-

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trols, and also quantified the expression of the HP-NAP gene implicated in *H. pylori* infection. The authors did not find *H. pylori* DNA in any of asthmatic children, but found it in 20.4% of the healthy controls, with some differences in HP-NAP gene expression among them, probably due to different endogenous gene expression levels or different environmental conditions that affect such expression.

In conclusion, the study suggests that HP-NAP is an important protein that protects children from asthma and can be regarded as an important candidate for novel strategies to prevent allergic diseases, shifting Th1/Th2 immune responses towards the Th1 phenotype. In future, some microorganisms, other than probiotics or parts of probiotics, could be used in infants to promote protective immune responses.

The main limitations of the study are the selection of patients and the assessment of *H. pylori* infection. The authors do not explain whether the predominance of males included in the study could affect the results, or whether the *H. pylori* positive ''healthy'' subjects showed gastric symptoms, or had any other complaints. On the other hand, the detection of *H. pylori* is based on quantitative PCR using the HP-NAP gene. The authors do not explain whether increased detection of the HP-NAP gene provides greater protection against asthma.

Some other issues remain to be addressed, for example: Are asthmatic/allergic patients better able to defend themselves against *H. pylori* than the non-atopic population? (reversal causation); or Could *H. pylori* infection be a confounding factor associated to other protective factors, such as overcrowding, time away from home, pets, number of siblings, or less access to antibiotics or the healthcare system? In other words, Is *H. pylori* a true ''protector'' or is it simply an epiphenomenon, a marker associated to other factors linked to poorer socioeconomic levels that have not been measured? Finally, the dual role of infectious diseases in preventing and promoting autoimmune and allergic diseases requires further investigation.

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