Asthma and gene-environment interaction: are we on the right path in our clinical practice?

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Emerging studies concerning pathophysiological mechanisms involved on the development and persistence of asthma reveal complex gene-environment interactions, in which identified genes interact with multiple environmental factors.[1,2] In clinical practice, important efforts are expended for control medications and the identification of physical-chemical and biological factors that trigger or aggravate asthma. However, in the outpatient follow-up of patients, the praxis of how to recognize and act over psychosocial factors strongly implied in asthma development, as well as other diseases, is still incipient on the biopsychosocial perspective.[3,4] Some of these psychosocial factors are studied under the denomination of ACE (Adverse Childhood Experiences), which include adverse experiences in the beginning of life, from the pregnancy until 18 years of age. These are examples of ACE: violence by intimate partner during pregnancy; separation from parents or caregivers; psychiatric diseases and alcohol and other drugs abuse by parents or caregivers; psychological, physical and sexual violence, among other situations.[5,6]

Studies concerning ACE and their biopsychosocial repercussions in adult life were initiated by Fellitie *et al*.[7,8] in the 1980s – the Adverse Childhood Experiences Study (ACE Study).[7,8] The discoveries of the "Decade of the Brain" and the Human Genome Project, both in 1990s, propelled even more the surveys on gene-environment interaction, highlighting the acting of epigenetics in the emergence of diseases throughout life.

Epigenetics is characterized by alterations in the gene expression that occur without alterations in DNA structure. In 2007, Ptashne[9] defined three criteria for the characterization of epigenetics as an alteration in the activity of a gene: 1) that does not involve a mutation; 2) and that is started by a sign; and 3) that may result in altered risk of disease in the absence of the sign that started its alteration. Classically, 4 epigenetic mechanisms were identified: 1) deoxyribonucleic acid methylation (DNAm); 2) modification of histones; 3) chromatin remodeling; and 4) small non-coding ribonucleic acids or microRNA (miRNAs).[1,9]

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The epigenetic information is partially stable in the course of mitosis and establishes a memory (or signature) of previous expositions, particularly in transitions of development. The periods of development more vulnerable to environment actions over the genes are the intrauterine period and the pre-puberty stage.[2,10] The meiotic epigenetic inheritance in germinative cells is being laboratory proven in *Caenorhabditis elegans*, the first animal that had its genome totally sequenced and functions as model of genetic study of many human diseases. This recognition that the epigenetic information can be transmitted throughout generations (that is, through meiosis) encourages studies about the transmissions of diseases in intergenerational, transgenerational and multigenerational manners.[2,11]

The inheritance is intergenerational when the maternal environmental expositions that have direct effects over the fetus and its germinative cells lead to the alteration of the phenotype of the child, and possibly of the grandchild. Transgenerational inheritance corresponds to environmental expositions of the father or mother before conception, with effects in the next generation and that is revealed in the affected descendants even in the absence of direct environmental exposition. The multigenerational inheritance occurs with the transmission of epigenetic information throughout generations in the absence of any direct environmental exposition or genetic manipulations.[11]

Also in 2007, the pediatrician Peter Gluckman *et al*.[12] proposed the Developmental Origins of Health and Disease (DOHaD), which reinforced the importance of considering the human biological plasticity towards the interaction with environmental events, especially those that occur in the beginning of life.[12] In this scenario, in the last decade studies about the response to toxic stress in the context of ACE were published. The toxic stress is a prolonged and intense immunoendocrine response of the body to stressful events, when there is a higher production of glucocorticoids and predisposition to epigenetic events.[6] With regard to asthma, it was demonstrated in animals that maternal stress during pregnancy might increase inflammation in the airways and the susceptibility to allergy in the offspring.[1,2]

Given the demonstrated evidence, it is possible to infer that psychosocial factors influence the severity of asthma, the response to prescribed treatment and, mainly, in the quality of life of patients and their families. Identifying and acting over toxic stress situations, as well as considering the intergenerationality of ACE may have a significant impact on the management of children and adolescents with asthma.

However, the identification and acting over possible psychosocial toxic contexts during consultations are challenging. The communication of the professional with patients and their families in order to triage situations of toxic stress is the first challenge to be considered.[13]Usually, the psychosocial approach of the patient in a situation of violence is not part of the curriculum of undergraduate courses in health sciences. The applying of validated tools to help the screening of violent contexts also does not seem to be frequent during consultations.[14,15]

The second challenge is the conduction of ACE cases liable of having support in the intersectoral care network. This modus operandi needs to be more publicized and expanded beyond the public health sector, in order to be also part of the routine of the private sector. The earlier our interventions over ACE, the higher the chances of decreasing deleterious effects for the biopsychosocial health of all people involved.

The prevalence of asthma is variable worldwide, but there is an increase since the second half of the last century, leading to higher impact in developing countries.[2,3] To identify and act over psychosocial factors that afflicts our patients may be a path for restoration not only for the management and prevalence of asthma, but for the countless clinical conditions that threat integrative health seem to have potential of being perpetuated for the next generations.

Author contribution

The author conceptualized the article and declared no conflict of interest.

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