



## Editorial

### [Translated article] With the Torch in the Mist of the United Airway Disease: Atopic March and Other Arguments in the Search for Evidence



### Con la antorcha entre la niebla de la vía aérea única: marcha atópica y otros argumentos en la búsqueda de la evidencia

Reality is almost always complex: in an ideal world, we would adhere to Seneca's maxim that the language of truth is simple and unvarnished, but this adage is difficult to apply to the concept of united airway disease.

The upper and lower airways are physically contiguous, they share similar histologies, and they respond to similar pathophysiological processes, so clinical manifestations may be the consequence of the same underlying disease.<sup>1</sup> Moreover, a nasobronchial reflex connecting both airways is well documented in animal models.<sup>2</sup> This has led some authors to describe the airway as a single united organ. This view is not new: in the second century, Galen of Pergamon in his publication "De usu partium" identified the effect of the upper airway on the lower airway, and defined the nose as a respiratory instrument.<sup>3</sup>

Epidemiologically, the relationship between the upper and lower airways appears strong. Rhinitis and asthma are highly prevalent diseases that often coexist in the same individual. Approximately 80% of asthma patients have rhinitis, and 10%–40% of patients with rhinitis have asthma.<sup>1,4</sup> Co-existence of both diseases in the same patient is higher than might be expected by chance, irrespective of allergic sensitization.<sup>5</sup>

From an anatomical and pathophysiological point of view, the upper and lower airways share several characteristics: they both have a ciliary epithelium with mucosal glands, they are highly vascularized, and demonstrate vagal and adrenergic innervation. Furthermore, the same inflammatory cells and mediators participate in the pathophysiology of both levels.<sup>6</sup>

The process known as atopic march could be considered a prototype of united airway disease that describes a temporal sequence, starting with atopic dermatitis (AD) and food allergies, and later progressing to asthma and rhinitis.<sup>7</sup> This concept has gained special prominence in the last 20 years with the development of the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative. This research group has been innovative in several areas: they have proposed a classification of allergic rhinitis that considers the persistence and

severity of symptoms; they have promoted the concept of concomitant asthma and rhinitis as a key factor in patient management; they have developed disease management guidelines; and they have adopted an evidence-based approach to the management of rhinitis.<sup>4</sup>

Several studies appear to support the concept of atopic march. The Tucson study, for example, found that the presence of AD in the first 2 years of life was associated with a significant increase in persistent wheezing at 6 years, with an OR of 2.4.<sup>8</sup>

Some factors associated with a greater probability of progression of the conventional atopic march have also been identified, such as polysensitization, parental atopy, persistent AD, younger age at disease onset, more severe AD, and the presence of filaggrin mutations.<sup>5</sup>

However, the atopic march model may be less common than initially thought. In a study of more than 9000 children, Belgrave et al. found that while cross-sectional studies seemed to support the concept, less than 7% of children with eczema follow a longitudinal trajectory typical of atopic march. These results suggest that the association between these diseases may be due to common pathophysiological mechanisms, but that they are independent, co-existing diseases.<sup>9</sup> Among the etiologies common to both asthma and rhinitis, environmental pollution has been associated with a higher prevalence and severity of both diseases and appears to be of particular relevance.<sup>10–12</sup> The impact of environmental factors on these diseases appears clear from studies that show that the prevalence of asthma or rhinitis has altered substantially within a few years in populations that are genetically very similar.<sup>13,14</sup>

Reverse atopic march has also been described. Barberio et al. followed a group of children aged 6–9 years with asthma but no food allergy or AD for a period of 9 years. In the follow-up period, 20% of these children developed AD.<sup>15</sup> Furthermore, in patients with non-allergic rhinitis, data consistent with the concept of united airway disease were also obtained, showing a significant association between this disease and asthma.<sup>1,7</sup>

Some links between rhinitis and asthma are well known, but further studies are still needed to achieve a more objective assessment of this interrelationship.<sup>4</sup> One aspect to consider is the effect

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of various interacting factors that are not usually analyzed together and which may influence the clinical expression of these diseases. A study of Spanish children with dust mite allergy found that a parental history of asthma or rhinitis was significantly associated with the development of the disease in offspring. Thus, a parental history of asthma was associated with a greater probability of asthma in the child and a parental history of rhinitis was associated with a greater probability of rhinitis in offspring.<sup>16</sup> Similarly, individuals with decreased filaggrin function are known to have a higher risk of AD and allergic asthma; however, in the absence of AD, decreased filaggrin function is not associated with a higher risk of asthma.<sup>17</sup>

Another important issue is the underdiagnosis of rhinitis, especially in adulthood. In a study conducted in 6 European countries, including Spain, among patients over 18 years of age diagnosed with asthma and treated with a combination of inhaled corticosteroids and long-term beta-agonists, rhinitis was evaluated in a question based on the ARIA guidelines on the intensity and frequency of nasal symptoms. It transpired that 65.7% of the patients with rhinitis had not been diagnosed.<sup>18</sup>

In conclusion, united airway disease, which may occur in some individuals, is a complex and multifactorial concept, and has probably been evaluated in an excessively simplified manner. A broader view that takes into account a range of pheno- and endotypes is needed.

#### Conflict of interests

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