



Bronchiectasthma and asthmectasis!

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Asthma and bronchiectasis: association or overlap <http://ow.ly/YHcJS>

Respiratory disease can be considered as a species in constant evolution. Due to population growth and ageing only, and apart from the current 1.1 billion smokers, there have never been more respiratory patients ever in history than today [1]. With the latest World Health Organization (WHO) worldwide estimates of 400 million individuals with rhinitis, 334 million asthmatics, 328 million chronic obstructive pulmonary disease (COPD) patients and over 100 million with sleep apnoea, there is plenty of opportunity for the concurrence of two or more respiratory diseases in the same person. Not surprisingly, it is now commonplace in medical journals and conferences to explore for syndromes that combine two respiratory conditions, such as COPD and sleep apnoea, asthma and COPD, lung cancer and pulmonary fibrosis, emphysema and bronchiectasis, *etc.* A relatively new kid on the block is, perhaps, bronchiectasis and asthma. Both chronic conditions are diagnosed clinically, with or without the help of imaging and lung function, and their flares (or exacerbations) share similar symptoms.

These diseases have individually been around for a while. Asthma was documented long before Hippocrates and the Egyptian Georg Ebers Papyrus, at the least nearly 5000 years ago by the Chinese *Nei Ching Su Wen* (*Classic of Internal Medicine*), written ~2697 BC, describing an asthma exacerbation. Conversely, bronchiectasis is as old as mankind, yet a definition was eluded until much more recently, when in 1819 René Laennec, and his stethoscope, reported it. The disease was researched in greater detail by Sir William Osler in the late 1800s, who actually died of complications from undiagnosed bronchiectasis [2].

Accordingly, asthma and bronchiectasis, or *vice versa*, are partners in an intense and complex, sometimes hot, relationship. They may have common aetiopathogenetic mechanisms, either genetic, environmental or immunological. Thus, certain mutations in the cystic fibrosis transmembrane conductance regulator gene are more frequent in nonallergic or neutrophilic asthma and in patients with disseminated bronchiectasis [3, 4]. Furthermore, α_1 -antitrypsin deficiency has also been associated with both diseases, although in the case of asthma there is no agreement on whether this relationship may be causal or simply corresponds to clinical misdiagnosis [5, 6]. With regard to environmental factors, respiratory tract infections in childhood have been considered as likely triggers of inflammatory mechanisms of the airways, which can lead to the future development of both diseases [7, 8]. Finally, several immunological mechanisms link asthma and bronchiectasis. On the one hand, the traditional association between bronchiectasis and immunodeficiencies, both primary and acquired, also includes asthma [9]. On the other hand, it has also been observed that innate immunity plays a role in the pathogenesis of some phenotypes of asthma and bronchiectasis. There are differences in neutrophilic, eosinophilic and paucigranulocytic asthma, both between these types and compared with healthy controls, in the expression of certain innate immune system receptors (Toll-like receptors 2 and 4, surfactant protein A and CD14), and in the production of certain cytokines (interleukin (IL)-8, IL-1 β and tumour necrosis factor- α). Some of these differences are also present in patients with bronchiectasis [10]. Moreover, asthma and bronchiectasis share protagonism in a clinical entity, allergic bronchopulmonary aspergillosis, where both constitute two of its diagnostic criteria [11]. In view of all these

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links, it is not surprising that the British Thoracic Society (BTS) recommended in its guideline for management of bronchiectasis that, in the absence of other possible aetiologies, asthma can be considered as a cause of bronchiectasis [12]. It is also worth considering that a completely opposite sequence of occurrence of both diseases, with the detection of bronchiectasis before a diagnosis of asthma, has also been reported [13].

Until recently, researchers have explored the influence in asthmatics of having bronchiectasis. In this regard, KANG *et al.* [14] observed a higher annual rate of asthma exacerbations, courses of systemic glucocorticoids and emergency room visits in a group of 50 asthmatics with bronchiectasis compared with 50 asthmatic controls. OGUZULGEN *et al.* [15] also detected a higher proportion of patients with a history of hospitalisation for acute asthma exacerbation in asthmatics with concomitant bronchiectasis (49%) compared with patients who only suffered asthma (17.6%). Moreover, in a recent analysis by the European Bronchiectasis Network (EMBARC) [16], involving 1258 patients and using the diagnostic criteria of the BTS, it was considered that asthma was the cause of bronchiectasis in 3.3% of cases; no significant differences in that proportion were appreciated depending on the severity of bronchiectasis. An unanswered question is whether asthma frequency is different within the newly suggested bronchiectasis phenotypes [17].

By contrast, the presence of bronchiectasis itself appears to increase depending on the severity of asthma. Comparing steroid-dependent asthma (SDA) and non-SDA (NSDA) patients, LUJÁN *et al.* [18] detected the presence of bronchiectasis in 20% of the SDA group and only in 4% of the NSDA group. In other series of patients with severe persistent asthma, the percentage of patients with bronchiectasis was much higher, reaching 44% [19]. In patients with both diseases, up to 49% have severe asthma [15].

In this issue of the *European Respiratory Journal*, MAO *et al.* [20] explore the opposite association, *i.e.* the influence of having asthma or not in a clinical cohort of patients with bronchiectasis. Apart from the novelty, other strengths of their research include the relatively high number of cases studied and that patients with bronchiectasis secondary to other diseases were reasonably excluded. Their most notable result was to observe that the presence of asthma was independently associated with experiencing at least one exacerbation of bronchiectasis during 1 year of follow-up (odds ratio 2.6, 95% CI 1.1–5.9; $p=0.02$).

However, a number of limitations, many of them mentioned by the authors, are worth discussing. As with all research studying possible links between asthma and bronchiectasis, MAO *et al.* [20] faced two serious challenges. First were the diagnostic difficulties in clinical practice involved with confirming the simultaneous presence of both diseases in the same patient. Quite often cases with bronchiectasis and bronchial hyperresponsiveness (BHR) were clinically and functionally indistinguishable from those of patients with bronchiectasis and asthma. BHR is very common among patients with bronchiectasis (33–45%) [21, 22] and is also associated with impaired lung function, regardless of whether or not there is concomitant asthma [23]. Secondly, it is necessary to consider the complexity of deciding whether an episode of clinical and functional impairment in a patient with asthma and bronchiectasis corresponds to an asthma attack, to an exacerbation of bronchiectasis or (perhaps more likely) to both conditions simultaneously. We must bear in mind that the symptoms of both types of episodes may be



FIGURE 1 Reconstruction of the first ever identification of bronchiectasis (plus asthma?). *Laennec and the Stethoscope*, from *A History of Medicine in Pictures*, presented by Parke, Davis & Company, directed by George A. Bender, painted by Robert A. Thom (1915–1979). Oil on canvas, creation date circa 1952, copyright 1960. Collection of the University of Michigan Health System, gift of Pfizer, Inc. Reproduced with permission from the University of Michigan Museum of Art (Ann Arbor, MI, USA).

similar or identical. In addition, there are several common causes of exacerbation of asthma and/or bronchiectasis, and also it is possible that any of the two exacerbated diseases can decompensate the other. Although the diagnostic criteria used by MAO *et al.* [20] for exacerbations of bronchiectasis seem quite robust (presence of four or more of the following symptoms/signs: change in sputum production, increased dyspnoea, increased cough, fever >38°C, increased wheezing, decreased exercise tolerance, fatigue, malaise, lethargy, reduced pulmonary function, changes in chest sounds or radiographic changes consistent with a new infectious process), it is clear that many of them also serve to diagnose asthma exacerbations. Finally, regardless of whether patients have an asthma attack or an exacerbation of bronchiectasis (or both at once), it seems logical that people with two bronchial diseases can present with “respiratory attacks” more often than subjects who only have one.

A philosophical approach to this problem could be that individuals suffering with asthma and bronchiectasis should comprise a different population and present a new syndrome worth studying and naming. The naming game in medicine has some unwritten rules. For instance, it has been recently noted that the term “syndrome” for asthma–COPD overlap syndrome is actually not well deserved [24], as some overlap may be predicted because asthma and COPD are common conditions, and there is no evidence this overlap has a distinctly known pathogenesis. However, recently, the WHO published global rules for naming new diseases [25]. In the (very unlikely) event that the overlap of asthma and bronchiectasis in the same individual were considered a new disease entity, we would present our eponym candidate to join the eminent list of doctors who helped to discover these diseases, as well as famous persons who suffered from them. Hence the Serrano–Soriano Syndrome (or the other way around) would hopefully help to identify new avenues for research, especially including those therapeutic measures that can simultaneously improve the control of both diseases, such as the treatment of airways inflammation (either with inhaled steroids [26] or macrolides [27]) or immunoglobulin replacement [28]. We will keep wondering if Laennec’s stethoscope (figure 1) and other tools will help to disentangle the overlap of asthma and bronchiectasis. Rather than suggesting bronchiectasthma and asthmectasis, we might restrain ourselves and live with asthma and bronchiectasis for the time being.

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