Airway disease: a confusion inside an enigma

Alyn H. Morice

Centre for Clinical Science, Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Hull, UK.

Corresponding author: Alyn H. Morice (a.h.morice@hull.ac.uk)

Shareable abstract (@ERSpublications)
Current diagnostic categories of airway disease are conflicting and contradictory. Historically, we were reliant on airway physiology. However, pathology is the study of disease. A reappraisal is necessary. https://bit.ly/3CZSqiQ

Cite this article as: Morice AH. Airway disease: a confusion inside an enigma. *ERJ Open Res* 2022; 8: 00519-2022 [DOI: 10.1183/23120541.00519-2022].

Copyright ©The authors 2022

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 5 Oct 2022
Accepted: 6 Oct 2022

The classification of airway disease is in a mess. When I was a medical student and dinosaurs walked the earth, there were four conditions: childhood asthma, late-onset asthma, chronic bronchitis, and emphysema. The latter two were then amalgamated, for reasons I still do not understand, into COPD, and defined on the basis of fixed airflow obstruction on spirometry. The two forms of asthma had similarities in that they had variable airflow obstruction and were steroid responsive. Childhood asthma was characterised by atopy, family history, and associated conditions such as eczema and rhinitis. Late-onset asthma rarely had these associations.

Today we have more conditions than you can shake a stick at. It is said that a camel is an animal that was designed by a committee. We have GOLD (the Global Initiative for Chronic Obstructive Lung Disease) and GINA (the Global Initiative for Asthma) and many other assemblies of the great and good advising us on the different phenotypes of COPD and asthma. However, all still cling to the idea that physiology can be used to define the disease, whereas pathology is the study of disease.

I well remember sitting in the hall at the European Respiratory Society congress when the results of the UPLIFT study [1] were first presented. Tiotropium caused a sustained and highly significant bronchodilation and I thought, "So the obstruction is no longer fixed". In the first study of metabolised inhaled steroids in asthma, the visionary Harry Morrow Brown observed that "Sputum examination in 59 cases [out of 60] showed a significant excess of eosinophil cells" and "The extent of the reversibility of the airways obstruction in each case varied widely" [2]. Pathology triumphed over physiology 50 years ago.

In this issue of *ERJ Open Research*, VAN DEN BERG *et al.* [3] report a retrospective observational study of over 2000 patients who attended the Isala Cough Clinic in the Netherlands. Chronic cough is a common but poorly recognised disease characterised by hypersensitivity of the vagus and its central nervous system projections [4]. The demographics of their population are typical of patients with chronic cough, being predominantly female with a mean age of 59 years. Over 90% had a Hull Airway Reflux Questionnaire (HARQ) score [5] above the upper limit of normal, comparable with the findings in patients with rigorously defined "refractory" chronic cough in the phase 3 studies of gefapixant [6]. What this current study reveals for the first time is that over half of the patients had an abnormal methacholine PC_{20} (provocative concentration causing a 20% fall in forced expiratory volume in 1 s), despite almost three-quarters having normal spirometry and a median exhaled nitric oxide fraction of 18 ppb. Blood eosinophilia ($>0.4\times10^9$ cells per L) was present in 6.4%.

So what does this study tell us? Chronic cough has a unique demographic, unlike asthma/COPD, however you define them. Biomarkers of these conditions are largely absent. Bronchial hyperresponsiveness (BHR) is, however, a prominent feature. It does not mean that the patient has asthma. We should define airway disease by the pathology and throw out terms such as "non-asthmatic eosinophilic bronchitis" (used for patients who do not have BHR) and "neurotrophic asthma" (which is just chronic bronchitis with wheezing). It is time for a rethink.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: A.H. Morice reports the following relationships outside the submitted work: grants or contracts received from MSD, Bayer, Shionogi, Bellus and NeRRi; royalties or licences from the HARQ questionnaire; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events received from MSD; and payment for expert testimony received from NICE. He is the chair of the task force on chronic cough for the European Respiratory Society and an associate editor of this journal.

References

1 Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
2 Brown HM, Storey G, George WH. Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. *Br Med J* 1972; 1: 585–590.
3 van den Berg JWK, Baxter CA, Edens MA, *et al.* The demographics, clinical characteristics and quality of life of patients with chronic cough from the Isala Cough Clinic in the Netherlands. *ERJ Open Res* 2022; 8: 00232-2022.
4 Morice AH, Millqvist E, Bieksiene K, *et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; 55: 1901136.
5 Morice AH, Faruqi S, Wright CE, *et al.* Cough hypersensitivity syndrome: a distinct clinical entity. *Lung* 2011; 189: 73–79.
6 McGarvey LP, Birring SS, Morice AH, *et al.* Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022; 399: 909–923.