Un-diagnosing persistent adult asthma

Lipworth, Brian J.; Jabbal, Sunny

Published in:
European Respiratory Journal

DOI:
10.1183/13993003.01433-2017

Publication date:
2017

Document Version
Peer reviewed version

EUROPEAN RESPIRATORY journal
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

Un-diagnosing persistent adult asthma

Journal:	*European Respiratory Journal*
Manuscript ID	ERJ-01433-2017.R1
Manuscript Type:	Research Letter
Date Submitted by the Author:	01-Aug-2017
Complete List of Authors:	Jabbal, Sunny; University of Dundee, Scottish Centre for Respiratory Research Lipworth, Brian; University of Dundee, Asthma & Allergy Research Group
Key Words:	exhaled nitric oxide, asthma, airway hyperresponsiveness

Un-diagnosing persistent adult asthma

[1]Brian J Lipworth, [1]Sunny Jabbal

[1]Scottish Centre for Respiratory Research, Ninewells Hospital & Medical School, Dundee, Scotland, DD1 9SY

Correspondence to: Dr BJ Lipworth, Scottish Centre for Respiratory Research, Ninewells Hospital & Medical School, University of Dundee, Dundee, DD1 9SY. Tel: +44 1382 383188 b.j.lipworth@dundee.ac.uk

The diagnosis of asthma is usually based on typical symptoms , family history , audible wheeze , peak flow , spirometry , possibly in conjunction with atopy and blood eosinophilia , as well as response to treatment . In cases where the diagnosis is less clear cut other tests may be required including impulse oscillometry (IOS), exhaled breath nitric oxide (FeNO) and bronchial challenge testing (Figure).

A commonly seen pattern in our asthma clinic would be a non-smoking patient presenting to primary care with an episode of viral associated persistent cough and wheeze, initially unresponsive to salbutamol and antibiotic, with a normal chest radiograph, negative sputum culture, normal peak flow , with or without normal spirometry. Such cases may then be given empirical treatment with inhaled corticosteroid (ICS) which may be continued in the longer term especially if symptoms take time to resolve. This also assumes that an alternative diagnosis has already been pursued in patients with persistent cough.

There is a psychological burden to an individual being diagnosed with asthma in addition to the on-going costs of treatment along with the potential for ICS related adverse effects. Once patients have been told they have asthma and on maintenance therapy it may be difficult to persuade them that either the initial diagnosis was incorrect or that they may have had an intermittent episode of asthma that subsequently resolved.

Diurnal variability on serial peak flow recordings may be a useful pointer to asthma but requires a motivated patient to properly perform and record accurate readings. Reversibility of spirometry to inhaled salbutamol (≥15% and ≥200ml increase in FEV1) is only useful for patients who have impaired FEV1 <80 % predicted where there is potential room for bronchodilator response. For patients with a preserved FEV1 >80% predicted , or for patients who cannot perform adequate spirometry ,it may be useful to consider using IOS which requires less cooperation being an effort independent test carried out during normal tidal breathing (1). A diagnosis of asthma may be supported by the

presence of heterogeneity of airway resistance as the difference between 5Hz and 20Hz (R5-R20>0.07 kPa/L.s) and salbutamol reversibility ≥ 40% (2, 3).

One of the hallmarks of asthmatic inflammation is the presence of underlying airway hyper-responsiveness (AHR), as measured by bronchial challenge testing using either direct (methacholine or histamine) or indirect (mannitol) acting stimuli (4) . Ideally such a challenge test should be performed having first stopped ICS for at least two weeks in order to avoid the possibility a false negative result. Our pragmatic regimen is to half the dose of ICS every week until a 200ug beclometasone equivalent dose is achieved, where upon it can be stopped, followed by repeat lung function and if required a challenge test two weeks later. The worsening of symptoms in association with obstructive lung function at this visit upon stopping ICS may be diagnostic in itself and obviate the need for performing challenge.

The dose related suppressive effects of ICS on AHR are more pronounced for indirect than direct acting challenges (5, 6). Hence if a challenge test is to be performed while still taking ICS, either methacholine or histamine should be used rather than mannitol. The American Thoracic Society advocate a cut off value for methacholine challenge as the provocative concentration to produce a 20% fall in FEV1 (PC20) of ≤4mg/ml being indicative of positive AHR, whereas a cut off >4≤8mg/ml is considered as being borderline (7). However, the guidelines do not stipulate whether these PC20 cut offs refer to patients on or off ICS. We and others recommend a pragmatic cut off value for PC20 ≤8 mg/ml for direct challenge (8, 9). We also advocate measuring FeNO off ICS, the reason for stopping treatment is that FeNO is maximally suppressed by low dose ICS after 1-2 weeks ,while values return back to baseline after 1 week of ICS washout (10) . ICS naïve patients with positive AHR (PC20 ≤8mg/ml) also have higher FeNO levels than those who are AHR negative (11). In this regard an elevated FeNO ≥ 35 parts per billion (12) is highly predictive of persistent asthma for a patient not currently using ICS .

Prior to challenge for patients taking combination inhalers the long acting beta-agonist (LABA) moiety should be stopped for one week while converting to ICS alone followed by tapering. The additional effect of LABA and leukotriene receptor antagonist (LTRA) on AHR amounts to less than one doubling dilution (13, 14), so that one week off such therapy should be sufficient washout in most cases. There is uncertainty about the protective effects of anti-cholinergics on AHR(15-17). Long acting muscarinic antagonists should be the first drug withdrawn for one week (18), prior to stopping LABA as part of sequential step down therapy.

In a real life study of community diagnosed asthma patients , there were 30 % who were non responsive to both methacholine and mannitol challenges , where the median beclometasone equivalent dose was 1000ug ,68% were taking LABA and 19% LTRA (9). In comparison to the 70% who were responders to challenge, there were significant differences in values for mean FEV1 (88 vs 100%), mean FeNO (26 vs 16 parts per billion), asthma control questionnaire score (1.07 vs 0.55) and skin prick positive response (79 vs 50%). A Canadian study found 28%

of patients with a physician based diagnosis who had no evidence of asthma when their treatment was tapered and evaluated using direct challenge testing , with an estimated cost saving £2100 for each un-diagnosed patient (19). In a further multicentre study from Canada using a similar protocol current asthma was ruled out in 33% of cases, and after further 12 month follow up 29% continued to have no evidence of asthma (8) .

Patients with a negative challenge test along with normal FeNO and IOS who have persistent symptoms having stopped ICS should then go on to have further tests perhaps including upper and lower airway endoscopy , high resolution CT thorax scan and gas diffusion in order to exclude possible alternative diagnoses such as chronic rhino-sinusitis , lung cancer, bronchiectasis and pulmonary embolism .

Word count = 1022

Figure Legend: Flow chart for decision making in difficult cases where there may be uncertainty about the diagnosis of persistent adult asthma.

References:

1. Galant SP, Komarow HD, Shin HW, Siddiqui S, Lipworth BJ. The case for impulse oscillometry in the management of asthma in children and adults. Ann Allergy Asthma Immunol. 2017;118(6):664-71.
2. Manoharan A, Anderson WJ, Lipworth J, Ibrahim I, Lipworth BJ. Small airway dysfunction is associated with poorer asthma control. The European respiratory journal. 44. England2014. p. 1353-5.
3. Short PM, Anderson WJ, Manoharan A, Lipworth BJ. Usefulness of impulse oscillometry for the assessment of airway hyperresponsiveness in mild-to-moderate adult asthma. Ann Allergy Asthma Immunol. 2015;115(1):17-20.
4. Chapman DG, Irvin CG. Mechanisms of airway hyper-responsiveness in asthma: the past, present and yet to come. Clin Exp Allergy. 2015;45(4):706-19.
5. Lipworth BJ, Fowler S, Wilson A, Crompton GK, Woodcock A, Daley-Yates PT. Fluticasone propionate bioavailability in asthma [1] (multiple letters). Lancet. 2000;356(9242):1681-2.
6. Currie GP, Stenback S, Lipworth BJ. Effects of fluticasone vs. fluticasone/salmeterol on airway calibre and airway hyperresponsiveness in mild persistent asthma. British Journal of Clinical Pharmacology. 2003;56(1):11-7.
7. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med. 2000;161(1):309-29.
8. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemiere C, et al. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. JAMA. 2017;317(3):269-79.

9. Manoharan A, Lipworth BJ, Craig E, Jackson C. The potential role of direct and indirect bronchial challenge testing to identify overtreatment of community managed asthma. Clin Exp Allergy. 2014;44(10):1240-5.
10. Anderson WJ, Short PM, Williamson PA, Lipworth BJ. Inhaled Corticosteroid Dose Response Using Domiciliary Exhaled Nitric Oxide in Persistent Asthma The FENotype Trial. Chest. 2012;142(6):1553-61.
11. Dupont LJ, Rochette F, Demedts MG, Verleden GM. Exhaled nitric oxide correlates with airway hyperresponsiveness in steroid-naive patients with mild asthma. American journal of respiratory and critical care medicine. 1998;157(3 Pt 1):894-8.
12. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602-15.
13. Currie GP, Jackson CM, Ogston SA, Lipworth BJ. Airway-stabilizing effect of long-acting beta2-agonists as add-on therapy to inhaled corticosteroids. QJM : monthly journal of the Association of Physicians. 2003;96(6):435-40.
14. Currie GP, Lipworth BJ. Bronchoprotective effects of leukotriene receptor antagonists in asthma: A meta-analysis. Chest. 2002;122(1):146-50.
15. Jabbal S, Manoharan A, Lipworth B. Bronchoprotective tolerance with indacaterol is not modified by concomitant tiotropium in persistent asthma. Clin Exp Allergy. 2017.
16. Britton J, Hanley SP, Garrett HV, Hadfield JW, Tattersfield AE. Dose related effects of salbutamol and ipratropium bromide on airway calibre and reactivity in subjects with asthma. Thorax. 1988;43(4):300-5.
17. Thomson NC, O'Byrne P, Hargreave FE. Prolonged asthmatic responses to inhaled methacholine. The Journal of allergy and clinical immunology. 1983;71(4):357-62.
18. O'Connor BJ, Towse LJ, Barnes PJ. Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. Am J Respir Crit Care Med. 1996;154(4 Pt 1):876-80.
19. Pakhale S, Sumner A, Coyle D, Vandemheen K, Aaron S. (Correcting) misdiagnoses of asthma: a cost effectiveness analysis. BMC Pulm Med. 2011;11:27.

192

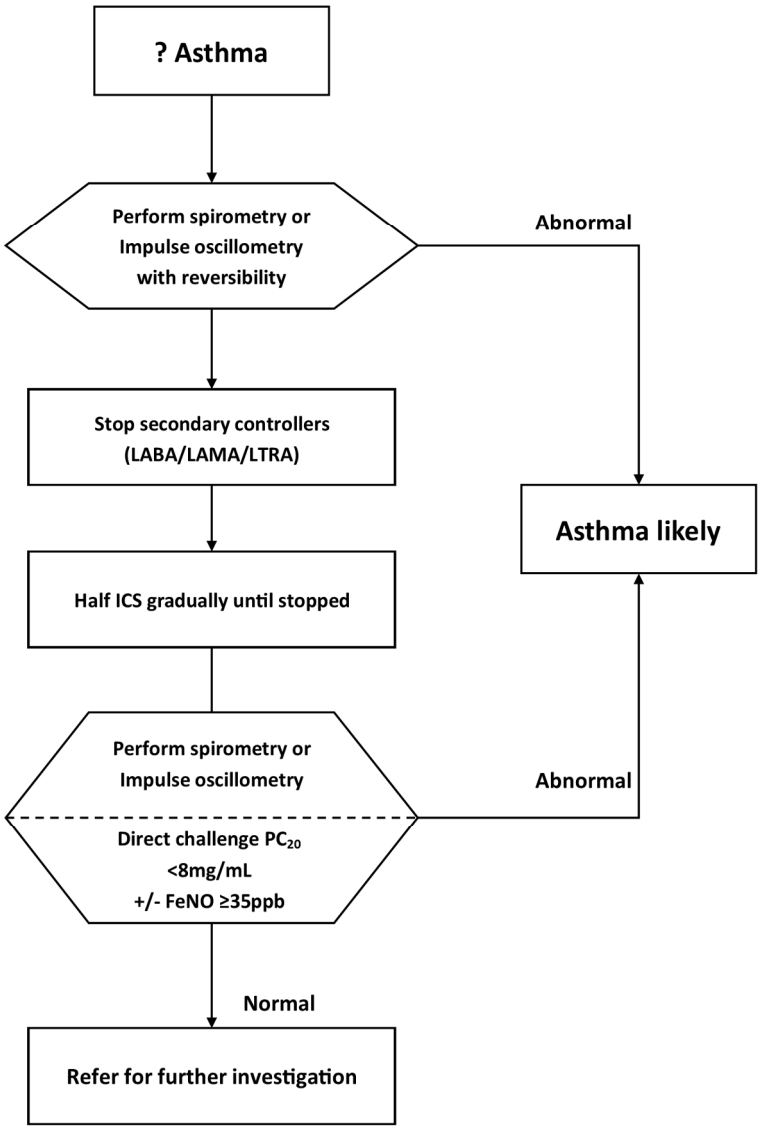

Figure Legend: Flow chart for decision making in difficult cases where there may be uncertainty about the diagnosis of persistent adult asthma.

445x623mm (96 x 96 DPI)