

Review of Diagnostic Challenges in Occupational Asthma

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Abstract

Purpose of review Occupational asthma (OA) is one of the most frequent occupational diseases and its diagnosis is often difficult. This review summarizes its current diagnostic challenges.

Recent findings OA is associated with significant health and socio-economic burden. It is underdiagnosed and physicians need to adopt a stepwise approach to confirm the diagnosis. Although early removal from exposure to the offending agent is associated with a better prognosis, physicians should try to confirm the diagnosis of work-related asthma before taking a worker off work. A proper occupational and medical history is very important but is not enough to make the diagnosis of OA. Objective evidence of work-related asthma is required and this represents a serious challenge to most physicians. Measurement of non-specific bronchial responsiveness (NSBR) and spirometry may confirm the diagnosis of asthma but do not confirm the diagnosis of OA. Serial monitoring of peak expiratory flows (PEF), NSBR, and airway inflammation at and off work may confirm the diagnosis of OA but are often difficult to perform. Confirming sensitization by skin prick tests or specific IgE may help to support the diagnosis of OA. Specific inhalation challenges (SIC) in the lab or at

work are considered the reference standard but are of limited access. Medical surveillance programs along with primary prevention (reducing exposure) may help to reduce the burden of OA, but the ideal program has yet to be defined.

Summary The diagnostic workup of OA remains a challenge and needs a rigorous stepwise evaluation.

Keywords Occupational asthma · Specific inhalation challenges · Monitoring · Peak expiratory flow

Introduction

Occupational asthma (OA) is one of the most frequent occupational respiratory diseases. Its annual incidence ranges between 22 and 40 cases per million of active workers and its prevalence is estimated around 16% of new onset adult asthma [1]. A recent American study showed that the proportion of incident asthma among adults that might be work-related was even greater, 18.2% [2]. OA, belonging to the category of work-related asthma, is defined by asthma due to causes and conditions attributable to a particular workplace environment and not to stimuli encountered outside the workplace [3]. The mean age at diagnosis is 38 years [4], making asthma a disease affecting a young population of workers. Workers diagnosed with OA tend to have more symptomatic days, more exacerbations, a greater utilization of healthcare resources, and a lower quality of life as compared to patients with non-work-related asthma, which is probably explained by the daily exposure to the offending agent at the workplace [5]. Furthermore, the prognosis of OA is often poor with the majority of subjects remaining either symptomatic or with abnormal lung function; however, early removal from exposure to the offending agent is the best way to improve outcome [6]. In terms of costs, several studies tried to address this point. Ayres

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et al. calculated the total lifetime costs (direct + indirect costs) for all cases of OA diagnosed in UK during 2003 [7]. The total lifetime cost for each individual OA case was estimated between 120,000 and 130,000 £. When these numbers were reported to the whole UK, the total lifetime cost for all OA cases diagnosed in 1 year (2003) ranged between 70 and 100 millions £. In Quebec, Malo et al. showed that the total costs for loss of income and compensation due to functional impairment were 61,300 CAN\$ per case, for the period 1988–2002 [8]. Higher costs of compensation for loss of income in men (but not in women) were associated with older age, rehabilitation programs, and married status [9]. The total direct costs for OA cases that required specialized care in 2008 in Spain were estimated to be around 18 millions € [10]. Among the risk factors, exposure intensity and the sensitizing properties of the involved agents are the main environmental risk factor whereas atopy (for high molecular weight agents), genetic factors (including genetic predictors involved in the early steps of OA [11]), the presence of occupational rhinitis, and, in some cases, smoking are individual risk factors for developing OA [12, 13]. Therefore, OA is a major concern in terms of public health, due to its high incidence and prevalence, its costs and the young age of workers at diagnosis.

The Diagnosis of OA: a Stepwise Approach

As stated in the most recent international guidelines [14, 15•] and in a recent review [16•] on work-related asthma and OA, clinicians have first to confirm the diagnosis of asthma, then establish the link between asthma and the workplace and finally identify the responsible agent. The investigation follows a stepwise approach.

The first step in the investigation of a worker suspected of OA is collecting the clinical and occupational history, which allows the clinician to estimate the clinical likelihood of the diagnosis of OA. In order to refine and strengthen this likelihood, a combination of different tests including spirometry, immunologic tests, measurement of non-specific bronchial responsiveness (NSBR), and monitoring of peak expiratory flow (PEF) at work and off work, coupled with monitoring of NSBR and airway inflammation, are often required [16•]. None of these tests alone is entirely specific to identify OA cases and their sensitivity varies considerably. Although specific inhalation challenges (SIC) are considered the reference standard for OA, they are not easily available and are expensive, time consuming, and can generate false-positive and false-negative results [17•].

Therefore, the diagnostic workup of OA cases is not straightforward and can be a challenge for clinicians. Every new adult-onset asthma case should be considered a potential case of OA and high level of suspicion is essential to prevent adverse outcomes. Early referral in specialized centers or early

investigation to establish the diagnosis of OA will hopefully reduce the burden of OA [18].

The aim of the review is to outline the limits and challenges in the clinical assessment of OA. We performed a search for French and English original studies and reviews using Pubmed for the period January 2011–June 2016.

Clinical and Occupational History

As the first step in the diagnosis workup, the clinical and occupational history has to focus on asthma symptoms (i.e., dyspnea, cough, wheezing, chest tightness) and their relationship with the work environment. However, OA is often under diagnosed, partly due to the fact that clinicians, even specialists, do not consider the possibility of the diagnosis [14, 19]. Chest physicians reported that low awareness of the disease and lack of knowledge and time are the main barriers to consider a potential diagnosis of OA [19]. Classically, respiratory symptoms are triggered by the workplace exposure, are worse at work and improve over the weekend and holidays. But, as shown by Tarlo et al., this pattern is highly non-specific as workers with non-work-related asthma also report some improvement during the weekend (41%) and on holidays (54%) [20]. Overall, although the worker recollection is often very sensitive, it is not very specific as confirmed by Malo et al. who showed that the positive predictive value of a history suggestive of OA was only 63% [21], meaning that in 37% of workers giving a history suggestive of OA, the diagnosis was not confirmed.

In order to improve this situation, several teams have developed and evaluated specific questionnaires. Pralong et al. have shown that a simple model based on 11 questions along with age and exposure duration has the ability to correctly discriminate 80% of workers suspected of OA in a clinical setting [22]. Among the 169 workers of this study, wheezing at work had the strongest positive predictive value for OA. Vandenplas et al. had shown in a previous study that wheezing, along with nasal and ocular itching, were positively associated with OA while loss of voice was negatively associated with OA to high molecular weight (HMW) agents [23]. Killom et al. have proposed the use of a work-related asthma screening questionnaire in the primary care setting in order to improve the diagnosis of work-related asthma and OA [24]. This questionnaire identified work-related symptoms and workplace exposures in 38 and 59% of subjects, respectively, which were not identified in standard care. Even if these models seem promising, they need prospective validation.

Besides symptoms, clinicians need to consider known risk factors for OA. Although industrial and environmental factors (e.g., agent, level and type of exposure, spills) are the main risk factors, personal risk factors should be considered when evaluating a worker with suspected OA. If genetic risk factors are not useful in clinical practice, inquiry about atopy,

presence of rhinitis, and previous history of asthma is essential [12]. Considering the united airway model, occupational rhinitis (OR) has been associated with OA in 58.4% of OA diagnoses in a large French study [25]. This association increased to 73.6% in OA cases due to HMW agents. Moreover, in 84.5% of cases, OR preceded or was concomitant with the diagnosis of OA. The close link between OR and OA and the finding that OR precedes the onset of OA in a majority of cases support OR as a risk factor for OA; the authors concluded that clinicians have to screen for rhinitis symptoms in workers at high risk of OA, especially in those exposed to HMW agents, in order to prevent the subsequent development of OA [25]. A previous history of asthma does not exclude the diagnosis of OA but is not a risk factor to develop OA.

Assessment of workplace exposure is an essential part of the occupational history and includes a detailed occupational history looking for the presence of potential sensitizers in the workplace. However, workers are often not aware of the nature of the agents they are exposed to at work, both directly or indirectly. Material and safety data sheets may help the clinician to identify potential sensitizers but they are often not complete, ignoring agents which are found in low concentrations [26]. A recent study demonstrated that clinicians are less efficient than occupational hygienists in identifying occupational agents [27]. That was especially true in a majority of workers who had a negative SIC in the laboratory, which may have resulted in some workers being misdiagnosed as not having OA. Therefore, the authors concluded that the evaluation of exposure by an occupational hygienist may be useful in situations when no causal agents can be identified by clinicians in workers with a history highly suggestive of OA. Therefore, as suggested by Tarlo, when a SIC in the laboratory is negative, physicians should consider seeking the input of an occupational hygienist to identify other potential sensitizers [28]. This could lead to additional challenges in the laboratory or a trial of return to work in the same conditions with a careful objective monitoring to detect changes in asthma related to work [28]. The latter is particularly true if no symptoms were elicited by the exposure in the lab—a specific challenge at work, which may be followed by serial monitoring of airway function and inflammation at and off work, may then confirm in some cases the diagnosis of OA [29].

Immunological Markers

Both skin prick tests and specific IgE measurements are sensitive for detecting type 1 sensitization and occupational asthma caused by most high molecular weight agents, acid anhydrides and some reactive dyes, but are not specific for diagnosing occupational asthma, as reported in the guidelines for the management of work-related asthma [15••]. Furthermore, there is a lack of standardization of the extracts of most

occupational agents because most extracts are made by each laboratory. Their usefulness in most cases of low molecular weight (LMW) agents is even more limited. In the case of isocyanate-induced OA, specific immunological markers have been evaluated: measurements of specific IgG and of isocyanate stimulation of monocyte chemoattractant protein-1 have however limited value in the diagnosis of OA although they may be used in some cases in order to improve the clinical probability of OA [30].

Biological Markers (EBC, Sputum, Exhaled Fraction of NO (FeNO))

Among the biological markers, induced sputum with eosinophils and neutrophils count and evaluation of different cytokines levels have been used to assess airway inflammation in OA. The use of sputum differential cell counts during the diagnostic workup of OA can add additional measures of airway inflammation [31]. A recent study looked at the sputum inflammatory cell profile, cytokines, and leukotrienes following SIC in workers with suspected OA [32]. The authors reported an increase in sputum eosinophils, neutrophils, and IL-10 concentration and a decrease in leukotriene B4 levels in workers with OA due to exposure to HMW agents but not in those exposed to LMW agents. They concluded that workers diagnosed with OA have different inflammatory profiles, depending on the type of causal agent (either HMW or LMW) they are exposed to. Lemiere et al. showed that workers with a low eosinophils count (<2%) in induced sputum at the time of the SIC had a lower FEV1, greater airflow obstruction, more increased NSBR, poorer control of their asthma, and a greater need of ICS during their follow-up several years after the diagnosis of OA [33]. They concluded that OA workers with a low eosinophils count in induced sputum had a poorer prognosis.

There has been an increased interest in the use of FeNO monitoring in the diagnosis workup of OA. Merget et al. published a case report of a baker unable to undergo SIC who had daily measure of FeNO during 1 month, at work and off work [34]. Whereas symptoms and FEV1 showed no change between at and off work periods, FeNO showed a significant increase from below 10 ppb off work to 75 ppb at work. Based on the variation of the FeNO values, a diagnostic of baker's asthma was made and the worker had to leave his job with some improvement in his symptoms 1 year later. This technique might therefore be helpful in selected cases but studies are needed to confirm the usefulness of serial FeNO measurements.

A recent study evaluated the change in FeNO following positive SIC among 16 workers exposed to LMW agents; 14/16 workers with a positive SIC had no statistically or clinically relevant increase in FeNO, and therefore, change in FeNO did not predict a positive SIC in this group [35].

Another study evaluating the change in FeNO following SIC found a significant (25%) increase of FeNO levels post SIC in the group with positive SIC, but, due to the low predictive diagnostic capacity of FeNO measurement, the authors concluded that FeNO could not be used as a surrogate marker to predict or assess SIC [36]. A review of the usefulness of FeNO levels in the investigation of OA by Lemiere showed conflicting results explained partly by some issues concerning the methods, treatment of inhaled corticosteroids, different phenotypes among OA workers, and the effect of bronchoconstriction on FeNO levels [31]. The author concluded that, despite some practical advantages over the analysis of induced sputum in OA, changes in FeNO are less sensitive than changes in sputum eosinophil counts in the case of positive SIC. Furthermore, the interpretation of FeNO levels remains more difficult than changes in sputum eosinophil counts. In settings where sputum eosinophil count is available, this test does complement the investigation of OA. Lemiere also showed that FeNO increased after SIC more consistently with HMW agents as opposed to LMW agents [37].

Peak Expiratory Flow Monitoring

Simple and portable devices have made easy the monitoring of PEF at and off work [14, 38, 39] in order to document objectively the relationship between worsening of asthma and work. The sensitivity and specificity of PEF monitoring in the diagnosis of OA are around 64 and 77%, respectively. We rely more on the visual analysis of the recording comparing changes in PEF between days at and off work—a change in PEF of at least 20% is usually considered significant [40]. The use of a computer-based system analysis of PEF (OASYS) has also been proposed by the group of S. Burge and has proven its usefulness [41–43]. However, there are many pitfalls in PEF monitoring, generating both false-positive and false-negative results. Indeed, PEFs may under- or over-estimate changes in airway caliber as assessed by FEV1 [44–46]. Peak expiratory flow monitoring also requires the collaboration of the worker which may not be obtained either by fear of losing his job or malingering to gain compensation benefits; however, this leads more often to underestimation of the PEF changes than overestimation [47, 48]. Finally, workers have to be exposed at work to the offending agent and to be symptomatic during the period of PEF monitoring. To improve its overall performance, PEF monitoring may be combined with serial measurements of NSBR [49] and, when possible, of sputum induction [50].

Spirometry and Non-specific Bronchial Responsiveness

Spirometry and the measurement of NSBR are essential components of the investigation of workers referred for OA.

Indeed, the presence of reversible airflow obstruction may confirm the diagnosis of asthma, but not of OA. However, when seen in the clinic, subjects with OA have often a normal spirometry. In that situation, the diagnosis of asthma may then be confirmed by increased NSBR as assessed by methacholine or histamine bronchial challenges, although it does not confirm the diagnosis of OA. However, on one hand, normal NSBR does not exclude the diagnosis of OA in a worker not exposed to the offending agent, as return to work may be associated with an increase in NSBR [51, 52]. On the other hand, it may be very useful in a worker still at work and symptomatic. In a large retrospective study of 1012 subjects, we have looked recently at the added value of the methacholine challenge in the investigation of workers suspected of OA and referred to our tertiary care clinic using SIC as the reference standard for diagnosing OA [4]. The overall negative predictive value (NPV) of the methacholine challenge was 86.3%. When considering only workers still exposed at work at the time of the methacholine challenge, the NPV increased to 95.2%. Furthermore, when considering all workers tested by a methacholine challenge at least once while at work, the NPV reached 97.7%. This study supported current guidelines suggesting that a negative methacholine challenge in a worker still exposed at work and symptomatic virtually excludes the diagnosis of OA. This stresses the importance to assess NSBR when the subject is still at work, and whenever possible, to confirm objectively the diagnosis of OA before withdrawing the subject from work to reduce the socio-economic burden of a wrong diagnosis. This is an important validation in the context of screening workers at risk of OA.

Specific Inhalation Challenge

A consensus statement has been published by the ERS task force on SIC with occupational agents [17••]. The key messages of the task force are the following: (1) general safety requirements, contraindications, and precautions should be strictly applied in order to minimize the risk of severe adverse events; (2) the duration or concentration of exposure to occupational agents should only be gradually increased under close monitoring of functional parameters; (3) a control challenge test with a 6–8-h period of spirometric monitoring on a separate day is required for the interpretation of SIC results; (4) changes in FEV1 should be the primary physiological outcome measure, but other functional indices (i.e., airway resistance/conductance) may be useful in subjects who cannot perform reproducible FEV1; and (5) NSBR should be measured at least at baseline and following a negative SIC—to reduce the risk of false-negative results as assessed by FEV1 changes, repeated (longer period of exposure) SIC should be performed when there is a significant increase in post-SIC NSBR or an increase in sputum eosinophils and FeNO. Although SIC

comes close to a gold standard, a negative SIC in a worker with otherwise good evidence of OA is not sufficient to exclude the diagnosis [15••]; SIC in the workplace or return to work with monitoring of PEF, NSBR and sputum induction should be considered [28, 29].

A European survey presented the results of 24 specialized centers performing SICs around the continent [53]. The access to SIC is not possible in every country: while some countries have several centers, many have none. The 12 centers with a high activity performed a median of 25 SICs annually (range: 12–124) as compared to a median of 8 SICs annually (range: 0.3–12) for the 12 centers with a low activity. SICs are systematically performed in 38% of centers, the remaining centers performing SICs only when other tests have failed to give an accurate diagnosis. In 54% of centers, a technician, a chemist, or a hygienist takes part to the procedure. FEV1 is used as the primary endpoint in 88% of centers, NSBR, sputum count, and FeNO being used as additional outcome parameters in 71, 46, and 67% of centers, respectively. The authors concluded that, structurally, there is a high degree of consistency between centers but more variation in procedure. They also encourage every country to offer access to SIC on a national level [53].

Medical Surveillance Programs

As recently reviewed, medical surveillance programs (MSP) are the cornerstone of secondary prevention for workers at risk of OA [54]. These programs are useful and should be implemented where primary prevention has failed or is impossible. Almost all MSP include a questionnaire, usually self-administered, even if no specific questionnaire has been validated for the screening of OA in the workplace. The purpose of the questionnaire is to identify workers who need further assessment and it should be therefore highly sensitive. One major issue with screening questionnaire is the accuracy with which it is completed as many workers being afraid to divulge their symptoms (i.e., fear of employer's judgment or of losing job). Partly dealing with this issue, many MSP include objective tests, such as spirometry and assessment of specific IgE sensitization. Despite the objectivity of spirometry, its usefulness has been questioned and while it is often normal even in subjects with asthma, the frequent poor quality of tests done in industry settings leads to unnecessary investigation [54]. This assertion is confirmed by a recent study evaluating the role of medical surveillance and spirometry in detecting OA in Finland [55]. Among the 60 cases of OA, 18% were detected by medical surveillance, and no case was detected on the basis of abnormal spirometry without respiratory symptoms. Most investigations were initiated by the presence of respiratory symptoms. Surveillance with regular screening for early sensitization as determined by specific IgE against a workplace agent has the potential to recognize an "asymptomatic sensitized" state, allowing relocation of sensitized workers to lower exposure area reducing the risk of developing OA [54, 56].

Evaluating to potential sensitizing effect of chemicals may improve our risk assessment and improve MSP. The group of Agius has developed a model based on the structure of the compound to predict if a chemical has the potential to cause OA [57]. This computer-based and easy-to-use model has been shown to correctly predict the asthmagenic potential of new organic low molecular weight chemicals [58]. A second version of the model has been refined recently, improving its overall performance in identifying chemicals as asthmagens (sensitivity 90%, specificity 96%). With an area under the receiver operating characteristic curve of 0.95, 95% of tested chemicals were correctly identified by the new model as asthmagenic or not [59]. This model needs to be validated externally before the generalization of its use.

Florentin et al. showed that FeNO cannot be used alone as a screening tool for OA among apprentices in two at-risk sectors (bakery and hairdressing) [60] but it may increase the performance of questionnaires used to screen for OA (overall NPV and PPV of FeNO >8.5 ppb + questionnaire: 97.0 and 32.6%, respectively). Further prospective studies are required before its implementation.

The findings of MSP should be shared with individual workers and, on a population level, reviewed by organizations in order to improve primary prevention. Unfortunately, Fischwick et al. showed that, even in high risk industries for OA, risks are often underestimated and, when specific risks are identified, MSP are carried only in a minority of industries with considerable variation among companies [61]. The authors concluded that MSP need to be more practical, evidence-based, and simple-to-follow, ensuring collaboration of workers, trade unions, and employers but also family physicians and health surveillance professionals.

Phenotypes

Two studies have evaluated different clinical phenotypes with very close results [37, 62]. The two teams showed marked differences in workers with a diagnosis of OA confirmed by SIC depending on the type of causal agents (HMW vs LMW agents). Workers exposed to LMW agents tended to have a lower prevalence of atopy and rhinitis, a lower sputum eosinophil count, no increase in FeNO, a higher prevalence of late airway response, and more increased NSBR. The authors suggested that these different phenotypes are probably due to the different pathogenic mechanisms underlying the different types of causal agents.

Conclusion

The diagnosis workup of OA remains a challenge and needs a rigorous stepwise approach in order to avoid false-positive and false-negative diagnosis. Due to the major public health

burden of OA, studies are needed to understand more precisely its pathogenic mechanisms and to develop new tests in order to simplify and improve the assessment of the workers.

Compliance with Ethical Standards

Conflict of Interest Drs. Pralong and Cartier declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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