REVIEWS

Work-Related Asthma: Diagnosis and Prognosis of Immunological Occupational Asthma and Work-Exacerbated Asthma

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■ **Abstract**

The incidence and prevalence of asthma are increasing. One reason for this trend is the rise in adult-onset asthma, especially occupational asthma, which is 1 of the 2 forms of work-related asthma. Occupational asthma is defined as asthma caused by agents that are present exclusively in the workplace. The presence of pre-existing asthma does not rule out the possibility of developing occupational asthma. A distinction has traditionally been made between immunological occupational asthma (whether IgE-mediated or not) and nonimmunological occupational asthma caused by irritants, the most characteristic example of which is reactive airway dysfunction syndrome. The other form of work-related asthma is known as work-exacerbated asthma, which affects persons with pre-existing or concurrent asthma that is worsened by work-related factors. It is important to differentiate between the 2 entities because their treatment, prognosis, and medical and social repercussions can differ widely. In this review, we discuss diagnostic methods, treatment, and avoidance/nonavoidance of the antigen in immunological occupational asthma and work-exacerbated asthma.

Key words: Specific inhalation challenge. Peak expiratory flow. Workplace. Irritants.

■ **Resumen**

La incidencia y prevalencia del asma van en aumento. El asma de inicio en la edad adulta y especialmente el asma ocupacional (AO) podrían ser una de las causas que influyeran en este incremento. El AO, una de las dos formas de asma relacionada con el trabajo (ART), se define como el asma causada por agentes que están presentes exclusivamente en el lugar de trabajo. Clásicamente, se ha realizado una distinción entre AO inmunológica (mediada o no por un mecanismo IgE) y AO no inmunológica causada por irritantes, cuyo ejemplo más característico es el síndrome reactivo de disfunción de la vía aérea. La presencia de asma previa no descarta la posibilidad de desarrollar AO. El asma exacerbada por el trabajo (AET) es la otra forma de ART y se define como aquel asma pre-existente o concurrente que empeora por factores relacionados con el trabajo. Diferenciar estas dos entidades es importante ya que su tratamiento, pronóstico y repercusiones médica y social, pueden diferir ampliamente. En esta revisión se discuten los diversos métodos diagnósticos, tratamientos y las diferentes estrategias de evitación / no evitación del antígeno tanto en el AO inmunológica como en el AET.

Palabras clave: Prueba de provocación bronquial específica. Pico flujo espiratorio. Lugar de trabajo. Irritantes.

Introduction

Bronchial asthma is a potentially serious disease, whose prevalence is increasing in most developed countries [1]. In Spain, the prevalence rates of asthma range between 5% and 14.5% depending on the region, and asthma is in the cause of approximately 28% of consultations in allergy services [2]. One of the reasons for this increase is the growing number of asthma cases that are first detected in adulthood [3]. In addition to the possible allergic origin that is typical of asthma in children, many other factors have been implicated in the etiology of adult-onset asthma, including obesity [4], environmental pollution [5], genetic variants in vitamin D receptors [6], psychological factors such as stress or anxiety [7], hormonal factors [8], use of specific drugs [9], exposure to tobacco smoke [10], and, most importantly, occupational exposure to specific agents [11-12].

In fact, occupational exposure is thought to account for up to 25% of all cases of adult-onset asthma [13-14]. This percentage is likely to increase, since new substances causing occupational asthma and new work situations that were previously unknown sources of exposure are being described in the literature [15-17]. Occupational exposure can cause asthma, but it can also aggravate a pre-existing condition. Occupational asthma (OA) is characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace [18]. Work-exacerbated asthma (WEA) can be observed in patients with pre-existing or concurrent asthma that is worsened by work-related factors [19]. Differentiation between the 2 entities is not easy, since OA may be diagnosed in patients with asthma prior to occupational exposure and WEA in patients whose asthma is not caused by occupational exposure but begins in adulthood when the individual is working. The current trend is to use the term work-related asthma (WRA) to designate asthma that is related to the work environment, regardless of whether it causes the condition (OA) or worsens it (WEA).

Once asthma has been confirmed, WRA is relatively simple to diagnose if physicians are alert to the possibility of its presence, because the availability of specific data and application of standard diagnostic procedures can settle with relative certainty whether the asthma is related to work [20]. Nevertheless, diagnosis of WRA is probably insufficient, and the distinction between OA and WEA is important because treatment, prognosis, and medical and social repercussions may differ widely [21-23]. Furthermore, OA is subdivided into immunological and nonimmunological forms (Figure 1), depending on the pathogenic mechanism involved. Immunological OA is characterized by asthma appearing after a latency period and can be caused by high- and low-molecular-weight agents that are either IgE-mediated or not. Nonimmunological OA is induced by irritants. The most common form is reactive airway dysfunction syndrome, which is easily diagnosed based on the medical record. The disease is considered to be stabilized when the following criteria are documented: absence of preceding respiratory complaints; onset of symptoms after a single specific exposure; exposure
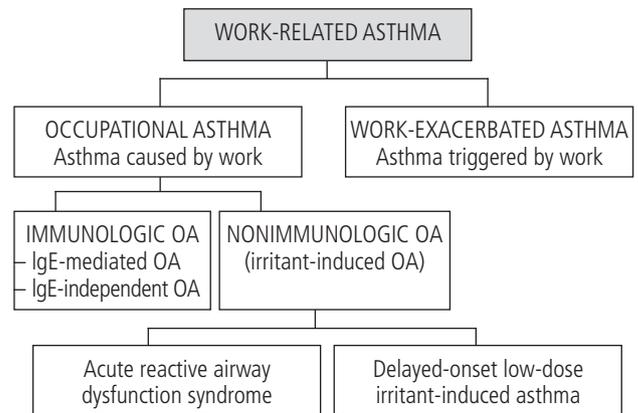

Figure 1. Types of work-related asthma.

to an irritant gas, smoke, fume, or vapor present in very high concentrations; onset of symptoms within 24 hours of exposure that persist for at least 3 months; symptoms suggestive of asthma with cough, wheezing, and dyspnea predominating; pulmonary function tests showing airflow obstruction; positive methacholine challenge test results; and exclusion of other types of pulmonary diseases [24]. An individual can also develop asthma after repeated moderate- and/or low-intensity exposure to irritants, although few data are available on the frequency, risk factors, pathophysiology, management, and prognosis of such exposure [25].

This review will focus on immunological OA and WEA, the types of WRA that are most frequently observed in clinical practice and present the greatest diagnostic challenge. Their treatment and prognosis are not well established.

Immunological Occupational Asthma

The diagnosis of immunological OA is based on the presence of bronchial asthma and a clear association with the individual's occupation [26]. Key factors for diagnosis are the medical record, immunological studies, and pulmonary function testing, including recordings of peak expiratory flow (PEF), and both specific and nonspecific bronchial challenge studies. Figure 2 presents a diagnostic algorithm of how and when to use these tests for the diagnosis of OA.

Medical Record

The characteristic medical record in OA includes a description of asthma symptoms that worsen during the working day and improve on weekends and during vacation periods. The latency period between starting work and the onset of symptoms is highly variable and may range from weeks to years. Sometimes, prior to the onset of asthma symptoms, and especially if the patient has been exposed to high-molecular-weight substances, ocular symptoms such as itching, tearing, or conjunctivitis and nasal symptoms such as congestion and rhinorrhea may be reported [27]. However, a history suggestive of OA, even in a patient exposed to an
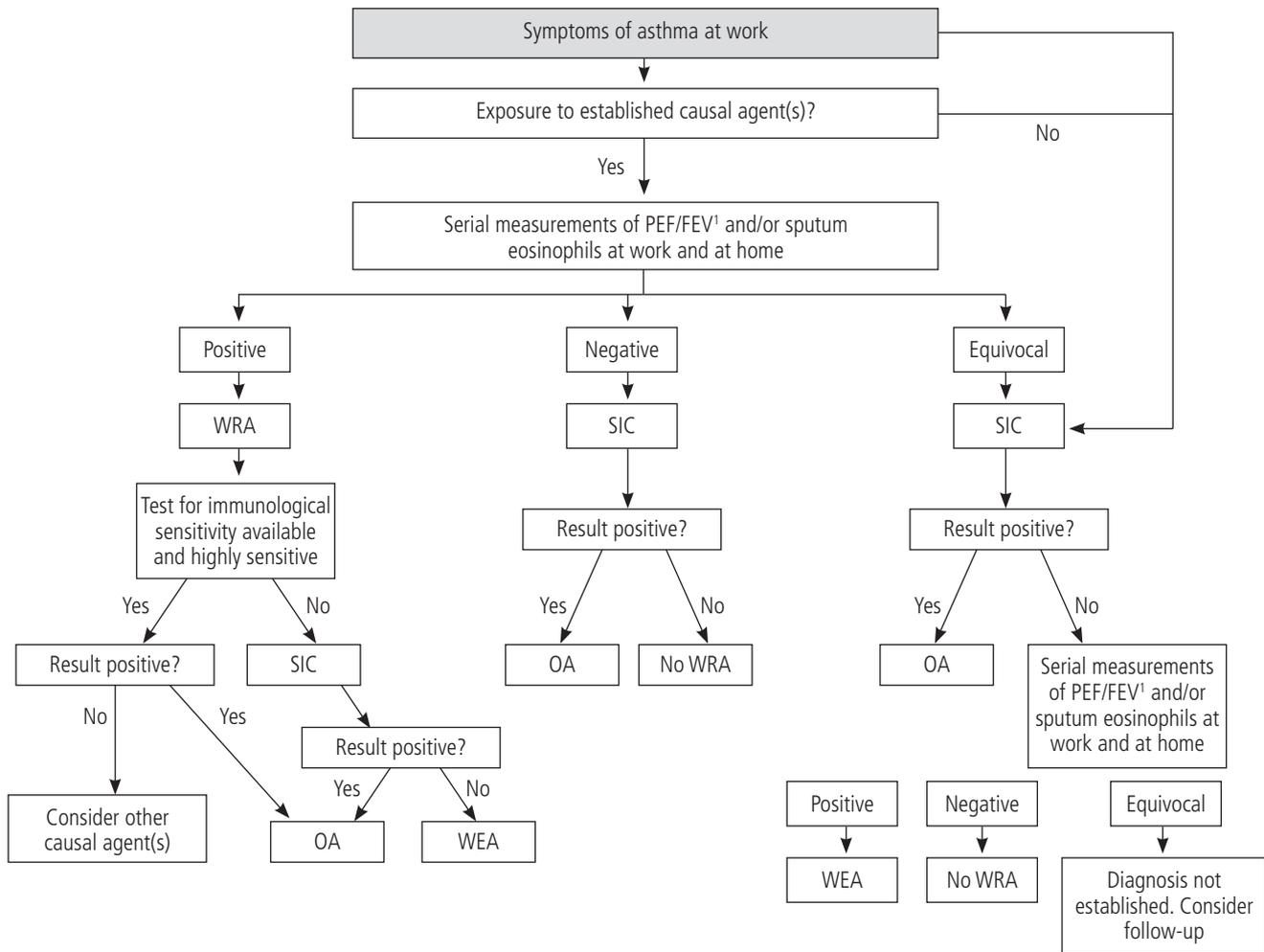
Figure 2. Algorithm for the diagnosis of occupational asthma diagnosis. FEV_1 indicates forced expiratory volume in 1 second; OA, occupational asthma; PEF, peak expiratory flow; SIC, specific inhalation challenge; WEA, work-exacerbated asthma; WRA, work-related asthma.

agent known to be capable of causing the condition, is not sufficient to confirm the diagnosis, since it has been shown that the correlation between the physician's suspicions and the final diagnosis was only borne out in half of the cases [28]. A recent study showed that the questions used to try to relate the symptoms to exposure—for instance, whether the patient's condition worsens or improves during periods of nonexposure—have high sensitivity but low specificity, since individuals with OA or respiratory symptoms not attributable to a particular disease will respond affirmatively to the same questions [29].

The medical record should also indicate the agent or types of agent to which the patient is exposed. These agents are generally classed according to their molecular weight into high-molecular-weight and low-molecular-weight substances, which have different mechanisms of action and, therefore, different clinical presentations. A recent evidence-based review of the literature identified 372 causative agents of immunological OA and 184 different causes of nonimmunological OA [30].

Immunological Tests

Demonstrating sensitization to agents present in the working environment can be of great help in diagnosing a patient with OA. In vivo techniques (skin tests) and in vitro techniques (specific antibody tests, mainly IgE) can be used to test this sensitization. However, it should be borne in mind that demonstrating sensitization does not imply causality or the presence of disease [31].

In the case of high-molecular-weight agents, whose mechanism of action is usually IgE-mediated, a negative result in an immunology test almost rules out the agent in question as the cause of the patient's symptoms [31]. SDS-PAGE and Western blot can identify and accurately characterize the antigenic protein bands causing occupational disease [32], and the quantification of antigens in the environment using ELISA and/or inhibition ELISA can be an additional aid in the diagnosis of OA, since this approach provides a measure of the concentration of these antigens in the work environment [33].

The situation is different in the case of low-molecular-weight compounds, since many are irritants and skin tests

are therefore not useful for diagnosis. Moreover, these agents may induce asthma via a nonspecific immune mechanism. Nevertheless, specific IgE to high-molecular-weight compounds has been reported [34].

Pulmonary Function Studies

Today, spirometry, specific and non-specific bronchial challenge tests, and determination of PEF during periods of exposure and nonexposure are considered essential tools for diagnosis of OA [35-36]. Within the nonspecific bronchial challenge tests, the methacholine test is considered the gold standard. This test is useful for diagnosing asthma [37], for establishing the relationship between asthma and work [38], and for interpreting the results of the specific inhalation challenge (SIC) [39]. Some authors believe that a negative methacholine challenge test result rules out the diagnosis of OA in a patient who is working [33], although a recent study has shown that it is more common to find a normal PC_{20} in the methacholine test in patients with OA than in patients with nonoccupational asthma [40].

The use of PEF during periods of exposure and nonexposure to diagnose OA was proposed about 30 years ago by Burge et al [41-42]. Initial studies of PEF showed that the sensitivity and specificity of this parameter were 81-87% and 74-89%, respectively, when it was interpreted by visual analysis and taking SIC as the reference approach [38,43]. In these studies, the PEF was interpreted by various observers, and the diagnosis of OA was based on consensus. However, in daily clinical practice, the test is interpreted by a single physician, with the result that sensitivity and specificity can differ greatly. In order to increase the yield of PEF, Gannon et al [44] developed a computerized system, OASYS-2, which had a sensitivity of 75% and a specificity of 98% for OA [44]. The system is based on plotting the maximum, mean, and minimum daily PEF and producing a score comparing periods at work and off work. It has been used mainly in the UK. The accuracy of PEF monitoring depends on patient adherence and honesty, which may account for differences in sensitivity and specificity levels according to the country studied. Indeed, 2 recent studies conducted in Canada [45] and Spain [46] based on habitual clinical practice found sensitivity values close to 70% with visual interpretation of the PEF and between 20% and 35% with OASYS-2, and specificity values of around 60% with visual interpretation and between 65% and 90% with OASYS-2. As other authors have suggested, this discrepancy could arise because the number of patients taking corticosteroids at the time these studies were performed was lower than now; hence, the differences in PEF in periods at and off work might have been more marked [42,47]. Other possible confounding factors in the interpretation of PEF are respiratory tract infections and possible falsification of the recordings [48].

Inflammation Studies Using Noninvasive Methods

Airway inflammation is a dominant feature of asthma and a hallmark of its pathophysiology, which is associated with airway hyperreactivity and airway remodeling. Airway inflammation has typically been assessed by histological examination of lung tissue (bronchial biopsy) and by bronchoalveolar lavage and/or bronchial washing. However, these techniques are invasive, and repeated measurements are not possible. Therefore, diagnostic tools, such as induced sputum (IS) and analysis of exhaled breath, have recently been developed and validated for less invasive evaluation of airway inflammation [49-53].

In patients with suspected OA, some studies have attempted to evaluate the usefulness of IS when workers are exposed in the workplace and when IS is performed along with SIC. Monitoring of the functional and inflammatory changes during periods in and away from the workplace has demonstrated that patients with OA mainly present eosinophilic airway inflammation after exposure to the causal agent when at work [53]. Although sputum eosinophilia seems to be the most relevant inflammatory profile in OA when at work, neutrophilic airway inflammation has also been described [54-55]. However, the significance of sputum neutrophilia remains unclear at present. In the context of SIC, analysis of IS can improve diagnosis of OA. In fact, it has been postulated that the increased sputum inflammatory cell counts observed following SIC in patients without OA may be an accurate parameter for predicting the development of an asthmatic response to subsequent challenges, especially when eosinophilic inflammation is present [56]. Furthermore, evaluating airway inflammation before and after SIC once outside the workplace has proved useful for follow-up of asthma; a rapid decrease in eosinophilic airway inflammation followed by an improvement in airway hyperreactivity was observed within 6 months outside the workplace in workers with OA, and patients with a noneosinophilic asthmatic reaction during SIC seem to have a poorer prognosis than those with eosinophilic airway inflammation [57].

Fractional exhaled NO (FeNO) concentration is the most extensively studied exhaled biomarker. Increased levels of FeNO have been documented in corticosteroid-naïve patients with asthma [58]. Nevertheless, only a few studies have examined the usefulness of FeNO in the assessment of OA; the results are inconsistent, owing to the low specificity of FeNO compared with IS and to several confounding factors that influence the results [59]. It has been suggested that increased levels of FeNO may be related to occupational agents that induce IgE-dependent asthma [60]. Assessment of changes in the FeNO level during SIC may be useful in patients who are unable to provide suitable sputum samples [61-62]. There have been conflicting data on changes in FeNO after SIC with occupational agents [39,63-65]. Sastre et al [66] found a significant increase in FeNO values over baseline in patients with a positive SIC result. However, when FeNO values obtained from patients with positive and negative SIC results were compared, this difference was not statistically significant. Santos et al [67] also found a significant increase in FeNO level only 24 hours after positive challenge, while there was a significant increase in sputum eosinophils at 7 hours. It is generally accepted that changes in FeNO are less discriminative than changes in sputum eosinophils. Further prospective studies are required to confirm the utility of FeNO in occupational settings [68].

A more recent method for noninvasive assessment of airway inflammation is the analysis of exhaled breath condensate (EBC). Toxic metals, trace elements, and specific chemical substances can be detected in the EBC of exposed

workers, thus underlining the ability of this method to supply extremely useful information on target tissue levels and doses of pneumotoxic compounds [69]. Increased levels of oxidative stress biomarkers have been reported in the EBC of hairdressers exposed to chemical agents with potentially irritant and sensitizing effects on the airways, albeit with no impairment of respiratory function [70]. One recent assessment of the utility of EBC pH during periods at work and off work found that a decrease of 0.4 between 2 weeks at work and 2 weeks off work in individuals with suspected OA had a specificity of 90% for definitive diagnosis of OA, indicating that this parameter could be incorporated in the diagnostic workup of OA [46]. Since information on the role of EBC pH in the context of SIC is still lacking, little is known about the degree to which EBC acidifies in patients with OA. One study found no association between asthmatic reactions induced by isocyanates and EBC acidification after SIC [71], and another monitored leukotrienes and 8-isoprostane in EBC before and after SIC, although the results cannot be considered conclusive [72].

Combination of Various Diagnostic Tests

Several studies have attempted to evaluate the diagnostic value of combining 2 or more diagnostic tests. In OA caused by high-molecular-weight agents, some studies have examined the combination of nonspecific bronchial challenge tests and specific skin prick tests. The pooled estimate of sensitivity was 61%, while the estimate of specificity was 82% [73]. A recent study in bakers found a sensitivity of 58% and specificity of 89% for the combination of the skin prick test and the nonspecific bronchial challenge test [74]. Very few studies have analyzed data on the diagnostic yield of the combination of PEF with specific skin prick tests, and the studies that combine nonspecific bronchial challenge tests with PEF did not show significant improvements in diagnosis [45]. Finally, some authors have proposed that the addition of the number of eosinophils in IS at work and off work to PEF may improve the sensitivity and specificity of the diagnosis of OA. Girard et al [45] showed that increases of 1% and 2% in the eosinophil count increase the specificity of the diagnosis of OA by 18% and 27%, respectively. Measurement of EBC pH during periods of exposure and nonexposure has also been shown to improve the diagnostic yield of PEF [46].

Specific Inhalation Challenge

SIC is the gold standard for the diagnosis of OA. It is a key technique for identifying new causative agents, for identifying the specific agent involved when a patient is exposed to more than 1 possible cause of OA in the workplace, and for establishing the pathogenic mechanisms through which the asthmatic reaction occurs. Although some authors do not recommend it on a routine basis given its complexity and the length of time required to administer it, many others have no doubt that it should be used if available, regardless of the results of complementary studies [63].

Exposure may be effected in 2 ways, depending on the nature of the causative agent. When the agent is soluble and the immunological mechanism is mediated by IgE, solutions are prepared with increasing concentrations of the agent and
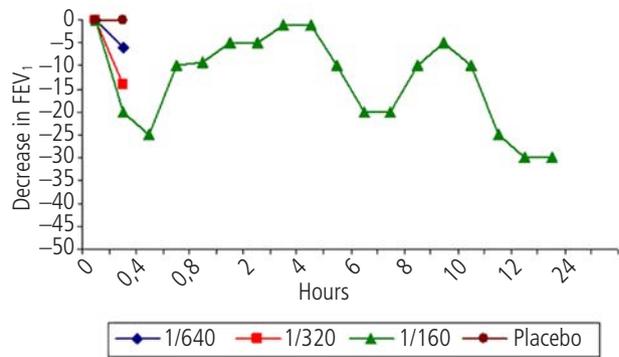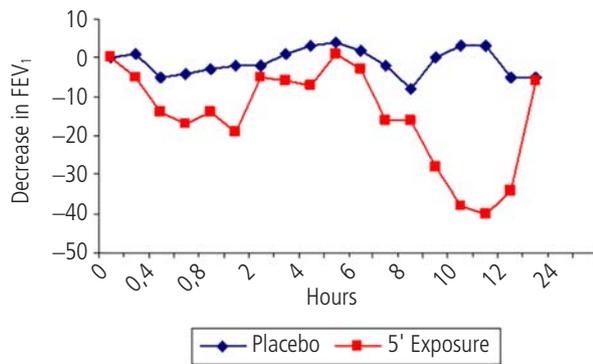

Figure 3. Specific inhalation challenge to a soluble agent (cochineal carmine, E120). The concentrations tested were 0.0015 (1/640), 0.003 (1/320), and 0.006 (1/160) mg/mL. These concentrations were calculated from the smallest antigen concentration capable of generating a positive skin response (0.006) and the methacholine PC_{20} (9.4 mg/mL) (see text and reference 70). FEV_1 indicates forced expiratory volume in 1 second.

administered as an aerosol using a nebulizer. The baseline concentration is calculated using a formula based on the PC_{20} of the methacholine test and the smallest antigen concentration able to generate a positive skin response [75]. Spirometry is performed at 2, 5, and 10 minutes after each nebulization. The test is considered positive when the fall in FEV_1 is above 20% compared with baseline. If a dosimeter is used, the results are expressed as the allergen PC_{20} or PD_{20}. It is important to monitor FEV_1 every hour during the 24 hours after inhalation in order to record a possible late response (Figure 3).

When the agent is not soluble, exposure should be performed in a challenge room [76]. The test is based on generating an atmosphere inside the room containing a known concentration of the agent. The production of this atmosphere also depends on the agent. If the test involves dust or powder, the patient tips the substance from one tray to another [77]. In the case of gases or vapors, the methods for generating a specific concentration can be static or dynamic. In static systems, a known quantity of gas is mixed with a quantity of air to produce a specific concentration, whereas in dynamic systems the airflow and the addition of gas to this airflow are controlled to produce a known level of dilution. These systems provide a continuous flow and enable a rapid, predictable change in concentration that favors mixing and minimizes the loss to absorption in the walls of the room [39]. Finally, sometimes the only alternative is to reproduce the working conditions in the challenge room itself [78]. Some specialist centers have devised closed circuit systems which obviate the need for the challenge room and, in theory, are able to better adjust the exposure and provide greater safety for health care professionals [79-80].

Once this atmosphere is created, the patient enters the room for a variable period of time depending on the characteristics of his/her asthma [81]. After exposure, the FEV_1 is measured every 10 minutes and then every hour for 24 hours. The test is considered positive when the fall in FEV_1 is greater than 20% compared with baseline (Figure 4), although some authors advocate reducing this requirement to 15%. If the test is negative, the exposure time is increased on successive days.

Figure 4. Specific inhalation challenge in a patient exposed to isocyanates. The patient was exposed (concentration of 7-15 ppb) in a challenge room. FEV_1 indicates forced expiratory volume in 1 second.

Some authors have proposed performing the SIC in the patient's workplace. Although this type of exposure is not standardized, the aim is to observe changes in baseline values of FEV_1, methacholine PC_{20}, and the number of eosinophils in IS. On the first day, the patient is exposed for 1 hour in his/her habitual place of work, and the FEV_1 is monitored during the following 24 hours. If no abnormalities are found, exposure is increased to 2 hours on day 2, to 4 hours on day 3, and to 8 hours on successive days for a total of 15 days, monitoring FEV_1 at all times. At 15 days, the methacholine PC_{20} and the eosinophil count in IS are measured again. If there are no significant changes in these variables, OA is definitively ruled out [64].

While the SIC is clearly the reference method for the diagnosis of OA, it is important to bear in mind that it can also generate false positives or negatives. In general, false positives can appear when the patient has labile asthma, when the ventilatory maneuvers of spirometry induce obstruction, or when, owing to the use of high concentrations of irritant agents, the agent causes reactive airway dysfunction syndrome. In contrast, false negatives may be observed if the patient receives a topical or systemic bronchodilator or anti-inflammatory treatment, if the period of nonexposure to the agent prior to the test was unduly long, or if the wrong agents are used.

Work-Exacerbated Asthma

WEA is a condition in which pre-existing or concomitant asthma is found to worsen as a result of environmental exposure in the workplace [19]. While WEA manifests as an increase in the frequency and/or severity of asthma symptoms and/or an increase in the medication needed to control the disease during workdays, diagnosis should be based on changes in airflow parameters, the degree of bronchial hyperresponsiveness, or levels of airway inflammation associated with occupational exposure [82]. It should be borne in mind that asthma may be pre-existing or concurrent with work; that is, it may start during the individual's working life, but it may not be caused by specific exposure in the workplace. Therefore, OA must always be ruled out before a diagnosis of WEA can be made [21], especially since the

study of PEF does not seem to be useful in differentiating between OA and WEA [83]. Furthermore, even though studies on inflammation demonstrate that neutrophilic inflammation may be predominant in cases of WEA, their results are not definitive [36,53,83]. In this setting, the SIC seems to be the best diagnostic method when there is some doubt about the clinical approach [63]. Indeed, with regard to the SIC, our group has shown that a decrease of more than 0.4 in the pH of EBC after SIC in patients with negative SIC has a high sensitivity and specificity for the diagnosis of WEA [84].

The prevalence of WEA varies between 13% and 38% of all adults with asthma according to different series [85-86], and the agents most implicated in its development are chemicals, dust, paints, cleaning products, hydrocarbons, isocyanates, wood, flour, and welding fumes [87-88]. Although data concerning the management of WEA are limited, professional organizations recommend minimizing exposure at work, optimizing standard medical management for asthma, and greater knowledge of the disease by the patient [19-21]. Nevertheless, a recent study demonstrated that asthmatic patients who are aware of their own allergic sensitizations do not seem to present better asthma control [89]. Both OA and WEA are associated with greater use of health care and 10-fold higher direct costs than asthma not related to work [83].

Prognosis and Treatment

For workers with OA caused by an immunological mechanism, complete and definitive removal from exposure to the sensitizing agent is usually recommended as the most efficient therapeutic approach [19], although some authors suggest similar clinical benefits with new biological treatments [90]. In contrast, as noted above, patients with WEA need not abandon their jobs if environmental conditions are improved and suitable medical treatment is provided [19-21,91-92].

The recommendation to avoid exposure in immunological OA, which is widely applied in practice, is based on 2 main findings. The first is that continued contact with the causative agent exacerbates asthma symptoms, aggravates airway obstruction and nonspecific bronchial hyperresponsiveness, and—in some patients—may even be fatal [93-94]. The second is that avoidance of exposure to the causative agent results in a significant improvement in these parameters, even though asthma may persist in approximately two-thirds of workers [95]. However, bearing in mind that cessation of exposure is often not feasible or is associated with adverse economic consequences for the worker, the employer, or society as a whole [96-97], a number of meta-analyses carried out in recent years have compared the effects of this management option [98-101]. The results indicate that available data on the prognosis of OA are insufficient to enable physicians to provide reliable, informed advice to patients with the disease.

The systematic review by Rachiotis et al [99] found that complete symptomatic recovery varied from 0% to 100%, with a pooled prevalence of 32%. Similar results were reported by Vandenplas et al [102], who found that avoidance of exposure led to recovery from asthma in less than one-third of affected workers. Several authors have tried to establish the factors that determine the persistence of asthma symptoms

after discontinuation of contact with the causative agent. The European Respiratory Society task force studied the contribution of host factors and workplace exposure to the outcome of OA and found that older age, high-molecular-weight agents, impaired lung function, and longer duration of exposure to the offending agent at the time of diagnosis had a negative effect on the outcome of OA. Atopy and smoking at diagnosis did not seem to influence the outcome of OA. A limited number of studies have considered gender and the pattern of asthmatic reaction on SIC and their findings were contradictory [103]. Recently, the FEV_1 value at diagnosis was also included as a prognostic factor for patients with OA due to isocyanates [104].

Conclusions

Work-related asthma, which includes OA and WEA, has become one of the most prevalent occupational lung diseases. WRA is easily diagnosed, but differentiating between OA and WEA is difficult. The distinction is important because the treatment and prognosis of both entities may differ significantly and medical-legal implications may also vary. A systematic literature search considered 5 key questions: diagnosis, risk factors, outcome of management options, medical screening and surveillance, and controlling exposure for primary prevention [105]. Recommendations were based on evidence. The authors established the importance of each recommendation (strong, moderate, or weak) and the degree of evidence (high, moderate, or low). In total, only 28 recommendations were made. Two of the recommendations graded as "strong" and with a "high" degree of evidence were that the diagnosis of OA should be confirmed by objective testing and that WRA should be recognized and diagnosed early in order to achieve the best outcome. However, other recommendations discussed in this review, such as avoidance of the causal agent, had only a moderate degree of evidence.

Given the limited evidence available, future studies should focus on improving diagnosis and prognosis, determining individual susceptibility, and establishing environmental measures aimed at reducing the incidence of this disease. These aspects are especially important in the case of WEA, as we know far less about this entity than about OA.

Acknowledgments

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