



New causes of immunologic occupational asthma 2014–2020

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Purpose of review

The purpose of this review was to list all new confirmed cases of immunological occupational asthma (IOA) described between mid-2014 and April 2020.

Findings

Several new agents, both of high and low molecular weight, have been identified in the last 6 years as potential respiratory sensitizers being able to induce immunological occupational asthma. This review confirms that new causes of IOA are still identified regularly, particularly in subjects exposed to high molecular agents, in the food industry (farming, pest control, food processing), pharmaceutical industry (antibiotics, various drugs) and cosmetic environment (dyes, powders).

Summary

It stressed the need for clinicians to stay alert and suspect occupational asthma in any adult with new onset asthma or newly uncontrolled asthma.

Keywords

causative agents, occupational allergy, occupational asthma, specific inhalation challenge

INTRODUCTION

Asthma is among the most prevalent occupational lung diseases in most industrialized countries and classically, 10–15% of adult-onset asthma is thought to be due to work [1]. While work-exacerbated asthma is pre-existing or concurrent asthma that is exacerbated at work, occupational asthma is defined as asthma caused by conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace [2]. Occupational asthma can be further distinguished between immunologic or nonimmunologic types, according to whether there is a latency period necessary to acquire an immunologic sensitization—this is called immunologic occupational asthma (IOA)—or not. The latter is characterized by asthma which develops within hours of a single exposure to high levels of inhaled irritants—variants of this type of asthma have been described following multiple exposures to irritants, and it is now called irritant-induced asthma.

More than 400 agents, both of high (>5–10 KD) and low molecular weight, have been associated with the development of IOA. New agents are described every year and the objective of this review is to list all new agents recognized as a cause of IOA since our last review in 2014 [3]. We have

deliberately kept only cases which have been confirmed by specific inhalation challenges (SIC) in the laboratory, considered the standard reference for the diagnosis of IOA [4^{••},5^{••}], and which allow the identification of the relevant cause of occupational asthma, as opposed to specific challenges at work or monitoring of peak expiratory flows (PEF) at and off work, coupled with monitoring of nonspecific bronchial responsiveness (NSBR) and sputum eosinophilia which can also confirm occupational asthma but do not allow to identify the responsible agent with certainty.

METHODS

Medline was searched for publications in English or French using the key words ‘occupational asthma’ and ‘occupational allergy’ between mid-2014 and

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KEY POINTS

- The diagnosis of IOA requires a high suspicion from clinicians and should be considered in any patient presenting with new onset asthma or newly uncontrolled asthma. The diagnosis should be confirmed by objective mean.
- Several new agents have been described in the last 6 years particularly in the food industry (farming, pest control and food processing), the pharmaceutical industry (antibiotics and various drugs) and cosmetic/hairdresser environment (dyes).

April 2020. Only studies which concerned agents not previously described as causing IOA (confirmed by SIC) were kept for review.

REVIEW

Several new agents were described as being responsible for IOA between mid-2014 and 2020. Tables 1 and 2 list the various agents recognized as new agents causing IOA according to their molecular weight, either high (HMW) or low (LMW) molecular weight, detailing the type of occupation/industry, duration of exposure before the onset of symptoms, other clinical manifestations associated with asthma, immunological tests to confirm sensitization (skin prick tests (SPT) and specific IgE when done), results of SIC, and other means of investigation.

The majority of new cases of IOA were associated with HMW agents and involved workers in the food industry (farming, food processing) or pharmaceutical industry. As expected, most cases of IOA

Table 1. List of new high molecular weight agents causing IOA

Agent	Type of work	# of subjects	Duration of exposure before onset of symptoms	Atopy	Clinical Symptoms	Immunological tests	SIC	Other means of investigation	Reference
Mediterranean Fruit fly (<i>Ceratitis capitata</i>)	Pest control, laboratory	#1 #2	3.6 y 3 y.	+ +	A, R A, R	SPT+, slgE+ SPT+, slgE+	EAR EAR	PEF + NS	[13]
Nematode (<i>Steinernema Feltia</i>)	Breeding nematodes for horticultural pest control	1	< 2y.	NS	A, RC	SPT+ slgE+	LATE and DUAL	Increase in NSBR post SIC	[14]
Parasitoid wasps (<i>E. Formosa</i> & <i>E. Emericus</i>)	Green house – using biological pest control	1	NS	NS	A, RC	SPT+, slgE+	EAR	NS	[15 ^a]
Pea parasite (<i>Bruchus Pisorum</i>)	Agronomists Farmers handling infested peas treated with aluminum phosphide	#1 #2 #3	NS	NS	A A, U A	SPT+, slgE+ SPT+, slgE+ SPT+, slgE+	+ (NS) + (NS) + (NS)	NS NS NS	[16]
Melon plant	Agricultural worker (melon harvest season)	1	NS	+	A, RC, U	SPT+ (melon plant and fruit)	EAR	Change in NSBR off and during harvest season	[17]
Lettuce	Farmers (harvesting & packaging)	1	NS	NS	A, U	SPT+, slgE+	EAR	NS	[18]
Anemon (<i>Actinia equina</i>)	Fisherman (mussels handling) Mussels treatment plant	#1 #2	NS NS	NS NS	A, RC, U A, RC	SPT+, slgE+ SPT+, slgE+	EAR DUAL	NS NS	[19]
Enzymes (pectinase & hemicellulase)	Wine cellar	1	18 y.	+	A	SPT+	+ (NS)	NS	[20]
Miracle tree (<i>Moringa Oleifera</i>)	Cosmetic industry	1	NS	NS	A, R	SPT+slgE+	EAR Vs DUAL	PEF +	[21]
Argan tree powder	Cosmetic factory	3	NS	+ (2/3)	A	SPT+ (1/3) slgE+ (3/3)	EAR (3/3)	NS	[22]
Royal jelly	Pharmacy laboratory	#1 #2	2 y. 0.25 y.	+ –	A, RC A, RC	SPT+ SPT+, slgE+	DUAL ND	Change in NSBR off and at work PEF +	[23]
FMOA (ferrimanitol ovalbumine)	Pharmaceutical company	1	1 y.	NS	A, R	SPT+, slgE+	EAR	NS	[7]
Cellulose	Machine operator (sanitary pad production)	1	NS	–	A, RC	SPT–, slgE–	LAR	PEF +	[24]

NS, not specified; y., years; m., months; A, asthma; R, rhinitis; RC, rhino-conjunctivitis; U, urticaria; SPT, Skin prick test; +, positive, –, negative; slgE, specific immunoglobulin E; SIC, specific inhalation challenge in the laboratory; EAR, early asthmatic reaction; DUAL, dual asthmatic reaction; LAR, late asthmatic reaction; PEF, monitoring of Peak expiratory flow rates at work and off work; NSBR, nonspecific bronchial responsiveness.

Table 2. List of new low molecular weight agents causing IOA

Agent	Type of work	# of subjects	Duration of exposure before onset of symptoms	Atopy	Clinical Symptoms	Immunological tests	SIC	Other means of investigation	Reference
Oxydative hair dyes Paraphenylenediamine mixed with oxydant	Hairdressers	5	4, 5, 6 & 20 (2) y.	+(2/5) -(3/5)	A, R (1), U (1)	SPT + (1/5)	EAR (3) DUAL (1) LATE (1)	PEF +	[25]
Sudan red dye (azoic dye)	Cosmetic packaging	1	1.5 y.	NS	A, RC	ND	DUAL	Increase in sputum eosinophils but no change in NSBR post-SIC	[26]
Tafenoquine	Pharmaceutical – drug preparation	1	NS	+	A, R	SPT ND, sIgE -	DUAL	NS	[27]
Ranitidine	Pharmaceutical laboratory	1	NS	+	A, R	SPT -	DUAL (?)	Negative NSBR pre and post-SIC	[28]
Clarithromycin	Pharmaceutical company	1	3.3 y.	NS	A	SPT -	LAR	Negative NSBR pre and post-SIC	[7]
Glucosamine hydrochloride	Janitor in a pharmaceutical company	1	3 y.	NS	A	NS	LAR	NS	[7]
Minoxidil	Beautician	1	3.3 y.	+	A, RC, dermatitis	SPT -	-	Significant increase in NSBR and sputum eosinophils	[7]
Ortho-phthalaldehyde	Endoscopic sterilisation	1	3 weeks	NS	A, C	ND	LATE	NS	[29]
Triclosan (Biocide)	Nursery – cleaning tables	1	NS	NS	A	NS	EAR	PEF+ Negative NSBR pre and post-SIC	[30]

induced by HMW agents were mediated by IgE sensitization and were associated with other allergic manifestations particularly rhinitis and in some cases conjunctivitis or contact urticaria. Several new low molecular weight (LMW) agents were also recognized as respiratory sensitizers although the mechanism of sensitization is unknown. The majority of cases involved workers in the pharmaceutical (antibiotics, drugs) and cosmetic industry (hairdressers, beautician) or exposed to disinfectants. Although less common than with HMW agents, rhinitis was also associated with IOA in some workers. Except in the case of oxidative hair dyes in hairdressers, most cases were single findings and we cannot speculate on the prevalence of IOA in the reported studies.

The diagnosis of IOA relied on positive SIC in the laboratory in all cases, except one, exposure to the offending agent eliciting either early, late or dual asthmatic reactions as reported in previous studies [6]. In one subject, the diagnosis of IOA (to minoxidil) was highly suspected by the history and significant changes in nonspecific bronchial responsiveness and increase in sputum eosinophils following SIC [7] although there was no change in spirometry following exposure in the laboratory. This pattern is highly suggestive of IOA [8].

We have not kept in this list of new agents those for whom the diagnosis was based on the history and either positive SPT, monitoring of PEF at and off work or improvement of NSBR after work withdrawal, for example, Methylisothiazolinone [9], 3D-printing [10], calf rennet [11] and quinoa [12] although the diagnosis in these cases is likely.

DISCUSSION AND CONCLUSION

The incidence of IOA seems to be decreasing in many countries in the last years although the incidence of work related asthma is still increasing in certain work settings such as cleaners and in food services [31–34]. This review confirms that new causes of IOA are still identified regularly particularly in subjects exposed to high molecular agents in the food industry (farming, pest control, food processing), pharmaceutical industry (antibiotics, various drugs) and cosmetic environment (dyes, powders). It stresses the need for clinicians to stay alert and consider the diagnosis of IOA in any adult presenting with new onset asthma or newly uncontrolled asthma particularly if symptoms seem to be related to work with improvement away from work. However, the diagnosis of occupational asthma should be confirmed objectively in all cases [5[¶]] and should not rely only on the history which is not specific although very sensitive [35].

Of interest to the reader, the Commission des Normes et de la Santé et Sécurité au travail (CNESST) of the province of Quebec, Canada, keeps an registry of all cases of occupational asthma which was updated in March 2020 and can be consulted at <https://www.csst.qc.ca/en/prevention/reptox/occupational-asthma/Pages/occupational-asthma.aspx>.

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Conflicts of interest

None.

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- of special interest
- of outstanding interest

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