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Research Article

Distribution of Sensitizer-Induced Occupational Asthma in R. Macedonia in the Period 2005-2014 by Occupation

Abstract

Introduction: Occupational asthma (OA) became an important public health problem worldwide in the last few decades. From two different OA types, sensitizer-induced OA accounts for approximately 90% of all OA cases. Aim of the study was to present the distribution of sensitizer-induced OA by occupation in R. Macedonia in the period 2005-2014.

Methods: Sensitizer-induced OA was diagnosed by serial measurement of peak expiratory flow (PEF) at and away from work or by combination of serial PEF measurement at and away from work and non-specific bronchial provocation at and away from work in subjects with diagnosed asthma and work-relatedness of the symptoms.

Results: The annual incidence rate of the diagnosed sensitizer-induced OA in the mentioned period varied from 1.8/100,000 working population in 2013 to 2.8/100,000 in 2006. Sensitizer-induced OA in bakers, cleaners, textile workers and agricultural workers accounted up to more than a third of the all diagnosed cases. Atopy was registered in approximately a half of the sensitized-induced OA cases. Majority of the cases with sensitizer-induced OA caused by HMW agents (i.e. OA in bakers, textile workers, tanners, herbal and fruit tea processors, and health care workers) was atopics and had positive prick tests to occupational allergens.

Conclusion: Our findings indicate the sectors with highest occurrence of sensitizer-induced OA in R. Macedonia in the period 2005-2014. The data obtained enable directing of adequate activities to prevent developing of the disease, as well as to identify affected ones and to prevent further respiratory impairment.

Introduction

Respiratory diseases rank as the third most prevalent work-related diseases (after ergonomic and stress-related diseases) according to a survey of occupational diseases in the European Union [1]. Work-related asthma (WRA) is the most common work-related lung disease in the last decades, causing significant morbidity, disability and high costs [2]. WRA includes two distinct categories in regard to its pathogenesis and management: occupational asthma (OA) and work-exacerbated (WEA). OA is a form of WRA induced by exposure to airborne dusts, vapors, or fumes in working environment, in subjects with or without pre-existing asthma. WEA is defined as a pre-existing or coincidental new-onset asthma worsened by non-specific factors in the workplace, such as cold and dry air, exertion, dust and fumes [3,4].

Despite the diagnosis is critical to prevent disease progression and its potential for morbidity and mortality, OA often remains undiagnosed or misdiagnosed as chronic bronchitis or chronic obstructive pulmonary disease (COPD) and is therefore either not treated at all or treated inappropriately [5,6].

In addition, two different OA categories can be distinguished:

sensitizer-induced and irritant-induced OA. Sensitizer-induced OA, which accounts for approximately 90% of all OA cases, is characterized by a latency period between first exposure to a respiratory sensitizer at work and the first presentation of symptoms, while irritantinduced OA starts typically within a few hours of a high-intensity exposure to an irritant gas, fumes or vapor encountered at work [3]. More than 250 occupational sensitizers causing OA have been described. According to their molecular weight these occupational agents are categorized into high-molecular-weight (HMW) agents (e.g. animal and plant proteins, flour and grain dust, latex, etc.) and low-molecular-weight (LMW) reactive chemicals (e.g. isocyanates, colophony, aldehydes, metal salts, etc.) Sensitization to most HMW and some LMW agents is through an immunoglobuline E (IgE) mechanisms and can be tested by skin tests, while most LMW agents cause allergic sensitization through IgE-independent mechanisms and an allergen-specific immune response can not be documented by skin tests [7].

A recent meat-analysis indicates that occupational factors account for approximately one in six cases of asthma in adults of working age [8]. The incidence of OA within the workforce depends on people's jobs and the workplace hazards to which they are exposed. The aim



of this study is to present the distribution of diagnosed sensitizer-induced OA by occupation in R. Macedonia in the period 2005-2014.

Materials and Methods

The present study is a report of the sensitizer-induced OA cases diagnosed in the period 2005-2014 at the Institute for Occupational Health of R. Macedonia, Skopje – World Health Organization Collaborating Center and GA 2 LEN Collaborating Center with respect to their occupation. The Institute is a referral center for WRA in R. Macedonia, i.e. all asthma cases with work-relatedness of the symptoms are referred to the Institute for further evaluation.

Sensitizer-induced OA was diagnosed according to the actual criteria for its medical case definition [3,10]. The subjects were considered having WRA in the cases of diagnosed asthma, association between symptoms of asthma and work and workplace exposure to an agent or process known to give rise to WRA. The cases with WEA were excluded by presence of the significant work-related changes in peak expiratory flow rate (PEFR) or in non-specific bronchial hyper responsiveness (BHR). In the mentioned period only two subjects with WRA met recommended criteria for diagnosis of irritant-induced asthma and they were excluded from this study group.

The serial PEFR measurement was performed in all patients (138 patients) according to the actual recommendations [4,5,9]. To obtain accurate readings and interpret them correctly, four readings per day were performed, at and away from work for a period of three weeks. The completed measurements were plotted as daily minimum, mean and maximum values, with calculation of an index of daily variability (maximum PEFR minus minimum PEFR divided by maximum PEFR). The test was considered positive, i.e. the significant work-related changes suggesting sensitizer-induced OA were registered, when PEFR varied by 20% or more during working days, as opposed to days off.

The non-specific bronchial provocation at and away from work was performed according to the actual recommendations [6,10,11] in the patients with border value of the serial PEFR measurement at and away from work (30 patients). The histamine challenge was carried out on a work day and then non-specific BHR was reassessed after at least two weeks away from work. The test was considered positive when BHR improved by at least two doubling concentrations of histamine while away from work.

Sensitization to common inhalant allergens (birch, grass mixed, plantain, *Dermatophagoides pteronyssinus*, dog hair, cat fur, and feathers mixed) and available occupational allergens was evaluated by skin prick test (SPT). The SPTs were performed on the volar part of the forearm using commercial allergen extracts. All tests included positive (1 mg/mL histamine) and negative (0.9 % saline) controls. Prick tests were considered positive if the mean wheal diameter 20 min after allergen application was at least 3 mm larger than the size of the negative control [13].

The annual incidence rate of the diagnosed sensitizer-induced OA in 100,000 working population was calculated as a ratio of new diagnosed cases occurring during one year and working population in R. Macedonia during the same period of time multiplied with 100,000 [12].

Results

In the period 2005-2014 at the Institute for Occupational Health of R. Macedonia, Skopje 138 cases of sensitizer-induced OA was diagnosed, varying from 12 cases in 2005, 2008, 2010, and 2013 to 18 cases in 2011. The annual incidence rate of the diagnosed sensitizer-induced OA in the period 2008-2013, varied from 1.8/100,000 working population in 2013 to 2.8/100,000 in 2006 (Table 1).

Table 2 summarizes the sensitizer-induced OA distribution by specific occupation of the workers.

Positive SPT so common inhalant allergens were registered in 48.5% (67/138) of the workers with sensitizer-induced OA. Table 3 is shown distribution of atopics among sensitizer-induced OA cases with particular occupation.

Positive SPT to available occupational allergens were registered in 29.8% (41/138) of the workers with sensitizer-induced OA, i.e. in the OA cases induced by HMW occupational agebts (Table 4). All sensitizer-induced OA cases with positive SPT to occupational allergens were atopics.

Discussion

Adult asthma attributable to occupational exposure became an important global public health problem in the last few decades. The population-attributable fraction appears to be similar in industrialized and developing countries characterized by rapid industrialization (13-15%), but lower in less industrialized developing countries (6%) [15]. While OA remains under-recognized, especially in developing countries, it remains poorly diagnosed and managed and inadequately compensated worldwide [4,15].

It is estimated that 11 million workers in the US in a wide range of industries and occupations are exposed to at least one of the numerous agents known to be associated with OA [16]. As it is estimated that OA accounts approximately 10% to 25% of adult onset asthma, the investigation of causal relationship between occupational exposure and asthma is indicated in approximately one of every 5 to 10 patients with adult-onset asthma [17,18].

Table 1: Annual incidence rate of the diagnosed sensitizer-induced OA in R. Macedonia in the period 2008-2013.

Year	New diagnosed cases with sensitizer-induced OA	Working Population (14)	Annual incidence rate/ 100,00 working population
2005	12	545,253	2.2
2006	16	570,404	2.8
2007	14	590,234	2.3
2008	12	609,015	2.0
2009	13	629,901	2.1
2010	12	637,855	1.9
2011	18	645,085	2.7
2012	14	655,554	2.1
2013	12	682,448	1.8
2014	15	687,465	2.1

Data are expressed as a number of new diagnosed cases with sensitizer-induced asthma during one year, total working population in R. Macedonia during the same period of time and their ratio multiplied with 100,000.

OA: occupational asthma.

Table 2: Sensitizer-induced OA cases by particular occupation in R. Macedonia in the period 2008-2013.

Sen	sitizer-induced
Occupation	cases
(n =	= 138)
Bakers (industrial and traditional),	
rain transporters, millers, pastry makers 17	(12.3%)
Cleaners	
domestic and non-domestic cleaners) 14 ((10.1%)
extile workers	
cotton and flax spinners, weavers and packers; 12 ((8.7%)
leachers)	
agricultural workers 12 ((8.7%)
Chemical industry workers 10 ((7.2%)
adhesive manufacturers, laminate manufacturers)	
Vood industry workers 9 (6	5.5%)
carpenters, furniture manufacturers, cabinet makers)	
Metal workers 7 (5	5.1%)
metal-parts manufacturers and fabricators)	
fairdressers 5 (3	3.6%)
Paint manufacturers 5 (3	3.6%)
Plastic industry workers 5 (3	3.6%)
plasticizers and insulation material manufacturers)	
Velders 5 (3	3.6%)
food technologists 5 (3	3.6%)
automobile spray painters 4 (2	2.9%)
Pharmaceutical industry workers 4 (2	2.9%)
dealthcare workers 4 (2	2.9%)
nurses, medical technicians, dentists, dental technicians)	
anners 3 (2	2.2%)
Packing material manufacturers 3 (2	2.2%)
/arnishes 3 (2	2.2%)
Solderers 2 (1	.4%)
Herbal and fruit tea processors 2 (1	.4%)
Retailers 2 (*	1.4%)
oundry mold makers 2 (1.4%)
irefighters 1 (0	0.7%)
Brewery workers 1 (0	0.7%)
aboratory animal workers 1 (0	0.7%)

Data are expressed as number and percentage of sensitizer-induced OA cases by particular occupation.

The aim of this study was to present the distribution of sensitizer-induced OA in R. Macedonia in the period 2005-2014 diagnosed at the IOH-WHO CC as a referral center for OA in R. Macedonia with respect to their occupations. The sensitizer-induced OA diagnosis was established by positive results of serial PEFR measurement at and away from work or by combination of serial PEFR measurement at and away from work and non-specific bronchial provocation at and away from work in the patients with diagnosed asthma and work-relatedness of the asthma symptoms. The gold standard for diagnosis of sensitizer-induced OA is a specific inhalation challenge (SIC) with the suspected occupational agent. However, such challenges are available in a few specialist centers only and the diagnosis of sensitizer-induced OA can be made without this test [19-21]. Evaluation of the serial PEFR measurement (when performed and interpreted according to the established protocols) as compared to SIC shows it

to be highly specific and sensitive (over 80%) [9,10,22]. To enhance sensitivity and specificity of serial PEFR measurement the test may be combined with non-specific bronchial provocation at and away from work [6]. We performed both tests to clarify the diagnosis in the cases with border value of the serial PEFR measurement and in all these cases significant changes in the BHR at the working days as compared to the days away from work were registered.

R. Macedonia is a developing country located in the Southeastern Europe. In the study carried out in 2003 including randomly selected subjects from six centers aged 20 to 44 years, the prevalence of adult asthma in R. Macedonia was found to be 5.4% that is in the range of its prevalence in the neighboring countries [23]. The annual incidence rates of diagnosed sensitizer-induced OA registered in this study are in the range of its incidence rate in the developing countries. According to the results from the literature, reported mean annual incidence of OA in developing countries varies less than 2 per 100,000 working population, 4.2 per 100,000 working population in West Midlands, UK, up to 18/100,000 in Scandinavian countries [15,24,25].

The incidence of sensitizer-induced OA varies with specific exposures. OA has been reported in 8% to 12% of laboratory animal workers, 7% to 9% of bakers, and 1.4% of health care workers exposed to natural rubber latex, but these percentages vary significantly depending on the study cited [26]. According to the results of the population-based study carried out by Kogevinas et al. [27] which included more than 15.000 people randomly selected from general population of 12 industrialized countries aged 20 to 44 years, the highest risk for OA was found for farmers, painters, plastic workers, cleaners, spray painters, and agricultural workers.

Table 3: Distribution of sensitizer-induced OA cases by atopic status.

Sensitizer-induced OA cases	Sensitizer-induced OA cases with positive SPT to common inhalant allergens (67/138)
Bakers, millers, pastry makers	14 /17
Cleaners	4 /14
Textile workers	10 /12
Agricultural workers	9 /12
Chemical industry workers	4 /10
Wood industry workers	4 /9
Metal workers	1 /7
Hairdressers	2/5
Paint manufacturers	0/5
Plastic industry workers	1/5
Welders	0/5
Food technologists	3 /5
Automobile spray painters	0/4
Pharmaceutical industry workers	3 /4
Healthcare workers	2 /4
Tanners	3 /3
Packing material manufacturers	2 /3
Varnishes	0/3
Solderers	0/2
Herbal and fruit tea processors	2/2
Retailers	1 /2
Foundry mold makers	0/2
Firefighters	0/1
Brewery workers	1/1
Laboratory animal workers	1/1

Data are expressed as number of sensitizer-induced OA cases with positive SPT to common inhalant allergens in regard to all sensitizer-induced OA cases with particular occupation.

OA: occupational asthma; SPT: skin prick test.

Table 4: Distribution of sensitizer-induced OA cases by sensitization to occupational allergens.

Occupation	Number of sensitizer-induced OA cases	Number of cases with positive SPT to occupational allergens	Occupational allergen
Bakers, grain transporters, millers, pastry	17	15	Wheat or/and meal
makers			Flour
Textile workers	12	9	Cotton or/and flax
Agricultural workers	12	8	Wheat flour, meal flour or/and grain
			dust
Healthcare workers	4	3	Latex
Tanners	3	3	Rabbit fur or hamster fur
Herbal and fruit tea processors	2	2	Lime or/and mugwort
Laboratory animal workers	1	1	Rat urine allergen

Data are expressed as total number of sensitizer-induced OA cases in the period 2005-2014 and number of sensitizer-induced OA cases sensitized to available occupational allergens.

OA: occupational asthma; SPT: skin prick test.

In addition, the high-risk occupations and industries associated with the development of OA vary depending on the dominant industrial sectors in a particular country. In our analysis sensitizer-induced asthma in bakers or workers related to bakery, cleaners, textile workers, and agricultural workers accounted more than a third of the all diagnosed cases of sensitizer-induced OA in the period 2005-2014. The rest of the OA cases are workers employed in other (more than 20) occupations and industries.

Baker's asthma is one of the leading causes of sensitizer-induced OA worldwide [28,29]. The disease is caused by inhalation of cereal flour allergens, enzymes and storage proteins, particularly wheat flour allergens [30]. It is well established that the cleaning products, i.e. products used to clean, disinfect, and control dust and mold on surfaces, can cause both sensitizer-induced and irritant-induced OA, as well as to aggravate pre-existing asthma [31-33]. There is sufficient evidence that the individuals can become sensitized and develop asthma from exposure to formaldehyde, glutaraldehyde, quaternary ammonium chloride compounds, and chlorine-containing compounds of chloramines-T, chlorhexidine and hexachlorophene. In addition, there is sufficient evidence that acute high level exposure to these compounds can also cause irritant-induced asthma [34,35]. It is also well established that occupational exposure in textile industry increases risks of chronic nonspecific lung disease including sensitizer-induced OA [36]. The high occurrence of sensitizer-induced OA among textile workers in our study is probably due to a large number of workers employed in textile industry in R. Macedonia. In addition, results of several study indicate that agricultural workers present a higher morbidity from OA than the general population as a consequence of their workplace exposure to organic dusts (grain, straw, hay, etc.), inorganic dust (silica, silicates, etc.), chemical products (pesticides, fertilizers, preservatives, etc.), as well as to gases and fumes (motor engines, slurry and silage) [37-39].

Atopy is considered as a risk factor for developing IgE-dependent sensitizer-induced OA, i.e. sensitizer-induced OA caused by most HMW and some LMW occupational agents (e.g. salts of platinum) [40,41]. On the other hand, it seems that atopy is not an important determinant of IgE-independent OA, i.e. OA caused by most LMW occupational agents [42,43]. Atopy, defined as the presence of at least one positive SPT to common inhalant allergens [44], was registered in approximately a half of the sensitizer-induced OA cases in this study. According to the findings of the case-control study carried out by Wang et al. [45] which investigated the relationship between

sensitizer-induced OA and atopic status of the patients, sensitizer-induced OA caused by HMW agents was significantly related to atopy, while the relationship between sensitizer-induced OA and LMW agents was inconsistent. Similar results were obtained in the present study. Namely, the most cases of sensitizer-induced OA caused by HMW agents (i.e. OA in bakers, textile workers, tanners, herbal and fruit tea processors, and health care workers) were atopics and had positive prick tests to occupational allergens. On the contrary, most of the workers with sensitizer-induced OA employed in cleaning, wood and chemical industry, metal and plastic manufacture, etc., i.e. the workers at the workplace dominantly exposed to LMW agents, were non-atopics and had negative prick tests to available occupational allergens.

Conclusion

In conclusion, our findings indicate the sectors with highest occurrence of sensitizer-induced OA (bakery, cleaning, textile industry, and agriculture) in R. Macedonia in the period 2005-2014. The data obtained enable directing of primary and secondary preventive strategies at controlling certain workplace exposures, accompanied by intense educational and managerial improvements, as well as at early removal from exposure to ensure that the worker has no further exposure to the causal agent, with preservation to income.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of R. Macedonia, Skopje – WHO Collaborating Center and GA²LEN Collaborating Center gave approval for performing the study and publishing the results obtained (03-788/11.2013).

Competing Interests

All authors hereby have declared that no competing interests exist.

Authors Participations

JM participated in the data collection, data analysis, and writing all versions of the manuscript. JKB participated in the data collection, data analysis, and writing all versions of the manuscript. KV participated in the data analysis. SRK, SS and DM participated in the data collection. All authors read and approved the final manuscript.



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