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Incidence of Immunological Occupational Asthma in 2015–2022 by Occupation: Macedonian Experience

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Abstract

BACKGROUND: Immunologic occupational asthma (OA), a more prevalent OA type than non-immunologic OA, became an important public health problem in the last decades worldwide.

AIM: To present the distribution of new diagnosed cases of immunologic OA in the RN Macedonia in the period 2015–2022 by occupation.

METHODS: Immunologic OA was diagnosed by the serial measurement of peak expiratory flow rate (PEFR) 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 workers with diagnosed asthma and work-relatedness of the symptoms. Sensitization to common inhalant and occupational allergens was evaluated by skin prick test.

RESULTS: The annual incidence rate of the diagnosed immunologic OA in this period varied from 1.9 / 100,000 working population in 2015–2.6 / 100,000 in 2022 with a drop in 2020 and 2021, i.e. in the period of COVID-19 pandemic (0.6 and 0.5, respectively). Cleaning, bakery, cleaning, textile manufacture, wood industry, agriculture, and metal-parts manufacture were the most important occupations for the development of immunologic OA. More than a half of the new diagnosed immunologic OA cases were atopics.

CONCLUSION: Our findings indicated the occupations with the highest incidence of immunologic OA that could enable targeting of preventive measures and activities to reduce the occurrence of immunologic OA as well as its adverse health outcomes.

Introduction

According to the existing evidence, work-related asthma (WRA) is considered as the most prevalent work-related pulmonary disease in industrialized countries in the last few decades. Exposures in the workplace can give rise to different types of WRA, i.e. WRA is not unique and homogeneous entity but includes types with significant difference in their pathogenesis, management, and medico-legal aspects, so there were its several classifications in the last decades. By the current classification, WRA includes three types, i.e. immunologic occupational asthma (OA), irritant-induced asthma (IIA), and work-exacerbated asthma, within each of these WRA forms further levels of heterogeneity and more phenotypes are recognized. The label "OA" encompasses immunologic OA (sensitizer-induced asthma OA or allergic OA) and IIA (non-immunologic OA or non-allergic OA), i.e. WRA types resulting from an inciting agent or condition only found at the workplace [1], [2], [3], [4].

The definition of immunologic OA, much like the definition of asthma itself, has changed over the years; therefore, it is difficult to determine the incidence and prevalence of the disorder. In addition, there is no simple test for immunologic OA with a sufficiently high level of accuracy. Instead, the diagnostic process combines different procedures in a stepwise manner, including detailed clinical and occupational history, immunologic testing, measurement of lung function parameters and airway inflammatory markers, as well as various methods that relate the changes in these functional and inflammatory indices to workplace exposure. The findings regarding the significance of occupation as a cause of immunologic OA vary based on the definition used and the methods for patient selection, as well as on the range of industries and occupations in particular country or region. On the other hand, workers who develop OA often leave the industry in which the illness began (a bias known as the "healthy worker effect"), even when OA has not yet been diagnosed. According to the existing evidence, up to 15% of all adult asthma cases may be occupational in origin, varying from 1% to 3% in food processing, 3–5% in wood workers exposed to dust from red west cedar, 7–9% in bakers and other workers exposed to flour, 3–30% in laboratory animal workers, 5–30% in automobile industry workers exposed to isocyanates to about 46% in workers exposed to platinum salts [5], [6], [7], [8].

The aim of the present study was to present the distribution of new diagnosed cases of immunologic OA in RN Macedonia in 2015–2022 by occupation.

Methods

The present study is a report of the immunologic OA cases diagnosed in the period 2015–2022 at the Institute for Occupational Health of RN 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 OA in RN Macedonia, i.e. all asthma cases with work-relatedness of the symptoms are referred to the Institute for further evaluation, and the present study is a continuum of the monitoring of OA incidence in the country by the same methodology used in our previous study on incidence of this OA type in the period 2005–2014 [9].

The diagnosis of immunologic OA was established in patients with diagnosed asthma and WRA symptoms by positive results from serial measurements of peak expiratory flow rate (PEFR) at and away from work and combination of serial PEFR measurements at and away from work and non-specific bronchial provocation at and away from work patients). Sensitization to common inhalant allergens and available occupational allergens was evaluated by skin prick test (SPT).

Serial PEFR measurements were performed in all patients according to the actual recommendations by four readings per day at and away from work for a period of 3 weeks. The completed measurements were plotted as daily minimum, mean and maximum values, with calculation of an index of daily variability ([maximum PEF-minimum PEF]/maximum PEF). The test was considered positive, i.e. the significant work-related changes suggesting immunologic OA, when PEFR varied by 20% or more during working days, as opposed to days off [10], [11].

Non-specific bronchial provocation at and away from work was performed according to the actual recommendations in the patients with border value of the serial PEF measurement at and away from work. The metacholine challenge was carried out on a work day and then non-specific bronchial hyperresponsiveness (BHR) was reassessed after at least 2 weeks away from work. The test was considered positive when BHR improved by at least two doubling concentrations of metacholine while away from work [12], [13], [14].

SPT to common inhalant allergens and available occupational allergens 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 [15].

The annual incidence rate of the diagnosed immunologic OA in 100,000 working population was calculated as a ratio of new diagnosed cases occurring during 1 year and working population in RN Macedonia during the period 2015–2022 multiplied with 100,000 [16], [17], [18].

Results

In the period 2015–2022 at the Institute for Occupational Health of R. Macedonia, Skopje 102 cases of immunologic OA were confirmed, varying from 4 cases in 2021 to 18 cases in 2022. The annual incidence rate of the diagnosed immunologic OA in this period varied from 1.9 / 100,000 working population in 2015 to 2.6 / 100,000 in 2022 with a drop in 2020 and 2021 (0.6 and 0.5, respectively) (Table 1). Serial PEFR measurements at and away from work were performed in all diagnosed cases. In 12 of them, i.e. in the cases in whom a border value of the serial PEFR measurements was registered, serial PEFR monitoring was combined with serial metacholine challenge, and in all these cases significant changes in the non-specific BHR at the working days as compared to the days away from work were registered.

Table 1: Annual incidence rate of the diagnosed immunologic OA in RN Macedonia in the period 2015–2022

Year	New diagnosed cases with immunologic OA	Working population [17], [18]	Annual incidence rate/100,000 working population
2015	14	711,380	1.9
2016	15	727,985	2.1
2017	17	743,451	2.3
2018	16	759,445	2.0
2019	13	799,546	2.1
2020	5	785,561	0.6
2021	4	796,681	0.5
2022	18	693,062	2.6

Data are expressed as a number of new diagnosed cases with immunologic OA per year, total working population in RN Macedonia during the mentioned year of time and their ratio multiplied with 100,000. OA: Occupational asthma.

The highest incidence rates of immunologic OA were registered in cleaners, bakers, textile workers, wood industry workers, metal workers, and agricultural workers, i.e., more than a half of all new diagnosed immunological OA cases (56.8%) were registered in these 6 occupations (Table 2).

Positive SPT so common inhalant allergens were registered in 61.8% (63 / 102) of the workers with immunologic OA. Table 3 shows the distribution of atopics among immunologic OA cases with particular occupation.

Positive SPT to available occupational allergens were registered in 24.5% (25 / 102) of the workers with immunologic OA (Table 4). All immunologic OA cases with positive SPT to occupational allergens were atopics.

Table 2: Immunologic OA cases by particular occupation in RN Macedonia in the period 2015–2022

Occupation	Immunologic OA cases (n = 102) (%)
Cleaners (domestic and non-domestic cleaners)	16 (15.7)
Bakers (industrial and traditional), grain transporters, millers, pastry makers	13 (12.7)
Textile workers (cotton and flax spinners, weavers and packers; bleachers)	9 (8.8)
Wood industry workers (carpenters, furniture manufacturers, cabinet makers)	8 (7.8)
Agricultural workers	6 (5.9)
Metal workers (metal-parts manufacturers and fabricators)	6 (5.9)
Chemical industry workers (adhesive manufacturers, laminate manufacturers)	5 (4.9)
Plastic industry workers (plasticizers and insulation material manufacturers)	5 (4.9)
Paint manufacturers	4 (3.9)
Food technologists	4 (3.9)
Pharmaceutical industry workers	4 (3.9)
Hairdressers	3 (2.9)
Healthcare workers (nurses, medical technicians, dentists, and dental technicians)	3 (2.9)
Automobile spray painters	2 (1.9)
Cosmetician	2 (1.9)
Packing material manufacturers	2 (1.9)
Varnishes	1 (0.9)
Upholsterers	1 (0.9)
Solderers	1 (0.9)
Herbal and fruit tea processors	1 (0.9)
Retailers	1 (0.9)
Brewery workers	1 (0.9)
Veterinary technicians	1 (0.9)
Animal handlers	1 (0.9)
Tanners	1 (0.9)
Welders	1 (0.9)

Data are expressed as number and percentage of new diagnosed immunologic OA cases by particular occupation. OA: Occupational asthma.

Discussion

As it is mentioned earlier, OA became the most prevalent occupational lung disease in the developed countries in the last few decades, i.e. it is estimated that in one of five to ten adult asthma patients the disease is occupational by its origin. By existing evidence, around 90% of all OA cases develop after sensitization to certain occupational sensitizer (immunologic OA), while the exposure to high concentrations of some respiratory irritants may lead to the development of OA in up to

Table 3: Distribution of immunologic OA cases by atopic status

Immunologic OA cases	Immunologic OA cases with positive SPT to common inhalant allergens (63/102)
Bakers, millers, pastry makers	9/13
Cleaners	8/16
Textile workers	8/9
Wood industry workers	5/8
Agricultural workers	4/6
Metal workers	3/6
Plastic industry workers	3/5
Food technologists	3/4
Chemical industry workers	2/5
Pharmaceutical industry workers	2/4
Healthcare workers	2/3
Hairdressers	2/3
Paint manufacturers	2/4
Packing material manufacturers	1/2
Cosmeticians	1/2
Varnishes	1/1
Upholsterers	1/1
Solderers	1/1
Herbal and fruit tea processors	1/1
Retailers	1/1
Brewery workers	1/1
Veterinary technicians	1/1
Tanners	1/1

Data are expressed as number of new diagnosed immunologic OA cases with positive SPT to common inhalant allergens in regard to all new diagnosed immunologic OA cases with particular occupation. OA: Occupational asthma; SPT: Skin prick test.

Table 4: Distribution of immunologic OA cases by sensitization to occupational allergens

Occupation	Number of immunologic OA cases (n = 102)	Number of cases with positive SPT to occupational allergens (25/102)	Occupational allergen
Bakers, grain transporters, millers, pastry makers	13	9	Wheat or/and meal flour
Textile workers	9	8	Cotton or/and flax
Agricultural workers	6	2	Wheat flour, meal flour or/and grain dust
Healthcare workers	3	3	Latex
Tanners	1	1	Rabbit fur or hamster fur
Herbal and fruit tea processors	1	1	Lime
Animal handlers	1	1	Rabbit fur

Data are expressed as total number of new diagnosed immunologic OA cases in the period 2015–2022 and number of new diagnosed immunologic OA cases sensitized to available occupational allergens. OA: Occupational asthma; SPT: Skin prick test.

10% of all OA cases (non-immunologic OA). So far, up to 300 occupational sensitizers causing immunologic 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 [13], [19], [20].

The aim of this study was to present the incidence of immunologic OA by occupation in RN Macedonia in the period 2015–2022 after it has been presented for the period 2005–2014. The OA diagnosis was established by serial PEFR measurements 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. Specific inhalation challenge (SIC) with the suspected occupational agent is considered as a gold standard for the diagnosis and confirmation of immunologic OA. However, this requires specialized facilities and is available at only a few centers, i.e. SIC should be performed when the diagnosis of immunologic OA remains in doubt after serial monitoring of PEFR and/or non-specific BHR or when a new agent is suspected of causing immunologic OA. 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%). Sensitivity and specificity of serial PEFR measurement should be enhanced by its combination with non-specific bronchial provocation at and away from work. As we did in our previous study, we performed both tests to clarify the diagnosis in the cases with border value of the serial PEFR monitoring at and away from work [6], [9], [21], [22].

The incidence rate of immunologic OA was similar in the period 2015–2019, its drop in 2020 and 2021 should be explained by limited access and activities in this field during the Covid-19 pandemic when

the whole health system was focused on management of patients with Covid-19, and its increase in 2022 when began normalization of the health system function. With exception of the incidence rates registered in 2020 and 2021, the incidence rates of immunologic OA in the period 2015–2022 were similar to those registered in the period 2005–2014, i.e. the mean annual incidence rate of immunologic OA is at the level of its mean annual incidence rates in developing countries [23].

Distribution of the new diagnosed cases of immunologic OA in the period 2015–2022 is also similar to those registered in the period 2005–2014. Cleaning (domestic and non-domestic), bakery (industrial and traditional), cleaning, textile manufacture, wood industry, agriculture, and metal-parts manufacture are the most important occupations for the development of immunologic OA, i.e. up to 60% of all immunologic OA cases in the period 2015–2022 developed in this six occupations. These findings may improve the targeting of the activities of primary prevention (reduction of exposure by maximal exposure limits and dust control when possible), as well as of secondary prevention (early detection of a disease process before the occurrence of clinically adverse health outcomes by preventive medical check-ups). Over the past decades years there has been an increased awareness and growing evidence that cleaners are at increased risk of developing immunologic OA, as well as other respiratory disorders. The use of spray products seemed to impart a higher risk than other types of cleaning agents. Chlorine bleach, ammonia, and air freshening sprays are considered as the most common cleaning agents related to immunologic OA. In addition, existing evidence indicates that cleaning agents can cause both immunologic and non-immunologic OA and aggravate pre-existing asthma [24], [25], [26], [27]. On the other side, baker's asthma remains one of the most common forms of immunologic OA at global level. Respiratory symptoms among bakers caused by exposure to flour dust identical to the baker's asthma symptoms had been described by Ramazzini in 1700. In addition, case reports from the beginning of the 20th century established the concept of baker's asthma as an allergic disease because of the observed combination of positive skin tests to flour extract and respiratory symptoms suggestive of asthma. In the meantime, a number of agents in cereal flours (wheat, rye, barley, rice, etc.), non-cereal flours (buckwheat, soybean flour) and other components in bakery dust (enzymes and additives, colors, spices, insects, moulds, etc.), that may induced the formation of IgE antibodies and allergic inflammation of the airways have been detected [28], [29], [30], [31].

Atopy is considered as a risk factor for developing IgE-dependent immunologic OA, i.e. immunologic OA caused by most HMW and some LMW occupational agents (e.g. salts of platinum). On the other hand, it seems that atopy is not an important determinant of IgE-independent immunologic OA, i.e. OA caused by most LMW occupational agents [5], [32], [33], [34], [35], [36]. Findings of our both studies also indicated that the most cases with immunologic OA caused by HMW agents were atopics (bakers, textile workers, agricultural workers, health care workers, etc.), whereas in a high proportion of the cases with immunologic OA probably caused by LMW agents (cleaners, chemical industry workers, paint manufacturers, etc.) SPT to standard inhalant allergens were negative.

Conclusion

In conclusion, results of the study indicate that annual incidence rate of immunologic OA in RN Macedonia in the period 2015–2022 of around 2%, with exception in the years of Covid-19 pandemic, that correspond with the results obtained for the period 2005–2014, as well as with its incidence rates in developing countries. Cleaning, bakery, textile manufacture, and agriculture were registered as occupations with the highest risk for its development. The results obtained could help in the improvement of preventive activities in order to reduce the incidence of the disease and its adverse health outcomes.

Authors Participations

JM and SS participated in the data collection, data analysis, and writing all versions of the manuscript. DM, AA, MPR, AND and DM participated in the data collection. All authors read and approved the final manuscript.

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