



Clinical Trial Paper

Can the ceramic industry be a new and hazardous sector for work-related asthma?

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ARTICLE INFO

Keywords:

Work-related asthma
Occupational asthma
Ceramic sector
Metal industry

ABSTRACT

Background: Work-related asthma (WRA) constitutes a significant proportion of all asthma cases and continues to be reported from different industries. The aim of the study was to identify the occupations that can be related to WRA and diagnostic steps used in suspected WRA patients.

Methods: We retrospectively reviewed the clinical records of WRA suspected patients who were referred to Ankara Occupational and Environmental Diseases Hospital, Turkey from January 2015 to January 2017. Detailed occupational history, the diagnostic steps such as pulmonary function testing (PFT), peak expiratory flow (PEF) monitoring and nonspecific bronchial provocation tests (NSBPT) were recorded.

Results: Among 160 patients, 148 were male and 12 were female. Only 2 of them were diagnosed as work-exacerbated asthma (WEA). Diagnosis of asthma was based on using reversible airflow limitation 28.8% (n = 46) or NSBPT 31.9% (n = 51). Toxicological analysis showed that 28 patients had heavy metal poisoning, 9 patients had solvent poisoning, 4 patients had both. According to occupations, 32 of them were ceramic workers (20.0%) and 27 of them were metal workers (16.9%). Plastic workers (4 ± 2.8 years), cleaners (6.2 ± 5.7 years), metal workers (7.4 ± 5.4 years), painters (10 ± 5.2 years), ceramic workers (10.8 ± 5.9 years) had the shortest exposure durations for development of occupational asthma (OA). An analysis of variance showed that the effect of heavy metal and solvent poisoning on mean time for onset of OA was not significant.

Conclusions: The results demonstrate that besides the sectors known to cause WRA, ceramic and metal industries can be related to important exposures related to WRA. Medical surveillance of employees in this sector is important in early detection.

1. Introduction

Asthma is a common respiratory condition characterized by variable pulmonary symptoms and variable expiratory airflow limitation [1]. Approximately 5–20% of newly diagnosed adult onset asthma cases are considered to be associated with occupational exposures [2]. When occupational exposures cause or exacerbate asthma, it is called work-related asthma (WRA) [3]. One of the subgroup of WRA is called work-exacerbated asthma (WEA), has been defined as pre-existing or coincident asthma that is worsened by workplace conditions not caused by workplace exposures. The second subgroup of WRA is called occupational asthma (OA) which is primarily caused by occupational exposures [4]. OA is mainly divided into two categories according to causative agents; allergic OA, also called sensitizer-induced OA, and non-allergic OA, also called irritant-induced OA [5]. Subgroups of WRA have similar clinical characteristics and can cause impairment/

disability due to work. Differential diagnosis among the types of WRA is important because there are some differences according to diagnosis, prognosis, and prevention [3].

The initial step in diagnosis of WRA is suspicion that a person's respiratory symptoms may be related to WRA. In the second step, confirmation of diagnosis of asthma is required both clinical and occupational history and objective measures of reversible airway obstruction. There is no simple test that would allow for diagnosing WRA with a sufficiently high level of confidence. It must be demonstrated that if there is a reversible airflow obstruction or a positive nonspecific bronchial provocation tests (NSBPT) by pulmonary function testing [2,3,5,6]. Positive NSBPT has a low specificity (48–64%) and accordingly a low positive predictive value (PPV) for diagnosing OA [7,8]. The next step is assessment of the association between asthma and workplace exposures. Approaches to this evaluation are serial peak expiratory flow (PEF) or forced expiratory volume in the first second

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(FEV1) measurements, serial testing of NSBPT, and if available, specific inhalation challenge (SIC) testing in the laboratory or in the workplace [8,9]. Although current guidelines for OA state that the most reliable method for diagnosis is the SIC testing [10–12]; it is not available in clinical settings in many countries and centers. The last step is differentiating types of WRA. Positive SIC test results generally can categorize the patient to a diagnosis of OA. If SIC testing is not available, differentiation of OA and WEA relies on the onset of asthma symptoms in relation to onset of the occupational exposure that is exacerbating the asthma. Where SIC testing is not clinically available, it has been suggested that alternatively combining serial measurements of NSBPT and/or PEF monitoring at work and away from work, immunologic tests can be used [9,13]. Two major problems in these diagnostic serial tests are that firstly the patients may be referred to clinics after quitting their jobs and secondly it is difficult to perform serial tests in the non-working period due to problems getting permission for time off work.

Recently, new cases of WRA due to workplace exposures in many sectors have been reported. The exposures related to WRA can vary from country to country in the same sectors. And also diagnostic steps used in WRA patients can vary according to possibilities for applying tests. Through this knowledge, we hoped to identify the occupations and sectors that can be related to suspected WRA in an Occupational Diseases Hospital. Additionally, we aimed to assess the distribution of OA and WEA patients and diagnostic steps used in suspected WRA patients.

2. Methods

2.1. Patients selection

We retrospectively reviewed the clinical records of 160 WRA suspected patients who were referred to Ankara Occupational and Environmental Diseases Hospital, Turkey from January 2015 to January 2017. Demographic characteristics, detailed occupational history, physical examination, results of pulmonary function testing, skin prick tests (SPTs), chest X-ray, and if available, NSBPT, serial PEF measurements, and high resolution computed tomography (HRCT) results were recorded. This study was approved by Hacettepe University Clinical Research Ethical Committee (Date and Number: 10/10/2017, GO-17/768-14). Demographic characteristics of patients are shown in Table 1. Records of 160 patients were reviewed, of whom 148 were male and 12 were female. Of them, 42.2% (n = 68) were diagnosed as having asthma before admission to our clinic and 57.8% (n = 92) of patients were referred to our clinic as suspected asthma.

2.2. Evaluation of asthma and WRA

The patients who were referred by occupational/workplace physicians from different workplaces having respiratory symptoms such as dyspnea, cough, wheezing and chest tightness were included in the study. For the first step evaluation and for diagnosing asthma, we demonstrated that there is a reversible airflow obstruction or positive NSBPT by pulmonary function testing (PFT). Airflow limitation was defined as FEV1/FVC < 70% [1,14] and reversibility was defined as an increase in FEV1 12% and 200 mL after administration of 400 µg salbutamol. After finding no reversible airflow limitation, patients underwent NSBPT. Positive test was defined as 20% fall in FEV1 from baseline of ≥20% with standard doses of methacholine (PC20 > 16 mg/mL as negative, 4–16 mg/mL as borderline BHR, 1–4 mg/mL as mild BHR, < 1 mg/mL as moderate to severe BHR) [1,15].

In the second step, patients were assessed for the relation of asthma with workplace exposures. Complete occupational anamnesis including duration of work, duration of symptoms and relationship between work and asthma symptoms, exposures in the workplace. If asthma were not present before working and occurred by workplace exposures, those patients were grouped as having suspected OA.

Table 1

Some demographic characteristics of patients.

Characteristics	
Mean Age (years)	42.6 ± 8
Gender	
Female	7.5% (n = 12)
Male	92.5% (n = 148)
Smoking status	
Never	21.3% (n = 34)
Current-smoker	46.9% (n = 75)
Ex-smoker	26.9% (n = 43)
Cigarette Pack-years	10.0 (1–45)
Mean working period (years)	13.2 ± 6.6
Mean time to onset of asthma (years)	9.6 ± 6.9
Working status	
working in the same job	60% (n = 96)
working in a different job	14.4% (n = 23)
quit their job	11.3% (n = 18)
has retired	9.4% (n = 15)
has been fired	4.4% (n = 7)
PFT results	
Mean value of FEV1	79.7 ± 16.5%
Mean value of FVC	88.6 ± 16.2%
Mean value of FEV1/FVC	74.8 ± 8.8%
Diagnosis of Asthma	
Reversible airflow obstruction	28.8% (n = 46)
Nonspecific bronchial hyperresponsiveness	31.9% (n = 51)
Chest X-ray	
Normal	71.3% (n = 114)
Reticulonodular opacities	20.0% (n = 32)
Air trapping	3.1% (n = 5)
HRCT	
reticulonodular	36.9% (n = 59)
normal	30.0% (n = 48)
nodular	7.5% (n = 12)
emphysema	1.9% (n = 3)
air trapping	1.3% (n = 2)

PFT: Pulmonary function testing, HRCT: High resolution computed tomography, FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity.

In the next step, after training to use PEFmeter, patients were asked to measure PEF rates three times per each practice and four times per day by writing the best measurement for each on a chart for 15 days at rest and 20 days at work. More than 20% PEF variability in at least 2/3 of working days and worsening of PEF values during work periods were suggestive OA. Skin prick test was performed only with a common panel of aeroallergens for evaluating atopy.

After these steps, patients were classified into three groups; non asthma, WRA and suspected but unconfirmed WRA that have workplace exposures related to asthma. Patients were also classified according to the sectors/occupations, exposures and processing fields.

2.3. Statistical analysis

Analysis of data was performed using the computer program IBM SPSS Statistics Version 21 (SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normality by the Kolmogorov–Smirnov test/Shapiro–Wilk's test. Values were presented as mean ± standard deviations or, in the case of nonnormally distributed data, as median with data range (minimum to maximum). The Chi-square test was used for the comparison of two independent groups for categorical data. The difference among the groups with normal distribution were evaluated by Student's t-test. The importance of the difference according to the means between groups was examined using analysis of variance. A P-value < 0.05 was considered to be statistically significant.

3. Results

The mean working period was 13.2 ± 6.6 years, and the mean time to onset of symptoms after starting work was 9.6 ± 6.9 years. Only 2 of

Table 2

Occupational distribution of study population.

	n	%
ceramic workers	32	20.0%
metal workers	27	16.9%
welders	20	12.5%
painters	15	9.4%
miners	13	8.1%
cleaners	7	4.4%
carpenters	5	3.1%
battery producers	5	3.1%
machine repairers	4	2.5%
plastic workers	3	1.9%
textile workers	3	1.9%
others	26	16.2%

160 patients were diagnosed as WEA according to their pre-existing asthma diagnosed before starting work. According to patients' occupations, 20.0% (n = 32) of them were ceramic workers, 16.9% (n = 27) were metal workers, 12.5% (n = 20) welders, 9.4% (n = 15) painters, 8.1% (n = 13) miners. According to different ceramics processing fields, 9.3% (n = 15) of them were working in raw material preparation, 5.6% (n = 9) of them were working in forming and shaping, 3.7% (n = 6) of them were working in glazing, painting or coating (Table 2).

All patients underwent PFT, mean value of FEV1 was $79.7 \pm 16.5\%$, mean value of FVC was $88.6 \pm 16.2\%$, mean value of FEV1/FVC was $74.8 \pm 8.8\%$. 97 patients were diagnosed as asthma by using reversible airflow limitation 28.8% (n = 46), or by using NSBPT 31.9% (n = 51). 8 patients were referred to pulmonary medicine clinic for differential diagnosis. 55 patients were classified as suspected asthma with probable workplace exposures and having variable symptoms but having normal PFT. Airflow limitation or positive NSBPT could not be shown and PEF monitoring could not be performed on these patients because of referring to our clinic after quitting their jobs (Fig. 1).

According to ILO (International Labour Organization) classification, 24.4% of workers were diagnosed as pneumoconiosis with 79.5% found to display in profusion category 1, 2.5% silicosis in profusion category 2, 1.3% silicosis in profusion category 3, 1.3% silicosis in profusion

Table 3

Distribution of exposures according to toxicological analysis.

Solvent	5.6% (n = 9)
Arsenic	5.0% (n = 8)
Lead + manganese	3.1% (n = 5)
Manganese	2.5% (n = 4)
Nickel	2.5% (n = 4)
PAH	1.9% (n = 3)
Lead	1.3% (n = 2)
Multiple heavy metals (more than 3)	1.3% (n = 2)
Other metals	1.9% (n = 3)

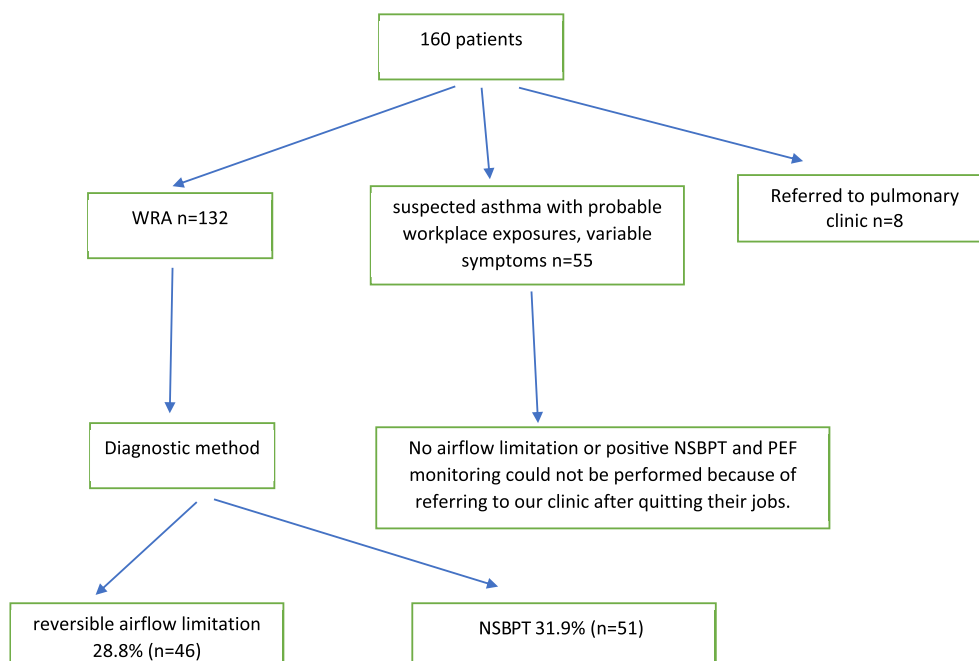
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The diagnosis of OA was made through PEF monitoring at work and at home with decrease in the PEF values in 24.4% (n = 39) of patients. Nearly 25% of patients could not perform PEF measurements because of quitting or retiring job or being fired. The others were diagnosed by detailed occupational history including their pre-existing asthma diagnosed before starting work.

Toxicological analysis showed that 28 patients had heavy metal poisoning including lead, manganese, cadmium, nickel, or combinations, 9 patients had solvent poisoning, 4 patients had both heavy metals and solvent poisoning (Table 3). A pie graph which is related to proportions in percent of the found exposures associated with WRA was shown (Fig. 2). Patients who had other work-related diseases were as follows; lumbar discopathy (n = 52), pneumoconiosis (n = 34), tinea pedis and/or unguis (n = 33), cervical discopathy (n = 17), carpal tunnel syndrome (n = 9), welder's lung (n = 8), allergic contact dermatitis (n = 7), irritant contact dermatitis (n = 5).

There was a significant relation between the occupations and mean time for onset of WRA. Among the occupations, marble workers (22.2 ± 3 years), repairmen (14.2 ± 14.4 years) carpenters (13.6 ± 10.5 years) had the longest exposure durations. And plastic and PVC workers (4 ± 2.8 years), cleaners (6.2 ± 5.7 years), metal workers (7.4 ± 5.4 years), painters (10 ± 5.2 years), ceramic workers (10.8 ± 5.9 years), welders (11 ± 4 years) had the shortest exposure durations. WEA patients' occupations were accumulator production worker and textile worker.

An analysis of variance showed that the effect of heavy metal poisoning on mean time for onset of OA was not significant. The mean time

**Fig. 1.** A flowchart of our retrospective study data.

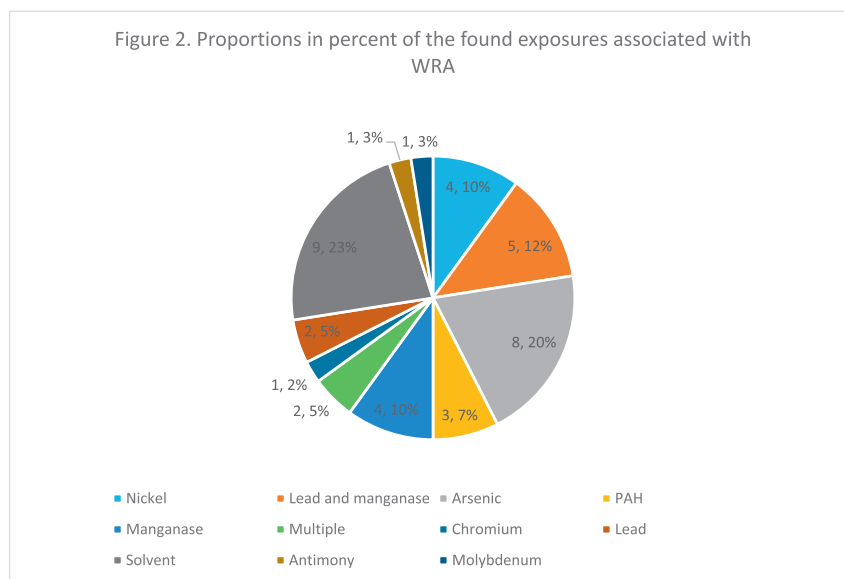


Fig. 2. Properties in percent of the found exposures associated with WRA.

for onset of OA who had heavy metal poisoning was 6.9 ± 5.3 years and the mean time for onset of OA who did not have heavy metal poisoning was 9.8 ± 6.6 . There was also no significant relation between mean time for onset of OA and solvent poisoning. The mean time for onset of OA who had solvent poisoning was 7.8 ± 3.3 years and the mean time for onset of OA who did not have solvent poisoning was 9.3 ± 6.9 .

4. Discussion

New workplace exposures causing WRA continue to be reported in different sectors. The best known agents related to WRA are animal and plant proteins (laboratory workers, bakers), metals (pharmaceutical workers, metal plating workers), diisocyanates (construction workers), paints, cotton dust (textile workers), acids, ammonia [16]. Existing nationally datasets have the potential to estimate trends in occupations and sectors. For example, there was a significant declining trend for OA attributed to wood, flour, aldehydes, isocyanates and latex, but there was a significant increasing trends reported were for quaternary ammonium products and cleaning products [17–19]. In our study, distribution of occupations were different from other current studies that ceramic workers, metal workers and welders were the largest groups that related to WRA. To our knowledge, ours is the first study to show different types of occupations especially ceramic workers that can be related to WRA. Especially the workers' processing fields which can contain hazardous exposures in ceramic industry are raw material preparation, forming and shaping, glazing, painting or coating.

Silica is a well known workplace exposure in ceramic sector. In addition to silica, ceramic workers are potentially exposed to beryllium, inorganic lead, lime, and aluminum [20]. The main raw materials of ceramic are clay, silica, alumina, magnesia, titania, iron oxide and zircon. But in these industries there are many different types of occupational exposures such as solvents, chemicals and metals. Heavy metals particulates or fumes (lead, cadmium, chromium, arsenic, copper, nickel, cobalt, manganese or tin) are found in glazes, colouring agents, films or coatings and also solvents such as xylene, toluene [21]. In this study, patients were asked for information related to exposures in the workplace and safety data sheets if available. Our findings also showed metal workers and welders are the second largest group of OA. These workers are exposed to a variety of agents like metals, irritating fumes and gases. These exposures have previously been associated with an increased risk of asthma [22,23]. A recent study have shown that ever-

exposure to metals was associated with fixed airway obstruction and a lower FEV1/FVC ratio [24]. In the same study, men were mostly metal, rubber, plastic product assemblers, glass, ceramics painters, mechanical and electrical technicians, painters, and sheet metal workers. Cobalt is one of the most important constituent present in ceramic industries. Glazers are the relevant workers when they are producing blue colored ceramic, causing occupational exposure to such metal. The decline in FEV1 and FEV1/FVC was higher in those who have exposed to cobalt compared to those who have not exposed [25].

A recent study has shown that the methacholine challenge has a high NPV for excluding the diagnosis of OA in a worker still at work and the authors advised that the methacholine challenges should be done while the patient is still exposed at work [7]. Nearly 25% of our study population were fired, quit or retired from their works. These subgroups are still difficult to demonstrate the accurate diagnosis of OA. So, despite of having a history of compatible with OA, there is a lack of in and off work assessments.

In this study, a significant proportion of WRA patients have a competent occupational history for diagnosis of OA. The reason for this may be due to the selection of patients from an Occupational Diseases Center. These results are similar but quite high proportion in favor of OA with the current studies [26]. In this study, we could not show an effect of heavy metal and solvent poisoning on mean time for onset of OA. One reason for this is in many workplaces toxicological analysis is performed for only common metals and solvents on workers. There can be some different exposures apart from the known ones.

Pneumoconiosis is the one of the most common type of occupational disease due to lack of adequate preventive measures in developing countries as similar to our study results [27]. And similar to a recent study, fortunately the common profusion of pneumoconiosis is stage 1 [27]. This can be explained by medical surveillance for early detection of silicosis cases.

In Turkey, among 597 occupational diseases, only 8 WRA cases out of 216 occupational lung diseases have been recorded in 2016 according to the recent Statistical Yearbook of Ministry of Labour and Security of Turkey [28]. These records are comprised of only workers covered by the social security system. Lower number than expected can be explained as due to poor detection and inadequate recording system. WRA was classified as allergic asthma, non allergic asthma and undifferentiated asthma in this official reference. This kind of classification is not compatible with the current WRA guidelines.

Our study has several limitations. A major limitation of our study is

that it is a retrospective study involving a relatively small number of patients. Second limitation may be that some of the occupational groups were small, so we were not able to make a subgroup analysis in different occupations. Another limitation of this study was the inability to perform SIC tests for accurate diagnosis of OA and demonstrating other different possible risk factors which may have contribute to asthma such as history of allergic diseases, exposure to aeroallergens, obesity, lower socioeconomic status and atopy. Only sixteen patients underwent skin prick testing and all of them were non-atopic.

5. Conclusions

In summary, there has been an increase in cases of WRA referred to occupational and environmental medicine clinics. However, studies regarding the importance of occupational exposures are still reporting conflicting results and many have a lack of specific exposure information. Moreover, there is a need for updated information regarding the impact of occupational exposures on WRA because production processes, raw-material and additives of products. Medical surveillance for early detection of cases who are working in these sectors such as ceramic and metal sectors apart from the known ones also can contribute to reducing the burden of impairment/disability owing to WRA.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgments

Author contributions: The study design was conceived by Ozlem Kar Kurt, clinical file data were extracted by Ozlem Kar Kurt and Dilek Ergun, and analyses performed by Ozlem Kar Kurt and Nursen Basaran. All coauthors contributed to the manuscript preparation and all approved the submitted version.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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