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Observation

WORK-RELATED ASTHMA IN AUTOMOBILE SPRAY PAINTERS: TWO CASE REPORTS

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This report describes two patients who had developed asthma after working as automobile painters with isocyanate-based aerosol paint for two years or over. In both patients asthma was confirmed using the standard diagnostic procedure. One of the subjects was atopic. One was ex-smoker and the other had never smoked. Neither had a family history of asthma. The symptoms occurred after workplace exposure lasting two years in one patient and three in the other. As both reported work-relatedness of the symptoms, they underwent serial peak expiratory flow rate (PEFR) measurement and bronchoprovocation testing. Significant work-related changes in PEFR diurnal variations and in non-specific bronchial hyperresponsiveness (NSBH) were observed in one patient, suggesting allergic occupational asthma (OA), while the other patient was diagnosed work-exacerbated asthma (WEA). Our data confirm that spray painting is an occupation with increased risk of respiratory impairment and asthma.

KEY WORDS: *bronchial provocation tests, isocyanates, occupational asthma, peak expiratory flow rate, work-exacerbated asthma*

Asthma rates are rising throughout the world, and environmental and occupational factors are being scrutinised in search of explanations. Workplace exposure can trigger or induce asthma and cause different types of work-related asthma (WRA) (1). WRA is a broad term encompassing occupational asthma (OA), that may be allergic and non-allergic or irritant-induced, and work-exacerbated asthma (WEA) (1, 2). Over the last few decades WRA has become the most common work-related respiratory disorder in the industrialised countries, contributing to 10 % to 29 % of all adult asthma cases (3-5). According to the results of a polycentric study carried out in 2003, the prevalence of asthma in the age group 20 to 44 years in Macedonia was 5.4 % and work-relatedness of the disease was reported in 24.7 % asthma patients (6).

There is evidence of WRA among spray painters using isocyanate-based aerosol paint. According to the European Community Respiratory Health Survey (ECRHS) classification, spray painting is considered an occupation with a high risk of respiratory impairment and asthma (occupational set "spray painters") (7, 8). It is well-established that workplace exposure to polyisocyanates, low-molecular-weight compounds used in the manufacture of polyurethane paints, varnishes, and plastics, may lead to respiratory impairment. Polyurethane paints containing isocyanate hardeners were introduced in the automobile refinishing market in the late 1960s to provide resistance to weather and sunlight, and came into wide use in the 1980s (9). Despite the acknowledged risk, widespread use of isocyanates in the paint systems used in the automotive repair and refinishing industry still entails exposure. This is an industry of primarily small, often family-owned repair shops with a few employed workers. The workers are

usually specialised in specific operations removal of damage, frame straightening, and welding are performed by mechanics while masking/taping, spraying basecoat and clearcoat, gun cleaning, untaping, compounding, washing, and detailing are performed by painters. Many studies indicate significant exposure to isocyanates in this industry (10-12).

Our study describes two automobile painters who developed different types of WRA working with isocyanate-based aerosol paint.

METHODS

Study design

This study included two subjects who were examined at the Institute of Occupational Health, Skopje (IOH) in 2006 and 2007. Asthma diagnosis was confirmed using the standard diagnostic procedure, while OA diagnosis was confirmed by serial monitoring of peak expiratory flow rate (PEFR) and by serial bronchoprovocation testing.

Clinical history

The presence of respiratory symptoms suggestive of asthma (wheezing, shortness of breath, chest tightness, cough, and asthma attacks) was documented using the ECRHS questionnaire (13). The subjects were asked about the onset (before or after entering the actual workplace; sudden or progressive) and work-relatedness of the symptoms (worsening of the symptoms during or after work shifts and improving during weekends and vacations).

We took and evaluated a detailed occupational history, including current and previous occupations. The subjects were asked about the characteristics of the working process, appliances and materials used, duration of the working shifts, and use of protective equipment. We also evaluated smoking history, family history of asthma and allergies (taking into account the first-degree relatives), accompanying disease, and use of medications.

Skin prick tests

Skin prick tests (SPT) to the common inhalant allergens were performed on the volar part of the forearm using allergen extracts (Torlak, Serbia) of birch (5000 PNU), lime (5000 PNU), mixed grass (*Agrostis alba, Alopecurus pralensis, Dactylis glomerata, Festuca pranesis, Phleum pratense, Poa pratensis, Secale cereale, Triticum aestivum,* and *Zea mais*; 5000 PNU), mugwort (5000 PNU), plantain (5000 PNU), mixed fungi (*Alternaria alternata, Aspergilus fumigatus, Mucor, Penicillium notatum, Cladosporium herbarum, Candida albicans*, and *Trychophyton*; 4000 PNU), *Dermatophagoides pteronyssinus* (4000 PNU), dog hair (4000 PNU), cat fur (4000 PNU), and mixed feathers (chicken and duck feathers; 4000 PNU). All tests included positive (1 mg mL^{-1} histamine) and negative (0.9 % saline) controls. Skin prick tests were considered positive if the mean wheal diameter 20 min after allergen application was at least 3 mm larger than negative control (14).

Spirometry

Spirometry, including measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, maximal expiratory flow at 50 %, 25 %, and 25 %-75 % of FVC (MEF_{50}, $MEF_{25,}$ and MEF_{25-75}, respectively), was performed recording the best of three measurements by spirometer Ganshorn SanoScope LF8 (Ganshorn Medizin Electronic GmbH, Germany). The results were expressed as percentages of the predicted values, according to the European Community for Coal and Steel (ECCS) standards (15).

Histamine challenge

The histamine challenge tests were performed according to the European Respiratory Society (ERS) recommendations (16). Concentrations of 0.5 mg mL^{-1}, 1 mg mL^{-1}, 2 mg mL^{-1}, 4 mg mL^{-1}, and 8 mg mL^{-1} histamine (Torlak, Serbia) were prepared by dilution with buffered saline. The doses of aerosol generated by Pari LC nebulizer (Pari GmbH, Germany) were inhaled through a mouthpiece. The subjects inhaled increasing concentrations of histamine using a tidal breathing method until FEV_1 fell by more than 20 % of its baseline value (provocative concentration 20 - PC20) or the highest concentration was reached. The test was considered positive if PC20 was equal or less than 4 mg mL^{-1}.

Asthma diagnosis

According to the American Thoracic Society (ATS) and Global Initiative for Asthma (GINA) recommendations (17, 18), current asthma is defined

as a presence of asthma-suggestive symptoms and positive histamine challenge.

Serial PEFR measurement

Serial PEFR measurements were performed using a PEFR-meter asmaPLAN+ (Vitalograph Ltd., Ireland) according to the ERS recommendations. To provide an adequate representation of days at work and days away from work, a positive record should include two weeks at work and two weekends away from work, and a negative record should include two weeks away from work, while PEFR measurements should be carried out at least 4 times a day (19).

Before taking PEFR self-measurements the subjects received instructions how to use the meter. They were instructed to record the highest of three readings only if the two best readings were within 20 L min^{-1} of each other. Measurements were taken four times a day from the morning till bedtime at similar times at and away from work. Readings were interpreted by analysing their diurnal variation. The test was considered positive when PEFR varied 20 % or more (calculated as maximum PEFR minus minimum PEFR divided by maximum PEFR) between working days, and days off work.

Serial nonspecific bronchoprovocation testing

Both subjects were also given serial histamine challenge on a work day and then nonspecific 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 (20).

Diagnosis of the WRA type

According to current ERS recommendations (1, 19, 20), allergic OA is defined as a diagnosed asthma that occurred after entering the current workplace with work-relatedness of the symptoms confirmed by serial PEFR monitoring or serial bronchoprovocation testing. Irritant-induced asthma (reactive airways dysfunctional syndrome - RADS) is defined as asthma with a sudden onset after an acute, high-level irritant exposure in a subject with documented absence of preceding respiratory complaints (1, 19). WEA is defined as a pre-existing or a new-onset asthma whose symptoms have worsened due to workplace environmental exposure, and is diagnosed by exclusion of OA (1).

Semi-quantitative risk assessment

We performed the semi-quantitative risk assessment at the subject's workplace according to the recommendations of "A Code of Practice for Risk Assessment, Advanced Techniques: June 2001" (21). The risk of adverse respiratory effects, rated as high, medium and low, was calculated taking account known and reasonably foreseeable hazards, effects that they could have, and probability of the event.

CASE REPORTS

Baseline clinical and functional data for the study patients are given in Table 1.

Subject 1.

Subject 1 was a 42-year old man who had never smoked, and had worked for four years in a car repair shop with 16 other workers. Before that he had worked as a driver for 17 years. At the current workplace he performed painting operations using isocyanate-based aerosol paints and his work shift was eight hours a day. These painting operations were performed in a large enclosed unit with an exhaust system consisting of a fan drawing air through filters into a plenum at the back of the unit and releasing it

Table 1 *Clinical and functional results of the two patients with WRA*

Subject	Age / years	Atopy	Smoking habit	Duration of exposure / years	Duration of symptoms / years	FEV_1 / % pred	FEV_1 / FVC / % pred
1	42	-	Never smoker	4	2	91	77
2	52	+	Ex- smoker	5	2	87	75

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: percentage of the predicted value.

outdoors. He reported painting about 20 to 25 cars per month, nearly every working day. His protective equipment consisted of protective clothing, gloves, and a simple air-filtering mask covering the nostrils. According to our semi-quantitative risk assessment, his workplace involved a medium risk of respiratory impairment.

At the first visit to the IOH Subject 1 reported progressive cough, shortness of breath, wheezing, and chest tightness over the previous two years. His symptoms typically occurred after the work shift, and on workdays he would wake at night with chest symptoms. The symptoms would improve with the application oral theophylline and/or inhaled salbutamol. During weekends and holidays the symptoms would completely clear, and he could stop taking medications. On his return to work the symptoms would recur within one or two days. He did not report any previous disease, and had no family history of asthma and allergies.

At his first visit, he was symptom-free, having been away from work for two weeks. He showed normal spirometric parameters, negative SPT to common inhalant allergens, and positive histamine challenge (PC20 = 4 mg mL^{-1}) which confirmed asthma diagnosis. As the subject reported work-relatedness of the symptoms and as there is a risk of allergic OA in spray painters, he underwent serial PEFR measurements and serial bronchoprovocation testing.

PEFR measurement showed significant changes between mean diurnal variations on days away from work and days at work (Figure 1).

Serial bronchoprovocation testing also showed significant differences in NSBH between days away from work and days at work; PC20 on days away from work was three double concentrations of histamine lower than on days at work (4 mg mL^{-1} *vs.* 0.5 mg mL^{-1}).

Significant work-related changes in mean PEFR diurnal variations and NSBH suggested allergic OA. Asthma management included moving the subject away from exposure and pharmacological anti-asthma treatment.

Subject 2

Subject 2 was a 52-year-old man who had worked for four years in a car repair shop with seven other workers, and before that he had worked as a shop assistant in spare parts and accessories store for 22 years. Similar to Subject 1, at the current workplace he performed painting operations using isocyanate-based aerosol paints, and his work shift also lasted eight hours a day. The painting operations were performed in a "home-made" booth without a ventilation system that had just been installed. He reported painting 12 to 15 cars per month, usually 4 to 5 times a week. Throughout the workshift he wore a working outfit, gloves, and simple mask for spraying. According to our semi-quantitative risk assessment his workplace involved a high risk of adverse respiratory effects.

He had a history of mild arterial hypertension over the last eight years and was treated with lysinopril. He also reported recurrent bronchitis in the childhood with productive cough and shortness of breath, but he

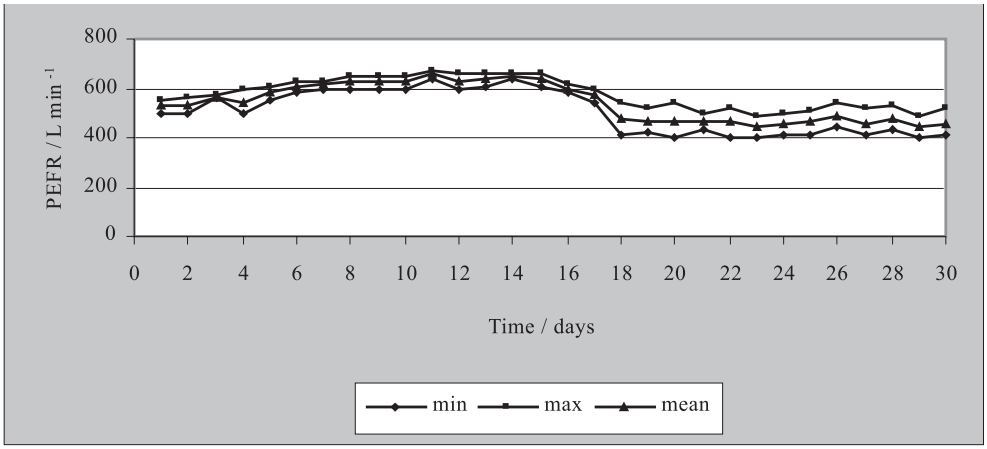

Figure 1 *Plot of maximum, mean, and minimum peak expiratory flow rate (PEFR) against time showing significant changes in mean PEFR diurnal variations on days away from work and days at work (8.1 % vs. 21.4 %, P = 0.000; independent samples t-test). Days away from work 1-15, days at work 16-30.*

was not evaluated for asthma at the time. However, he had had no respiratory complaint in the last 30 years. His mother suffered from seasonal allergic rhinitis, but he had no family history of asthma. He nad not been smoking for the last eight years, and before that he had smoked 20 cigarettes a day for 20 years.

He had been symptom-free until three years before his first visit to IOH, at which time he had rhinorrhoea, cough, shortness of breath, wheezing, and exercise intolerance. These symptoms occurred progressively and were more pronounced during and after work, occasionally causing him to wake at night. His symptoms improved with inhaled salbutamol, and decreased after two weeks away from work. They returned after two days at work and were controlled by inhaled salbutamol two to three times daily.

At the first visit, the subject reported only a mild cough, having been away from work for two weeks. Spirometry showed normal FVC, $FEV_{1,}$ and FEV_1/FVC % with an obstruction of the small airways. Skin prick tests were positive to birch, mixed grass, mugwort, and *Dermatophagoides pteronyssinus*. Histamine challenge was also positive (PC20 = 4 mg mL^{-1}), confirming asthma diagnosis. Consequently, we performed serial PEFR measurement and bronchoprovocation testing.

Mean diurnal PEFR variations did not show significant difference between days at work and away from work (Figure 2).

Bronchoprovocation testing on days away from work and days at work showed a difference in PC20 which did not reach two double concentrations of histamine (4 mg mL^{-1} *vs.* 2 mg mL^{-1}).

As PEFR and NSBH changes did not significantly differ between days at work and days away from work, our diagnosis was WEA. Its management included pharmacological anti-asthma treatment and we recommended that the subject should avoid the current workplace if the disease could not be controlled by optimised therapy and improved working conditions after the installation of the new ventilation system.

DISCUSSION

Due to its growing prevalence over the last few decades, WRA has been recognized by public health authorities as a priority issue in many countries worldwide. As WRA claims rate in Washington State increased over 55 % in the period 1991-1999, Washington added WRA as a disease physicians must report to the state health officials. High-risk industries for WRA in Washington State include sawmills, plastic products manufacture, and car repair (3).

Currently, isocyanate-containing coatings are found on almost every vehicle. Results from a Yale study (22) showed a 20 % prevalence of respiratory symptoms in automobile painters using isocyanate-based aerosol paints, but the production and use of these paints continues to grow (9). These chemicals are also considered an important cause of allergic occupational asthma in many countries throughout the world (e. g. US, Canada, and South Korea) (3, 11, 23).

Because of the many controversies, WRA diagnosis should not be made lightly. It is important

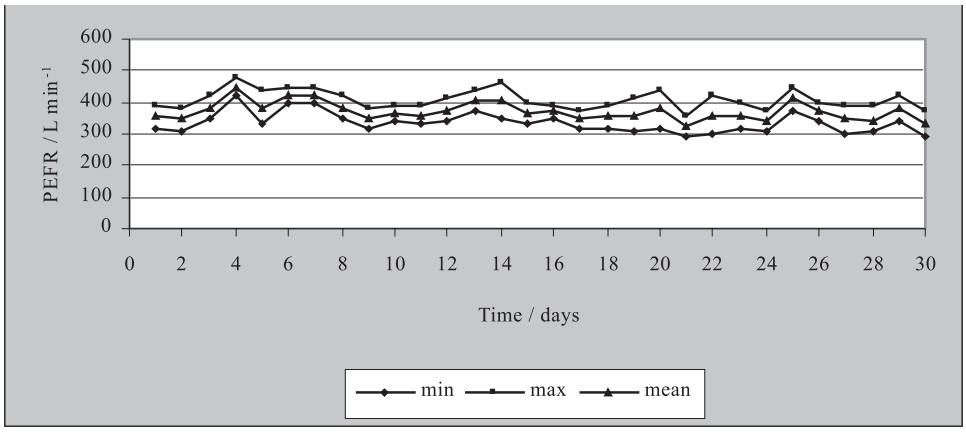

Figure 2 *Plot of maximum, mean, and minimum peak expiratory flow rate (PEFR) against time showing non-significant changes in mean PEFR diurnal variations on days away from work and days at work (16.6 % vs. 18.5 %, P = 0.423; independent samples t-test). Days away from work 1-15, days at work 16-30.*

to distinguish different types of WRA, since their prevention and treatment may differ significantly (1). Underdiagnosing and overdiagnosing OA can both create a substantial burden for patients, their families, employers, health-care insurance providers, and the society as a whole (24).

Automobile spray painters using isocyanate-containing aerosol paints in our study were employed in two autobody repair shops different in the size of business and premises. In fact, every autobody repair shop is an unique environment (9) that differs from others in work practices, workload, and the level of coating, and no two shops are the same. Literature describes different types of WRA in subjects employed in car repair industry. OA induced by isocyanates has become the model of allergic OA caused by low-molecular-weight compounds (25, 26). According to Mapp et al. (26), the estimated prevalence of WRA among painters using isocyanate-based aerosol paints was 7.1 %. Toluene diisocyanae (TDI), methylene diphenyldiisocyanate (MDI), and hexamethilene diisocyanate (HDI) are known causative agents of allergic OA (27). Although the isocyanate-induced effects are widely cited, their pathways, as well as the importance of intensity, duration, and frequency of exposure are still not well understood (9, 20).

As neither of our subjects had elements for the diagnosis of RADS, our work-up included confirmation or exclusion of allergic OA. The gold standard for diagnosing allergic OA is the specific inhalation challenge (SIC), but it is not frequently used. It is expensive and time-consuming, and carries a significant health risk to the person being tested. Finally, the challenge may not provide the correct exposure and may produce false negative and false positive results. When performed in a laboratory, the challenge is controlled, but also artificial (24, 28). Commonly performed in routine practice are the "stop-resume" work tests using serial measurements of PEFR, NSBH and/or sputum eosinophilia (26, 29). As Chiry et al. (29) reported that in some cases serial PEFR measurement failed to distinguish allergic OA from WEA, and indicated a need of additional tests, such as changes in airway responsiveness and immunologic tests, we reassessed the work-relatedness of asthma in our cases by serial bronchoprovocation testing. Similar to our previous study (30), in both cases the results of the two methods repeated each other, confirming the conclusion of Côté et al. (31) that the combination of serial PEFR measurement with serial measurement of NSBH does not add anything in differentiation between allergic OA and WEA to monitoring by PEFR alone.

We were unable to perform isocyanate challenge, so we did not confirm isocyanate as a causative agent of allergic OA in Subject 1. Even though isocyanates are the probable cause of allergic sensitisation and OA, other agents used by this subject (e.g. organic solvents) are not to be excluded. Allergy testing has a limited role in the diagnosis of isocyanate-induced asthma, as it is caused by non IgE-mediated mechanisms. In a study including 43 TDI-induced OA patients of whom 81 % were spray painters, Park & Nahm (23) found specific IgE-antibody to isocyanate conjugates in 40 %, with no relation between its presence and any clinical parameter. On the other hand, it is well known that positive allergy tests to workplace allergens can not confirm the diagnosis of allergic OA, as they identify sensitisation, and not the disease itself (32). Subject 1 was a never-smoker and his SPTs to common inhalant allergens were negative. Several studies have suggested that atopy and smoking may be associated with development of allergic OA caused by isocyanates (33, 34). In contrast, other studies indicated that atopy and smoking did not contribute to specific sensitisation and development of isocyanate-induced asthma (35).

We can speculate whether WEA diagnosed in Subject 2 is reactivation of an undiagnosed pre-existing childhood asthma with a long symptom-free period, triggered by current workplace exposure. It remains controversial whether the worsening of pre-existing asthma induced by a high-level inhalation of irritants should be categorised as an "acute irritant-induced asthma" or as WEA (36). Several investigators have proposed to extend the spectrum of irritant-induced asthma to include new-onset asthma and reactivation of quiescent asthma in subjects repeatedly exposed to "moderate" or "excessive", although poorly documented, concentrations of irritants at the workplace (37, 38). The evidence supporting this concept of "not-so-sudden RADS" is still very weak. We agree with the proposition of Vandenplas & Malo (1) that the delayed-onset asthma following repeated exposure to moderate or excessive concentrations of irritants can not be considered OA because the causal relationship between workplace exposure and the development of asthma can not be ascertained with a sufficient level of confidence.

The reader should note that our study has some limitations. We were unable to perform environmental measurements at the workplaces of the affected

subjects, so we could not document the effect of the level of exposure on WRA. Testing with workplace allergens could better present allergic sensitisation and its implications for the respiratory impairment in the affected subjects. As we did not perform SIC, we could not establish a relationship between its results and the data obtained from the serial PEFR and bronchoprovocation testing.

In conclusion, our findings confirm that spray painting is an occupation which involves the risk of respiratory impairment and WRA. They also confirm the need of regular medical examinations and implementation of appropriate measures to prevent adverse respiratory effects of workplace exposure in automobile spray painters.

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Sažetak

PROFESIONALNA ASTMA U AUTOLAKIRERA: OPIS DVAJU SLUČAJEVA

U radu su opisana dva bolesnika koji su nakon rada s aerosolskom bojom na bazi izocijanata u autolakirerskoj radionici dobili astmu. U oba je slučaja dijagnoza potvrđena standardnim postupkom. Jedan je bolesnik bio atopičan. Jedan je bivši pušač, a drugi nikad nije pušio. U obiteljskoj anamnezi nije bilo astme ni u jednog bolesnika. Simptomi su se javili nakon profesionalne izloženosti u trajanju od dvije odnosno tri godine. Budući da su oba bolesnika povezivala simptome s poslom, podvrgnuti su mjerenju vršnog ekspiratornog protoka (engl. *peak expiratory flow rate*, krat. PEFR) te nizu bronhoprovokacijskih testova. U jednoga su bolesnika zamijećene značajne profesionalne dnevne promjene u PEFR-u i nespecifične bronhalne hiperreaktivnosti, što upućuje na profesionalnu alergijsku astmu, dok je u drugoga ispitanika dijagnosticirano pogoršanje astme povezano s profesionalnom izloženosti. Naši podaci potvrđuju pretpostavku da posao autolakiranja sprejem nosi povećani rizik od respiratornih tegoba i astme.

KLJUČNE RIJEČI: *bronhoprovokacijski test, izocijanati, respiratorne tegobe, vršni ekspiratorni protok*

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