Case report
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Late asthmatic reaction caused by naphthylene-1,5 diisocyanate

by Xaver Baur, MD,¹ Dagmar Wieners, MD,¹ Boleslaw Marczynski, PhD¹

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After occupational exposure to naphthylene-1,5 diisocyanate (NDI) for 2 years, a 33-year-old female worker developed work-related asthma attacks. Occupational-type exposure tests with NDI resulted in a late asthmatic response, whereas a corresponding challenge test with 4,4'-methylenediphenyl diisocyanate was negative. We conclude that NDI exposure in the range of its occupational exposure limit caused occupational asthma in this subject.

Key terms exposure test, isocyanates, late asthmatic reaction, lung function, occupational asthma, occupational exposure limits.

We report the case of a female worker in the plastics industry suffering from occupational asthma due to naphthylene diisocyanate (NDI) exposure.

Case description

Before starting her job in the plastics industry, the patient, aged 33 years, did not suffer from a respiratory disorder. She neither smoked nor kept domestic animals. Between 1992 and 1996 she worked in the production of plastic molds and elastomers on a polyurethane base. She was exposed to NDI (Desmodur 15).

In spite of the exhaust equipment in the work area, there was a strong smell and a substantial amount of smoke. Workplace measurements by the technical supervising authority yielded NDI concentrations of up to 0.156 mg/m³ [threshold limit value (TLV) 0.087 mg/m³].

Work-related cough, wheezing, and dyspnea started in 1994 after 2 years of activity without complaints. The symptoms regularly increased in the course of the afternoon and frequently persisted on the way home from work and during the following night. On weekends and vacations, the patient’s health state improved. After the 1st or 2nd day at work a relapse occurred. A seasonal influence could not be found.

In March of 1996 the patient consulted a pneumologist. He diagnosed a slightly obstructive ventilation pattern. Since this diagnosis, her therapy has consisted of inhalative corticosteroids and β₂ sympathomimetics. On account of her disease, the patient was, in April 1996, transferred to a workplace in the company’s dispatch department. This transfer led to immediate improvement. Cough and dyspnea became rare and was no longer directly related to occupational activity. Since June 1997, the patient has been on paid maternity leave. The leave has resulted in a further improvement of her state of health. At present, only occasional seizures of cough and nocturnal respiratory complaints of unknown etiology occur. Her current therapy consists of an inhalative corticosteroid and β₂ sympathomimetics on demand.

Clinical examinations

After a period of 30 months without exposure to isocyanates, the lung function test showed neither an obstructive nor a restrictive ventilation pattern. The methacholine challenge test revealed bronchial hyperreactivity (provocation dose for significant increase of specific airway resistance, PD_{100}β₂ = 0.3 mg methacholine) (1). The skin prick test with 20 ubiquitary and HSA-conjugated (HSA = human serum albumin) isocyanates, 4,4' methylenediphenyl diisocyanate (MDI), toluene diisocyanate (TDI), and hexamethylene diisocyanate (HDI) merely demonstrated a mild positive immediate-type

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reaction to cat dander (corresponding to 50% of the histamine reaction; no corresponding exposure ascertainable). Total immunoglobulin (Ig) E amounted to 80 kU/l (normal range <100 kU/l). Specific IgE antibodies to cat dander existed (radioallergosorbent class 2). Specific IgE or IgG antibodies to the HSA-bound isocyanates MDI, TDI, HDI, NDI, and acid anhydrides could not be detected. The epicutaneous test with the European standard antigens and the chemical rubber antigens did not lead to a skin reaction according to type I and type IV sensitization.

Exposure tests were routinely performed in a 12-m³ chamber with monomeric-oligomeric 4,4'-MDI (Merck, Darmstadt, Germany) and, using an adapted method, also with NDI (Bayer, Leverkusen, Germany). MDI atmospheres were generated by heating monomeric-oligomeric 4,4'-MDI to 110—130°C; constant air concentrations of 3 ppb were maintained for 10 minutes and afterwards of 5 ppb (TLV) for 110 minutes (2). We used a similar scheme for the NDI tests [ie, 5 ppb over 10 minutes and 10 ppb (TLV) over 110 minutes]. The air concentrations of MDI and NDI were continuously monitored by a continuous toxic gas monitor (series 7100, MDA Scientific Corporation, Lincolnshire, Illinois, United States). The instrument had been newly calibrated 1 week before the isocyanate tests were started.

The MDI exposure test did not induce lung function changes or symptoms. In the NDI test, the late asthmatic reaction described in the case history could be reproduced (figure 1). There was no indication of extrinsic allergic alveolitis since neither systemic symptoms nor a restrictive ventilation pattern occurred.

Discussion

Several studies on humans and animals showed that chronic or high inhalative exposure to isocyanates can lead to desquamation and inflammatory reactions of the airway mucosa with the clinical diagnosis of obstructive bronchitis and bronchial asthma (3—5). Ten to thirty percent of employees exposed to isocyanates and suffering from an obstructive airway disease show specific IgE antibodies, while patients suffering from isocyanate alveolitis typically have specific IgG antibodies (6, 7).

Only single cases of airway diseases due to NDI have been described (8—11). Alexandersson et al (8) examined 23 workers exposed to NDI and 20 referents to clarify the question of the extent to which the occupational exposure is concomitant with an elevated prevalence of respiratory complaints and lung function impairment. NDI concentrations between 0.02 mg/m³ (2.3 ppb) and 0.07 mg/m³ (8 ppb) over an average period of 18 months were associated with increased prevalences of irritation of the eyes, cough, and exertion dyspnea. The lung function tests showed a closing volume increase of 6%. Five workers with respiratory complaints due to NDI
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exposure demonstrated a reduction in forced expiratory vital capacity (FVC) reduction of ≥0.6 liters in addition to an elevated closing volume in comparison with the reference value (P=0.06).

Harries et al (9) examined 3 workers exposed to NDI in rubber production. While the challenge tests with MDI and TDI were negative, NDI induced significant bronchial obstruction [forced expiratory volume in 1 second (FEV₁₀) decline >15%] in 3 of 3 subjects.

Fuortes et al (10) described the cases of 3 female workers exposed to NDI in a factory producing rubber tires. They developed work-related cough, wheezing, dyspnea, and significant lung function impairments during the workshift. The FVC decreased from 3.6 to 0.85 liters (ie, from 112% to 26%), and the FEV₁₀ declined from 2.9 to 0.67 liters (ie, from 105% to 25%) of the reference mean value according to Knudson (12). These authors also examined 26 people exposed to NDI in the same enterprise and 20 referents without exposure. Seventeen NDI-exposed subjects reported work-related bronchial asthma. In 3 cases, the lung function measurements showed an FEV₁₀ and peak expiratory flow (PEF) decline between 12.5% and 20% during the workshift.

Tee et al (11) examined 58 patients with bronchial asthma due to isocyanate exposure in order to determine the diagnostic importance of specific IgE antibodies to isocyanates. Among others, they performed NDI challenge tests (concentrations were not measured) in 2 cases which induced significant bronchial obstructions (FEV₁₀ decline >15%).

The conditions in our patient’s workplace were prone to induce an obstructive airway disease. The NDI TLV was at least temporarily exceeded. The causal connection between occupational NDI exposure and obstructive airway disease with late asthmatic responses in the absence of IgE antibodies could be proved in spite of a private period of 30 months. The specificity of the reaction was confirmed by the fact that an also nonspecific hyperreactive referent did not develop bronchial obstruction in a homogeneous NDI challenge test.

The airway disease of our patient must, therefore, in accordance with the positive workplace-related exposure test, the case history data, and the course of the disease, be attributed to the occupational NDI exposure. There was no evidence for other factors that may have caused the disease. Thus a causal link between occupational NDI exposure and liability exists. We recommended the recognition of German occupational disease number 1315 (isocyanate disorder) according to the decree on occupational diseases, including the impairment of job performance entitling to a pension. The impairment results from persistent, clinically manifest bronchial hyperreactivity which requires the administration of medicaments. The consequence is that the patient can no longer be exposed to any kind of airway irritants in the workplace (restricted possibilities on the labor market).

According to current information, this is the 12th reported case of obstructive airway disease caused by NDI (8-11). For the first time, a workplace-related NDI exposure test using a standardized procedure with exactly generated and continuously monitored NDI concentrations was performed. This possibility is now generally available for diagnostics.

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