

Sensitization and irritant-induced occupational asthma with latency are clinically indistinguishable

P. S. Burge, V. C. Moore and A. S. Robertson

Correspondence to: P. S. Burge, Occupational Lung Disease Unit, Birmingham Heartlands Hospital, Birmingham B9 5SS, UK. Tel: +44 (0)1214240734; fax +44 (0)1217720292; e-mail: sherwood.burge@heartofengland.nhs.uk

Background	Acute irritant exposures at work are well-recognized causes of asthma. In the occupational setting, low-dose exposure to the same agent does not provoke asthma. Occupational asthma (OA) with latency due to irritants is not widely accepted.
Aims	To compare workers with OA with latency likely to be due to irritant exposures with workers with the more usual sensitization-induced OA.
Methods	Following identification of a worker who fulfils all the criteria for irritant-induced OA with latency whose investigation documented lime dust as a cause for his OA, we searched the Shield reporting scheme database between 1989 and 2010 for entries where the OA was more likely to be due to irritant than allergic mechanisms and compared these with the remainder where allergic mechanisms were likely. Outcome measures were latent interval from first exposure to first work-related symptom, non-specific bronchial reactivity, smoking, atopy and the presence of pre-existing asthma.
Results	A previously fit lecturer teaching bricklaying had irritant-induced OA with latency without unusual exposures with an immediate asthmatic reaction following exposure to a sand/lime mixture (pH 8). The Shield database identified 127 workers with likely irritant-induced asthma with latency and 1646 with hypersensitivity-induced OA. The two groups were indistinguishable in terms of pre-existing asthma, atopy, age, latent interval, non-specific reactivity and smoking.
Conclusions	Irritant exposure is a cause of OA with latency currently clinically indistinguishable from OA due to sensitization.
Key words	Lime; low-dose irritant; occupational asthma; Shield.

Introduction

Most definitions of occupational asthma (OA) with latency require an allergic or hypersensitivity mechanism [1–3]. In 1985, Brooks *et al.* [4] described a group with acute onset asthma after a sudden exposure to a major respiratory irritant, typically chlorine gas. Individuals had to have no pre-existing asthma and asthma starting within 24 h of the exposure together with increased non-specific reactivity persisting for at least 3 months after the incident. He called this reactive airways dysfunction syndrome, now generally called acute irritant-induced asthma. There is no latent interval, and those affected are not affected by usual low-dose exposure to the causative agent, i.e. they have not become sensitized. If the exposure was at work, subsequent employment is not usually threatened. Later, it became clear that less acute exposures could cause similar problems, Brooks *et al.* [5] coined the term ‘not-so-sudden onset irritant induced asthma’. The exposures could be less intense

than acute irritant-induced asthma but must be <4 months. There was an excess of atopics and those with childhood asthma in this group suggesting that reactivation of childhood asthma was sometimes a mechanism. We believe that there is a third group of irritant-induced OA, where there is no high-level exposure and asthma develops after a symptomless latent interval that may be several years. Once asthma has developed, usual exposures result in asthma, similar to OA with sensitization. We suggest that this is called irritant-induced OA with latency (or just irritant-induced OA), the criteria for which would be (i) no prior asthma, (ii) a latent interval from first exposure to disease, (iii) no massive acute exposure, (iv) symptoms related to usual exposure to the causative agent, (v) reproducibility of the asthma from either workplace challenges or specific inhalation challenge or valid serial measurements of peak expiratory flow (PEF) measurements and (vi) an allergic mechanism is very unlikely.

We describe a worker whom we believe has the typical features of this disease and have reviewed reports of OA to

the Shield notification system (covering the West Midlands, UK) [6,7] and identified workers who might fit an irritant mechanism with latency more easily than an allergic mechanism.

Methods

The Shield surveillance scheme (a voluntary reporting scheme for OA in the West Midlands, UK) [6,7] was searched for entries between 1989 and 2010 where the most likely causative agent was one for which there was evidence of an irritant mechanism from other studies. We selected all welders (44), those exposed to building dust and cement (16), acids (9), ammonium chloride (7), aluminium casting (10), bleach (7), caustic soda (1), chlorine and chloramines (10), coal dust (3), cigarette smoke (3) and diesel exhaust (17). The characteristics of these workers were compared with the remainder using X^2 or t -tests. The worker described in this report is one of only nine from the 'irritant' group who had specific inhalation challenge tests. The others had positive challenges to sidestream cigarette smoke (one immediate reaction), nitrogen trichloride (one immediate, one dual reaction) [8], aluminium chloride (one dual reaction) [9], formic acid (one dual reaction) and ammonium/zinc chloride (two immediate and one dual reaction). Atopy was defined as a positive skin prick test >3 mm to a common environmental antigen with a negative control. The method used for non-specific reactivity changed from histamine by Wrights nebulizer (normal > 8 mg/ml) to methacholine using the Yan method (normal >2000 μ g) during the years studied. The analysis of the serial measurements of PEF in the index case used the Oasys computer-assisted analytical system which utilises four principal methods of separating occupational from non-occupational changes in PEF. The Oasys score is based on pattern recognition and a discriminant analysis designed to mimic an expert reviewer, a positive score is >2.51 [10]. The area between the curve (ABC) analysis compares the differences between mean hourly PEF measurements on days at and away from work as shown in Figure 1, a positive score in ≥ 15 l/min/h [11], and the timepoint analysis is a statistical method based on the ABC plot which calculated the 95% confidence interval (CI) for PEF on days away from work and identifies mean workday values that are below this, a positive score is ≥ 1 non-waking timepoint [12]. The final method compares the mean PEF on all work and rest days, differences >15 l/min are positive [13].

The individual worker described has read this manuscript and given written consent for publication. The data from the Shield database are anonymous and come from routinely collected clinical information and as such is regarded as audit by our institutional review board and not needing prospective approval.

Results

A 49-year-old lifelong non-smoker worked as a bricklaying lecturer. He had no prior history of allergies or lung disease. He started training landscape gardeners 13 years previously where the bricklaying was taught in the open. After 5 years instruction, he moved indoors and taught general construction bricklaying. After 8 years, he developed work-related sore throat, runny eyes and runny nose. Four years later, he had asthma symptoms for the first time with cough, wheeze and breathlessness that sometimes woke him from sleep. Symptoms started towards the end of the working day progressed throughout the working week and improved on days off and on holidays. Bricks were laid with a mixture of nine parts of sand and two parts of lime (no cement was used as the constructions had to be demolished regularly to make room for more practice walls). The whole construction hall was dusty with sand and lime. The lime (calcium carbonate) is a natural product and may also contain magnesium oxide, silicon oxide and smaller amounts of aluminium oxide and iron oxide and is alkaline (pH 8).

When first seen, he was taking Seretide 125/25 2 puffs twice daily, his spirometry was normal [forced expiratory volume in 1 s (FEV1) 104% predicted, forced vital capacity 106% predicted] and methacholine reactivity >4800 μ g by the Yan method (normal >2000 μ g). He had a single positive skin prick test to *Dermatophagoides pteronyssinus* and normal blood eosinophils ($0.11 \times 10^9/l$). Exhaled breath nitric oxide (NO) was raised at 67 p.p.b. (normal < 22). Two hourly measurements of PEF confirmed OA with an Oasys score of 3.86 (cut-off for OA ≥ 2.51 [10]). Figure 1 from the Oasys analysis shows the ABC score of 47 l/min/h (cut-off for OA ≥ 15 [11]) and 5 timepoints with significant reductions compared with days away from work [12]. The mean rest day–workday PEF was 42 l/min (normal < 16) or 8.5% predicted (normal $< 2.8\%$) [13]. The mean whole record diurnal variation in PEF was 22%.

He was admitted for specific challenge testing by tipping the test materials between two trays for 20 min. The results of the control day using tiling adhesive and the sand/lime day are shown in Figure 2. There was an immediate reaction following the sand/lime exposure. His methacholine reactivity had become positive at 709 μ g when measured the day before specific challenges, it decreased further the day after the sand/lime exposure to 252 μ g and returned to normal (>4800 μ g) after removal from indoor bricklaying, working outdoors teaching slab laying. He however remained asthmatic requiring Seretide 250/25 two puffs twice daily but no longer had work-related PEF changes, and his exhaled NO had come down to 29 p.p.b. A similar challenge with sand/lime was negative in a methacholine reactive (PC₂₀ 1878 μ g) brick maker with a positive challenge to coolant pond water.

This case fulfils the usual criteria for OA including a latent interval from first exposure, the development

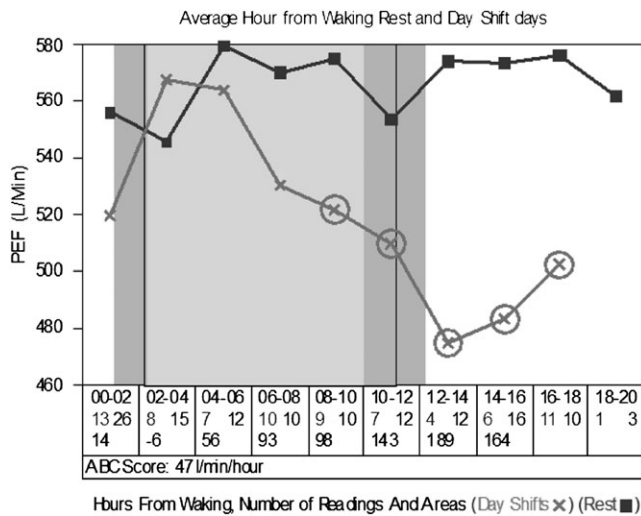


Figure 1. Mean 2-hourly PEF from waking on days away from work (upper line with squares) and on day shifts (lower line with crosses). The work times are shaded (vertical black lines mode work time 2–11 h from waking) and the darker shading shows the earliest and latest times. The circles show the timepoints where the mean workday value is significantly lower than the mean rest day value (timepoint analysis). The lower block shows the number of measurement used at each timepoint (workdays on the left, rest days on the right). The mean difference between the two lines (the ABCs) is 47 l/min/h.

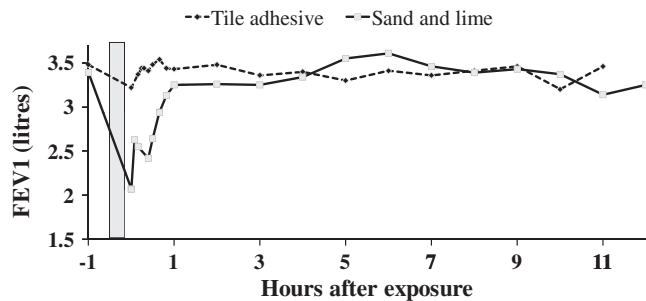


Figure 2. Specific inhalation challenge testing to 20 min exposure to tipped tile adhesive (upper line) and sand/lime mix (lower line) showing an immediate reaction to the sand/lime exposure. Methacholine PD₂₀ was 709 µg the day before the challenges and 252 µg the day after the sand/lime exposure. Exhaled nitric oxide (FeNO) was 54 p.p.b. 24 h after control exposure and 61 p.p.b. after the sand/lime mixture (a non-significant change).

of non-specific reactivity, daily deterioration with usual exposure and a positive specific inhalation challenge. It however seems very improbable that the sand/lime mix was acting via an allergic mechanism. It contained no additives and was alkaline. We suggest that this is an example of irritant-induced OA with latency.

Table 1 shows the comparison demographics between the predefined irritant group and the probable hypersensitivity mechanism group reported to Shield between 1989 and 2010. Some of the fields were incomplete in some reports as the data form has changed over the years: percentages are of those with data. Age, atopy, smoking,

Table 1. Comparison between workers with OA reported to the Shield database with presumed irritant and hypersensitivity mechanisms

	Presumed hypersensitivity, n = 1646	Presumed irritant, n = 127
Mean age	44 years	43 years
Atopic	44%	53%
Non-specific reactivity during exposure	42%	52%
Current/ex-smoker/never-smoker %	24/45/31	22/48/30
Male	70%	89%
Pre-existing asthma	14%	16%
Mean latent interval	7.3 years	10.2 years

There were no statistically significant differences between the groups.

pre-existing asthma, latent interval and the presence of non-specific reactivity while exposed did not differ significantly between the groups.

Discussion

Analysis of the Shield database shows no significant difference in the features of OA with presumed hypersensitivity and presumed irritant causation. The case we present also demonstrates that OA with latency can result from prolonged exposure to respiratory irritants and that without the exposure, the worker would not have developed asthma. Once developed, OA due to hypersensitivity and irritation is clinically indistinguishable. Both groups have similar non-specific reactivity, latent interval, regular deterioration on workdays and improvement away from exposure and similar prevalences of smoking, atopy and pre-existing asthma. Exposure to usual levels of irritants is not well described or widely accepted as a cause of OA with latency. Three of the 10 cases of irritant-induced OA described by Tarlo and Broder [14] probably fulfil the same criteria, with exposures to welding fume, calcium oxide, phosgene and hydrochloric acid.

The main strength of this study is its size, reporting much the largest series of workers with OA investigated in a single unit using similar methodology. Clinicians are not involved in compensation decisions in the UK, so the diagnosis can be made unrelated to limitations of the compensation system. The main weakness is the assumption of underlying mechanism, both in those assumed to be due to hypersensitivity and those due to irritation. The identification of workers where the mechanism was more likely to be irritant was done on grounds of plausibility and published studies showing irritant effects of the agents. Diesel exhaust particulates have been shown to cause bronchial inflammation in normal

volunteers [15] and OA in bus garage workers [16]. Nitrogen trichloride has caused epithelial leakage of surfactant proteins derived from alveolar lining fluid (surfactant protein-A and surfactant protein-B) in swimmers exposed to indoor swimming pool air [17] and OA in pool attendants [8]. Potroom asthma from aluminium smelting has often been regarded as an irritant reaction and sometimes called 'asthma-like syndrome' [18] because of the relationships of the disease with airborne fluoride levels. There is a dose-response relationship between exposure and the onset of asthma and non-specific responsiveness [19]. There is therefore precedent in the identification of the 'irritant' group in this study. There is no evidence that serial measurements of PEF can separate those due to allergy from those due to irritation. The finding of a delayed reaction in PEF (Figure 1) is against an acute irritant effect and supports a more gradual effect with more usual exposures. There is good evidence that regular high-level irritant exposures (e.g., grain dust $> 30 \text{ mg/m}^3$) in asymptomatic workers does not cause mean PEF differences in serial PEF between work and rest days exceeding 16 l/min or 2.8% of predicted PEF (the upper 95% CI for this variable [13]) and good evidence that the difference in area under the curve for serial measurements of PEF between work and rest days in non-occupational asthmatics does not exceed 15 l/min/h [11]; both clearly exceeded in our index worker. The one comparison study of serial PEF measurements in work-exacerbated asthma (WEA) and allergic OA found smaller differences in WEA but no differences in expert interpretation but defined WEA as those with a negative specific challenge (despite finding work-related PEF changes) [20]. The identification of the cause of the OA in our irritant group was confirmed by specific inhalation testing in nine workers, and even then it was not possible to separate irritant from allergic mechanisms. Although most had isolated immediate reactions, dual asthmatic reactions were seen in four workers.

Some argue that the workers exposed to irritants would have developed asthma anyway and that the daily deterioration in asthma related to usual level exposure to the irritant are examples of WEA, rather than OA, where the exposure is the cause of the asthma. Case series of this type are unable to answer this question, for which epidemiological studies of the incidence of asthma in exposed populations is required. If the asthma was going to occur anyway, and the exposure to irritants merely exacerbated their asthma, asthma incidence should not be increased in exposed populations. However, population studies showing an increased incidence of asthma in workers exposed to many of the agents characterized as irritant in this paper are available. The Finnish population register from 1986 to 1998 was used to calculate age-adjusted relative risks (RR) for asthma incidence in 24 construction occupations. The risk was increased in nearly all occupations studied but was highest among welders and flame cutters

(RR 2.34), asphalt roofing workers (RR 2.04), plumbers (RR 1.90) and brick layers and tile setters (RR 1.83) [21]. Also an odds ratio for asthma in welders was 7.0 (95% CI, 1.2–41.6) in a prospective study of rural workers in Denmark [22]. The British Occupational Health Research Foundation guidelines for occupation asthma [23] list cleaners (bleach exposure), mechanics and storage workers (diesel exhaust exposure), waiters (environmental tobacco exposure) and welders as having an increased incidence of asthma. The fact that there is an increased incidence of asthma in a particular occupationally exposed group does not imply that all those with incident asthma in that group are caused by the exposure but does suggest that the increase in incidence above the background level is likely to be related to the exposures of that group. In this study, the requirement for regular deterioration at work and improvement away from work increases the likelihood that the occupational exposures were the cause of the asthma.

A similar situation exists with contact dermatitis, where irritant mechanisms are recognized as more common than allergic ones. The skin often looks the same and histology is also indistinguishable [24]. Continuous low-dose irritation causes chronic damage to the epidermis so that usual low-level exposure results in dermatitis, which would not affect those with the same exposure on normal skin. Perhaps the purest example of low-dose irritant-induced asthma is in elite cross-country skiers, $>50\%$ of whom develop asthma. Biopsy studies have shown changes in the bronchial epithelium very similar to allergic asthma [25], some with and some without eosinophil infiltration.

The similarity in the workers reported to Shield with presumed irritant and hypersensitivity mechanisms suggests that both routes can present in similar ways and suggests that this is different from 'not-so-sudden onset OA' where atopy and pre-existing asthma are more common [5]. Whether the prognosis of irritant-induced OA is different awaits further studies.

Key points

- Continued exposure to an occupational irritant can cause new-onset occupational asthma after years of exposure.
- Irritant-induced occupational asthma with latency is clinically indistinguishable from hypersensitivity-induced occupational asthma.
- Continued exposure to respiratory irritants should be included in the causes of occupational asthma.

Conflicts of interest

None declared.

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