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Extrinsic allergic alveolitis caused by misting fountains ☆

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Summary Recently, an increasing number of patients were presented to our clinics with febrile and respiratory symptoms associated with exposure to a new type of domestic ultrasonic humidifier.

We report on 11 patients who developed recurrent episodes of fever, cough and dyspnea after repeated exposure to ultrasonic misting fountains at home. A diagnosis of extrinsic allergic alveolitis (EAA) or toxic alveolitis was made on the basis of the history and the clinical, radiological, laboratory and immunological findings. Eight patients were subjected to inhalative challenge tests with their own ultrasonic misting fountains, and all of them exhibited positive reactions.

Nine patients were diagnosed with an EAA (humidifier lung) and two patients with a toxic alveolitis (humidifier fever).

This study demonstrates the potential for ultrasonic misting fountains to cause illness in the home. In view of the increasing popularity of these devices, humidifier lung and humidifier fever should be considered in the differential diagnosis of patients with unexplained pulmonary or flu-like illnesses with fever.

Introduction

The use of ultrasonic misting fountains for domestic decoration, aromatherapy, air purification and humidification has recently become widespread, and this has resulted in a new exposure group at risk of developing humidifier-associated illnesses.

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In 1959, Pestalozzi described the ''mysterious occupational disease'' caused by humidifiers of 12 cabinetmakers in Switzerland and termed it ''humidifier fever''.[1] After 11 years, the same symptoms (fever, cough and dyspnea) were seen in four office workers in an office with air conditioners in the USA, and until recently it was mainly an occupational disease.[2,3] Over the course of time, the term ''humidifier lung'' became more accepted for this type of extrinsic allergic alveolitis (EAA). A lot of symptoms of humidifier lung occur after inhalation of particles containing endotoxins without that antigens are involved. This toxic alveolitis (or organic dust toxic syndrome (ODTS)) is called today ''humidifier fever''.[4] The incidence of humidifier fever amongst exposed people is estimated at 40–50%, while the incidence of humidifier lung is estimated at 10%.[5–7]

Thermophilic actinomycetes, other bacterial antigens, moulds, yeasts and sometimes parasites have been isolated from the humidifier water or ventilatory systems.[8,9]

We now report 11 cases of humidifier lung or humidifier fever caused by home ultrasonic misting fountains, and present the clinical features, immunological evidence, microbiological findings and the results of bronchoalveolar lavage fluid (BALF) analysis. Furthermore, in eight cases, an inhalation challenge was performed with the original misting fountain. One case from this series has already been published as a case report of EAA without finding specific serum antibodies.[10] A further case is due to be published as the first case report of EAA with identification of specific serum antibodies in association with ultrasonic misting fountain exposure.[11]

Figure 1 Domestic ultrasonic misting fountain.

Material and methods

Patients

Eleven patients (seven male, four female, aged 17–73 years) with humidifier-associated illnesses were studied. All had used ultrasonic misting fountains at home, which are a modern type of humidifier (Fig. 1). All patients had complained of fever, and most had also complained of cough and dyspnea.

Laboratory studies

Pulmonary function tests and capillary blood gas analysis were performed on all patients in the initial phase of investigation, and on six patients during the inhalative challenges. Chest radiographs were taken of all patients, and high-resolution computer tomography of the thorax was performed on six patients. A transbronchial biopsy was taken from one patient. Other laboratory studies included hemograms, immunoglobulins, erythrocyte sedimentation rate and quantification of C-reactive protein (CRP). Bronchoalveolar lavage (BAL) was performed on seven patients for a differential cell count and to characterize the phenotype of the T-cells recovered from the BALF (OKT4 (anti-CD4) and OKT 8 (anti-CD8)). In five cases the humidifier water was assayed for the concentration of endotoxins, using the chromogenic modification of the *Limulus* amebocyte lysate test (Whittaker Bioproducts) as recommended by the Workgroup on Agents in Organic Dusts.[12] The results were reported in terms of endotoxin units per millilitre and were interpreted according to the criteria of the Dutch Expert Committee on Occupational Standards 1998.[13]

Immunological studies

All serum samples obtained from the patients were tested using the double diffusion test according to Ouchterlony in gel by visible precipitin lines. The IgG-ELISA method was performed as solid phase technique on 96 wells ''BreakApart microplates MaxiSorb'' (Nunc, Wiesbaden, Germany) using the coating buffer $Na_2CO_3/NaHCO_3$, pH 9.6. Anti-IgG (Sigma Aldrich, Steinheim, Germany) was peroxidase coated. A water sample of each misting fountain was coated in this way onto the walls of the wells of the microplates. Coating the moulds and bacteria was done by the same way.

Challenge test

Inhalation challenge tests using each patient's own ultrasonic misting fountain and the original water were performed on eight patients after obtaining written informed consent. The tests were performed in a clinical setting which mimicked the home situation. In six cases, the following parameters were documented at 2, 4, 6, 8, (12) and 24 h after an exposure of 2 h: symptoms and clinical status, pulmonary function tests, capillary blood gas analysis and hemogram. Pulmonary function tests were not performed in the remaining two cases. The challenge tests were interpreted according to the criteria of the German working group on EAA.[14]

Results

Clinical findings

The clinical features of the patients are summarized in Table 1. All 11 patients (seven men and four women) had a history of exposure to ultrasonic misting fountains. In all cases, distilled water had been used to fill the humidifiers. All patients had complained of fever, 10 patients also had dyspnea, and nine had suffered with cough.

The chest radiographs of six patients, which were taken in the initial phase of investigation or after inhalative challenge, revealed diffuse patchy infiltrates predominantly in the lower lobes. All of these patients were followed up, and the radiographic findings returned to normal with the avoidance of humidifier use. High- resolution computer tomography scans were performed on six patients, and showed diffuse ground-glass opacities in five cases.

Pulmonary function tests showed moderate restrictive impairment in six patients, with an average vital capacity of 51% predicted and an average total lung capacity of 63% predicted. Three patients had a mild restrictive impairment with an average vital capacity of 77% predicted and an average total lung capacity of 79% predicted. Two patients had normal lung function during the investigations. The diffusing capacity in three cases was severely reduced to an average of 38% predicted. Mild to moderate reductions in diffusing capacity were seen in three cases (average 71% predicted). Five patients had a normal diffusing capacity.

BAL was performed on seven patients. In six cases, the total cell counts of the BALF was elevated between 20 and 60×10^6 cells. The differential cell counts showed in all cases an increase in lymphocytes of between 17% and 39%. The phenotypes of the T-cells which were recovered from the BALF (OKT4 [anti-CD4] and OKT 8 [anti-CD8]) were inconsistent.

In the case of one patient, a transbronchial lung biopsy was performed, and the specimens revealed alveolitis with lymphocytic and histiocytic infiltration.

Eight patients were subjected to inhalative challenge tests with their own ultrasonic misting fountains. All patients exhibited a positive response. A combined systemic (fever, chills and leucocytosis in peripheral blood) and pulmonary (dyspnea, cough, hypoxemia and a restrictive lung

Table 1 Summary of clinical data.

Number of patients	11
Age of patients (average)	17–73 (40) years
Sex (women:men)	36:64%
Signs and symptoms	($N = 11$)
Fever	100%
Cough	81%
Dyspnea	91%
Hypoxemia	64%
Radiography	($N = 11$)
Chest radiograph	
Diffuse infiltrates	55%
Nodules	9%
HRCT	($N = 6$)
Ground-glass opacities	83%
Pulmonary function testing	($N = 11$)
Vital capacity (% of predicted)	
Normal	18%
Mild reduction (∅77%)	27%
Moderate reduction (∅51%)	55%
Total lung capacity (% of predicted)	
Normal	18%
Mild reduction (∅79%)	27%
Moderate reduction (∅63%)	55%
Diffusing capacity (% of predicted)	
Normal	45%
Mild/moderate reduction (∅71%)	27%
Severe reduction (∅38%)	27%
Inhalation challenge	($N = 8$)
With systemic and pulmonary response	75%
With systemic response	25%

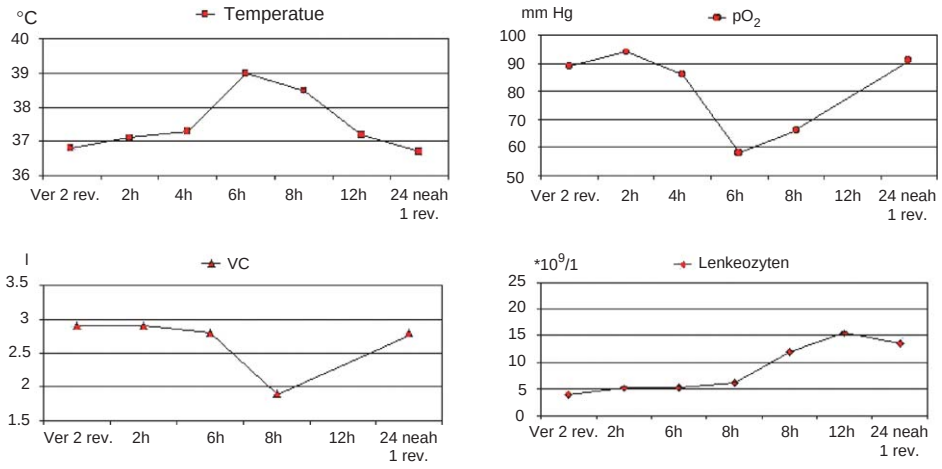

Figure 2 A representative result of a challenge test with systemic and pulmonary responses.

function pattern) reaction was seen in six cases. Two patients had only a systemic response with fever but without any pulmonary reaction. A representative result of a challenge test with systemic and pulmonary responses is shown in Fig. 2.

Immunological and microbiological findings

In the cultures of the humidifier water grew a variety of bacteria, moulds and yeasts. The organisms that were identified are listed in Table 2. Thermophilic actinomycetes were not detected.

In nine patients, serum-specific IgG antibodies (ELISA) were found against the used humidifier water, and in five cases positive precipitating antibodies (Ouchterlony test) to the water were detected. Four patients had serum-specific IgG antibodies (ELISA) against organisms (Bacillus sp., Pseudomonas sp., Stenotrophomonas sp. and Mucores) cultured from the humidifier water. No precipitating antibodies to these organisms were found.

In one case of humidifier fever we found a high concentration of endotoxin (9100 EU/ml), which could be responsible for this toxic alveolitis.

Table 2 Laboratory data.

Number of patients	11
Organisms cultured from the humidifier water	($N = 11$)
Staphylococcus sp.	9%
Bacillus sp.	45%
Pseudomonas sp.	27%
Stenotrophomonas sp.	9%
Acinetobacter sp.	9%
Mucor sp.	18%
Penicillium sp.	18%
Candida sp.	9%
Saccharomyces sp.	9%
Serum precipitins (Ouchterlony)	($N = 11$)
To the humidifier water	45%
To the organisms cultured from the humidifier water	0%
Serum-specific IgG antibodies (ELISA)	($N = 11$)
To the humidifier water	81%
To the organisms cultured from the humidifier water	36%
Endotoxin in the water	($N = 5$)
Normal	80%
High	20%

Discussion

There has recently been an increase in the use of ultrasonic misting fountains in homes. These humidifiers readily disperse droplets ranging in size from 0.5 to 3 μm that can easily reach the distal airway spaces. In addition to this, ultrasonic humidifiers contain relatively inaccessible parts which are difficult to clean, such as the aerosol dispersion nozzle and the transducer chamber. To prevent contamination of the humidifier the water must be changed frequently and all parts must be cleaned thoroughly.[15]

In this paper we described nine cases of humidifier lung (hypersensitivity pneumonitis) and two cases of humidifier fever (ODTS) resulting from domestic exposure to ultrasonic misting fountains. The diagnosis of humidifier lung was made in six

cases by detection of appropriate serum antibodies, a restrictive lung function pattern, and a predominant lymphocytosis in the BAL. The diagnosis was confirmed by inhalation challenges which led to typical systemic and pulmonary responses. In one patient, we diagnosed humidifier lung without detection of serum antibodies against the humidifier water or against the microorganisms identified within the water. In this case, the combination of radiological results (chest radiographs and computer tomography), histological findings of transbronchial biopsy specimens, predominance of lymphocytes in the BALF and the inhalative challenge confirmed the diagnosis. In two cases, we diagnosed humidifier lung based on the history and clinical, laboratory and immunological findings without inhalation challenge.[14,16-19]

The two patients with diagnosis of humidifier fever had shown positive systemic responses to inhalative challenges, but no pulmonary responses. In one of these cases we identified a high concentration of endotoxin in the humidifier water as the causative agent for the toxic alveolitis.[13,20]

The above cases illustrate a causal relationship between domestic exposure to ultrasonic misting fountains and the development of humidifier lung and humidifier fever. Because of the recent popularity of these humidifier devices it is likely that the incidence of humidifier-associated illnesses will increase. Therefore, a diagnosis of humidifier fever or humidifier lung should be considered in otherwise healthy people who present with unexplained fever and pulmonary symptoms, and clinicians should consider asking about domestic misting fountains exposure in their interviews.

To help prevent humidifier-associated illness, purchasers of ultrasonic misting fountains should be advised of the potential risks associated with the use and should be instructed on how to keep both water and humidifier clean. However, in the operating manuals for these humidifiers we found no exact instructions for the manner or frequency of cleaning. It is the duty of the manufacturers to give more detailed instructions regarding the manner and frequency for cleaning these devices to prevent humidifier-associated illnesses. Until this is realized, we would advise against the use of these ultrasonic humidifier devices.

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