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Increased Neutrophil Chemotactic Activity is Noted in Alminum-induced Occupational Asthma

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A worker with occupational exposure to aluminum powder developed asthmatic symptoms three years and six months after starting work. Skin tests (prick and intradermal) to aluminum chloride ($AlCl_3$) were negative. Inhalation challenge test with 10 mg of aluminum powder and 10 mg/ml of $AlCl_3$ solution induced an early asthmatic response. Sodium cromoglycate pre-treatment reduced $AlCl_3$-induced bronchoconstriction. Neutrophil chemotactic activity was markedly increased one and seven hours after the challenge procedure, which was lessened with sodium cromoglycate pre-treatment. Aluminum can induce occupational asthma in exposed worker, which may be mediated by a non- immunologic mechanism and the possible role of neutrophils was suggested.

Key Words : *Occupation asthma, Aluminum, Neutrophil*

INTRODUCTION

Aluminum is known to cause occupational asthma very rarely[1]. Some investigators[2-4] have reported asthmatic symptoms and the presence of nonspecific bronchial reactivity in potroom workers. Pot fume emissions include gaseous and particulate fluorides, alumina and carbon dusts, sulfur dioxide (SO2), carbon monoxide (CO) and particulate polycyclic organic matter. There are no distinctive respiratory sensitizers. However, workers exposed to aluminum fluoride have been shown to have increased bronchial reactivity and to develop asthma, which improves away from exposure[5].

Here we report a case of occupational asthma induced by aluminum powder.

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MATERIALS AND METHODS

1. Case History

The subject was a 38 year old man, nonsmoker and non-atopic who had started work in a safe-making factory 5 years ago. He had participated in mixing aluminum and minimal amounts of cement powders to make safes in the closed room. Three years and six months after starting work, he began to experience dyspnea associated with cough and sputum production. These symptoms usually appeared one hour after beginning work and were more severe in the evening and night following work, improving during or after holidays. He took some medication prescribed at a private clinic and felt some improvement, but his symptoms recurred when he stopped medication.

Questionnaire revealed neither past history of asthma or lung diseases nor any familial and personal atopic history. There were no pets or birds at his home. When first evaluated, he had stopped working for seven

days. Physical examination showed a healthy-appearing male except for a sporadic cough. No abnormal sign was noted in both lungs. Chest X-ray showed no abnormal finding. Pulmonary function test showed mild degree of restrictive and obstructive pattern (FVC was 71% of predicted value and FEV1/FVC was 70%).

2. Investigations

1) Skin Tests

Skin prick tests to common inhalant allergens and $AlCl_3$ (1.0 and 10 mg/ml) gave no immediate wheal or flare reactions. An intradermal skin test to $AlCl_3$ (10 mg/ml) was negative response, as well as patch tests with a routine battery including $AlCl_3$.

2) Inhalation Challenge Studies

A methacholine bronchial challenge test, performed according to modified Chai's method[6], gave a PC20 of 0.44 mg/ml. Two types of specific bronchoprovocation tests were performed as follows. On a control day, lactose powder (10mg) in an intal capsule (Fison Co. U.K.) was inhaled with a spinhaler. Forced expiratory volume in one second (FEV1) and maximal mid-expiratory flow (MMEF) were measured with a spirometer (HI 298, Chest, Japan) before exposure, then every ten minutes for a 30-minutes period, and hourly for 8 hours. There was no significant change in FEV1 as shown in Fig. 1. On a different day, 10 mg of aluminum powder in the same kind of capsule was inhaled via a spinhaler. There was a significant fall in FEV1 20 minutes after the inhalation which continued up to 4 hours after the end of exposure (Fig. 1). Cough and dyspnea were noted with an expiratory wheezing sound in both lower lung fields. After seven days, a bronchoprovocation test with $AlCl_3$ solution was carried out. The test solution was delivered by a Devilbiss 646 nebulizer, adjusted to a flow rate of 6/ℓ min, and the patient inhaled the nebulized aerosol from residual volume to total lung capacity five times. Normal saline was inhaled to determine the baseline value. Initially, 1 mg/ml of $AlCl_3$ solution was inhaled. As

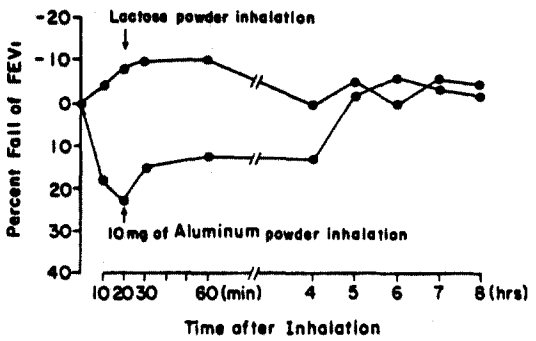

Fig. 1. The results of bronchoprovocation test with lactose and 10 mg of aluminum powder.

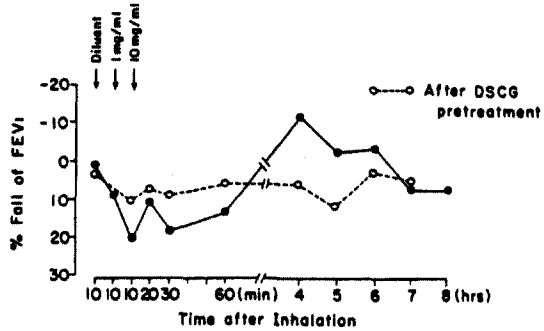

Fig. 2. Result of bronchoprovocation test with AlCl3 solution with and without DSCG pre-treatment.

there was no significant change in FEV1 after 10 minutes, 10 mg/ml of $AlCl_3$ solution was inhaled. There was more than a 20% fall of FEV1 and he felt chest tightness (Fig. 2). His symptoms recovered immediately and there was no significant change in FEV1 during the following eight hours. A follow-up methacholine bronchial challenge test was performed 24 hours after the bronchoprovocation test in a similar stage of initial baseline FEV1. His methacholine PC20 decreased to 0.15 mg/ml in comparison with the initial level of 0.44 mg/ml. On a different day, 4 mg of sodium cromoglycate was inhaled one time by a spinhaler and then the bronchoprovocation test with 10 mg/ml of $AlCl_3$ solution was performed in a similar lung function state. There was a 10 % fall in FEV1 after the inhalation, which continued up

Table 1. Neutrophil Chemotactic Activity in Sera during the $AlCl_3$ Bronchoprovocation Test with and without Sodium Cromoglycate Pre-treatment

$AlCl_3$ bronchoprovocation test	Sodium cromoglycate (-)	pre-treatment (+)
baseline	100	100
10 minutes	119	117
60 minutes	211	109
7 hours	216	137

to five hours, while there were no respiratory symptoms (Fig. 2).

3) Measurement of Neutrophil Chemotactic Activity

Neutrophils were obtained from heparinized whole blood of AB type normal volunteers by sedimentation in 6% dextran dextrose solution followed by centrifugation on Ficoll- Hypaque solution (specific gravity of 1.077) and hypotonic lysis[7]. Cells containing neutrophils more than 95% were suspended in Hank's balanced salt solution (HBSS) with 0.4% of bovine serum albumin (BSA) at the concentration of $1x10^6$ cells/ml. The chamber was incubated for 90 minutes at 37℃ in a humidified incubator containing 5% CO2. Thereafter the filter was removed, fixed in 100% methanol, and subsequently stained with Diff Quick stain solution. The number of neutrophils which migrated through the filter was determined microscopically by 40x objective. Ten fields were counted per well and all experiments were conducted in quadriple. The results were expressed as the percent ratio of the mean number of neutrophils migrated per field in the post-challenge sample to the mean number of neutrophils per field of the pre-challenge sample. Ten mole of f-MLP was used in positive control and HBSS with BSA in negative control. As shown in Table 1, the neutrophil chemotactic activity was markedly increased during the challenge procedure. In contrast, sodium cromoglycate pre-treatment significantly blocked the increased neutrophil chemotactic activity.

DISCUSSION

More than 200 substances can cause occupational asthma[8], but metal asthma is a rare phenomenon. Metals that are known to cause asthma are nickel[9-12], platinum[13], chromium[11, 14], cobalt[15, 16], vanadium[17] and zinc[8]. In 1985, Simonsson et al[5]. reported two types of aluminum salt (aluminum fluoride and sulfate) associated with occupational asthma. Kongerud and Soyseth[19] reported that the prevalence of work-related asthmatic symptoms in a cross-sectional study of 337 aluminum potroom workers was 9%. Bronchial hyperresponsiveness was noted in 12% of them. Female gender, past smoking history and airflow limitation were predictors of methacholine responsiveness. Our subject showed a significant bronchoconstriction after the inhalation of aluminum powder and $AlCl_3$ solution. Follow-up methacholine PC20 was decreased after the bronchoprovocation test. These data suggested that aluminum dust can induce occupational asthma in exposed patient.

Some investigators[11, 20] have postulated that low-weight metal (less than 500 daltons of molecular weight) could act as haptens in vivo following conjugation with serum proteins to be antigens, and this has been shown for platinum[3], nickel[14], cobalt[16] and chromium[11] at least in some exposed workers. Mackay et al[21]. studied serum levels of IgM, IgG, IgA, immune complexes and IgE in 33 asthmatic and 127 non-asthmatic potroom workers. Asthmatic workers differed only by lower mean serum levels of IgM. There has been no report of specific IgE antibody to aluminum. Simonson et al[5]. suggested that aluminum could irritate the bronchial mucosa, increasing the excitability of irritant receptors and/or c-fibers, lowering the threshold to stimulants which result in the development of airway hyperresponsiveness[22].

Knogerud et al[4, 23] reported that subjects exposed for more than 10 years to aluminum

are at higher risk for development of work-related dyspnea and wheezing. This effect of cumulative exposure may suggest that pathogenetic mechanisms due to irritants might be acting. They also reported that fluoride exposure and smoking could be related to asthmatic symptoms in potroom workers, whether or not this increased sensitivity is due to chemical irritation with an inflammatory reaction. We do not know whether the hypersensitivity is due to changes in the airway mucosa, the neural structures or the bronchiolar smooth muscles. Particulate materials of Al_2O_3, Fe_2O_3 and Cr_2O_3 can release histamine in vitro from rat peritoneal mast cells[24]. Such particulates may, thus, also act in an non- antigenic way on mast cells. Moreover, aluminum salts are known to change antigen sensitivity in animals. Indeed, in animal studies, aluminum increases the reactive capacity of mast cells and lung tissue to ovalbumin, an effect which is accompanied by increased levels of IgE or IgG2-antibodies. Such non-specific precipitation of allergy has not been established in humans, however, and Bergstrom et al[25]. had not noted a general increase of IgE response with aluminum-salt exposure. In our subject, the intradermal skin test as well as the prick test and a patch test with aluminum chloride solution were negative response. Total IgE level by PRIST was 180 IU/ml. These do not support an IgE- mediated sensitization process.

Neutrophilia had been noted in bronchoalveolar lavage fluid in the late asthmatic reaction induced by isocyanate challenge test[26]. Kay[27] reported that peripheral blood mononuclear cells, from patients with severe acute asthma, generated significantly greater amounts of neutrophil chemotactic activity into the culture supernatant after 24 hours, as compared with all control groups which reduced after 1 week of therapy. Various kinds of inflammatory cells produce different types of neutrophil chemotactic factors from those of mast cells[28]. In our patient, post-challenge neutrophil chemotactic activity was markedly increased in comparison with that of pre-challenge time, which was blunted by sodnum cromoglycate pretreatment. In other in vivo study, accumulation and activation of neutrophils, eosinophils and macrophages after allergen bronchial challenge were reduced by sodium cromoglycate[29]. These data suggested the possible role of neutrophils in the pathogenesis of aluminum-induced occupational asthma.

It is suggested that aluminum powder might induce bronchoconstriction, which was mediated by non-immunologic mechanism. Possible role of neutrophils in aluminum-induced bronchoconstriction was also suggested.

REFERENCES

1. Josephs LK, Gregg I, Mullee MA, Holgate ST. *Nonspecific bronchial reactivity and its relationship to the clinical expression of asthma. Am Rev Respir Dis 1989; 140:350-357.*
2. Abramson MJ, Wlodarczyk JH, Saunders NA, Hensley MJ. *Does aluminum smelting cause lung disease? Am Rev Respir Dis 1989; 139:1042-1057.*
3. Sarlc M, Godnic-Cvar J, Gomzi M, Stilinovic L. *The role of atopy in potroom workers asthma. A, J Ind Med 1986; 9:239-242.*
4. Kongerud J, Samuelsen SO. *A longitudinal study of respiratory symptoms in aluminium potroom workers. Am Rev Respir Dis 1991; 144 :10-16.*
5. Simonsson BG, Sjoberg A, Rolf C, Haeger-Aronsen B. *Acute and long term airway hypersensitivity in aluminum-salt exposed workers with natural asthma. Eur J Respir Dis 1985; 66:05-118.*
6. Chai H, Farr RS, Foehlich LA, Mathison DA, McLean JA, Rosenthal RR, Sheffer AL, Spector SL, Townley RG. *Standardization of bronchial inhalation challenge procedures. J Allergy Clin Immunol 1975; 56:323-327.*
7. Boym A : Separation of leukocytes from blood and bone marrow. *Scand J Clin Lab Invest 1968; 21:1968-1975.*
8. Davies RJ, Blainey AD. *Occupational asthma : Classification and clinical aspects. Seminars Respir Med 1984; 5:229-247.*
9. Malo JL, Cartier A, Doepner M, Nieboer E,

Dolovich J. *Occupational asthma caused by nickel sulfate. J Allergy Clin Immunol 1982: 69:55-59.*
10. Malo JL, Cartier A, Gagnon G, Evans S, Dolovich J. *Isolated late asthmatic reaction due to nickel sulfate without antibodies to nickel. Clin Allergy 1985: 15:95-99.*
11. Novey HS, Habib M, Wells ID. *Asthma and IgE antibodies induced chromium and IgE antibodies induced by chromium and nickel sulfate. J Allergy Clin Immunol 1983: 72: 407-412.*
12. Shirakawa T, Kusaka T, Fujimura N, Kato M, Heki S, Morimoto K. *Hard metal asthma: Cross immunological and respiratory reactivity between cobalt and nickel. Thorax 1990: 45:267-271.*
13. Cromwell O, Pepys J, Parish WE, Hughes EG. *Specific IgE antibodies to platinum salts in sensitized workers. Clin Allergy 1979: 9:09-117.*
14. Olaguibel JM, Basomba A. *Occupational asthma induced by chromium salts. Allergol et Immunopathol 1989: 17:33-136.*
15. Gheysens B, Auwerx J, den Eeckhout AV, Demedts M. *Cobalt-induced bronchial asthma in diamond polishers. Chest 1985: 88: 740-744.*
16. Shirakawa T, Kusaka Y, Fujimura N, Goto S, Kato M, Heki S, Morimoto K. *Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. Chest 1989: 95:29-37.*
17. Musk W, Tees G. *Asthma caused by occupational exposure to vanadium compounds. Med J Aust 1982: 1:183-184.*
18. Malo JL, Cartier A. *Occupational asthma due to fumes of galvanized metal. Chest 1987: 92:375-377.*
19. Kongerud J, Soyseth V. *Methacholine responsiveness, respiratory symptoms and pulmonary function in aluminum potroom workers. Eur Respir J 1991: 4:159-168.*
20. Popa V, Teculescu D, Stanescu D, Gavrilescu N. *Bronchial asthma and asthmatic bronchitis determined by simple chemicals. Dis Chest 1969: 56:395-404.*
21. Mackay IR, Oliphant RC, Laby B, Smith MM, Fisher JN, Mitchell RJ, Propert DN, Tait BD. *An immunologic and genetic study of asthma in workers in an aluminum smelter. J Occup Med 1990: 32:1022-1026.*
22. Simmonson BG. *Bronchial hyperreactivity. Eur J Respir Dis 61(Suppl) 1980: 108:21-28.*
23. Kongerud J, Gronnesby JK, Magnus P. *Respiratory symptoms and lung function of aluminum potroom workers. Scand J Work Environ Health 1990: 16:270-277.*
24. Casarelt MG, Casarett LJ, Hodge HC. *An in vitro study of mast cell response to particulate materials. Pharmacology 1968: 1:271-282.*
25. Bergstrand H, Andersson I, Nystrom I, Pauwels R, Bazin H. *The non-specific enhancement of allergy. Allergy 1983: 38: 247-260.*
26. Fabbri LLM, Boschetto P, Zocca E, Milani G, Pivicotto F, Plepari M, Burlina A, Licata B, Mappe E. *Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. Am Rev Respir Dis 1987: 136:36-42.*
27. Kay AB, Corrigan CJ Frew AJ. *The role of cellular immunology in asthma. Eur Respir J 4(Suppl. 13):105S, 1991*
28. Haeger EB, Wasserman SI. Chemotactic factors. *In Bierman CW, Lee TH. eds. Immunol Allergy Clin North Am. Allergic mediators and bronchial hyperresponsiveness. I Philadelphia: WB Sanders, 355-363, 1990*
29. Church MK. *Drugs in asthma treatment.* In Holgate ST, Charch M. *Allergy 1st ed., London 1993: p15.1-15.12.*
30. Pepys J, Hargreave FE, Chan M, Mc Carthy DS. *Inhibitory effects of disodium cromoglycate on allergen inhalation tests. Lancet 1968: 2:134-138.*
31. Jackson DM, Richards IM. *The effects of sodium cromoglycate on histamine aerosol-induced reflex bronchoconstriction in the anesthetized dog. Br J Pharmacol 1977: 61:257-261.*