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CLINICAL STUDY

Silica and Asbestos Exposure in ANCA-Associated Vasculitis with Pulmonary Involvement

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Silica and asbestos exposure are thought to belong to the triggering factors of antineutrophil cytoplasm antibodies (ANCA)-associated vasculitis. We carried out a study to find out whether patients with pulmonary involvement attributable to ANCA-associated vasculitis (AAV) have been exposed to silicon-containing materials. Thirty-one patients (12 women, 19 men, median age 51 years) were interviewed using a structured questionnaire. Occupational exposure to silicon-containing chemicals was reported by 22.6% of the patients (12.9% to SiO_2, 9.7% to asbestos), compared with 0% of control subjects ($p<0.05$). Our findings support the pathophysiologic role of silica in AAV.

Keywords ANCA, asbestos, etiology, silica, vasculitis

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INTRODUCTION

The ANCA-associated vasculitides (AAV) are complex, immune-mediated disorders characterized by a necrotizing pauci-immune vasculitis affecting multiple organs, especially the respiratory tract and kidney. These AAV include three major categories: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss Syndrome (CSS). They are strongly associated with the presence of antineutrophil cytoplasmic antibodies (ANCA). The ANCA are most often directed to either proteinase 3 (PR3-ANCA) or to myeloperoxidase (MPO-ANCA). Both PR3 and MPO are located in the azurophilic granules of neutrophils and the peroxidase-positive lysosomes of monocytes.[1]

The tissue injury in AAV results from the interplay between an initiating inflammatory event and a highly specific pathogenic immune response to previously shielded epitopes of neutrophil granule proteins. This generates high-titer ANCA directed against antigens within the primary granules of neutrophils and monocytes. These antibodies produce tissue damage via interactions with primed neutrophils and endothelial cells. The exact events leading to the initiation of the disease

Table 1
Detailed analysis of patients exposed to silica or asbestos

No	Sex	Age/yrs	ANCA	Dg.	Exposure	T1/yrs	T2/yrs	Smoker	Profession
1	Man	64	P	MPA	SiO_2	5	30	Yes	Fireplace building
2	Man	67	C	WG	SiO_2	8	8	Yes	Ceramics teacher
3	Woman	75	P	WG	SiO_2	2.5	48	No	Stonework labourer
4	Man	22	C	WG	SiO_2	2	2	Yes	Glass industry
5	Man	38	C	WG	Asbestos	7	17	Yes	Heating engineer
6	Man	36	P	MPA	Asbestos	1	1	Yes	Floorer (floor coverings)
7	Man	59	P	MPA	Asbestos	2	15	No	Traffic policeman

Abbreviations are: T1 = the length of exposure, T2 = the period between the start of exposure and the diagnosis.

are unclear. Infectious, genetic, and environmental risk factors and combinations of all three have been suggested.[2]

The first symptoms of WG very often occur in the respiratory tract. Exposure to infectious and noninfectious agents or toxins is, therefore, believed to be an inciting event. One of the possible candidates is silicon-containing dust. Exposure to silica dust has been repeatedly reported to be significantly higher in patients with ANCA and AAV than in healthy controls, lupus nephritis, or other conditions.[3,4] Recently, occupational exposure to asbestos, another silicon-containing mineral, even without typical signs of asbestosis such as interstitial lung fibrosis, has been reported to result in ANCA positivity.[5] We have, therefore, focused on occupational histories and established the silica and asbestos exposures in our patients with pulmonary AAV.

PATIENTS AND METHODS

We included a total of 31 patients with AAV with pulmonary and renal involvement diagnosed in our center between the years 1993 and 2002.

The diagnosis of AAV was determined in all cases by a renal biopsy showing pauci-immune crescentic glomerulonephritis and ANCA positivity. Positive ANCA findings were defined as a C-ANCA or P-ANCA staining pattern for ethanol-fixed human neutrophils, as determined by indirect immunofluorescent microscopy. All P-ANCA were further characterized as MPO-specific and all C-ANCA as PR3-specific by enzyme-linked immunosorbent assay. Pulmonary involvement in patients with AAV was defined by the presence of hemoptysis, pulmonary hemorrhage, respiratory failure, and/or radiographic proof of infiltrates in the absence of evidence of any other cause, mainly infectious.

The patients were asked to complete questionnaires designed by the occupational health physicians to evaluate their exposure to silica-containing chemicals and estimate their extent by the intensity $\times$ frequen-frequency $\times$ duration.

The control subjects provided by the Occupational Medicine Department were age, sex, and residence-matched healthy individuals, working as office employees. All but one with borderline positivity of MPO-ANCA, clinically insignificant, was ANCA-negative.

The statistical analysis was performed using a test of hypothesis of equality of two relative frequencies. P values <0.05 were considered significant.

RESULTS

The group of patients consisted of 12 women and 19 men. Their median age at diagnosis was 51 years (range 18–75 years). Their respective diagnoses according to the Chapel Hill Consensus Conference definitions[6] were as follows: 22 had WG, 8 had MPA, and one patient had CSS. All patients were ANCA positive, 21 of them had C-ANCA (anti-PR3), and 10 P-ANCA (anti-MPO).

All patients had pulmonary involvement diagnosed by clinical signs and/or abnormal findings on chest x-ray. Twenty-three of them had alveolar or diffuse hazy opacities, the remaining eight patients had cavitating nodules. Eleven patients presented with hemoptysis. Twenty-four patients had spirometry performed at some stage of the disease. Lung functions were normal in 10 patients, 11 had airflow obstruction, two had restrictive impairment, and one patient had a mixed obstructive and restrictive pattern. Fourteen patients had the transfer factor for carbon monoxide (TLCO) tested. It was normal in five cases, slightly reduced in another five, and more severely reduced in four cases. Exposure to smoking was comparable in the AAV and control groups (41.9% vs. 43.3% of smokers).

A total of seven AAV patients (22.6%) had a former exposure to silicon-containing chemicals (12.9% to SiO_2,

9.7% to asbestos). The mean length of exposure was almost 4 years, in all cases the exposure was considered as low. We explored the possibility that the exposure was more likely to be associated with sex, smoking, and specific ANCA pattern or disease category. None of these was proven significant, although there was a tendency towards higher exposure in the MPO group. The detailed analysis including the occupational histories of the exposed patients is shown in Table 1. The results were compared to those of 30 age, sex, and residence-matched controls, where no patients were found to have any previous occupational exposure to silicon-containing materials. The difference was statistically significant ($p<0.05$).

DISCUSSION

Environmental factors are thought to play a role in the development of autoimmune diseases. Since the beginning of the last century an increased prevalence of different autoimmune diseases (rheumatoid arthritis, scleroderma, systemic lupus erythematosus) in patients exposed to silica has been reported.[7–9] A combination of risk factors is involved in susceptibility to AAV. It is largely accepted that AAV is genetically based but environmentally triggered. Since 1960, several patients with silicosis developed pauci-immune necrotizing crescentic glomerulonephritis. Later on, it was reported that these patients had ANCA that was, in most cases, directed to myeloperoxidase. In one study, 27% of chronically silica-exposed individuals had anti-MPO antibodies.[10]

Furthermore, several case reports, case series, and case-control studies have demonstrated an association between AAV and exposure to silica-containing materials.[11–14] In summary, there is increasing evidence of a pathophysiologic role of silica in AAV, although the mechanisms by which silica may induce AAV are not well known.

Silica (silicon dioxide, SiO_2) is the earth's most abundant mineral.[11] SiO_2 occurs in a noncrystalline (amorphous) or a crystalline form. The crystalline forms are constituents of soil, rock, and sand. When these materials are processed and subsequently used, the workers can be exposed to respirable crystalline silica.[14] The mechanisms by which silica-containing compounds induce acute and chronic lung damage are well described and understood.[15] It has been shown that silica aspirated through the airway may activate alveolar macrophages and not only induce inflammation and activation of fibroblasts, but also stimulate lymphocytes through T-cell receptors and attract neutrophils, which are the source of MPO. Myeloperoxidase (MPO) secondarily taken up by alveolar macrophages may be presented to immunocompetent cells to develop autoimmunity against MPO.[16,17] Silica is also considered to induce apoptosis of monocytes, macrophages, and possibly neutrophils. Surface expression of MPO during apoptosis of neutrophils in the absence of priming has been shown. The ANCA may bind to the antigen on apoptotic cells, resulting in an amplified release of cytokines, oxygen radicals, and lysosomal enzymes operative in vasculitis.[15] Silica, therefore, affects the immune response in many ways and the host's genetic susceptibility is probably the factor that decides whether or not the affected (exposed) individual will develop the autoimmune disease. Similarly to silica, the inhaled asbestos fibers persist in the respiratory systems for decades. A higher rate of ANCA positivity was found in asbestos-exposed patients who did not show any signs of asbestosis in the form of interstitial lung fibrosis, but had asbestos-induced pleural hyalinoses. Therefore, asbestos seems to have a more pronounced effect on the formation of ANCA than silica.[5]

We focused our attention on patients with AAV with pulmonary involvement. The pulmonary involvement in all patients was attributable to AAV; none of the patients was diagnosed with any kind of pneumoconiosis. Spirometry findings in patients with AAV have not been satisfactorily discussed in literature. Both restrictive and obstructive patterns can be found.[18] The majority of our patients had an obstructive disease, which is consistent with the literature.[18] Spirometry in our patients was performed irrespective of the stage of the disease, mostly in remission. The findings, therefore, reflect the consequences of pulmonary AAV attributable to vasculitis damage, and not the vasculitis activity. The reduced carbon monoxide transfer factor (TLCO) in pulmonary AAV is also a finding that confirms the available literary data. Unlike the lung function, which frequently improves following treatment, the diffusing capacity may not return to normal.[18] The impaired TLCO in our patients did not correspond to any ventilation abnormality. Four patients with reduced TLCO had normal ventilation parameters, three had a moderate airflow obstruction and two had a restrictive pattern on spirometry. Three patients with normal TLCO had a mild obstruction and two had normal ventilation. We have not detected any case of abnormally high TLCO, which comes under conditions of alveolar bleeding, again because the patients were not tested at the time of diagnosis.

We were able to show a significantly higher anamnestic exposure to silicon-containing compounds in our group of AAV patients compared to the control group. Case-control studies are known to frequently involve biases, especially with respect to the selection of control subjects and the recall of exposure history. We are certain

that none of the control subjects had AAV. In keeping with the published data,[11,14,15] we found a tendency to higher exposure in the P-ANCA subgroup, none of the other factors studied (sex, diagnosis, smoking) were significant.

CONCLUSION

The results of this study indicate that activities and environments known to cause higher levels of exposure to silica dust are associated with AAV. Silica and asbestos dust exposure is, therefore, likely to be a factor that facilitates the pathogenesis of AAV in the Czech population. The exact mechanisms of causality must be further explored on a larger population of AAV patients.

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