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Occupational exposure in patients with the antisynthetase syndrome

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ABSTRACT

Interstitial lung disease (ILD) is common in patients with myositis and is related with the presence of antisynthetase autoantibodies (aSA). Together with other manifestations, the resulting condition is known as the antisynthetase syndrome (ASS). Contact with certain environmental and occupational agents is also associated with the development of ILD. The objective of this study was to analyze occupational exposure and associated clinical manifestations in a cohort of patients with ASS. aSA had been identified by line immunoassay and confirmed by immunoprecipitation. Serial pulmonary function tests had been carried out to assess lung function. Thirty-two ASS patients and a control group of 32 myositis patients without aSA underwent a specific questionnaire interview to evaluate their cumulative exposure to biological dust, mineral dust, and gases/fumes up to disease onset. Comparisons were done with the Fisher exact test and Mann–Whitney test. Out from 32 ASS patients (median age, 42.7 yeras; IQR 32.2–52.5), twenty-six patients had anti-Jo-1, three anti-PL-12, and three anti-PL-7. Nine had polymyositis, 15 dermatomyositis, one amyopathic dermatomyositis, and seven pure ILD without myositis. Sixteen ASS patients (50 %) and seven (22 %) myositis patients without aSA had ever been highly exposed to dust, gases, or fumes ($p < 0.05$). A more than 10 % improvement in forced vital capacity occurred in 61 % of highly exposed patients and 23 % of those with low/no exposure ($p = 0.06$) over the observation period. In

conclusion, a high percentage of patients with ASS had been exposed to dusts, gases, or fumes.

INTRODUCTION

Idiopathic inflammatory myopathies, such as dermatomyositis (DM) and polymyositis (PM) are systemic autoimmune diseases characterized by skeletal muscle inflammation. [*1*] Nearly half these patients have interstitial lung disease (ILD), which is related to the presence of a characteristic group of myositis-specific autoantibodies, the antisynthetase antibodies (aSA). [*2*, *3*] Anti-histidyl-transfer RNA (tRNA) (anti-Jo-1) antibody, found in approximately 20 to 30 % of PM and DM patients, is the most common of these autoantibodies. [*4*]

Lung involvement often coexists with, and sometimes precedes, the development of myositis. This temporal sequence raises the possibility that exposure to inhaled antigens could be a precipitating event that initiates an immune reaction in the lung and later involves muscle and other organs. [*5*] The presence of a proteolytically sensitive conformation of the histidyl-tRNA synthetase in the lung and data reported by some authors regarding the antisynthetase syndrome further supports this idea. [*6–9*]

Exposure to environmental agents and occupational dust has been related to the development of ILD. Several studies have reported an association between cryptogenic fibrosing alveolitis and occupational exposure to various agents, especially metal and wood dust but also cleaning products and paints, among others [*10–16*].

Our objective was to analyze the exposure to inhaled environmental or occupational agents in a cohort of patients with antisynthetase syndrome (ASS) and to examine clinical and immunological associations.

PATIENTS AND METHODS

Patient population

This is a cohort study with retrospectively collected data. Sixty patients positive for aSA were identified from a cohort of 179 adult patients with idiopathic inflammatory myopathies, seen at Vall d'Hebrón General Hospital in Barcelona (Spain) between 1983 and 2012. From this group, 32 patients were personally interviewed by one of the investigators with a specific questionnaire to assess lifetime occupational exposure to biological dust, mineral dust, and gases/fumes and were classified as having high exposure or no/low exposure. The other 28 cases were not included in the study for the following reasons: deceased (12 patients), lost to follow-up (12 patients), and refused participation in the study (4 patients). Six patients, three from each exposure group, were excluded from the lung function analysis because of insufficient data. A random sample of 32 myositis patients without aSA from our cohort of inflammatory myopathies was used as a control group. Controls were also personally interviewed, and the results were compared with those of ASS patients. Data on clinical and serologic features, pulmonary function testing, and therapies were obtained by review of the patients' medical records and laboratory databases. The clinical variables included the presence or absence of inflammatory myopathy, ILD, arthritis, Raynaud's phenomenon, mechanic's hands, fever, and a history of smoking. The diagnoses of DM and PM were based on the criteria of Bohan and

Peter [*17*], and only patients with definite or probable disease were included. The Sontheimer criteria [*18*] were used to diagnose amyopathic dermatomyositis (ADM). The diagnosis of ILD was established by high-resolution CT study. Spirometry was performed using a Datospir 200 (Sibel, Barcelona, Spain) according to the European Respiratory Society (ERS) guidelines [*19*]. The reference values used were those proposed by Roca et al. [*20*] for the Mediterranean population. Spirometry was performed in all patients at the time of the ILD diagnosis and during the course of the disease. An average of two tests were carried out per year. After the ILD diagnosis, avoidance of occupational exposure by inhalation was recommended. A consistent change in the forced vital capacity (FVC) of 10 % in the absence of an alternate explanation was considered an improvement or progression of ILD. [*21*]
The study was approved by the Vall d'Hebron University Hospital Ethics Committee for Clinical Research [PR (AG) 112/2009], and all patients gave oral consent to the analysis and publication of their data.

Determination of autoantibodies and HLA typing
aSA were identified by ELISA or line immunoassay (Myositis Profile Euroline, Euroimmun, Lübeck, Germany) [*22*] and were confirmed by RNA or protein immunoprecipitation assay with radiolabeled HeLa cells [*4*]. HLA class II was detected with a sequence-specific primer and sequence-specific oligonucleotide polymerase chain reaction technique.

Occupational exposure assessment
Information on lifetime occupational history was obtained from the 32 patients and 32 controls using a structured interviewer-led questionnaire. The job title, type of industry, and starting and ending years were recorded for all jobs held for more than 12 consecutive months and at least 20 h per week. Jobs were coded using the Spanish version of the International Standard Classification of Occupations, 1988, (ISCO-88) system. [*23*] Job codes were linked to a general population job exposure matrix, [*24*, *25*] classifying each individual job as associated with no, low, or high exposure to biological dust, mineral dust, or gases/fumes. Cumulative exposure to each of the three agents was determined using the total number of years the individual had worked in jobs with the assigned exposure until the onset of the disease.
Comparisons between exposed and unexposed patients and between patients with ASS and the control group of myositis patients without aSA were performed using Fisher's exact test and the Mann–Whitney test. Significance was set at a p value of less than 0.05

RESULTS

Thirty-two patients (22 women) with ASS and ILD were interviewed. The median age was 42.7 years (Interquartile range (IQR) 32.2–52.5) (Table 1). The median time to the diagnosis of ILD in our sample was 1.6 months (IQR 0–29). Median follow-up after the ILD diagnosis was 61 months (IQR 32–120). Twenty-six patients tested positive for anti-Jo-1, three to anti-PL-12, and three to anti-PL-7. These patients were classified as having PM (9 cases), DM (15 cases), or ADM (1 case), and the remaining patients (7 cases) had pure ILD without myositis. Twenty-two patients (69 %) were carriers of the HLA-DRB1*03 haplotype.

[TABLE 1]

High occupational exposure to biological dust, mineral dust, or gases/fumes had occurred in 11, 10, and 13 patients, respectively (Table 2). Reported occupations are summarized in Table 3. Sixteen of the 32 ASS patients had ever been highly exposed to any of the three agents analyzed, whereas only seven from a random sample of 32 patients from our myositis cohort without aSA had such exposure (50 % vs 22 %; $p < 0.05$). Other parameters, such as ILD ($p < 0.05$), mechanic's hands ($p < 0.05$), HLA-DRB1*03 ($p = 0.05$), and fever ($p = 0.06$) were also more frequent in the ASS group, as would be expected (Table 1). ILD tended to be more common in patients with a history of high occupational exposure: 15 of 16 with ILD and high exposure versus 12 of 16 with ILD and no/low exposure (94 % vs. 75 %), although statistical significance was not reached ($p = 0.17$). No association was found between the presence of pure ILD without myositis and exposure to any of the agents studied. No statistically significant differences were found in the severity of ILD, determined by FVC at onset, between patients with high or no/low exposure. No statistically significant association was found between the presence of arthritis, mechanic's hands, fever, Raynaud's phenomenon, type of myositis, positive status to HLA-DRB1*03 haplotype, or type of aSA and high exposure to any of the three agents. There were no statistically significant differences in the number of immunosuppressive drugs used between patients with high or no/low exposure. A consistent improvement of more than 10 % in FVC during follow-up was observed in 61 % of highly exposed patients (8 of 13) and only 23 % (3 of 13) of those with no or low exposure ($p = 0.06$) (Table 4). Thus, in patients with a history of high exposure to dust, gases, or fumes, avoidance of exposure after the ILD diagnosis seemed to be associated with a better prognosis.

[TABLE 2] [TABLE 3][TABLE 4]

DISCUSSION

In this study, performed in a cohort of patients with ASS, we found that half the patients had been highly exposed to dust, fumes, or gases before the onset of the disease. ILD comprises a group of relatively rare lung conditions that involve varying degrees of acute and chronic inflammation that can progress to end-stage fibrosis. Environmental exposure to various agents, such as metal dust, wood dust, and dust containing steel, brass, lead, pine wood, or solvents, has been linked to an increased risk of developing pulmonary fibrosis. [*9–16*]

Several studies, mainly case reports, have described the development of rheumatic disease after different types of environmental exposures. A varied spectrum of clinical and serological autoimmune disorders, including scleroderma-like illnesses and lupus-like syndromes, has been reported after exposure to agents like solvents or silica. [*26–30*]

ASS-associated ILD is a heterogeneous entity that ranges from a benign stable disease to rapidly progressive and treatment-resistant pneumonitis [*2*] Lung involvement seems to be even more strongly associated with these autoantibodies than muscle, and ILD often precedes myositis symptoms. [*3*] These facts have led to hypotheses that the immune reaction starts in the lungs after exposure to certain

environmental factors, as in other interstitial pneumonias, and later spreads to other organs such as muscles and joints. [*5*] The finding of a more cleavable conformation of the hystidyl-tRNA synthetase enzyme in the lung, which makes it more antigenic, suggests that immunity may start in the lung. [*6*]

To date, there are no studies investigating the role of occupational exposure to inhaled agents in the pathogenesis of patients with ASS. The single related study from Tillie et al. [*7*] reported a high occupational exposure rate (39 %) in a cohort of 32 ASS patients with ILD, with 26 % being employees in the cleaning industry. The authors suggested the possibility of exposure to abrasive agents as the triggering cause of pulmonary inflammation. According to an epidemiological research study carried out by Chinoy et al. [*31*] related to tobacco and ASS, there was a higher frequency of anti-Jo-1 antibodies in patients who were positive for DRB1*03 and smokers, compared with DRB1*03-positive nonsmokers. Although the difference did not reach statistical significance, it suggests a gene–environment interaction in the development of anti-Jo-1 antibodies. Our results support this idea, since more than two thirds of the patients studied were positive for HLA-DRB1*03.

In our report, 50 % of patients diagnosed with ASS were highly exposed to biological dust, mineral dust, and/or gases and fumes, whereas only 22 % of patients from our myositis cohort without aSA had such exposure. In any case, this figure is much higher than the 13 % prevalence reported in a general population sample in our area. [*32*, *33*] Moreover, when these highly exposed patients were compared with ASS patients with no or low exposure, a consistent improvement in FVC was observed. Avoidance of the offending agent after the ILD diagnosis could be a possible explanation. However, the retrospective nature of the study and the absence of reliable data that these patients systematically avoided exposure detract from these findings. Further studies are needed to clarify this issue.

There are several limitations to this study but also some strengths. The main limitations include the small patient sample due to the rarity of the syndrome, its retrospective nature, and possible recall bias in reporting the occupational history. The strengths of the study include the presence of a well-characterized comparison group and an external reference from a general population sample from the study area to compare the prevalence of exposure. In addition, the exposure assessment was based on established methods combining a structured face-to-face questionnaire on lifetime occupational history with a job exposure matrix. In summary, a high percentage of patients with ASS had been exposed to dusts, gases, or fumes before disease onset. These findings lend support to the idea that occupational exposure could play a role in the pathogenesis of some cases of ASS-associated ILD.

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Disclosures

None.

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TABLES AND FIGURES

Table 1
Clinical characteristics and epidemiological data of the cohort of patients with antisynthetase syndrome and the control group

	Cases (n = 32)	**Controls (n = 32)**	**p**
Female gender	22 (69)	27 (84)	0.16
Median age at symptoms onset, years (IQR)	42.7 (32.2–52.5)	44.1 (32.2–52.6)	0.84
Median time working to clinical manifestations, years (IQR)	20.2 (8.5–35.6)	13.2 (8.0–31.2)	0.20
Any job with high exposure[a]	16 (50)	7 (22)	<0.05*
Smoking	19 (59.4)	DU	—
Interstitial lung disease myositis[b]	27 (84.4)	7 (22)	<0.05
Dermatomyositis	15 (46.8)	23 (71)	0.05
Polymyositis	9 (28.1)	7 (22)	0.6
Amyopathic dermatomyositis	1 (3.1)	1 (3.1)	—
Fever	9 (28.1)	3 (1)	0.06
Raynaud's phenomenon	15 (46.8)	9 (28)	0.13
Mechanic's hands	18 (56.2)	4 (12.5)	<0.05
HLA-DRB1*03	22 (68.7)	14 (43)	0.05

Data are expressed as number (%), unless otherwise indicated
IQR interquartile range, DU data unavailable
*Statistically significant. (p = 0.04 after gender adjustment)

[a]Occupational exposure to dust, gases, or fumes
[b]Seven patients had pure interstitial lung disease without myositis

Table 2
Descriptive statistics of lifetime occupational exposure up to clinical appearance, n (%)

Variables	**No exposure**	**Low exposure**	**High exposure**
Biological dust	12 (37.5)	9 (28.1)	11 (34.4)
Mineral dust	14 (43.7)	8 (25)	10 (31.3)
Gases and fumes	12 (37.5)	7 (21.9)	13 (40.6)
Dusts, gases, and/or fumes	9 (28.1)	7 (21.9)	16 (50)

Duration of exposure until appearance of first symptoms ranged from 1 to 52 years

Table 3
Most frequently reported occupations, n (%)

Complete occupational history (included 91 different jobs) [32 patients]	**Ever high exposure to dusts, gases and/or fumes (Included 29 different jobs) [16 patients]**
Administrative, 17 (19)	Agricultural workers, 9 (31)
Agricultural workers, 9 (10)	Chemical products machine operators, 4 (14)
Manufacturing workers, 9 (10)	Construction workers, 2 (7)
Cleaners and related, 8 (9)	Machinery mechanics and fitters, 2 (7)
Managers, 5 (5)	Food and related products machine operators, 2 (7)
Textile workers, 4 (4)	Other, 10 (34)
Other, 39 (43)	

Table 4
Associations between lifetime occupational exposure and clinical characteristics, n (%)

Clinical characteristics	**Exposed* (n = 16)**	**Nonexposed (n = 16)**	**Statistical significance (p)**
ILD	15 (94)	12 (75)	0.17
Arthritis	15 (94)	14 (87)	0.50
Myositis	12 (75)	13 (81)	0.50
Fever	4 (25)	5 (30)	0.50
Mechanic’s hands 10 (62)	10 (62)	8 (50)	0.36
FVC improvement[#] (>10 %)	8 (61)	3 (23)	0.06
Raynaud’s phenomenon	7 (44)	8 (50)	0.50
HLA-DRB1*03	10 (62)	12 (75)	0.36

FVC forced vital capacity

*Ever worked in a job involving high exposure to dusts, gases, or fumes. p value obtained using Fisher’s exact test
[#]Percentage is calculated after excluding 3 patients in each group bacause of insufficient data