Multiple clinical and biological autoimmune manifestations in 50 workers after occupational exposure to silica

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Abstract

Objectives—A self referred group of four workers from a factory producing scouring powder with a high silica content showed a surprisingly high number of features compatible with a connective tissue disease. Further subjects working at the same factory were subsequently studied to evaluate the relation between this exposure and the development of autoimmune processes.

Methods—A total of 50 subjects (44 women, six men; mean (SD) age 43.7 (5.5) years; mean duration of employment 6.1 years) underwent a prospective study including clinical history and physical examination, an immunobiological study, HLA typing, radiological and functional oesophageal and respiratory examination, ophthalmological examination, and isotopic testing of salivary glands.

Results—Symptoms of a systemic illness were present in 32 (64%) subjects: six with Sjögren's syndrome; five with the criteria for systemic sclerosis; three with systemic lupus erythematosus (SLE); five with an 'overlap syndrome'; and 13 with undifferentiated findings not meeting the criteria for a defined disease. Antinuclear antibodies were present in 36 (72%) subjects; four had antibodies to native DNA, including two subjects with SLE, one with systemic sclerosis associated with secondary Sjögren's syndrome, and one with overlap syndrome. Anticentromere antibodies were not detected. The frequency of HLA-DR3 was increased in the clinically affected subjects, but did not reach statistical significance.

Conclusions—This descriptive study emphasises the high probability of workers occupationally exposed to silica developing a multiple spectrum of clinical and serological autoimmune manifestations.

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In 1914 Bramwell¹ showed an increase in the occurrence of scleroderma in stone masons and in 1953 Caplan² reported a relation between a pulmonary disease in patients with silicosis and rheumatoid arthritis, although he did not establish a relation between silica exposure and the development of polyarthritis.

Erasmus,³ in 1957, and Rodnan *et al*,⁴ in 1966, showed an association between silicosis and the development of a specific systemic disease, scleroderma. Since then, isolated studies reporting various alterations in the immune response in subjects exposed to silica have been reported. This paper describes the clinical and biological manifestations observed in 50 subjects occupationally exposed to silica and analyses the surprising heterogeneity of these manifestations.

Subjects and methods

STUDY POPULATION

The study group consisted of an opportunistic sample of 50 workers (six men and 44 women) who had been working for a mean of 6.1 years at a scouring powder factory located in the outskirts of Seville, Spain. The workers ground and handled the silica that was the main component (about 90%) of a scouring powder. The first four subjects were self referred because of clinical symptoms. When it was realised that these subjects had a high number of collagen disease related symptoms in common, they were encouraged to contact their ex-colleagues and siblings exposed to the same agent, even if they had no subjective disease, to evaluate their clinical status. In this sense, some of the later subjects were 'recruited'. The only selection criterion was to have been working at the factory and handling the powder. Most of the data about the working environment came from the subjects themselves; the factory had been closed for about 10 years before the first subjects were studied.

STUDY PLAN

The subjects were evaluated by a protocol established by the unit for collagen diseases.

Clinical history and physical examination data were obtained by members of the unit for collagen diseases. The American Rheumatism Association (ARA) criteria for the diagnosis of the connective tissue diseases were applied. For systemic lupus erythematosus (SLE) the ARA criteria applied were those of Tan *et al*⁵ and for systemic sclerosis the criteria of the Subcommittee for Scleroderma Criteria of the ARA were used.⁶ Patients with 'overlap syndrome' express evident features of SLE and systemic sclerosis. 'Undefined collagen disease' was classified as described by De Portugal *et al*⁷

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and Le Roy *et al.*⁸ Sjögren's syndrome was diagnosed by the existence of (a) keratoconjunctivitis sicca lachrymal hyposecretion (Schirmer's test) coexistent with 'punctate or filamentary keratitis' (positivity to rose bengal and slit lamp) or (b) abnormalities in the salivary glands explored by gammagraphy with technetium-99 labelled sodium pertechnetate.⁹

For the immunobiological studies, the levels of serum immunoglobulins C3 and C4 (lower limit of normal values 800 and 200 mg/l respectively) were measured by nephelometry. Rheumatoid factor was measured by latex agglutination. The presence of cryoglobulins was evaluated by serum precipitation of 1°C. Antinuclear antibodies were measured by indirect immunofluorescence on unfixed rat tissue (liver, kidney, and stomach). Native DNA was determined on a *Crithidia luciliae* substrate and anticentromere antibodies and antinuclear antibodies on HEp-2 cells. Results were considered positive if fluorescence was present at a titre of 1/40 or higher for the rat and HEp-2 substrates and 1/10 for *Crithidia luciliae*. Autoantibodies against extractable nuclear antigens were measured by immunodiffusion and counterimmunoelectrophoresis using rabbit thymus and human spleen extracts as the source of antigens.

HLA class I and II antigens were typed using the standard National Institutes of Health microlymphocytotoxicity assay with the International Histocompatibility Workshop reagents and locally available serum samples.

Radiological studies (UICC classification)¹⁰ and functional studies of the lungs included conventional spirometry and measurement of total lung capacity, maximum inspiratory pressure, and arterial blood gases.

Oesophageal studies included morphological (barium roentgenogram) and functional studies using a method modified from Tolin and Fisher¹¹: administration of 5.55 kBq colloidal technetium-99m diluted in 15 ml water in decubitus in one swallow. Computer images were obtained at a rate of one frame a second for 60 seconds and one frame a 15 second for 10 minutes.

Ophthalmological studies included Schirmer's test and biomicroscopy after staining with rose bengal.

Isotopic testing of the salivary gland function was performed by gammagraphy after intravenous administration of 185–370 kBq technetium-99m labelled pertechnetate.

STATISTICAL ANALYSIS

Data were analysed by Student's *t* test (continuous variables) and the χ^2 test with Yates's correction and Fisher's exact test (categorical variables). A difference was considered statistically significant if $p \leq 0.05$.

Results

EPIDEMIOLOGICAL DATA

The subjects were studied 10 years after working with silica. We calculated that about

300 subjects had been exposed during the 10 years of factory operation (this figure was obtained by data provided by the workers themselves and from legal documents related to claims for compensation). The 50 subjects studied represent 17% of the total number of workers. There were six men and 44 women; the workers reported that there was an overall predominance of women in the factory. Their mean (SD) age was 43.7 (5.5) years ranging from 34 to 60 years. In this study group, five pairs of siblings and two groups of three siblings were found (brothers and sisters).

The workers were all exposed to the same agent in one single room, with no other known hazardous exposures in the workplace. The intensity of the individual exposure was difficult to evaluate due to a lack of available data. Only the exposure time was available as a measure of the approximate exposure intensity. The mean (SD) exposure time in the whole series was 6.1 (3.4) years with a range between 2 and 10 years. In the subjects with features of connective tissue diseases it was slightly longer (mean value 6.4 years) than in those without disease (mean value 5.7 years); these differences did not reach statistical significance ($p=0.6685$). The mean times of exposure for the various diseases were 5.3 years for SLE, eight for systemic sclerosis, and 6.7 for SLE/systemic sclerosis; these differences were not statistically significant ($p=0.09$). The latency time from first exposure until the appearance of symptoms was 11.8 (5.9) years.

CLINICAL MANIFESTATIONS

Thirty two (64%) subjects had features of a systemic disease; the most relevant are given in table 1. Three cases of primary Sjögren's syndrome (not associated with another collagen disease) are included in the group 'undefined

Table 1 Clinical data of the 50 subjects studied. Values are No (%) of subjects with the clinical manifestation

Cutaneous manifestations	32 (64)
Malar erythema	12 (24)
Cutaneous sclerosis	10 (20)
Generalised sclerosis	2 (4)
Limited to extremities	8 (16)
Sclerodactyly	2 (4)
Digital ulcers	7 (14)
Digital necrosis	1 (1)
Calcinosis	1 (2)
Dryness of eyes or mouth, or both	29 (58)
Complete Sjögren's syndrome	9 (18)
Primary Sjögren's syndrome	3 (6)
Raynaud's phenomenon	14 (28)
Oesophageal abnormalities	
Subjective manifestations	10 (20)
Radiological abnormalities	11 (22)
Delay in isotopic transit*	21 (42(72))
Oesophagomanometric abnormalities†	4 (8(57))
Respiratory abnormalities	19 (38)
Dyspnoea	17 (34)
Chest radiographic abnormalities	24 (48)
Silicotic pattern	18 (36)
Diffuse pulmonary fibrosis	14 (28)
Pleural thickening	3 (6)
Pleural effusion	2 (4)
'Eggshell' nodes	7 (14)
Functional study abnormalities*	16 (32)
Articular manifestations	21 (42)
Arthralgias	20 (40)
Morning stiffness	11 (22)
Non-erosive arthritis	5 (10)
Neurological abnormalities	1 (2)

*Twenty nine subjects.

†Seven subjects.

collagen diseases'. The remaining six cases were secondary and associated with two cases of systemic sclerosis, one SLE, and three cases of overlap syndrome (SLE/systemic sclerosis). The presence of Raynaud's phenomenon was closely correlated with the presence of sicca syndrome ($p<0.01$).

We specifically analysed the respiratory aspects related to silicosis; 18 (36%) subjects had compatible lesions (four without features of systemic diseases; five with defined connective tissue disease—one with systemic sclerosis, one with SLE, and three with overlap syndrome; nine with 'undefined collagen diseases'). We therefore detected a silicotic pattern in four (28%) of 18 patients without symptoms and in 14 (43%) of 32 patients with immunological abnormalities; these differences are not statistically significant ($p=0.11$). Functional respiratory studies were performed in 29 patients; in 16 (32%) subjects several abnormalities were detected, sometimes several in the same patient: five (31%) had restrictive spirographic patterns and three (20%) obstructive patterns.

With respect to articular symptoms, non-erosive arthritis of the hands was present in five patients: two with SLE, one with systemic sclerosis, and two with overlap syndromes.

The only neurological abnormality detected was a sensory neuropathy of the V cranial nerve in a patient with overlap syndrome.

In summary, consistent features of systemic disease were found in 32 (64%) subjects (29 women and three men) (table 2). The higher prevalence in women is apparent, but only reflects the imbalance of men and women in the group studied ($p=0.99$).

LABORATORY TESTS

Table 3 gives a summary of the biological and immunological abnormalities. Anaemia corresponded to the type of chronic inflammatory disease. Fifteen subjects were repeatedly defined as having leucopenia (leucocytes $<4.5 \times 10^9/l$; for the SLE criteria a value of less than $4 \times 10^9/l$ was applied). No quantitative abnormalities were shown in the thrombocytes.

Antinuclear antibodies were positive in 36 (72%) subjects. They included 28 (88%) of the 32 subjects with symptoms of rheumatic or connective tissue diseases. The cumulative frequency curve showed 25 subjects with a titre equal to or greater than 1/80, and 19 equal to or greater than 1/160. The highest titres (1/1280) were detected in five subjects. The most common finding was the mixed pattern,¹²

Table 2 Clinical diagnosis in 50 subjects exposed to silica. Values are No (%) of subjects studied

Systemic sclerosis (SSc)	5 (10)
Systemic lupus erythematosus (SLE)	3 (6)
Overlap syndrome (SLE/SSc)	5 (10)
Secondary Sjögren's syndrome*	6 (12)
Undefined collagen diseases†	19 (38)
Asymptomatic subjects	18 (36)

*Included in the three first clinical diagnosis.

†Including three cases of primary Sjögren's syndrome.

Table 3 Biological and immunological data. Values are No (%) or subjects affected

Anaemia (haemoglobin <110 g/l)	6 (12)
Leucopenia ($<4.5 \times 10^9/l$)	15 (30)
Lymphopenia ($<1.5 \times 10^9/l$)	21 (42)
Increased erythrocyte sedimentation rate (>30 mm/h)	19 (38)
Abnormal muscular enzymes	4 (8)
Presence of rheumatoid factor	12 (22)
Presence of C reactive protein	13 (26)
Hypergammaglobulinaemia (>18 g/l)	13 (26)
Decreased C3 or C4, or both	12 (22)
Presence of cryoproteins*	16 (32(43))
Antinuclear antibodies†	36 (72)
Antibodies to native DNA	4 (8)
HEp-2 substrate patterns‡	
Homogeneous	21 (42)
Antinucleolar	9 (18)
Speckled non-anticentromere	11 (22)
Anticentromere	0 (0)
Negative	14 (28)

*Thirty seven subjects.

†Rat liver, kidney, stomach; titre $>1/20$.

‡Some patterns were concomitant.

present in 27 serum samples. In spite of the scleroderma-like features found in these subjects, none had anticentromere antibodies. The study of antibodies against extractable nucleas antigens showed two (4%) subjects positive for SS-B, two (4%) for SS-A, one (2%) for Sm, one (2%) for nRNP, and two (4%) for Scl-70. Some of these specificities were found in the same patient.

Tissues were typed for HLA-A and HLA-B antigens in 48 of 50 subjects; in 41 of these HLA-DR typing was also performed. Owing to the lack of a control population not exposed to silica from the same environment and the presence of several pairs of siblings in the population studied, only a comparison of the HLA antigen frequencies between affected and non-affected subjects was made. The frequency of the HLA antigens was not significantly different between the two groups. The DR3 antigen had a high prevalence in the affected subjects, whereas the prevalence in healthy subjects was close to the frequency in the general population of Spain,¹³ although this was not statistically significant (see table 4). A comparison of clinical diagnosis, autoantibody type, and HLA phenotype in each pair of siblings did not reveal any influence of the HLA phenotype on the occurrence of a silica related illness (see table 5).

Discussion

Caplan was the first to report an association between rheumatoid arthritis and a specific variety of pulmonary lesions in subjects exposed to silica.² His discussion did not analyse the possible role of silica in triggering autoimmune processes as he considered the disease to be a simple anatomoclinical form of

Table 4 Results of tissue typing. Values are No (%) of subjects studied

Patients	DR3+	DR3-	Total
Affected	15 (58)	11 (42)	26
Not affected	4 (27)	11 (73)	15
Total	19	22	41

χ^2 test = 3.68; χ^2 with Yates's correction = 2.54, $p<0.106$; Fisher's exact test $p=0.054$.

Table 5 Serological, diagnostic, and genetic correlations in siblings exposed to silica

Family/members	Diagnosis*	Antibodies†	No of shared haplotypes
1-A	SLE/SSc/SSS	Mix., Nuc.‡, SS-B, SS-A	(DR3+)>0§
1-B	Sc/SSS	Mix., Nuc‡, SS-B, Scl-70	(DR3+)>0§
2-A	SLE/SSc/SSS	Spe.‡, Sm, SS-A	(DR3+)>1
2-B	UD	Mix.	(DR3-)>1
3-A	SLE	Mix.‡, DNAn+	(DR3-)>1
3-B	SLE/SSS	Mix.‡	(DR3+)>0§
4-A	SLE/SSc/SSS	Mix.‡, Nuc., Scl-70	(DR3+)>1
4-B	UD	Mix.	(DR3+)>2
4-C	SSc/SSS	Mix.‡	(DR3-)>0
5-A	No	Mix.	(DR3+)>2
5-B¶	No	a-SMA	(DR3+)>2
5-C	UD	Mix.	(DR3+)>2
6-A	UD/PSS	Mix.‡, Nuc.	(NT)>2
6-B	No	Mix.	(NT)>2
7-A	No	Negative	(NT)>2
7-B	UD	Mix.	(NT)>2

*SLE=Systemic lupus erythematosus; SSc=systemic sclerosis; SSS=secondary Sjögren's syndrome; UD=undefined collagen disease; No=no clinics; PSS=primary Sjögren's syndrome.
†Antinuclear antibody patterns: Mix.=mixed; Nuc.=nucleolar; Spe.=speckled; a-SMA=anti-smooth muscle antibodies.
‡Very high titre of antibodies.
§DR3 inherited from a haplotype different to the DR3 of the sister(s), NT=Not tested.
¶Male.

pulmonary disease coexisting with arthritis in the same subject.

Bramwell,¹ Erasmus,³ and Rodnan *et al*⁴ first reported a relation between silica exposure and systemic diseases, specifically systemic sclerosis. This disease shows a surprising coincidence with silicosis in two aspects: first, from the pathological point of view the systemic sclerosis is also characterised by a greatly accelerated fibroblast activity, higher than in other systemic processes;¹⁴ and secondly, in systemic sclerosis there is an extremely high production of interleukin 1 by macrophages.^{15 16} Subsequently other workers have reported a high rate of association between silicosis and systemic sclerosis.^{17 18}

Silica particles can act on macrophages, increasing the production and secretion of interleukin 1.¹⁹⁻²¹ This powerful mediator of inflammation is known to promote the stimulation and proliferation of fibroblasts in silicosis and in other pulmonary fibrosing diseases.^{22 23} Because of its relevant role in the immune response, the increase in interleukin 1 could be the pivotal point on which multiple autoimmune abnormalities observed over a period of time in subjects exposed to silica depend.

Scouring powder for domestic use, such as that produced by our patients, is composed of 70-90% powdered quartz.²⁴ The development of silicosis in detergent factory workers has been reported previously²⁵⁻²⁷ and Gong and Tashkin²⁸ reported a woman with silicosis linked to a vasculitis syndrome, positive for rheumatoid factor and antinuclear antibodies, who had deeply inhaled a household scouring powder with a 90% silica content on a daily basis for 10 months.

The relation between exposure to silica and connective tissue diseases other than scleroderma is not well known. Lippman *et al*²⁹ and Soutar *et al*³⁰ reported a higher frequency of antinuclear antibodies and rheumatoid factor in coal miners; Benedek *et al*³¹ detected a strong association between rheumatoid factor and pneumoconiosis and Jones *et al*³² reported a high prevalence of antinuclear antibodies in subjects exposed to silica. Giles *et al*³³ reported

rapidly progressive glomerulonephritis in a patient with an acute silicoproteinosis; Hatron *et al*³⁴ reported four cases of SLE in coal miners; and Bernardini and Iannacone³⁵ and Cledes *et al*³⁶ reported silicosis associated with SLE.

This study describes a high prevalence of autoimmune abnormalities in a restricted cohort chronically exposed to silica. Auto-immune processes were present in 32 (64%) of the 50 subjects studied.

Even if we assume that the remaining 250 factory workers had not been affected, the frequency of systemic diseases in this group would be 10.6%. The prevalence for SLE in the general population is 1-3/100 000 subjects,³⁷ but in this series it increased to 16% (three with SLE and five with SLE/systemic sclerosis); even if we reduce this proportion to 2.6% the difference is definite. Systemic sclerosis appeared in 10 (20%) patients (five with systemic sclerosis and five with systemic sclerosis/SLE), with 2 (3%) as a minimum, whereas its prevalence in the general population is even lower than that of SLE; the calculated annual incidence is 4.5-12/10⁶ subjects.³⁸ Although some workers^{4 17} have found a male predominance in scleroderma secondary to silica exposure, our experience shows a higher frequency (around 10:1) in women. The first published series was from an environment in which only men work (coal mining), whereas our group predominantly consists of women; there was no difference (p=0.99) between the ratio of men to women in the studied series (6:44) and the affected subjects (3:29). The apparent imbalance depends on the sex bias of the group studied.

The latency time from first exposure until the appearance of symptoms was long (11.8 years), but the average exposure time in the whole series (6.1 years), in the subjects with features of connective tissue diseases (6.4 years), or in those without disease (5.7 years) was not statistically significant. Therefore the appearance of systemic disease did not correlate with the exposure time.

The frequency of siblings in our patient population is high (five pairs and two groups of three). This raises the question of whether, in addition to the fundamental factor of massive and long term exposure to silica, genetic background could be important as a predisposing factor. The frequency of clinical disorders in the whole group reached 64% (32/50). In the subgroup of siblings it was 75% (12/16). Even if we eliminate the related subjects, however, the frequency of disease is still high (20/34 (59%)).

A possible implication of the HLA system in the susceptibility for developing autoimmune diseases after exposure to silica was investigated. When we compare the frequencies of HLA antigens in healthy and affected subjects, we observe a high frequency of HLA-DR3 in the second group; however, this is not statistically significant. On the other hand, comparing each pair of siblings and their respective diagnosis, antibody type and titre, and the number of HLA shared haplotypes, no

association between HLA antigens and the type of immunopathological manifestation can be detected.

We also observed a surprising variability in the clinical response, with a wide range of features present in the various systemic diseases. There was an overall predominance of the pattern of 'undefined collagen diseases' and 'overlap syndromes'. Nevertheless, we observed a number of patients with SLE or systemic sclerosis whose features were the same as in the primary forms of these diseases. A striking feature, however, was the constant absence of anticentromere antibodies, common in systemic sclerosis (particularly in localised forms), and the presence of an antibody to Sm in a patient with a predominance of systemic sclerosis features.

In conclusion, we have described a group of subjects exposed to the same exogenous insult, silica, who developed systemic diseases or autoantibodies, or both, of considerable heterogeneity, which do not seem to be linked to any particular HLA phenotype.

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