

Systemic Sclerosis in DRw52-positive Silica-exposed Males: A Case Report

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Abstract

The aims of this paper were to describe clinical and laboratory details of 4 siblings, of whom 2 have systemic sclerosis and to describe this family in the context of reported cases of familial systemic sclerosis.

The proband and his affected male sibling share the tissue typing antigens: HLA11, B57, DR13, DRw52,- and DQ2,6. Both were concordant for gender, silica exposure, marital status, migration history and antinuclear factor status but discordant for systemic sclerosis subtype, age at disease onset and ENA status. One non-affected sibling had no disease despite concordance for gender, HLA status, silica exposure, marital status, and migration history.

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Introduction

Familial scleroderma was first documented in 1953 by Rees and Bennett who described the occurrence of a localised disease in a father and daughter.¹ The first documentation of familial systemic disease was by Orabona and Albano who reported its occurrence in two sisters some five years later.²

Since then there have been other sporadic reports of familial disease. These have spanned four decades of medical literature, and have covered many racial groups, different disease manifestations and various intrafamilial relationships.

We present the relevant medical history of a family in whom 2 male siblings have systemic sclerosis. Both are DRw52-positive and had similar occupational exposure to silica.

Case Report

Proband

The proband, born in 1936, was a married Greek male who worked on a small multipurpose farm until 1963 when he and his family migrated to Australia. He subsequently worked as a labourer and jackhammer operator until 1972 when he presented with a 2-year history of generalised arthralgia, weakness, malaise and occasional dyspnoea.

Past history was unremarkable apart from a diagnosis of silicosis made in 1982 on the basis of his occupational history, atypical chest pain, the radiological development of calcified hilar lymph nodes with scattered fine punctate calcification throughout the upper lobes, and exclusion of mycobacterial infection.

On examination there was evidence of scleroderma

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affecting the hands, mid-forearms and face, facial telangiectasiae, knee crepitus and low grade fever. The diagnosis of systemic sclerosis was made and treatment commenced. Raynaud's phenomenon, pulp space narrowing, oesophageal involvement and progression of skin involvement to just above the elbows developed over the ensuing years. No calcinosis, lower bowel, or cardiovascular involvement was noted.

He was treated with D-penicillamine for 6 months, chlorambucil for 30 months, colchicine since 1980 and low dose prednisone since 1972.

Investigations revealed airways restriction and bilateral basal reticular markings consistent with pulmonary fibrosis. Serum creatinine was 0.08 mm/l, tissue typing HLA A11,23, B44,57, DR3,13, DRw52,-, DQ2,6, antinuclear factor-positive 1 / 160 (speckled and homogeneous pattern), ENA negative for SS-A, SS-B, RNP and Sm. He was also anticentromere antibody and antitopoisomerase antibody negative.

Affected Sibling

The proband has a brother, born in 1942, also with systemic sclerosis. This sibling has a similar occupational history, having worked on the same small farm before migrating to Sydney, Australia, and having subsequently worked as a labourer on both building sites and in water pipe laying and maintenance until the present day.

He first presented in 1989 with a 3-year history of mild Raynaud's phenomenon, finger stiffness and knee arthralgia. He had no sicca symptoms or any symptoms relating to the gastrointestinal; respiratory, or cardiovascular systems. Clinically he had sclerodactyly but no scleroderma, digital pitting, pulp atrophy, telangiectasiae or calcinosis. He was normotensive and examination of his respiratory and cardiovascular systems was normal. Initial investigations included: antinuclear factor positive 1 / 160 (speckled pattern), erythrocyte sedimentation rate 52 mm/first hour, rheumatoid factor positive 1: 128. Incomplete CREST (Calcinosis, Raynaud's, Oesophageal dysmotility, Sclerodactyly, Telangiectasia) syndrome was diagnosed on the basis of Raynaud's phenomenon, sclerodactyly and a positive speckled antinuclear antibody.

He remains in the same occupation. Currently the skin changes remain unchanged. He is virtually symptom free, with only mild Raynaud's during the winter months, and mild intermittent dysphagia.

Relevant investigations included: antinuclear antibody positive 1/2560 (speckled pattern), with anticentromere antibody staining, ENA positive for SS-A and SS-B, tissue typing HLA A3,11, B35,57, DR3,w13, DRw52,-, DQ2,6. A recent chest X-ray showed accentuation of upper lung field markings but no pleural plaques or calcification.

In summary, although the affected sibling's disease could be construed to be an undifferentiated connective tissue disease or a connective tissue disease-in-evolution, the features suggestive of limited scleroderma included Raynaud's, sclerodactyly, positive anticentromere antibody staining and mild intermittent dysphagia, which, though not investigated, may indicate oesophageal dysmotility.

Unaffected Siblings

Two other siblings remain disease free. One, a married male born in 1940, has an identical work history to the proband, having worked on the same small multipurpose farm until migrating with his family to Australia in 1963. Since then he has worked as a labourer and jackhammer operator, maintaining and laying water pipes. Dust control measures are employed in his current occupation. He has remained free of symptoms relating to connective tissue disease or occupational dust exposure. Relevant investigations included: antinuclear factor positive 1/160 (speckled pattern), ENA negative, tissue typing HLA A3,11 B35,57, DR3,w13, DRw52,-, DQ2,6. A recent chest X-ray revealed a well-defined nodular appearance in both upper and middle zones with some calcified hilar lymph nodes, suggesting the possibility of silicosis. Nail-fold capillaroscopy was normal.

The last sibling, a married female born in 1938, was a machinist and is currently a home manager. She has a history of cervical and lumbar back pain and hypertension and has no symptoms referable to connective tissue diseases. She has only a weakly positive antinuclear antibody titre of 1:40, a negative ENA and her tissue typing is HLA A3,11 B35,57, DR3,w13 DRw52,-, DQ2,6.

Other Relatives

The mother is deceased and the elderly father declined to be involved.

Discussion

Inclusion of this Sydney family increases the number of published cases of familial systemic sclerosis to 35¹⁻³⁰ while highlighting the rarity of its occurrence.

Analysis of the family's details is informative in a number of respects. Despite protection afforded by the male gender,³¹ both affected siblings were male. They had similar occupation and similar occupational exposure to silica dust, which has been incriminated in systemic sclerosis aetiopathogenesis.³²⁻³⁵ Both shared the HLA antigen DRw52, which has been associated with systemic sclerosis of both limited and diffuse subtypes.³⁶ Neither was positive for DR5, a Class II antigen reported from a number of studies³⁷⁻³⁹ to occur with increased frequency in systemic sclerosis patients. Here the similarity ends. The ages at disease onset, as estimated by the age at first disease symptom, were dispa-

TABLE I: REVIEW OF FAMILIAL SYSTEMIC SCLEROSIS CASES

Author/Year	Family member	Disease subtype	HLA	Unaffected siblings
Orabana 1958 ¹	Sister	L	NM	NM
	Sister	L		
McAndrew 1965 ²	Brother	L	NM	NM
	Brother	NM		
Blanchard 1965 ³	Brother	D	NM	NM
	Brother	D		
Schimke 1967 ⁴	Sister	L	NM	1 S + 1 B
	Sister	NM		
Burge 1969 ⁵	Sister	NM	NM	Nil
	Sister	L		
Rendell 1974 ⁶	Sister	D	NM	3 s
	Sister	D		
	Sister	L		
Greger 1975 ⁷	Father	D	NM	4 S + 1 B
	Son	D		
Sasaki 1977 ⁸	Mother	L	A9Bw40	1 S
	Daughter	L	A9,10Bw40	
Gray 1977 ⁹	Mother	D	NM	NM
	Son	D	A2,24,B7,22	
Frayha 1977 ¹⁰	Mother	L	NM	1 S + 1 B
	Daughter	L	NM	
Muralidar 1978 ¹¹	Sister	?D	NM	5 B
	Sister	D	NM	
Mund 1978 ¹²	Mother	L	A1,11,B17,w22	NM
	Daughter	L	A11,w31Bw22,w35	
Sheldon 1981 ¹³	Brother	L	A2,B12,21DR4,7	3 S + 2 B
	Sister	?D	Aw32,Bw35,DRw2	
	Brother	L	A2,B12,21,DRw4,7	
Gusseva 1981 ¹⁴	Sister	L	A3,9,B7,12	Nil
	Sister	L	A3,9,B7,12	
Stephens 1992 ¹⁵	Father	D	DR3,4 DQ2,8	NM
	Daughter	D	DR3,4 DQ2,8	
Soppi 1982 ¹⁶	Sister	NM	A2,3,B8,14	4 S + 2 B
	Brother	NM	A2,3,B8,14(15)	
Tuffanelli 1983 ¹⁷	Mother	?D	NM	NM
	Daughter	?L		
McGregor 1988 ¹⁹	Brother	?D	A1,24,B37,w60DR4,w10	6 S + 2 S
	Brother	?D	A1,2,B18,35,DR2,7	
McHugh 1994 ²⁰	Sister	L	DRB1 0407 0801	1 B
	Sister	L	DRB1 1501 0801	
Cook 1993 ²¹	Sister	?D	A1,11,B17,27,Cw2,6,DR5,7,DRw52	NM
	Sister	L	A1,11,B17,27,Cw2,6,DR5,7,DRw52	
De Juan 1994 ²²	Sister	?	A2,25,B35,51,DR4,11,DRw7,8	2 S + 4 B
	Sister	L	A1,23,B27,39,Cw2,DR8,13a3	
	Sister	L	Ax,11,B27,40,DR6,7.1	2 S + 1 B
	Sister	L	A2,11,B27,51,DR7.1,13a3	
Doutre 1986 ²³	Sister	L	A10,19,B12,Y1	NM
	Sister	L	A1,2,B15,17	
Matucci-Cerinic 1988 ²⁴	Sister	NM	A11,26,B8,40,w6,DR3,5	NM
	Sister	NM	A26,30-1,B8,13,w4,6,DR3	
McColl 1994 ²⁵	Sister	L	A3,24,B27,60,DR5,8	NM
	Sister	L	A3,24,B27,60,DR5,8	
	Grandmother	L	NM	1 S
	Grandson	L	A2,B44,DR10,12,DRw52	
Tajima 1995 ²⁶	Mother	NM	NM	1B
	Daughter	L		
Morse 1989 ²⁷	Father	D	A11,23,B7,-DR2,5,DRw52	NM
	Daughter	D	A-,23,B-,14,DR1,5,DRw52	
Sasaki 1991 ²⁸	Sister	D	NM	2 S + 5 B

TABLE I: Contd.

Author/Year	Family member	Disease subtype	HLA	Unaffected siblings
Stephens 1994 ²⁹	Sister	L	A24,B51,w52,C52,w3,DR2,w6	
	Father	D	DR3,4,DQ2,8	
	Daughter	D	DR3,4,DQ2,8	NM
	Mother	L	DR4,7,DQ7,9	
	Daughter	L	DR5,7,DQ2,7	NM
Manolios 1995 ³⁰	Sister	L	A2,31,B13,44,DR4,4	2 S + 4 B
	Sister	L	A2,31,B13,44,DR4,4	
	Sister	D	A24,31,B51,44,DR12.1,x	2 S + 1 B
	Sister	D	A3,24,B18,51,DRw11,15	
	Mother	L	A3,3,B7,44,DR1,w15	
	Daughter	L	A3,31,B7,13,DR4,w15	1 S
	Sister	L	A1,28,B44,57,DR1,9	2 S + 3 B
	Sister	L	A1,28,B44,57,DR1,9	
	Brother	D	A3,11,B35,57,DR3,13,DRw52,-	1 S + 1 B
	Brother	L	A3,11,B35,57,DR3,13,DRw52,-	

NM: no mention; D: diffuse disease; L: limited disease; S: sister; B: brother

rate by 10 years. Furthermore, there was variability in the pattern of organ involvement and disease subtype, with diffuse disease in the **proband**, and limited disease in the affected sibling. Serology also differed, with the **proband** being ENA negative, and the affected sibling being SS-A and SS-B positive.

Also of interest is the absence of disease to date in the unaffected male currently 57 years of age, that is, 13 and 23 years older than the ages at which systemic sclerosis began in his male siblings. His occupational history was similar to those of his male siblings, he has radiological evidence of silicosis (as does the **proband**), shares an identical class 1 and class 2 haplotype with one of the affected siblings, is weakly antinuclear antibody positive but to date has normal nail-fold capillaroscopy findings and remains asymptomatic. In summary he is concordant with one affected sibling in the following four respects-identical haplotype, sex, occupational history and similar age-but remains discordant for the disease.

This suggests that the unaffected male sibling may be in a preclinical disease phase preceding the development of abnormal nail-fold capillaries. Alternatively he is currently protected from the disease either by virtue of not possessing a non-HLA associated systemic sclerosis-susceptibility gene or not having been exposed to another environmental triggering agent. The observation that he is 13 years and 23 years older than the ages at which systemic sclerosis symptoms began in his affected siblings argues against the former hypothesis.

This family's data add in the previously mentioned ways to other documented cases¹⁻³⁰ which are summarised in Table I. These cases demonstrate that the occurrence of familial systemic sclerosis is not restricted by race, gender or nationality. However, interestingly, no

instances of familial systemic sclerosis have yet been documented in patients of Chinese extraction.

Of the 35 documented familial cases, 23 were between siblings, 11 were parent-child pairs and one was a maternal grandmother-grandson combination. The 23 instances of familial disease between siblings comprised disease in 21 sibling pairs, and 2 families in each of which the disease allegedly involved 3 siblings.

Of the 11 parent-child relationships, maternal involvement outweighed paternal involvement by 8 to 3, approximating the expected female to male gender ratio of 3:1.^{31,36,40} A cumulative total of 15 daughters and 6 sons were born to this cohort and their spouses. Of these, 9 daughters (60%) and 2 sons (33%) were affected (odds ratio 3.0; 95% CI: 0.3-35.2). Where disease subtype could be ascertained, the disease concordance to discordance ratio was 9:0, and limited disease slightly predominated over diffuse disease in a 5 to 4 ratio.

Of the 23 families with between-siblings familial disease, the number and gender of unaffected siblings were documented in 16. These comprised 57 females and 42 males of whom 27 females (47%) and 7 males (17%) had systemic sclerosis. Within these 16 families, the female gender remained a systemic sclerosis risk factor with an odds ratio of 4.5 (95% CI: 1.6-13.3).

The disease subtype concordance to discordance ratio within sibling pairs was 4:1. Assuming limited disease accounts for 80% of disease subtype expression,⁴¹ the expected concordance to discordance ratio for sibling pairs (i.e. LL + DD:LD) can be estimated at 17:8. This is lower than the observed concordance to discordance ratio in both parent-child and between-sibling familial disease. This suggests that the disease subtype in a subsequent family member is not a random occurrence solely determined by those factors governing limited to

diffuse subtype ratio in an idiopathic systemic sclerosis population. Although evidence is lacking, this "non-randomness" suggests a factor or factors which are more likely of genetic than environmental origins.

Where differentiation into disease subtype was possible, limited disease occurred in 25 siblings and diffuse disease in 14 siblings. Although limited disease predominated, the proportion of familial cases with diffuse disease is higher than expected from surveys of idiopathic disease.⁴²

A number of tentative conclusions may be drawn from analysis of mixed histocompatibility complex data detailed in Table I. First, inter-family comparison of Class I tissue antigens failed to demonstrate any one recurrently occurring antigen. Secondly, although Class II data are less complete, inter-family comparison of Class II tissue antigens also failed to demonstrate any one recurrently occurring antigen. The occurrence of familial disease therefore may be explained either by the presence of a genetic determinant distant from the MHC region on the sixth chromosome and/or the presence of (an) environment determinant(s). Thirdly, the presence of an identical HLA haplotype between siblings-the 2 affected and 2 unaffected brothers of Sheldon and colleagues and the affected and unaffected siblings from this study-was not invariably associated with disease concordance.

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