

EXTENDED REPORTS

Systemic sclerosis in Iceland. A nationwide epidemiological study

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Abstract

Objectives—To investigate the incidence, prevalence and clinical features of systemic sclerosis (SS) in Iceland.

Methods—All patients diagnosed with SS from 1975-90 were included. Retrieval for the study began in 1980 and was carried out by computerised search from registers of all hospitals and health care clinics and death registration files, and with personal communication with doctors in Iceland

Results—Over a 16 year period from 1975-90, 15 new cases were found with an incidence of 0.7 and 0.05/100 000, for females and males at risk respectively, and 0.38 for both sexes. At the end of 1990 there were 18 patients alive with SS, 13 with limited and five with diffuse cutaneous involvement. The age standardised prevalence was 11.9 and 1.5/100 000 for females and males at risk respectively. The crude prevalence rate for both sexes was 7.1/100 000. There were five deaths, two patients died of SS related causes, one had SS renal disease. The relative risk of death was similar to that in the general population. The calculated five year survival rate was 100% and the 10 year survival rate 81%. No HLA antigen association was found.

Conclusion—Compared with previous surveys this study shows a low incidence of systemic sclerosis and a high proportion of patients with limited cutaneous involvement.

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Systemic sclerosis (scleroderma) is a rare disease affecting skin and internal organs. The aetiology is largely unknown, the role of genetic factors is unclear, but environmental factors, such as, polyvinyl chloride, silica and coal are thought to be of importance in inducing symptoms and to have implications in the progression of the disease.¹ Systemic sclerosis (SS) has been considered to run a progressive course with a rather bleak prognosis. Of importance is that virtually all the descriptive epidemiology of SS is derived from studies on selected patient materials. Such studies tend to overestimate the gravity of diseases such as SS.² In the present study the 1980 ARA criteria were applied for the classification of SS in an unselected population. The structure of the

study allows us to conclude that we have probably screened the whole population for SS. It is of interest to study a disease such as SS in an ethnically homogeneous community like Iceland where potentially noxious environmental factors are minimal compared with highly industrialised countries.

Materials and methods

The Icelandic population (255 708 on 1 December 1990) is homogeneous with ethnic origin from the Nordic countries and Ireland. The health care system in Iceland is community-based and medical service is readily available; the small size of the country facilitates easy flow of information.³ Retrieval for the study began in 1980 and was ongoing during the study period. It was carried out by a computer search in the registers of all hospitals and health care centres in Iceland, at health care centres without computerised registration a personal contact was made with the local doctors, to look for patients with the diagnosis of systemic sclerosis. A questionnaire asking for that diagnosis was sent to: district medical doctors, private practitioners, internists, neurologists, paediatricians, dermatologists, nephrologists, and rheumatologists as well as other physicians likely to have information on patients who had never been admitted to hospitals with this diagnosis. Death registration and necropsy reports for suspected cases were also checked. The diagnosis was made in hospital in 78% of the cases and the remainder was diagnosed outside hospitals. In this way we believe we screened the whole population for systemic sclerosis. The records of all patients registered with this diagnosis from 1 January 1975 through 31 December 1990 were reviewed and the 18 patients alive with this diagnosis called for examination. Patients with overlap features of lupus, scleroderma and polymyositis and the solitary presence of high titre anti-RNP antibodies were considered mixed connective tissue disease cases and not included in the study.

The 1980 ARA criteria used for the classification of systemic sclerosis were applied.⁴ Patients were classified as having limited systemic sclerosis or CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasias) if truncal scleroderma was absent and, classified as having diffuse systemic sclerosis if truncal scleroderma was present. A predefined protocol was used to fulfill clinical and laboratory

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parameters serially for every patient. Patients with a localised form of scleroderma, that is, linear scleroderma or scleroderma morphea, were not included in the study.

The annual incidence of systemic scleroderma was calculated from the number of patients first registered as having systemic sclerosis during the 16 year period. The prevalence of systemic sclerosis was calculated from the number of patients alive on 31 December 1990. Incidence and prevalence rates were standardised to the world population as defined by Segi.⁵ Survival rates were calculated by the Kaplan Meyer life table method from the year of diagnosis until 31 December 1990.

An overall clinical assessment, including skin score, laboratory profile and urinalysis was performed three times annually from 1988–90 for each of the 18 patients alive with the disease.

HLA-typing for class I antigens was done on 20 patients and 333 controls, and class II antigens were tested on 17 patients and 50 controls, with the methods of Vartal *et al.*⁶ Statistical analysis was carried out with a Chi square contingency table.⁷

Antinuclear antibody (ANA) was detected by a standardised immunofluorescence technique, using a rat liver as a substrate.⁸ A positive ANA was defined as a titre of more than 1/20, where 95% of the normal population had a titre of 1/20 or less. An ELISA technique was used to detect antibodies against the Scl-70 and SSA nuclear elements.⁹ Cellular ELISA was used to detect antibodies against endothelial cells.¹⁰ Anti-centromere antibody testing was carried out on prepared mitotic cells from Immuno Concepts California by immunofluorescence technique.¹¹

Results

The response rate to the questionnaire was over 95%. In the 16 year period there were 15 new cases, 14 females and one male classified as systemic sclerosis. The mean age at the time of diagnosis was 43.8 years (range 5–70). The age specific annual incidence rates are shown in table 1. The crude rate for both sexes was 0.38/100 000/year, the age standardised annual incidence rate was 0.7 for women and 0.05 for men respectively. At the end of 1990 there were 18 patients alive, 16 women and 2 men, with a total crude prevalence rate of 7.1/100 000. The age standardised prevalence rate was 11.9 for women and 1.5/100 000 for men. For the 18 patients alive at the end of 1990 the mean disease duration from onset of subjective feeling of skin swelling and thickening on the fingers, was 9.9 years (range 1–27), the mean age was 53.5 years (range 15–85). Clinical features of the 18 patients alive at the end of 1990 are shown in table 2. Thirteen were classified as having limited and five as having diffuse systemic sclerosis. Clinically relevant kidney disease as shown by increased serum creatinine, hypertension, formed elements in the urine, significant proteinuria or haematuria was not found in any of the 18 patients on close follow up over three

Table 1 Annual age specific incidence rates of systemic sclerosis in Iceland from 1975–90

| Age groups | Females | | Males | |
|--------------------------------|---------|--------|-------|--------|
| | No* | Rate** | No* | Rate** |
| 0–9 | 1 | 1 | 0 | 0 |
| 10–19 | 0 | 0 | 0 | 0 |
| 20–29 | 2 | 2 | 0 | 0 |
| 30–39 | 2 | 2 | 0 | 0 |
| 40–49 | 4 | 4 | 1 | 1 |
| 50–59 | 3 | 3 | 0 | 0 |
| 60–69 | 1 | 1 | 0 | 0 |
| 70–79 | 1 | 2 | 0 | 0 |
| 80+ | 0 | 0 | 0 | 0 |
| Overall age Standardised rate† | | 0.7 | | 0.05 |

*Total number of new systemic sclerosis cases in a 16 year period.

**Rates per 100 000 population risk per year.

†Standardised to the world population.

years (1988–91) or in the patients' previous records. Positive ANA was found in 15 patients, anti-nucleolar pattern was found in 11 patients, antibodies against Scl 70 in four and against SSA in three. Antibodies against endothelial cells were found in six patients. Anti-centromere antibodies were found in two patients with limited SS and in no patient with diffuse SS. Autoantibody profiles are shown in table 3.

Testing for class I and II HLA antigens revealed no significant association (table 4)

Mean values for haemoglobin, sedimentation rate, serum creatinine and CRP were within normal limits for the group as a whole.

There were five deaths during the study period, three males and two females. The mean (SD) age at death was 66 (13.8) years range 53–85). The expected number of deaths according to mortality in the general population and age and sex distribution of the study group was 1.2 for women and one for men; thus the risk ratio is 1.7 (95% confidence interval 0.2–6.1), and 3.0 (95% confidence interval 0.6–8.8) respectively. The calculated five year survival rate was 100% and the 10 year survival rate 81%. The mean disease duration at the time of death was 12.5 years. One of five patients who died had diffuse SS, the other four had limited SS. One of the five patients had evidence of renal involvement with increased creatinin and abnormal urinalysis at the time of death. Three of the patients died from cardiovascular causes, one from cancer, and one from unknown causes. In two cases the deaths could be related directly to systemic sclerosis, one of the two had SS renal disease and the other SS cardiac disease.

Discussion

In our nationwide survey the 1980 ARA criteria were applied for the classification of systemic sclerosis. The structure of the study allows us to conclude that we probably screened the whole population for systemic sclerosis. The under-ascertainment was thought to be minimal since retrieval for the study has been ongoing since 1980. Published reports show a variable incidence of systemic sclerosis; the incidence in Iceland of 3.8 per million is in the lower range.² Recent data from

Table 2 Organ involvement in 18 patients with systemic sclerosis

| | Diffuse SS (no 5) | | Limited SS (no 13) | |
|--|-------------------|-------|--------------------|------|
| | No | % | No | % |
| Peripheral vascular (Raynaud's phenomenon) | 5 | (100) | 12 | (92) |
| Arthritis/tenosynovitis | 3 | (60) | 12 | (92) |
| Gastrointestinal | 4 | (80) | 10 | (77) |
| Cardiac | 3 | (60) | 6 | (46) |
| Pulmonary | 5 | (100) | 8 | (62) |
| Renal | 0 | | 0 | |
| Mucosal membranes (Sjögren's s.) | 0 | | 4 | (31) |

Table 3 Autoantibodies in 18 patients with systemic sclerosis

| | No | % |
|------------------|----|------|
| ANA | 15 | (83) |
| Anti-Scl 70 | 4 | (22) |
| Anti-nucleolar | 11 | (61) |
| SS A | 3 | (17) |
| Anti-endothelial | 6 | (33) |
| Anti-centromere | 2 | (11) |

Table 4 HLA-association with systemic sclerosis in Iceland

| Antigen | Patients | | Controls | | RR | X2 | P (correction for number of antigens by Bonferroni inequality method) |
|---------|----------|----|----------|-----|-------|-------|---|
| | h | k | H | K | | | |
| A1 | 7 | 13 | 120 | 213 | 0.984 | 0.209 | NS |
| A11 | 6 | 14 | 65 | 268 | 1.838 | 1.627 | NS |
| B5 | 2 | 18 | 6 | 327 | 6.809 | 1.627 | NS |
| B8 | 7 | 13 | 51 | 282 | 3.047 | 5.666 | NS |
| B15 | 1 | 19 | 66 | 267 | 0.309 | 2.417 | NS |
| B18 | 3 | 17 | 21 | 312 | 2.907 | 3.216 | NS |
| DR1 | 6 | 11 | 6 | 44 | 3.870 | 4.683 | NS |
| DR4 | 3 | 14 | 19 | 31 | 3.900 | 2.230 | NS |
| DR5 | 3 | 14 | 3 | 47 | 3.276 | 2.397 | NS |
| DR8 | 4 | 13 | 3 | 47 | 4.524 | 4.201 | NS |

h = patients positive for the antigen, k = patients negative for the antigen, H = controls positive for the antigen, K = controls negative for the antigen, RR = relative risk.

X2 = statistical significance of the difference from RR.

P = probability corrected for the number of antigens by Bonferroni inequality method.

NS = Not significant.

Pittsburgh based on a 20 year survey of hospital diagnosed cases suggest a higher incidence or 19.1 per million for the last 10 years of the study.¹² The prevalence in Iceland was found to be 7.1/100 000, a community survey in South Carolina¹³ found a prevalence more than four times higher than that. Conversely, other studies show incidence and prevalence figures closer to ours.² The nature of our study, where the whole population was screened for systemic sclerosis, makes comparison with other studies difficult, but the disease is probably rarer in Iceland than in other countries. This may be unexpected considering the cold climate and the fact that Raynaud's phenomenon is a prominent manifestation of SS. The reason for the low prevalence might be the absence of environmental factors. There are no coal or silica mines¹⁴ or plastic industries using polyvinyl chloride¹⁵ in Iceland and pollution is low. On the other hand, the high prevalence rate in Pittsburgh might be due to silica exposure of the large local mining population. To our knowledge similar studies in other Nordic countries have not been done. The importance of genetic factors is still unclear.

Renal involvement is rare at diagnosis in systemic sclerosis but emerges in 45% of the patients on the average 3.2 years after diagnosis.¹⁶ This is shown by haematuria, proteinuria and abnormal urinary sediment,

hypertension and decreased glomerular filtration. The good prognosis in Icelandic patients may in part be explained by the fact that, for some reason, they seem to have less renal involvement even though involvement of other internal organs is as common as elsewhere. The unselected nature of our study might partly be the reason for the relatively high proportion of mild cases, which was also noted for patients with lupus in Iceland, where there was low incidence of renal involvement.³ The renal protective factor is unknown; it could be on a genetic basis or due to the absence of noxious environmental factors. The patients diagnosed before 1984 were treated with a combination of hydralazine 25 mg three times a day glutamine 200 mg twice a day and penicillamine 500–750 mg four times a day, according to Asboe-Hansen,^{17 18} this was not carried out in a controlled fashion, but may have had a bearing on the outcome.

Systemic sclerosis is characterised by sclerosis of the skin, yet involvement of internal organs is predictive for survival.^{19 20} Reduced survival rates in systemic sclerosis are most apparent during the first two years of the disease and tend to be related to older age, male sex, anaemia, a high sedimentation rate and evidence of renal, cardiac or pulmonary involvement.²¹ A low haemoglobin level in younger patients and impaired renal function in older patients are the best predictors of mortality.²² There have been a number of studies on survival in systemic sclerosis, all showing survival at five and 10 years to be 44–73% and 42–59% respectively.^{23 31} In Iceland the overall survival rate of patients with systemic sclerosis seems to be considerably higher where five year survival was found to be 100% and 10 year survival 81%, this may be a reflection of the fact that most of the patients have limited cutaneous involvement that is considered to carry a better prognosis. The risk of death among patients with systemic sclerosis is similar to that of the general sex- and age-matched Icelandic population. The small size of the study population, however, makes it hard to draw any conclusions regarding survival rates, but at least it can be said that systemic sclerosis in Iceland is a benign disease.

The association of systemic sclerosis with the HLA antigens has been weak. Numerous early reports suggested an association with B8^{32 33} but this has not been a universal finding. Later testing for class II antigens suggested an association with DR3 and DR.² In our study we found no association with the HLA antigens. The patients came from all over Iceland and are not related, and are not of the 'rheuma' families in Iceland, nor was there any time clustering apparent.

In summary, our nationwide study of an unselected population, found systemic sclerosis to be rarer, and the prognosis better in Iceland than previously reported elsewhere.

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