Incidence of scleroderma spectrum disorders in Slovenia

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ABSTRACT

Objectives. *This paper aims to investigate the incidence of scleroderma spectrum disorders (SDS) in Slovenia.*

Methods. *From 01.01.2007 to 31.12.2009 we prospectively examined all patients over 18 years of age suspected of suffering from SDS who were referred to our department, which is the only Rheumatology referral centre in the Ljubljana region serving a population of 518.921 Caucasians over 18. Patient work-up consisted of clinical assessment, laboratory and imaging studies, and functional tests. The working classification of SDS proposed by Maricq and Valter was used to classify patients as having CREST syndrome, digital scleroderma disease (SD), intermediate SD, diffuse SD, undifferentiated connective tissue disease with SD features, and SD sine scleroderma. Patients with certain features of SDS who did not fit any specific class were classified as having prescleroderma using LeRoy's classification of early systemic sclerosis.*

Results. *We examined 100 patients. Forty-one new cases of SDS were diagnosed (37 females, 4 males), aged 58.9±15.1 years (24–86 years).*

Conclusion. *The overall age-adjusted annual incidence of SDS in Slovenia is 2.6 per 100.000 adults per year (95%CI=1.7–3.5).*

Introduction

Scleroderma spectrum disorders (SDS), including systemic sclerosis (SSc) as defined by the American College of Rheumatology preliminary criteria for the classification of SSc (ACR 1980), are characterised by skin thickening, micro-vascular damage and autoimmunity (1). SDS show large individual variability in the extent of skin and organ involvement, disease progression pace and prognosis. Epidemiological studies of SDS have been hampered by the rarity of these diseases, the variability of their clinical manifestations, and the tendency of the features of SDS to overlap with those of other recognised connective tissue diseases. Published estimates of the prevalence and incidence of SDS vary widely depending on the period of observation, methods of case ascertainment, and the geographic area of the study.

Epidemiological data on SDS are scarce; hence we decided to further the insight into the epidemiology of SDS by determination of the overall age-adjusted annual incidence of SDS in Slovenia. To our knowledge, this is the first report of the incidence of SDS in the available literature ascertained by prospective evaluation of all suspected subjects in a well-defined region (3-12).

Patients and methods

Patients

We prospectively examined all patients without prior diagnosis of any scleroderma spectrum disorder older than 18 years suspected of suffering from SDS referred to our outpatient clinic or admitted to our department from 01.01.2007 to 31.12.2009. Since some SDS patients seek help from dermatologists, pulmonologists, angiologists, and gastroenterologists, these sub-specialists were informed about the study and requested to refer these patients to our department. Our department is the only rheumatology referral centre in the Ljubljana region which has a Caucasian population of 518.921 aged 18 or above (Source: Statistical Office of the Republic of Slovenia, Department of Demographic and Social Statistics). The study was approved by the national ethical commission. All patients gave written informed consent.

Patient work-up

All patients were examined by a single physician and assessed using the definitions listed in Table I. All patients were tested for anti-nuclear antibodies (ANA), and antibodies against extractable nuclear antigens. Anti-nuclear an-

tibodies were determined by indirect immunofluorescence on HEp-2 cell line substrate (Immunoconcepts, Sacramento, CA, USA). Titer of ANAs 1:160 and higher were considered positive. Anti-SS/A, anti-SS/B, anti-Scl-70, anti-U1RNP, anti-Ku, anti-PM/Scl, anti-PCNA, anti-Sm, anti-Jo1, anti-SL antibodies were determined by counter-immuno-electrophoresis (14). Anti-centromere and anti-RNA polymerase antibodies were determined based on typical immunofluorescence patterns on HEp-2 cell line substrate (Immunoconcepts, Sacramento, CA, USA). Nail-fold capillaroscopy was performed in all patients. Depending on presentation, additional tests were ordered, *e.g.* further biochemistries, EKG, pulmonary function tests, measurement of diffusing capacity of the lung for carbon monoxide (D_{LCO}), chest x-ray, echocardiogram, esophageal x-ray, hand and feet x-ray.

Table I. Definitions of pathological nail-fold capillaroscopy findings and organ involvement.

Nail-fold capillaroscopy
(Adapted from Cutolo, 2004) (13)

- Enlarged/giant capillaries
- Loss of capillaries
- Disorganisation of the capillary arrays
- Ramified/bushy capillaries
- Haemorrhages
- Micro-thromboses

Raynaud phenomenon
Recurrent spasms of small digital arterioles/arteries in fingers and toes, usually triggered by cold and emotional stress. Patients report of sudden pallor, in severe cases followed by cyanosis, and finally resolving with reactive hyperemia upon cessation of stress or rewarming.

Digital tip ischaemia
Digital pitting scars, ulcerations or gangrene, or both.

Skin thickness
Modified Rodnan total skin thickness score by clinically scoring each of the 17 body areas on a scale of 0–3.

Pulmonary involvement
- SD associated pulmonary fibrosis
  - Other causes of lung fibrosis were excluded and
  - Bilateral fibrosis confirmed by chest x-ray, high resolution CT scan and/or
  - Pulmonary function tests show restrictive pattern and D_{LCO} <80%.
- Pulmonary arterial hypertension

Gastrointestinal involvement
- Patient history of dysphagia, intermittent heart burn, nausea, constipation, diarrhoea and/or
- Proof of gastrointestinal motility changes, esophageal stenosis, gastro-esophageal reflux disease, intestinal pseudo-obstruction using radiology, endoscopy or esophageal manometry.

Kidney involvement

Cardiac involvement

Skeletal muscle disease

Joint involvement

Soft tissue calcifications are shown on x-ray of hands and feet.

SD: scleroderma disease.

Classification of patients
We used the working classification of SDS proposed by Maricq and Valter to classify the patients as having CREST syndrome (calcinosis, Raynaud phenomenon [RP], esophagopathy, sclerodactyly and telangiectasia), digital scleroderma disease (SD), intermediate SD, diffuse SD, undifferentiated connective tissue disease with SD features (UCTD-SD), and SD sine scleroderma (2). Additionally, we used LeRoy's criteria for early systemic sclerosis to classify the patients presenting with RP, pathological capillaroscopy, and autoantibodies suggestive of SD as having prescleroderma (Table II) (15).

Table II. Classification of scleroderma spectrum disorders (Adapted from Maricq and Valter) (2).

Prescleroderma
Raynaud phenomenon, pathological capillaroscopy, ANA or other auto-antibodies suggestive of SSc

Diffuse SD
Skin involvement proximal to elbows/knees, includes trunk

Intermediate SD
Skin involvement proximal to MCP/MTP, distal to elbows and knees, trunk not involved

Digital SD
Patients meeting minor ACRs criteria (sclerodactyly, digital pitting scars or loss of substance from the finger pads, bibasilar pulmonary fibrosis)

CREST syndrome
No skin involvement or sclerodactyly only, T is required with one or more other acronyms, ACA is required with any two or more acronyms

UCTD-SD
SD features, sclerodactyly only, no ACA, no telangiectasias.

SD sine scleroderma
SSc features, no skin involvement, no ACA, no telangiectasias.

ACA: anti-centromere antibodies; ACR: American college of Rheumatology; ANA: anti-nuclear antibodies; CREST: calcinosis, Raynaud phenomenon, esophagopathy, sclerodactyly, and telangiectasia; MCP: metacarpophalangeal joints; MTP: metatarsophalangeal joints; SD: scleroderma disease; UCTD-SD: undifferentiated connective tissue disease with features of scleroderma disease; SSc: systemic sclerosis.

Statistical analysis
The exact 95% confidence interval (CI) based on binomial distribution was calculated for the incidence estimate.

Results

During the 3-year study period we examined 100 patients suspected of having SDS. Forty-one (41%; 37 women, 4 men) were diagnosed as having SDS. Their mean age was 58.9±15.1 years (range 24–86). Male to female ratio was 1:9. Distribution into SDS subsets as defined in Table II is presented in Table III. Only 10 out of 41 (24%) patients classified as having SDS also fulfilled the ACR 1980 classification criteria for SSc (Table III). The autoantibody profile of the patients with SDS is shown in Table IV.

Fifty-four patients (42 women, 12 men) had elements of SDS, but fit in no subset, four patients had no elements of SDS during the catchment period, and one patient could not be classified since he refused any further tests (Table III). Patients with primary RP were on average younger (mean, 48±SD, 16 years), more often male (male:female ratio 1:4), and had had RP for a longer time (mean, 76±99 months) before presenting to a rheumatologist than the patients with SDS (mean, 29±21 months).

Two patients, one diagnosed with CREST syndrome and the other with UCTD-SD, were diagnosed a few months later with T cell lymphoma and colon cancer, respectively. One patient with primary RP was diagnosed with systemic lupus erythematous (SLE) a year later, and one patient with RP and anti-Ro auto-antibodies was diagnosed with Sjögren syndrome two years later. Based on the catchment population and using the working classification of SDS proposed by Maricq and Valter, the age-

Table III. Results – distribution of patients by year of inclusion and diagnosis.

	2007	2008	2009	Total	ACR 1980 criteria fulfilled
Patients included	31	33	36	100	10
SDS (all)	**18**	**10**	**13**	**41**	**10**
Prescleroderma	0	2	0	2	0
Digital SD	1	0	0	1	1
CREST	7	5	9	21	5
Intermediate SD	1	0	0	1	1
Diffuse SD	1	0	0	1	1
UCTD-SD	4	1	3	8	2
SD sine scleroderma	4	2	1	7	0
Non SDS (all)	**13**	**23**	**23**	**59**	**–**
Primary RP	5	16	14	35	–
RP with pathologic capillaroscopy	4	4	7	15	–
RP with SD autoantibodies	1	3	0	4	–
Unproven RP	3	0	0	3	–
Unclassified	0	0	1	1	–
Primary biliary cirrhosis/CREST	0	0	1	1	–

CREST: calcinosis, Raynaud phenomenon, esophagopathy, sclerodactyly, and telangiectasia; RP: Raynaud phenomenon; SD: scleroderma disease; UCTD-SD: undifferentiated connective tissue disease with features of scleroderma disease.

Table IV. Autoantibodies in patients classified as SDS.

	ANA	ACA	Anti-Scl70	Anti-PM/Scl	Anti-Ku	No auto anti-bodies
SDS (n=41, %)	**36 (87.8%)**	**19 (46.3%)**	**1 (2.4%)**	**2 (4.8%)**	**1 (2.4%)**	**5 (12.2%)**
Prescleroderma (n=2)	2	1	0	0	0	0
Digital SD (n=1)	1	0	1	0	0	0
CREST (n=21)	20	18	0	0	0	1
Intermediate SD (n=1)	1	0	0	0	0	0
Diffuse SD (n=1)	1	0	0	0	0	0
UCTD-SD (n=8)	7	0	0	1	1	1
SD sine scleroderma (n=7)	4	0	0	1	0	3

CREST: calcinosis, Raynaud phenomenon, esophagopathy, sclerodactyly, and telangiectasia; RP: Raynaud phenomenon; SD: scleroderma disease; UCTD-SD: undifferentiated connective tissue disease with features of scleroderma disease; SDS: scleroderma spectrum disorder; ACA: anti-centromere antibodies, ANA: anti-nuclear antibodies.

adjusted annual incidence for SDS is 2.5 per 100.000 inhabitants older than 18 years (95%CI = 1.4–3.6). If we used the LeRoy's criteria for early SSc, the age-adjusted annual incidence was 2.6 per 100.000 adults (95%CI = 1.7–3.5). If we considered only the patients with definitive SSc, diagnosed by 1980 ACR criteria, the age-adjusted annual incidence was 0.64 per 100.000 adults (95%CI = 0.1–1.2).

Since the Slovenian population of two million is demographically homogenous, we can probably assume that the incidence figures are representative for the entire country.

Discussion

In the past forty years, only few estimates of annual incidence of SSc in the USA, Canada, Australia, New Zealand, Japan and Europe were published (3-12). The reported annual incidence of SSc ranged from 0.06–12.2 per 100.000. High variability of the reported incidence estimates probably stems from differences in the period of observation, methods of case ascertainment, classification criteria used and the geographic area of the study.

Depending on the classification criteria, the incidence of SDS in Slovenia was 0.64, 2.5, 2.6 per 100.000 adults, when the ACR 1980, the working classification of SDS proposed by Maricq and Valter, or Leroy's criteria for early SSc were used, respectively.

The annual incidence of definite SSc cases according to the ACR 1980 criteria in Slovenia is comparable to the incidences reported in Greece, Minnesota, New Zealand, and Japan (0.37–1.3 per 100.000) (3, 8-10). Interestingly, the annual incidence in Greece (1.3 per 100.000) is higher than in Slovenia, and much higher than in Iceland (0.38 per 100.000). This is in line with the previously observed north-south gradient of SSc occurrence in Europe, which so far has no explanation. On the other hand, a very recent study from north-eastern part of Italy which borders Slovenia on the west reported a higher incidence of SSc (3.2 and 4.3 per 100.000 patients older than 16 years, when the ACR 1980 and LeRoy's criteria were used, respectively) (12).

Although we used different methods of case ascertainment and different classification criteria than the aforementioned studies, the age and sex distribution were comparable with those in other European studies. The mean age of patients at diagnosis was 58.9±15.1, which is comparable with 59.8±13.3 in the Lugo region in Spain (3). The male:female ratio of 1:9 is comparable with that in other European countries where it ranges 1:7–11 (5, 12). Interestingly, men are affected more often in Australia, New Zealand, Canada, and in some US states, where the male:female ratio ranges 1:1.5–6 (5).

Our study had several strengths. Firstly, it was a prospective study. Secondly, a single evaluator assessed all included patients. Thirdly, we used classification criteria that tend to detect patients in earlier and atypical forms of the disease, which nowadays represent the target population for therapeutic interventions. However, our study also had two major limitations. Firstly, the catchment population was relatively small. Secondly, it is likely that not all cases of SDS were recognised as such by the above mentioned sub-specialists and have therefore not been referred to our department, thus, our estimate of incidence of SDS is probably too conservative.

Further epidemiological investigations into early and atypical forms of SDS are needed to determine their medico-socio-economical impact.

In conclusion, we prospecitvely determined age-adjusted annual incidence of SDS in Slovenia, annual incidence of SDS. which is 2.6 per 100.000 (95%CI = 1.7–3.5), and finally, the annual incidence of systemic sclerosis, which is 0.64 per 100.000 (95%CI = 0.1–1.2).

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