Epidemiology of systemic sclerosis in a district of northern Italy

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ABSTRACT

Objective. *To estimate, using both the American College of Rheumatology-ACR 1980 classification criteria and revised LeRoy and Medsger 2001 criteria, the incidence and prevalence of systemic sclerosis (SSc) in an area in north-eastern Italy with a referral base population of about 346,000 inhabitants.*

Methods. *Retrospective examination of all patients 16 years and older of native Italian origin and resident in the Ferrara district who had either been admitted to hospital or referred to our outpatient clinic with a diagnosis of SSc between 1st January 1999 and 31st December 2007. SSc subjects were identified both by a search of hospital discharge code 710.1, as per the international classification of disease-9 codes, and using a computerised search for this pathology code in the national health care system. The subjects referred to our outpatient clinic were identified from a dedicated data base. Incidence and prevalence rates were calculated as the number of cases per 100,000 inhabitants (population data based on the October 2001 national census). The medical records of each potential case were accurately examined and reviewed by the same physician who determined whether those patients identified as having a diagnosis of SSc did indeed meet the ACR 1980 classification criteria for SSc and/or the LeRoy and Medsger 2001 criteria.*

Results. *After reviewing all cases, of the 118 patients meeting the LeRoy-Medsger 2001 criteria, only 88 patients had a definitive diagnosis of SSc according to the ACR 1980 criteria. Considering the ACR criteria, the prevalence rate was 25.4 cases per 100,000 (95% CI: 22.2–28.6), and the annual incidence rate over the study period was 3.2 per 100,000 (95% CI: 2.0–4.4). Considering the LeRoy and Medsger criteria epidemiological data were respectively 34.1 cases per 100,000 (95% CI: 30.4–37.8) and 4.3 cases per 100,000 (95% CI: 3.0–5.6). According to the LeRoy and Medsger criteria, the SSc subsets were broken down as follows: 20 limited-SSc (19.2%), 76 limited cutaneous-SSc (62.1%), 22 diffuse cutaneous-SSc (18.7%). The female/male ratio was 9.7:1.*

Conclusion. *Incidence and prevalence of SSc observed in an area in north-eastern Italy were found to be higher than reported in the various geographical area (UK, US, Australia, etc) but similar to another Italian study adopting, as here, the LeRoy-Medsger criteria. The different diagnostic criteria adopted may explain some of the differences found in comparison to the studies based only on the ACR criteria, however, regional discrepancies in disease occurrence cannot easily be dismissed only on the basis of methodological approaches to case definition or ascertainment; genetic, ethnic and environmental factors should also be considered. Currently the main challenge remains to determine the scientific basis for the observed differences, distinguishing between changes deriving from geographic/ethnic features and from the analytic methods.*

Introduction

Systemic sclerosis (SSc) is a complex disease the main features of which are extensive fibrosis, vascular alterations, and auto-antibodies against various cellular antigens. In the commonly accepted classification of the disease, two major subgroups are considered: limited cutaneous scleroderma (lcSSc) and diffuse cutaneous scleroderma (dcSSc). In lcSSc, fibrosis is mainly restricted to the hands, arms, and face; Raynaud's phenomenon is present for several years before fibrosis appears; pulmonary hypertension is frequent; and anti-centromere antibodies occur in 50 to 90% of all patients. Diffuse cutaneous scleroderma is a rapidly progressing disorder that affects large areas of the skin and compromises internal

organs; women are at much higher risk for scleroderma than men (ratio ranging from 3:1 to 14:1) (1).

Although aetiology remains unknown, several aspects such as familial disease clustering, high frequency of other autoimmune disorders in relatives, different phenotypes among race and ethnic groups appear to suggest that genetic factors do play a role in pathogenesis (2-4). Furthermore, SSc-associated polymorphisms have been reported for gene encoding cytokines, cytokine receptors, chemokines, and extracellular proteins (5). Alongside these aspects, it is known that environmental factors (*e.g.* viruses, drugs, vinyl chloride, and silica) may induce clinical phenotypes like SSc (6). Apart from the factors mentioned above, diagnostic criteria and ascertainment methods employed may also affect the results of epidemiological data.

As a consequence, studies on the prevalence and incidence of SSc have given conflicting results. The available data indicate a prevalence ranging from 50 to 300 cases per million/inhabitants and an incidence ranging from 2.3 to 22.8 cases per million/inhabitants/year (7). The largest epidemiology study has been published by Steen and Medsger from the city of Pittsburgh and Allegheny County (8). During this 20-year survey were identified a total annual incidence of 13,9 per million population, with an evident increase (rate doubled) during the second decade especially in women. The Authors justified these observations due to improved detection and medical record techniques over time, although a true increase in the incidence of SSc was even suggested. In Europe, a north-south gradient has been observed (in England 88/million/inhabitants in 2000; in France 158/million/inhabitants in 2001), while an unusually high number of SSc cases (from 3 to 1,000 times greater than expected) have been reported for some limited areas (near London's airports, rural area close to Rome) (9, 10). Little epidemiological data is available from southern Europe and what we do have often comes from heterogeneous ethnic groups in a limited geographical area.

As regards to methodological approach-related variability, the American College of Rheumatology (ACR) 1980 classification criteria for SSc (former ARA criteria) are usually applied for epidemiological purposes, although this set does not include the diagnostic relevance of several other disease markers routinely considered in clinical practice (*i.e.* Raynaud phenomenon, anti-centromeric/topoisomerase I antibodies, capillaroscopic pattern) (11). A decade ago, Le Roy and Medsger Jr. proposed a set of criteria (Le Roy-Medsger criteria) in which naifold capillary findings and autoimmune serology were considered in the diagnosis of multisystem, multistage disorder, marked by variable expression like SSc, with the aim to increase diagnostic sensitivity in the early phases of the disease (12).

The aim of the present study was to investigate the prevalence and the incidence of SSc, considering both ACR criteria and the revised LeRoy-Medsger criteria in a district in north-eastern Italy over a period of 8 years.

Methods

According to the national census estimates of October 2001, the study area (district of Ferrara) has a population of about 346,000 inhabitants. The population is almost entirely Caucasian. Ferrara is the largest town in the district with a population of about 131,000; the remaining rural area has about 215,000 inhabitants. The city of Ferrara has a single 700-bed teaching hospital. Our Department is the only tertiary referral centre for rheumatic diseases and has long had a section dedicated to SSc and other connective tissue diseases.

The SSc patients residing in the study area who were admitted to hospital (to our Rheumatology Unit, other departments in our hospital, to any of the 3 other hospitals of the district, and/or to other Italian hospitals) or referred to our outpatient clinic with a diagnosis of SSc between 1st January 1999 and 31st December 2007 were retrospectively evaluated. Subjects enrolled in the study were identified both by a search for hospital discharge code 710.1, according to the International Classification Disease-9 (ICD-9) codes, and using a computerised search for this disease code (*i.e.* SSc) in the national health care system, including all patients living in the Ferrara district. The subjects referred to our outpatient clinic were identified by dedicated data base. The patients aged 16 years and older, of Caucasian origin and residing in the study area for at least 6 months prior to diagnosis were included in the study. Patients with localised scleroderma (*i.e.* morphea or linear scleroderma) were excluded from the study.

The medical records of each case were accurately examined and reviewed in order to determine whether the patients fulfilled the ACR and LeRoy-Medsger criteria (10, 11). Given the retrospective nature of the study, each patient file was re-evaluated by the same experienced physician and both sets of SSc classification criteria were adopted to define each case. SSc subtypes were classified according to LeRoy *et al.* (13). All patients were assessed for the presence of anti-nuclear antibodies (ANA) by the routine screening of indirect immunofluorescence (IIF) ANA testing using commercial Hep-2 cell lines as a substrate at the initial dilution of 1:80. ANA were considered positive at a dilution of 1:160 or greater. Detection of antibodies to the topoisomerase I-Scl70 antigen was performed using ELISA kits.

Incidence and prevalence of the disease were calculated as number of cases per 100,000 inhabitants.

Results

The demographic and clinical characteristics of SSc patients diagnosed during the study period and residing in the district are showed in Table I. Thirty-eight patients followed in other hospitals within the Ferrara district were re-evaluated following the ACR and LeRoy-Medsger criteria for SSc (11, 12). Diagnosis was retained for only 14 of them; 10 patients had also been followed in our unit and the other 14 did not meet the ACR or LeRoy-Medsger criteria. In conclusion, using the LeRoy-Medsger criteria a total of 118 cases were diagnosed as having SSc while 88 met the ACR diagnostic criteria.

Considering the ACR criteria, the prevalence rate was 25.4 cases per 100,000

Table I. Clinical characteristics of the patients.

Total number of patients	118
Women/men	107/11 (ratio 9.7:1)
Mean age at diagnosis (years)	59.7 (median 62; range 22-83 yrs)
Mean disease duration (months)	124 (median 84, range 5-600)
Skin involvement:	
Limited	20 (19.2%)
Limited cutaneous	76 (62.1%)
Diffuse cutaneous	22 (18.7%)
Intestitial lung disease (ILD)	52 (44%)
Esophageal involvement	89 (75.4%)
Renal involvement	5§ (4%)
Pulmonary hypertension*	3 (without ILD)(2.5%)
Autoantibody:	
ACA	71 (60%9)
Scl-70	24 (20%)
nucleolar	12 (10%)

§one patient with penicillamine-related nephrosic syndrome.
*considering the patients evaluated by echocardiography (cut-off: >40 mmHg) and then by cardiac catheterism.

Table II. SSc epidemiological data reported from different countries.

Authors	Study period	Incidence (pts/100,000/year)	Prevalence (pts/100,000)	Country
Tamaky *et al*.[23]	1988	-	2.1-5.3§	Tokyo (Japan)
Mayes *et al*.[24]	1989-1991	1.9	27.6^	Detroit (US)
Robert-Thomson *et al*.[25]	1993-2002	0.1	2.1^	South Australia
Maricq *et al*.[16]	1989	-	67 to 265†	South Carolina (US)
Le Guern *et al*.[26]	2001	-	15.8°§	Seine-Saint-Denis area- Paris (France)
Silman *et al*.[27]	1988	0.1/0.6	1.3/4.8*§	West Midlands Region (UK)
Allcock *et al*.[28]	2000	-	8.8§	Northeast England
Alamanos *et al*.[29]	1981-2002	0.1	1.5§	Northwest Greece
Valesini *et al*.[9]	1993	-	87.4§	Rural area close to Rome (Italy)
Present study	1999-2007	4.3°(3.2)§	34°(25.4)§	Ferrara (north Italy)
Thompson *et al*.[15]	2002	-	28§	Woodstock-Ontario (Canada)
Valter *et al*.[14]	1997	-	35§†	Estonia
Aias-Nuñez *et al*.[18]	1988-2006	2.3º(1.2)§	27.7º§	Spain
Airò *et al*.[22]	2004	-	33.9º(26.1)§	Valtrompia (north Italy)

†It considering SSC spectrum disorders; *Respectively in males and women; °With Le Roy-Medsger criteria; §With >ACR 1980 criteria; ^Using 1980 ACR criteria for define SSc or by rheumatologist's diagnosis, documented sclerodactyly, and at least 2 other features of CREST syndrome for probable SSc.

inhabitants (95% Confidence Intervals (CI): 22.2–28.6), and the annual incidence rate over the study period was 3.2 per 100,000/inhabitants/year (95% CI: 2.0–4.4;). Considering the LeRoy criteria, prevalence and incidence were respectively 34 cases per 100,000 (95% CI: 30.4–37.8) and 4.3 cases per 100,000/ inhabitants/year (95% CI: 3.0–5.6). The incidence rate was stable without any significant increase over time. The female/male ratio was 9.7:1. The mean age at diagnosis was 59.7 yrs (median 62 yrs; range 23–83 yrs) and the mean disease duration at the time of this study was 124 months (median 84 months; range 5–600). According to the LeRoy criteria, the SSc subsets were as follows: 20 limited-SSc (lSSc, 19.2%), 76 limited cutaneous-SSc (lcSSc, 62.1%), 22 diffuse cutaneous-SSc (dcSSc, 18.7%). During the study period 5 patients died (1 of sepsis, 3 of congestive heart failure all of whom had severe SSc-lung involvement, 1 of small-cell lung cancer). As regards the auto-antibodies profile, anti-centromeric antibodies (ACA) were present in 71 cases (60%), anti-topoisomerase I in 24 (20%), anti-nucleolar in 12 (10%) while the remaining patients were only ANA positive with non-specific IIF pattern. No patient was found free of anti-nuclear antibodies.

Discussion

The discrepancies in epidemiological data for the disease drawn from different geographical areas are profoundly affected by 3 main aspects: genetic background and ethnic features, environmental factors and methodological differences in case ascertainment. Unfortunately, there is a lack of knowledge on the relationship between SSc and each of these points; only hypotheses can be made about how these aspects relate to SSc aetiopathogenesis. This is why there is such great variability in SSc epidemiological data from around the world.

In the available literature the prevalence of SSc ranged from 7 to 489 per million/inhabitants and the incidence from 0.6 to 122 per million/inhabitants per year. Many geographical variations have also been reported, prevalence being higher in the USA (276 per million/inhabitants in 1990) and Australia (233 per million/inhabitants in 1999) than in Japan (38 per million/inhabitants) and Europe; moreover a north-south gradient has been observed (5).

Other discrepancies have also been reported such as the high prevalence (350 per million/inhabitants or 2800 per million when overlapping syndromes SSc sine-scleroderma and undifferentiated connective tissue disease with scleroderma features are included), found in an Eastern European country (Estonia

(14). An unusual prevalence of SSc (3, 5, or 1000 times greater than expected) has been reported in some areas (Ontario, Rome, near London's airports), suggesting particular geographical clustering, although no defined determinants have been identified (9, 10, 15).

In Italy only one study – from a small geographic cluster in a rural area close to Rome – reported a trend in this disease with a prevalence of 489 per million/inhabitants, several times higher than expected (9). Recently, Thompson and Pope described another geographic cluster in Ontario, Canada (15). The Authors reported a prevalence of 28 per 100,000/inhabitants and an even higher prevalence was reported by Maricq *et al*. in a population-based study performed in South Carolina (16). The latter data seem to be in agreement with the recent report by Bernatsky et al. where, on the basis of population-based administrative data, a prevalence of 74.4/100,000 and 13.3/100,000 inhabitants were reported, respectively, in women and men (17). Although it is likely that these discrepancies from different countries reflect methodological variations in case ascertainment, different genetic-ethnic factors and factors related to a specific geographical area (environmental factors) cannot be ruled out.

With regard to case ascertainment, recently some Authors have underscored the relevance of the criteria adopted for the diagnosis of SSc in order to evaluate their influence on epidemiological data. In fact, the ACR criteria formally used for research purposes have poor sensitivity in early diagnosis. Although use of the criteria proposed by LeRoy and Medsger to establish incidence and prevalence could be controversial as they have not yet been validated, these criteria are widely applied in the everyday clinical practice. On the other hand, in recent years, several reports have described patients without skin involvement who have clinical and laboratory aspects consistent with SSc. It would be anachronistic not to apply such useful tools as nailfold capillaroscopy and autoantibody profile, and not only for early diagnosis of a potentially life-threatening disease but also as a prognostic factor (18-21). In the study by Aries-Nuňez *et al*., approximately 40% of the patients did not meet the ACR criteria: this is not surprising given that these criteria were designed for research purposes and thus do not including cases with early or milder forms, or with limited disease (18).

Considering the different criteria, differences in prevalence and incidence rate have been observed. With the ACR criteria the prevalence was 25.4 cases per 100,000/inhabitants and the annual incidence rate over the 8-year study period was 2.7 per 100,000/inhabitants/years. Employing the LeRoy-Medsger criteria prevalence and incidence rose to 34 cases per 100,000/inhabitants and 3.7 cases per 100,000/inhabitants/years. Our data are in agreement with those of Airò *et al*. which showed a prevalence of 33.9 cases per 100,000/inhabitants, in a geographical area in northern Italy, near the Ferrara district. In both studies, higher SSc-prevalence was found using LeRoy-Medsger criteria than the ACR criteria (22). Although the retrospective nature of this study represents one of the major drawback, these data may more faithfully represent the real epidemiology of SSc, as it can include milder forms of the disease which are undoubtedly more frequent.

Notwithstanding the critical issue of the diagnostic criteria adopted, wide variations are reported for the population and/or geographical area considered, and no key determinants are currently known to justify this variability. Apart from genetic aspects, a relationship has been described between higher incidence/prevalence of SSc and different rural areas. In the study reported above, a higher incidence of SSc was observed in small rural communities (Woodstock, Sarnia and Windsor in southwestern Ontario, Canada). In particular a significant cluster was observed in Woodstock (prevalence 28/100,000) without any significant differences in chemical exposure or other environmental factors, thus ruling out the higher number of agricultural industries in this area as compared to the other communities considered (15). Interestingly, even in the present study, about 70% of the population lives in small rural communities. Unfortunately, there has been no previous focus on this topic in Italy, making impossible to compare our observations with other data from the same country.

Another relevant point, that may help explain the recent higher SSc incidence rates, is the rise in physician awareness of this disease which has reduced diagnostic delay, especially for those patients with mild forms of disease (lSSc and lcSSc). Clinical features of these subtypes are often difficult to pinpoint and diagnosis may be underestimated *vs*. the diffuse form of disease. Moreover, improvement in the diagnostic tools and advances in treatment, which improve survival rates, could be another reason for the rise in SSc prevalence in recent years. In spite of these considerations, it is difficult to write off geographical discrepancies in disease prevalence as simply the result of different methodological approaches to case definition or ascertainment; it is highly likely that genetic and ethnic factors as well as exposure to putative environmental triggers also come into play in the development of SSc. In conclusion, SSc is difficult to study epidemiologically because tricky cases may go undiagnosed. Many relevant question are open, in particular whether the epidemiological data and disease expression are similar in all the populations and in all geographic areas. The main challenge remains to determine the scientific basis for the observed differences, distinguishing between changes in ascertainment methods and true changes in disease expression due to genetic and environmental factors.

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