Peer reviewed article

Clinical diagnosis compared to classification criteria in a cohort of 54 patients with systemic sclerosis and associated disorders

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Summary

Objective: To compare clinical diagnosis with two validated classification criteria for systemic sclerosis (SSc) in a cohort of Swiss patients with SSc and associated disorders.

Methods: Charts of 54 patients with SSc and associated disorders were reviewed and compared with data obtained at a thorough clinical examination using a standardised protocol (Raynaud's phenomen [RP], skin involvement, nailfold capillary microscopy and determination of autoantibody pattern).

Results: According to patient records 6 patients had diffuse cutaneous SSc (dcSSc), 23 limited cutaneous SSc (lcSSc) and 20 were not classified. Two patients had mixed connective tissue disease (MCTD) and 3 overlap syndromes. At the time of clinical examination, 7 patients showed dcSSc (6 plus 1 patient originally classified as lcSSc), 26 lcSSc (20 plus 6 originally not classified) and 16 patients had severe RP which was arbitrarily classified as Raynaud's syndrome (RS). 15 of the latter 16 were antinuclear antibody positive and 7 exhibited pathological nailfold capillaries. On the basis of LeRoy and Medsger's criteria, 6 of these patients could be further classified as limited SSc (lSSc). Of 49 sera tested, 14 contained centromere antibodies at clinical examination, 16 Scl-70, 5 RNA-pol, 1 Ku, 12 antibodies with unknown specificity, and one serum was autoantibody negative.

Conclusions: A substantial number of patients with minor cutaneous manifestations do not fulfil ACR classification criteria, though they have typical clinical signs of SSc. Characteristic features in these patients are presence of Raynaud's phenomenon, antinuclear antibodies and pathological changes in nailfold capillary microscopy. Application of the diagnostic criteria recently proposed by LeRoy and Medsger makes it possible to name many of these patients. The use of these criteria is recommended for clinical management.

Key words: systemic sclerosis; scleroderma; cohort; Raynaud's phenomen; nailfold capillary microscopy; antinuclear antibody

Introduction

Systemic sclerosis (SSc) is an autoimmune multisystemic connective tissue disorder characterised by inflammatory and fibrosing processes which result in changes to skin, blood vessels and internal organs such as lung, gut, kidney and heart [1]. According to the extent of skin involvement – proximal or distal of elbows – SSc is classified as diffuse cutaneous (dcSSc) or limited cutaneous (lcSSc) respectively [2]. It is important to note that dcSSc and lcSSc show striking differences in disease evolution kinetics. Whereas in the diffuse cutaneous form visceral involvement may develop within weeks, patients with the limited cutaneous

Abbreviations

ANA	antinuclear antibodies
cm	centromere antibodies
MCTD	mixed connective tissue disease
mRSS	modified Rodnan skin thickness score
dcSSc	diffuse cutaneous systemic sclerosis
lcSSc	limited cutaneous systemic sclerosis
lSSC	limited systemic sclerosis
SSc	systemic sclerosis
RP	Raynaud phenomen
RS	Raynaud's syndrome

No financial support declared.

Table 1

ARA 1980 Classification Criteria [1].

One major or two or more minor criteria have to be fulfilled.
A Major criterion
Proximal scleroderma: thickening, tautness of fingers and the skin proximal of metacarpophalangeal and metatarsophalangeal joints
B Minor criteria
1. Sclerodactyly: thickening, tautness of the skin, limited on fingers
2. Digital pitting scars of fingertips or loss of substance of distal finger pad
3. Bibasilar pulmonary fibrosis

Table 2

2001 LeRoy and Medsger proposed criteria for limited forms of SSc (lSSc) [11].

Raynaud's phenomenon (RP), objectively documented
plus
abnormal widefield nailfold capillaroscopy (consisting of dilatation and/or avascular areas)
or
SSc selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III in a titer of 1:100 or higher)
If RP is subjective only, both SSc capillary pattern and SSc selective autoantibodies (in titre >1:100) are required to define lSSc. lSSc can overlap with other disease.

form typically remain stable for many years, but finally may develop late visceral complications. Correlations between the disease-specific antibodies Scl-70, RNA-pol and centromere antibodies and organ involvement have recently been documented [3, 4]. Patients with Scl-70 antibodies are prone to development of pulmonary fibrosis, RNA-pol antibodies are associated with an increased risk of renal crisis and centromere antibodies with pulmonary hypertension [5, 6].

This study set out to describe a cohort of SSc patients diagnosed and treated at our university centre between 1990–2000 and to compare the data with a recent clinical examination, with a view to verifying clinical diagnosis and fulfilment of ACR classification criteria of 1980 (table 1) [1] and more recently proposed criteria for early systemic sclerosis (table 2) [7].

Patients and methods

All patients diagnosed and treated at the Department of Rheumatology, Clinical Immunology and Allergology of Bern University Hospital between 1990 and 2000 were identified using International Classification of Disease codes (ICD-9: 710.1, 710.8, 710.9 and ICD-10: M34.0, M34.1, M34.8, M34.9). The patient records were checked for correct coding, and thereafter patients were invited to participate in a clinical and laboratory workup programme. In addition we invited patients from the SSc patient organisation to participate in the study. The study protocol was accepted by the local ethical committee and all patients gave written informed consent.

The workup (assessment) included the patient's history, a thorough clinical examination and nailfold-capillaroscopy using a standardised protocol [8]. All patients were examined by RU or JB, supervised by the senior physicians HRZ, MO or PMV.

RP was graded according to an evaluation sheet [9] into grade 0: no Raynaud's; grade 1: probable RP, defined as uniphasique episodes of pallor, cyanosis of fingers, toes or in the face on cold exposure; grade 2: definite RP, defined as episodes of biphasique change of pallor, cyanosis, suffusion on fingers, toes or in the face on cold exposure or at room temperature; grade 3: severe RP, defined as 2 with in addition paraesthesia or numbness.

Skin involvement was documented with the modified Rodnan skin thickness score (mRSS) [10–12]. The score was checked by a senior physician. Other disease-typical skin alterations such as teleangiectasia, melanoderma, calcinosis cutis and finger tip ulcers were recorded. Nailfold capillary microscopy was performed and recorded in a standardised form, and the most profound changes were documented by digital photography [9, 13].

Sera were collected at the time of clinical examinations, stored at –20 ºC and collectively analysed at the Rheumaforschungsinstitut in Aachen/Germany by RM. ANA were analysed and characterised by indirect immunfluorescence on HEp-2-cells [14]. If positive, antigen specificity was determined using immunodiffusion on agarose gels [15, 16], enzyme-immunoassays [17], immunoblot with HeLa-cell extracts [14], line-immunoassays and/or immunoprecipitation tests. The following antigens were analysed: centromeres, Scl-70 (DNA-topoisomerase I), RNA-polymerases, U1-RNP, fibrillarin, Ku, SL and aminoacyl-tRNA synthetases (Jo-1).

Results

102 patients with the diagnosis of SSc (limited cutaneous including CREST syndrome, dcSSc or unspecified SSc) or overlap syndrome were identified by ICD codes and confirmed by patient records. 16 patients (15.7%) had died (8 deaths related to SSc according to patient charts, 6 of these with dcSSc; in 8 cases the cause of death is unknown). 48 patients were able and willing to participate in the study. Reasons not to participate were: living too far away (n = 6), not feeling ill at all (n = 10), not being able to travel (living in nursing home, handicapped, n = 20), opposition by the family doctor (n = 2). 6 patients were recruited from the Swiss patient organisation for SSc. Finally 54 patients were included in the study, 46 female, 9 male (f:m = 5:1), mean age 57.3 years (fig. 1).

In 24 of 48 patient records (44%) the diagno-

sis corresponded to the classification at clinical workup: 6 patients with dcSSc, 13 with lcSSc, 3 with MCTD (mixed connective tissue disease) and 2 with overlap syndromes. 14 cases of unspecified SSc could be allocated to lcSSc, one case with lcSSc had developed into dcSSc according to the patient chart. In summary, we classified 7 patients as dcSSc, and 26 as lcSSc fulfilling 1980 ACR criteria on the examination day. However, 16 patients had severe Raynaud's phenomenon but did not fulfil ACR 1980 classification criteria. Using the criteria proposed in 2001 by LeRoy and Medsger [2], 6 of these 16 patients could be classified as limited SSc (table 3). If reporting of Raynaud's phenomenon was judged to be objective, 16 would have to be classified as lSSc and only 1 remained in the RS group.

When applying the ACR 1980 classification criteria, patients with dcSSc were younger at disease onset compared to lcSSc (47 ± 10 and 50 ± 14 years respectively) and had a shorter disease duration (5 ± 4 and 8, ± 6 years respectively) (table 4). In patients classified as RS the disease onset was latest (mean 55 ± 12 years) and the mean age was highest at the day of workup examination (60 ± 12 years). The mean time lapse between the first visit mentioned in patient charts and assessment was 4 years (range 0–9) for the seven patients classified as dcSSc, 6 years (range 0–21) for the 26 classified as lcSSc and 4 years (range 0–9) for the 16 cases with RP.

The 33 patients fulfilling ACR 1980 criteria reported as first symptoms Raynaud's phenomenon (73%), finger-tip ulcers (42%), oedema of the skin (36%), general stiffness (33%) and arthralgia (26%). The 16 patients with RS mentioned RP (55%), general pain (44%), oedema of the skin (25%), arthralgia (25%) and fatigue (19%) as first symptoms.

The 33 ACR 1980 classified patients showed a mean modified Rodnan skin score of 10 (range 3–28), in dcSSc mean skin score was 19 (range 12-28, SD ± 8), in lcSSc 9 (range 3-16, SD ± 4) with significant differences between these two classification groups (p = 0.015). The 16 patients classified as RS had a mean skin score of 1 (range 0–4, SD ± 1). Six of these latter patients had skin changes such as tightening and/or thickening, sclerodactyly and/or teleangiectasia.

Nailfold capillary microscopy could not be performed in 4 patients due to massive flexion contractures of fingers (3 dcSSc, 1 lcSSc), leaving the results of 50 patients for analysis. No or minor changes were found in 16 patients (9 with RS, 6 lcSSc and 1 overlap syndrome). Avascular fields were present in all cases with dcSSc, but only in 56% of lcSSc and 25% RS patients. Enlarged capillaries were found in 75% of dcSSc, in 56% of lcSSc, and in 50% of RS patients. No correlation could be found between the type and frequency of capillary changes and type of SSc (i.e. dcSSc versus lcSSc).

Figure 1
Flow-chart.

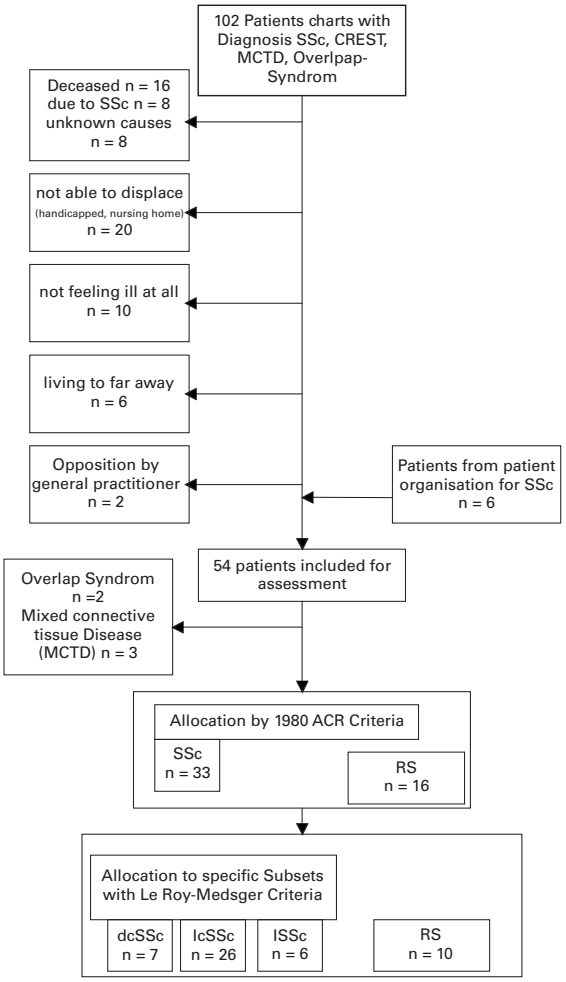

Table 3
Diagnosis at first visit and ACR 1980 respectively.

	Clinical diagnosis in patient records	SSc* Subsets fulfilling ACR 1980 classification at assessment	SSc* Subsets fulfilling "LeRoy/Medsger 2001" classification at assessment
Diffuse cutaneous SSc	6 (3)#	7 (3)#	7(3)#
Limited cutaneous SSc, (incl. CREST-syndrome)	23 (2)#	26 (3)#	26 (3#)
Limited SSc	0 (0)#	0 (0)#	6 (1)#
Not further specified SSc	20 (2)#	0 (0)#	0 (0)#
Raynaud's Syndrome	0 (0)#	16 (1)#	10 (0)#
Mixed connective tissue disease (MCTD)	3 (0)#	3 (0)#	3(0)#
Overlap syndrome	2 (2)#	2 (2)#	2(2)#
TOTAL	54 (9)#	54 (9)#	54 (9)#

"LeRoy/Medsger 2001" Classification at follow-up * SSc: Systemic sclerosis, # in brackets: men

Table 4

Characteristics of patients with Raynaud syndrome (RS), limited cutaneous systemic sclerosis (lcSSc) or diffuse cutaneous systemic sclerosis (dcSSc) fulfilling the ACR 1980 classification at assessment. Number of patients with different autoantibodies.

	RS (n = 16)	lcSSc (n = 26)	dcSSc (n = 7)
Female : male	5.5:1	12:1	1,3:1
Age at disease onset (yr)	55 + 12	50 + 14	47 + 10
Range (yr)	32-72	11-71	27-56
Age at the examination day (yr)	60 + 12	59 + 12	52 + 21
Range (yr)	37-77	21-80	38-57
Disease duration (yr)	6 + 3	8+ 5	5 + 4
Range (yr)	0-11	0-25	0-11
Anti-Scl-70	2	8	6
Anti-centromere	8	5	1*
Anti-RNA polymerase	3	2	0
Anti-Ku	0	1	0
Unidentified autoantibodies	2	9	1
ANA negativ	1	1	0

*1 patient with dcSSc had anticentromere and anti-scl-70 antibodies.

Sera of 49 patients were analysed for the presence and specificity of autoantibodies. In 47 cases ANA were present. The following specificities were found: Scl-70 in 16 cases, centromere in 14, RNA-Pol in 5 and Ku in 1 patient. In 12 sera ANA of unknown specificity were detected and one serum did not contain detectable ANA.

Discussion

The main finding of this study was the identification of a substantial number of SSc patients presenting with RP and typical clinical findings of SSc, but without or with very limited skin involvement. These patients do not fulfil the ACR classification criteria of 1980 but the more recent classification criteria proposed by LeRoy and Medsger [7].

The ACR criteria of 1980 were designed to be highly specific but, as a consequence, their sensitivity is rather low. It is remarkable that the original publication mentions the dilemma regarding patients with Raynaud's phenomenon and sclerodactyly [1]. A retrospective analysis of two large cohorts revealed that 41% and 66% respectively of lcSSc did not meet ACR criteria, but they were nevertheless classified as SSc [18]. These figures correspond to the percentage of patients with RS in our cohort. In agreement with this interpretation, our RS patients display a high percentage of other typical SSc features such as presence of antinuclear antibodies, abnormalities in nailfold capillaries or sclerodactyly as a typical skin manifestation.

Nothing is known about the long-term prognosis of this minor variant of SSc patients. The fact that certain autoantibodies correlated with severe visceral involvement were also found in this subset of SSc patients raises concern about the prognosis (two patients with Scl-70, three with RNA-polymerase autoantibodies). Prospective monitoring of these patients should show whether these RS patients represent a true "minor" variant of SSc and whether autoantibodies have a higher prognostic value than skin involvement.

The literature describes a variety of pathognomonic changes in nailfold capillaroscopy, such as avascular areas, enlarged capillaries and loss of capillaries [18, 19]. The differences in percentages of these capillary changes in relation to type of SSc implied diagnostic information. However, they did not reach statistical significance in our cohort. It appears likely that this was due to the limited number of subjects. It would be helpful if the quality or quantity of such changes correlated with disease activity or predicted progress. So far only two publications have addressed this issue [20, 21]. However, the number of patients in these cohorts was too limited to allow calculations of predictive values. Such clinically important issues should be addressed by large patient cohorts such as the recently developed EUSTAR registry [28].

The fact that only 60% of candidates could be recruited for a follow-up examination raises the question whether our cohort is representative for the Swiss SSc population. Several recent publications on the prevalence of SSc in European countries are available for comparison [22–27]. It is notable that the estimated prevalence in Switzerland is similar to the numbers published for other countries. Other academic centres had comparable drop-out rates (26%) for follow-up examinations [26], in part due to the disease-related death of approximately 30% of patients [22]. Furthermore, comparison of patient characteristics revealed very similar data in the largest European

cohort as regards age and disease duration [22]. The f:m ratios in other studies varied between 3:1 and 7.8:1 [22, 23, 26]. Mean disease duration in patients with dcSSc was shorter than in patients with lcSSc (5.4 and 8.5 years respectively). Collectively it appears likely that the patient characteristics of our cohort can be considered representative for this country.

In conclusion, our results support the notion that the new classification criteria of LeRoy and Medsger are more suitable for everyday clinical practice than the ACR 1980 criteria. Even if these criteria are rigidly applied (e.g. in demanding a proven Raynaud's phenomenon), SSc as the connective tissue disorder with the worst prognosis will probably remain underdiagnosed. Clues for early diagnosis are the presence of antinuclear antibodies and nailfold capillary changes.

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