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The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement

N. Hunzelmann[1], E. Genth[2], T. Krieg[1], W. Lehmacher[3], I. Melchers[4], M. Meurer[5], P. Moinzadeh[1], U. Müller-Ladner[6], C. Pfeiffer[5], G. Riemekasten[7], E. Schulze-Lohoff[8], C. Sunderkoetter[9], M. Weber[8], M. Worm[10], P. Klaus[10], A. Rubbert[11], K. Steinbrink[12], B. Grundt[12], R. Hein[13], K. Scharffetter-Kochanek[14], R. Hinrichs[14], K. Walker[14], R.-M. Szeimies[15], S. Karrer[15], A. Müller[16], C. Seitz[17], E. Schmidt[17], P. Lehmann[18], I. Foeldvári[19], F. Reichenberger[20], W. L. Gross[21], A. Kuhn[22], M. Haust[22], K. Reich[23], M. Böhm[9], P. Saar[16], G. Fierlbeck[24], I. Kötter[25], H.-M. Lorenz[26], N. Blank[26], K. Gräfenstein[27], A. Juche[27], E. Aberer[28], G. Bali[28], C. Fiehn[29], R. Stadler[30] and V. Bartels[30]

Objective. Systemic sclerosis (SSc) is a rare, heterogeneous disease, which affects different organs and therefore requires interdisciplinary diagnostic and therapeutic management. To improve the detection and follow-up of patients presenting with different disease manifestations, an interdisciplinary registry was founded with contributions from different subspecialties involved in the care of patients with SSc.

Methods. A questionnaire was developed to collect a core set of clinical data to determine the current disease status. Patients were grouped into five descriptive disease subsets, i.e. lcSSc, dcSSc, SSc sine scleroderma, overlap-syndrome and UCTD with scleroderma features.

Results. Of the 1483 patients, 45.5% of patients had lcSSc and 32.7% dcSSc. Overlap syndrome was diagnosed in 10.9% of patients, while 8.8% had an undifferentiated form. SSc sine scleroderma was present in 1.5% of patients. Organ involvement was markedly different between subsets; pulmonary fibrosis for instance was significantly more frequent in dcSSc (56.1%) than in overlap syndrome (30.6%) or lcSSc (20.8%). Pulmonary hypertension was more common in dcSSc (18.5%) compared with lcSSc (14.9%), overlap syndrome (8.2%) and undifferentiated disease (4.1%). Musculoskeletal involvement was typical for overlap syndromes (67.6%). A family history of rheumatic disease was reported in 17.2% of patients and was associated with early disease onset ($P < 0.005$).

Conclusion. In this nationwide register, a descriptive classification of patients with disease manifestations characteristic of SSc in five groups allows to include a broader spectrum of patients with features of SSc.

Key words: Systemic sclerosis, Scleroderma, Connective tissue disease, Overlap syndrome, Undifferentiated disease.

[1]Department of Dermatology and Venerology, University of Cologne, Cologne, [2]Department of Rheumatology, University of Aachen, Aachen, [3]Institute of Biostatistics, Informatics and Epidemiology, University of Cologne, Cologne, [4]Clinical Research Unit for Rheumatology, University Medical Center Freiburg, Freiburg, [5]Department of Dermatology, Dresden University Hospital, Dresden, [6]Department of Rheumatology and Clinical Immunology, Kerckhoff Clinic, Bad Nauheim, [7]Rheumatology and Clinical Immunology, Charité, Berlin, [8]Hospital Cologne-Merheim, Medical Clinic I, [9]Department of Dermatology, University of Münster, Münster, [10]Department of Dermatology, Venerology and Allergology, University Hospital Charité, Berlin, [11]Department of Rheumatology, University of Cologne, Cologne, [12]Department of Dermatology, University of Mainz, Mainz, [13]Department of Dermatology and Allergology, University of Munich, Munich, [14]Department of Dermatology and Allergology, University of Ulm, Ulm, [15]Department of Dermatology, [16]Department of Internal Medicine, University of Regensburg, Regensburg, [17]Department of Internal Medicine, University of Regensburg, Regensburg, [18]Department of Dermatology, Allergology and Environmental Medicine, Private University Witten-Herdecke, HELIOS Klinikum Wuppertal, Wuppertal, [19]Hospital Eilbek, Hamburg, [20]Department of Internal Medicine, University of Giessen, Giessen, [21]Clinic for Rheumatology, Bad Bramstedt, [22]Department of Dermatology, University of Düsseldorf, Düsseldorf, [23]Department of Dermatology and Venerology,Georg-August-University of Göttingen, Göttingen, [24]Department of Dermatology, University of Tübingen, Tübingen, [25]Department of Internal Medicine, University of Tübingen, Tübingen, [26]Department of Internal Medicine, University of Heidelberg, Heidelberg, [27]Johanniter Hospital in Fläming gGmbH, Center of Rheumatology of Brandenburg, Germany, [28]Department of Dermatology and Venerology, University of Graz, Graz, Austria, [29]Department of Internal Medicine, Center of Rheumatology, Baden-Baden and [30]Department of Dermatology, Clinic of Minden, Minden, Germany.

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Correspondence to: N. Hunzelmann, Department of Dermatology and Venerology, University of Cologne, Kerpener Str. 62, 50924 Cologne, Germany. E-mail: Sklerodermie-Netzwerk@uk-koeln.de

Introduction

Systemic sclerosis (SSc) is a rare, multisystem disease showing a large individual variability in the extent of skin and organ involvement as well as in disease progression and prognosis. SSc is predominantly a female-oriented disease with reported female to male ratios between 3 : 1 and 6 : 1, most likely influenced by ethnical and regional factors [1–6]. The annual incidence was estimated to range between 0.6 and 19 cases per million populations, depending on methodological differences in case definition and ascertainment, the time period, different genetic and ethnic backgrounds. Accordingly, reported prevalence rates were reported between 4 and 242 cases per million populations [5, 7–11]. It has also been reported that SSc occurs significantly more frequent in families with SSc than in the general population. As of yet, the strongest risk factor identified for SSc is a positive family history of SSc. However, the absolute risk for each family member remains rather low (<1%) [12]. SSc is associated with a markedly increased mortality, depending on racial differences, presence and severity of internal organ involvement, age at diagnosis and gender [5]. Thus, the reported 5 yr survival rates vary considerable between 50% and 80% [8, 13].

In 1980, the ACR published preliminary classification criteria showing a 97% sensitivity and 98% specificity for SSc to classify patients with established disease [14]. During recent years, a descriptive sub-classification of lcSSc *vs* dcSSc, based on a number of clinical characteristics elaborated by Le Roy *et al.* [15], has been widely accepted and used in clinical practice. However, none of these classifications are satisfactory for daily clinical practice. For instance, a subset of patients presents with virtually no scleroderma, but has RP, pulmonary hypertension or other

scleroderma features as well as ACAs or other scleroderma-associated autoantibodies. This subset has been described as SSc (scleroderma) sine scleroderma [16, 17]. Also, a significant number of patients belong to a subgroup with symptoms of SSc occurring simultaneously with those of other CTDs like myositis, SS or lupus erythematodes. These patients are often classified as scleroderma overlap syndrome and are characterized by typical autoantibodies, e.g. most frequently anti-U1-RNP- or anti-PmScl-antibodies [18]. Furthermore, due to improved health care and activity of patients' associations, patients present earlier in the course of the disease with symptoms suggestive of, but not conclusive for a diagnosis of definite SSc, e.g. RP and scleroderma-specific ANAs; these symptoms have been described as UCTD [19, 20].

To date, there exist no data on the occurrence of these additional disease subsets in a large population. In order to improve clinical care and to develop recommendations for the diagnosis and treatment of SSc, the German Network for Systemic Scleroderma (DNSS) was established in October 2003, funded by the German Federal Ministry of Education and Research (BMBF). A core activity of this network is a patient registry that comprises centres in all parts of Germany as well as one centre in Graz (Austria). A major goal of the network was to ensure acquisition of patients with different disease presentations and clinical variants of this heterogenous disease. This goal was not only facilitated by a country-wide network, but also by cooperation of different subspecialties being primarily involved in the care of patients with SSc in Germany, i.e. rheumatologists, dermatologists, pulmonologists and nephrologists.

This report is a large cross-sectional analysis of SSc disease subsets extending over the classification of Le Roy on a nationwide basis. The data presented herein strongly indicate that an improved classification is needed. Together with international registries such as EULAR Scleroderma Trials and Research (EUSTAR) [21], the data form a basis for clinical trials and evidence-based recommendations for diagnosis and therapy.

Patients and methods

The DNSS was founded in October 2003 on a grant by the BMBF. The network is based on different subspecialties consisting of dermatologists, rheumatologists, pulmonologists and nephrologists from altogether 27 centres. Among these, 10 are rheumatological centres (Aachen, Bad Bramstedt, Baden-Baden, Bad Nauheim, Berlin, Freiburg, Hamburg, Heidelberg, Regensburg and Treuenbrietzen), 12 are dermatological centres (Berlin, Dresden, Göttingen, Cologne, Mainz, Minden, Munich, Münster, Regensburg, Ulm, Wuppertal and Würzburg) and in two centres the Departments of Dermatology and Rheumatology jointly register their patients (Düsseldorf and Tübingen). In addition, a pulmonary centre each in Giessen and Graz, and a nephrological centre in Cologne-Merheim took part, adding their expertise with regard to the specific complications of pulmonary or renal involvement of SSc.

The ethics committee of the coordinating centre, i.e. the Cologne University Hospital, gave a positive vote on a patient information and consent form for the registry. On the basis of this document, informed patient consent as well as the approval of the local ethics committees in all participating centres was obtained prior to registering patients. By April 2007, more than 1483 SSc patients had been registered.

In 2003, a disease- and organ-specific questionnaire was designed with the consent of all network members, including information on gender, date of birth, height, weight, family history for inflammatory rheumatic disease signs and symptoms of organ involvement of skin, heart, lung, gastrointestinal tract, kidney, musculoskeletal system, nervous system and characteristic laboratory data such as ANA.

Two reference documents were prepared to ensure consistency of registered patients' data in the network centres. These documents included definitions of questionnaire items and recommendations for diagnostic procedures.

Organ involvement was defined as follows: RP was characterized by recurrent spasms of small digital arterioles/arteries at fingers and toes, usually triggered by cold and emotional stress. Clinically a sudden pallor of individual digits was followed by reactive hyperaemia, in severe cases also by cyanosis [22]. Age at RP onset was considered to be the age at which this symptom appears. We defined the first non-RP onset as the time/age when the first skin changes (puffy fingers, sclerodactily, truncal scleroderma) developed and the second non-RP onset as the time/age at which first organ lesions occurred. All registered patients were asked for the date/age when RP, skin changes and organ manifestations were noticed/diagnosed.

Skin involvement was evaluated using the Rodnan skin score that assesses the skin thickness by clinical palpation of 17 body areas on a scale of 0–3 [23, 24]. Thickening and fibrosis of the skin as one of the first recognized phenomenon in SSc still forms the basis of most classification criteria and proposed subsets of the disease [15, 25, 26]. With respect to these symptoms the participants of the centres were trained several times by meetings of the network or EUSTAR-organized Rodnan skin score courses (Budapest, January 2005; Bad Nauheim, January 2007) to ensure standardized and correct performance of skin scoring within the network.

Digital tip ischaemia was associated with digital pitting scars, ulcerations or gangrene, or both.

Pulmonary manifestation was established, when pulmonary interstitial fibrosis and/or isolated pulmonary hypertension were found. *Isolated pulmonary hypertension* was defined as clinical evidence of right heart failure and/or increased mean pulmonary arterial pressure (PAPm >25 mmHg at rest or PAPm >30 mmHg during exercise) as determined by right heart catheterization. In addition, an estimated right ventricular systolic pressure (RVSP) >40 mmHg as determined by echocardiography was used to define likely PAH. Patients with dyspnoea [New York Heart Association (NYHA) Grade II and upwards] show often isolated impairments of carbon monoxide transfer factor (TLCO) with $<75\%$ of the predictive values with the forced vital capacity $<80\%$. *Pulmonary interstitial fibrosis* was defined as SSc associated, when other possible causes of lung fibrosis were excluded and bilateral fibrosis confirmed by chest X-ray, high-resolution CT scan and/or restrictive pulmonary abnormalities on pulmonary function tests (TLC $<80\%$) were found.

Gastrointestinal involvement was defined as gastrointestinal motility disturbance, dysphagia, nausea, malabsorption, oesophageal stenosis, gastro-oesophageal reflux or intestinal pseudo-obstruction. *Oesophageal dysphagia and reflux* were suggested by subjective symptoms like not able to swallow liquid or hard food as well as intermittent heart burn and by the oesophageal manometric examination and gastroscopy.

Kidney involvement was defined as the presence of renal insufficiency encompassing renal insufficiency due to acute renal crisis (age-related creatinine clearance <80 ml/min). For the diagnosis of proteinuria we used a urine microelectrophoresis that indicated very early disturbances in the renal filter function (albuminuria ≥ 30 mg/24 h or ≥ 20 mg/l; proteinuria ≥ 300 mg/24 h or ≥ 200 mg/l).

Cardiac disease was defined as one of the following: palpitations, conduction disturbance and diastolic dysfunction on the echocardiogram.

Skeletal muscle disease was defined as proximal muscle weakness or atrophy recorded on clinical evaluation and raised serum muscle enzyme levels. The item musculoskeletal system (Table 2) summarizes musculoskeletal involvement (with muscle weakness, atrophia and CK elevation) as well as articular involvement (with synovitis, joint contractures).

Articular involvement was defined as synovitis with swelling, with or without tenderness to palpation, in one or more joints. We also recorded any kind of joint contracture (limitation in active as well as passive movements) or tendon friction rubs. Nervous system involvement was defined as trigeminal neuralgia, carpal tunnel syndrome or polyneuropathy. Sicca symptoms were defined as decreased secretion of one or more adenoids and the masticatory organ was characterized by microstomia, defined as obvious decreased mouth opening clearly detected by the investigators due to the disease and/or fibrosis of the lingual frenulum.

To ensure the detection of disease heterogeneity, the registry defined additional distinct subsets apart from lcSSc and dcSSc, i.e. overlap syndrome, UCTD with features of scleroderma and SSc sine scleroderma.

The dcSSc was defined as a progressive form with an early onset of RP, usually within 1 yr of onset of skin changes. This subset is characterized by rapid involvement of trunk, face, proximal and distal extremities. Very frequently, anti-Scl 70 (anti-topoisomerase-I) antibodies are present [15].

The lcSSc was defined by skin affection of the extremities distal to the knee and elbow joints, facial skin and occurrence of RP. These patients often (50–70%) have ACAs [15].

Overlap syndrome was defined as a disease occurring with clinical aspects of SSc (according to the ACR criteria) or main symptoms of SSc simultaneously with those of other CTDs/other autoimmune diseases such as dermatomyositis, SS or lupus erythematodes. These patients are mostly positive for anti-U1-RNP- or anti-PmScl-antibodies [18].

Sclerosis (scleroderma) sine scleroderma was defined by a positive RP, no skin alterations, pulmonary arterial hypertension (PAH), cardiac, pulmonary and gastrointestinal involvement [16, 17, 26].

Undifferentiated SSc was defined as positive RP (at least bicolour) and at least one further feature of SSc (typical nail-fold capillary alterations, puffy fingers, pulmonary hypertension) and/or detectable scleroderma-specific autoantibodies without fulfilling the ACR criteria for SSc [19, 20].

Data recording and statistical analyses

The DNSS maintains a centralized online patient registry that includes all SSc-patient data in a standardized four-page DNSS questionnaire. The Central Office for Coordination (CoC) was set up at the Department of Dermatology and Venerology at the University of Cologne and acts as data manager. The DNSS cooperates closely with the Cologne Center for Clinical Studies (KKSK) that developed a DNSS online patient registry using the MACRO software for Clinical Trials (Infermed Ltd., London). Seven clinical centres currently use the option to register their patients online. The remaining centres perform their registrations on paper and send the filled-in questionnaires to the central office for coordination, where the registration forms are validated and entered into the online registry.

The analysis is a cross-sectional study. The data were statistically analysed using Microsoft Office Excel 2003 and SPSS 14.0 for Windows for tabular and graphic representation. Statistical evaluation was performed using contingency table tests (χ^2-test or Fisher's exact t-test) to describe significant differences or associations. When multiple tests were performed, only P-values <0.0001 are mentioned. Bivariate analysis was performed for comparison of subtypes. For most data sets, $<2\%$ of data were missing (Table 2). However, in some sets the percentage of missing data is higher, e.g. family case history, masticatory organ, DLCO. This is largely due to the fact that these parameters were added to the questionnaire after the registry was initiated.

Results

As of February 2007, a total of 1483 patients had been enrolled in the registry. The female to male ratio was 5:1. The mean age was 55.7 ± 13.7 yrs (±S.D.). On average, female patients 56.1 ± 13.9 yrs were older than male 53.9 ± 12.4 yrs patients. A family history of rheumatic diseases was reported by 17.2% of all patients (Table 1) and was significantly associated with a lower mean age and earlier disease onset of RP, skin involvement and internal organ involvement (Fig. 1).

A detailed analysis of age at disease onset, skin and organ involvement for the different disease subsets is shown in Table 1.

Disease presentation in different subsets

The frequency of the disease subsets is shown in Table 2. The most frequent subset was the limited cutaneous form (45.5%), followed by the diffuse cutaneous type (32.7%), overlap syndrome (10.9%) and undifferentiated form (8.8%). SSc sine scleroderma was found in 1.5% of all registered patients. The description of skin involvement in patients characterized as sclerosis sine scleroderma represents the presence of puffy fingers and not sclerodactily. However, due to the low frequency in the registry, this subset was excluded from further statistical analysis. The female to male ratio ranged from 3.2 : 1 in dcSSc to 7.2 : 1 in lcSSc and was around 5 : 1 in overlap syndrome and the undifferentiated subset.

The time interval between the onset of the RP and skin and internal organ involvement varied significantly between disease subsets (Fig. 2), being shortest for the dcSSc variant and longest for the lcSSc disease variant. On average, skin involvement preceded internal organ involvement in all subsets.

Organ involvement for the different disease subsets is shown in Fig. 3. Here, the dcSSc subset shows the highest frequencies for pulmonary fibrosis, pulmonary hypertension, kidney and heart involvement. Kidney involvement was more common in the diffuse subset ($P < 0.001$), but did not reach the level of significance ($P < 0.0001$). Clinically prominent symptoms as digital ulcers, joint contractures, proteinuria, conduction blocks and restrictive pulmonary function were also most frequent in the dcSSc subset. In contrast, gastrointestinal involvement did not show significant differences between the subsets of dcSSc, lcSSc and overlap syndrome.

Pulmonary fibrosis had a frequency of 56.1% in dcSSc compared with 30.6% in overlap syndrome and 20.8% in lcSSc. Pulmonary hypertension was also most frequent with 18.5% in

TABLE 1. Distribution of age, onset of organ involvement and disease subsets

	Age (yrs)	Age at RP onset (yrs)	Age at skin involvement (yrs)	Age at organ involvement (yrs)
Total	55.7 ± 13.7	44.3 ± 15.6	47.9 ± 14.4	50.3 ± 14.2
Family case history	53.7 ± 13.0	41.5 ± 15.4	46.1 ± 14.0	47.9 ± 13.6
Female	56.0 ± 13.9	44.2 ± 15.8	48.1 ± 14.6	50.5 ± 14.5
Male	53.9 ± 12.4	45.1 ± 14.6	47.0 ± 13.4	49.1 ± 12.4
Overlap-S.	50.9 ± 13.5	40.5 ± 15.7	43.6 ± 15.5	45.0 ± 14.6
Undiff. Scl.	54.7 ± 12.5	46.8 ± 14.6	49.6 ± 12.5	50.9 ± 13.3
Scl. sine Scl.	54.1 ± 15.8	42.7 ± 14.9	48.1 ± 14.3	48.2 ± 16.0
dcssc	54.1 ± 14.1	44.5 ± 15.2	46.4 ± 14.3	48.6 ± 14.3
lcSSc	58.5 ± 12.7	44.7 ± 15.8	49.9 ± 14.0	52.2 ± 13.7

Values expressed as mean ± S.D. Overlap-S: Overlap syndrome; Undiff. Scl: Undifferentiated scleroderma; Scl. sine Scl.: sclerosis (scleroderma) sine scleroderma; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis.

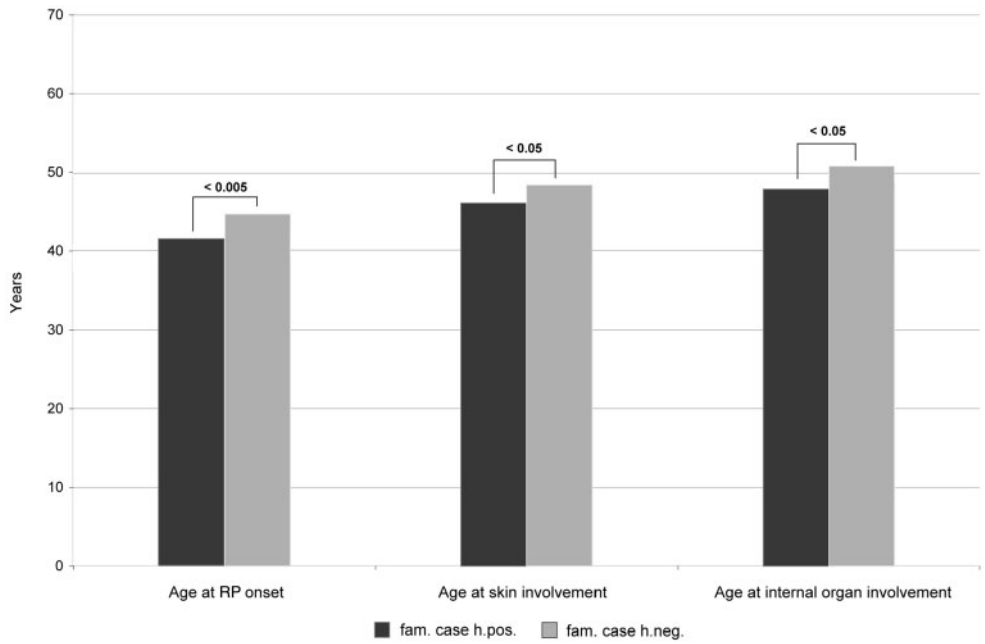

FIG. 1. Mean ages of RP onset and organ involvement by family history.

TABLE 2. Patient characteristics

	Total	Missing data	lcSSc	dcSSc	Overlap-S.	Undiff. Scl.	Scl. sine Scl.
Number of patients, *n* (%)	1483 (100)	0 (0)	674 (45.5)	484 (32.7)	162 (10.9)	130 (8.8)	22 (1.5)
Female	83.4	0.2	87.8	76.1	84.2	84.3	90.9
Male	16.4	0.2	12.2	23.9	15.8	15.7	9.1
Family case history	17.2	19.8	20.2	23.5	25.8	24.1	18.8
ANA positive	90.4	1	92.9	93.9	95.2	83.5	95
Scl 70 positive	27.6	1.2	16.2	55.8	15.1	10.7	40
ACA positive	36.4	1	61.5	11.2	16.4	34.7	35
SSc-associated antibodies	32.5	1	27.6	31.6	68.5	35.5	30
Elevated acute-phase reactants (>30 mm/h)	15.9	16.3	13.4	17.8	14.8	17.7	4.5
Percentage of organ involvement by SSc subsets							
RP	94.4	0.1	96.3	94.2	95.9	89.3	95.5
Skin involvement	87.8	0.3	91.5	97.6	82.3	60	63.6
PAH	15.8	0.1	14.9	18.5	8.2	4.1	13.6
Pulmonary fibrosis	34.5	0.1	20.8	56.1	30.6	18.2	59.1
Oesophagus	60	0.1	59.2	69.3	61.2	35.5	72.7
Stomach	14.2	0.2	15.3	15.6	14.3	8.3	27.3
Intestine	5.7	0.2	6.1	5.3	5.4	7.4	18.2
Kidney	10.5	0.2	9.1	15.9	6.1	8.3	22.7
Heart	14.6	0.2	12	23	10.2	8.3	13.6
Musculoskeletal system	47.5	1.4	44.9	56.6	67.6	44.6	45.5
Nervous system	6.4	2.2	4.1	7.1	10.3	6.6	4.5
Sicca-symptoms	39.5	2.5	43.5	39.7	38.9	43.3	45.5
Masticatory organ	24.1	7.2	23.7	34.1	24.4	18.5	15
Percentage of present symptoms by SSc subsets							
Digital ulcers	24.4	2.2	23.8	34.4	21.2	9.9	33.3
Synovitis	15.1	3.4	11.7	19.2	22.7	14.9	33.3
Joint contractures	26.1	3	22.6	39.7	21.8	15.7	22.2
Tendon friction rubs	8.3	3.2	6.6	13.1	9.9	8.3	27.8
CK elevation	9.2	2.8	5.5	12.1	22.8	6.7	11.1
Muscle weakness	27.7	2	24.7	33.5	40.4	22.3	33.3
Muscle atrophy	16.9	3	14.3	21.4	25.4	9.1	16.7
Dysphagia, reflux	60.4	1.9	60.8	69.2	63	43	61.1
Satiety, nausea	16.5	3.6	17.9	16.4	20.6	19.8	33.3
Diarrhoea, constipation	24.2	3.6	27.2	25.2	22.1	32.2	35.3
Hypertension	24	2.2	28.2	24.5	19.9	29.8	38.9
Renal insufficiency	13.7	2.6	16.5	15.6	8.3	8.3	22.2
Proteinuria	9.5	3.1	8.9	15.2	9.7	6.7	11.1
Dyspnoea	31.2	2	32	40.4	23.3	18.2	50
Palpitations	22.3	2.8	23.1	20.1	21.5	23.1	27.8
Conduction block	12.9	2.6	10.8	19.2	10.3	8.3	16.7
Diastolic dysfunction	14.1	3.4	14.9	19	9.1	8.3	17.6
Lung restrictive disease	23.7	2.8	16.1	40.7	18.6	10	33.3
Polyneuropathy	8	4.9	6.8	8	8.8	5.9	0
Trigeminal neuralgia	1.6	4.7	1.1	2.6	1.5	1.7	0
DLCO (≤ 75%	24.8	51.9	23.6	31.4	21	10.8	9.1
mRSS (mean ± S.D.)	9.2 ± 9.2	13.1	6.9 ± 6.2	15.2 ± 10.9	6.9 ± 7.9	2.7 ± 4.3	0.6 ± 0.8

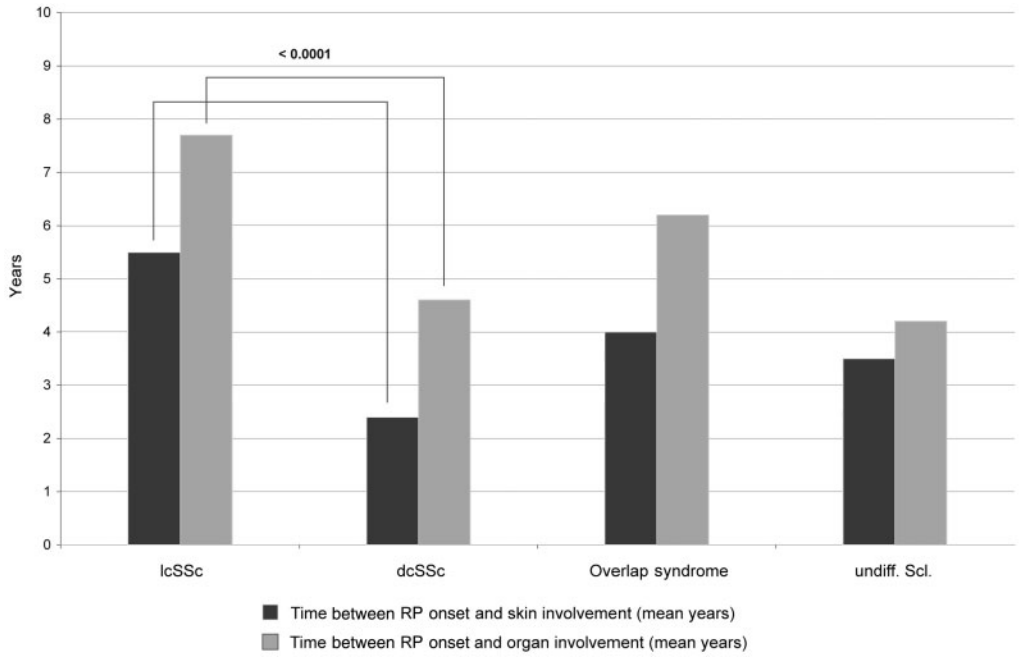

FIG. 2. Mean time interval between RP onset and organ involvement by disease.

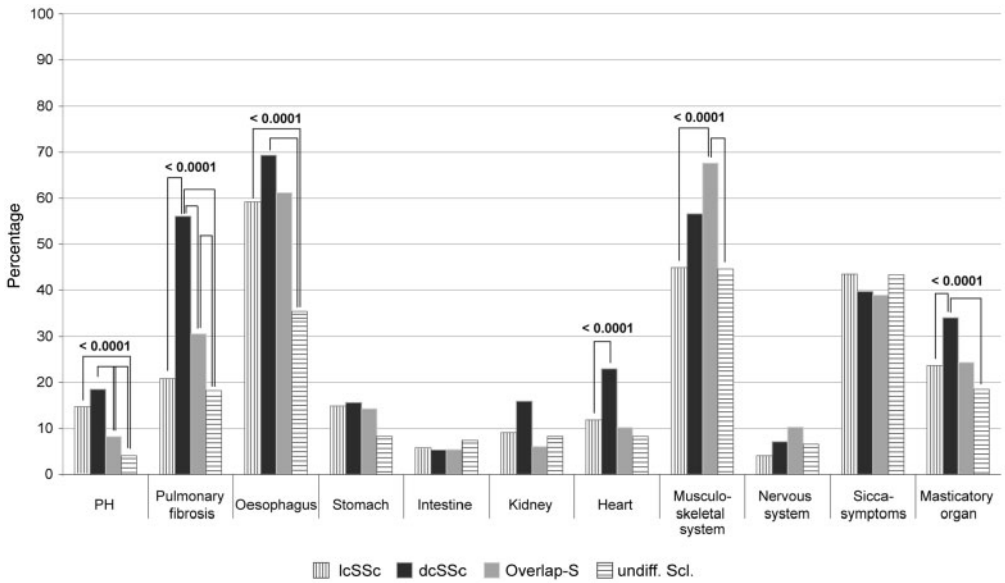

FIG. 3. Relative frequency of organ involvement by different subsets.

dcSSc compared with 14.9% in lcSSc and 8.2% in overlap syndrome. A finding of interest was a substantial proportion of patients with isolated pulmonary hypertension without lung fibrosis both in the dcSSc and lcSSc subsets (27.7% *vs* 60%; $P < 0.001$).

Digital ulcers were reported most frequently in the dcSSc subset (34.4%), but also to a significant degree in overlap syndrome patients (21.2%). Oral involvement was reported in 34.1% of patients with dcSSc and in 23.7% of patients with lcSSc. Involvement of the nervous system presenting as polyneuropathy was reported in 6–8% of patients with no difference between subsets. Trigeminal neuralgia was reported in percentages around 1–3% for all subsets.

Musculoskeletal symptoms were most prominent in patients with overlap syndrome, with signs such as CK elevation and synovitis being more frequent when compared with other subsets ($P < 0.0001$). CK elevation was reported significantly more often in 22.8% of overlap syndrome patients compared with 12.1% in the dcSSc subset and 5.5% in the lcSSc subset ($P < 0.0001$), respectively.

Differences between medical subspecialties

Different disease characteristics and different disease subsets may determine which specialist provides primary care to the patient, e.g. rheumatologist or dermatologist. Interestingly, regarding the four major subsets a significant difference in subset frequency was only found for the overlap syndrome. Overlap syndrome, which is usually characterized by prominent musculoskeletal involvement, was more frequently diagnosed in rheumatological centres

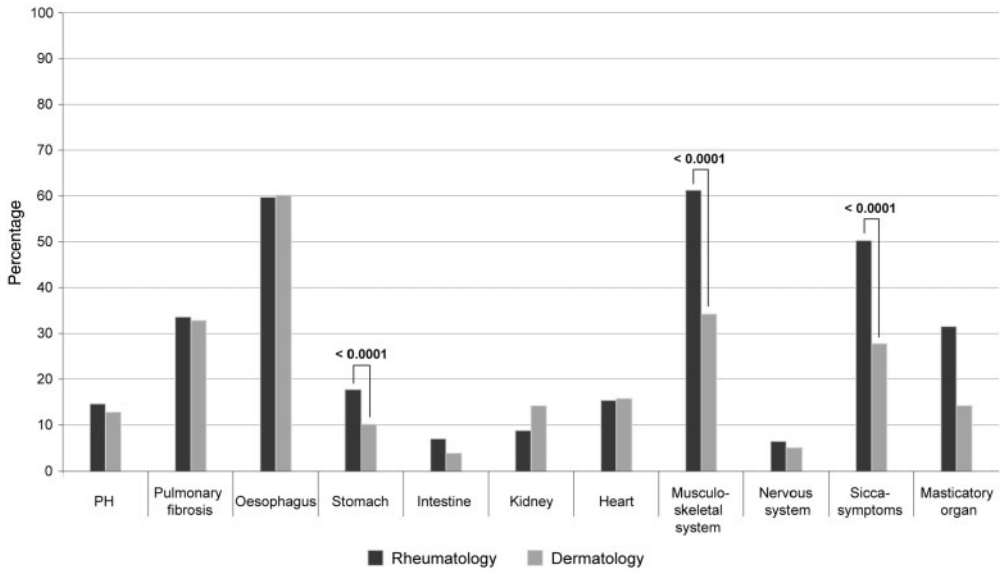

FIG. 4. Relative frequency of organ involvement of SSc patients in dermatological and rheumatological centres.

($P < 0.01$). The frequency of dcSSc and lcSSc in the two specialties showed no significant difference.

Results of the analysis of organ involvement and symptoms of patients presenting to rheumatological or dermatological clinics are shown in Fig. 4. Symptoms indicating prominent involvement of the musculoskeletal system (including joint contractures, synovitis, muscle weakness and atrophy) were more prevalent in rheumatological centres ($P < 0.001$). This was also found for subjective symptoms such as sicca complaints, palpitations and signs such as diastolic dysfunction or arterial hypertension. Digital ulcers were equally prevalent in dermatological vs rheumatological centres (25.5% *vs* 23.8%; $P < 0.05$).

In contrast, pulmonary fibrosis, pulmonary hypertension, conduction blocks or digital ulcers were equally prevalent in rheumatological and dermatological centres.

Discussion

SSc is characterized by a remarkable disease heterogeneity in organ involvement, severity and prognosis. The 1980 ACR criteria were established to classify patients with definite disease. In clinical practice, the classification of lcSSc *vs* dcSSc [15] is nowadays widely used. However, a significant number of patients belongs to subgroups, which do not fit into this classification, e.g. who are presenting with symptoms of SSc occurring simultaneously with symptoms of other CTDs such as myositis, SS or lupus erythematodes. These patients have been classified as scleroderma overlap syndrome being characterized by typical autoantibodies, e.g. detectable anti-U1-RNP- or anti-PmScl-antibodies [18], although the usefulness of this category is controversial. Also, due to improved health care, patients present early in the disease course with symptoms suggestive but not yet sufficient to diagnose definite SSc (e.g. RP and scleroderma-specific ANA).

In SSc, as in other rare diseases, large registries are a prerequisite to identify more uniform cohorts of patients to be able to recruit patients into clinical studies with comparable criteria for outcome measurement. Nevertheless, previous studies also suggested that, even with standardized definitions in larger registries, there may be considerable heterogeneity in patient samples reflecting, e.g. genetic and ethnic heterogeneity, the profile of centres with a propensity of referral cases or less-severe community cases. Therefore, in an attempt to reduce the referral bias, this network tried to broaden the clinical scope of the patients being registered by relying on several medical subspecialties, i.e. rheumatological, dermatological, pulmonary and nephrological centres with a long-standing expertise in the care of SSc patients.

Depending on the study, the percentage of SSc patients with the diffuse type of the disease varies considerably (33.8% [9]; 17% [26]; 44.6% [27]; 36.9% [21]) with the percentage of this study (32.7%) being well within this range. The observed variation may be partly due to regional differences in the patient population, as e.g. Afro-American individuals have been found to suffer from the diffuse disease type more frequently than a Caucasian population as in this study. The lower percentage in our study can also be attributed to the fact that this study considers more subsets, distinguishing not only between the limited and diffuse type of the disease but also between overlap syndromes and undifferentiated disease. Accordingly, the limited disease variant was found in 45.5%, which is lower when compared with previous studies of e.g. 57.5% in Walker *et al*. [21] or 55.8% in Ferri *et al*. [28]. In our study, patients not fitting into the categories of Le Roy *et al*. [15] were classified into three additional subsets. Here, we can show that 10.9% of patients belonged to the overlap syndrome subtype and 8.8% of patients to the undifferentiated subset, indicating that in clinical practice a considerable number of patients (i.e. ~20%) present with clinical symptoms that are not fully compatible with the definition of Le Roy (1988) for the limited and diffuse cutaneous subset. The patients with overlap syndrome can certainly be included into the Le Roy categories; however, they clearly have a different course of the disease. Thereby, in the present study, we have made the attempt to use the cohort available to test the hypothesis, whether these patients could represent a distinct subset. The data of this cohort indicate that the clinical presentation is different and the subset appears to influence the choice of the care provider (i.e. patients with overlap syndrome were predominantly taken care by rheumatologists) as well as the therapeutic approach (Hunzelmann *et al*., 2008, unpublished observation). The data of this cohort therefore support the view to consider overlap syndrome as a distinct entity.

The average age of disease onset (defined as onset of RP) of about 44.3 yrs was similar to the value described previously in the EUSTAR cohort [21]. Notably, a family history of rheumatic diseases was significantly associated with a lower mean age and

earlier disease onset of RP, skin involvement and internal organ involvement, underlining the potential role of common genetic traits in the pathophysiology of rheumatic diseases. However, a comparison with other studies is difficult due to variations in the definition of diagnosis and disease onset. The female to male ratio of 5.08 is in the range of previous reports (7.4 [28]; 3.2 [9]). The values for involvement of the kidney (10.5%), the heart (14.6%), the lung (34.5%) and the oesophagus (60%) in this report are also within the range of previous data [9, 21, 27, 28]; however, marked differences could be elucidated between disease subsets.

The detection frequency of anti-topoisomerase (27.6%) autoantibodies corresponds well with previous data in the study of Ioannidis *et al.* [27] (25.3%) but is less than that reported in the EUSTAR registry (~40%). This study also confirms the results of Walker *et al.* [21], which indicates that, to a significant degree (28.6%), pulmonary hypertension may occur in the diffuse subset without pulmonary fibrosis, underlining the necessity to screen for pulmonary hypertension irrespective of the subset.

Patients with the subset of scleroderma sine scleroderma were described in 1.5% of registered patients. However, these patients had similar characteristics than the limited subtype and not a specific antibody profile i.e. a preponderance of ACAs. Nevertheless, our study supports the results of Poormoghim *et al.* [16], which concluded that this subset is a clinical variant of the limited subtype and should not be considered a distinct disorder.

Oral involvement characterized by decreased mouth opening and resulting in poor dental status was reported in 34.1% of dcSSc patients indicating an important, to date underrated contribution to disease-associated morbidity and a need for specialized care. Trigeminal neuralgia, which has been reported to be associated with the dcSSc subset [15], appeared at a low frequency but markedly higher than that in the general population (0.1/1000).

SSc is a multisystem disease and a number of subspecialties are involved in the care of SSc patients. Care for these patients differs from country to country, depending on the history as well as the financial and organizational structure of the health care system. In Germany, rheumatologists and dermatologists have traditionally taken care of SSc patients. It can be hypothesized that this registry, in contrast to registries established by rheumatologists, may therefore include more patients with mild disease, as patients with limited organ involvement (e.g. RP, acrosclerosis) may first be seen by a dermatologist. Indeed, the data of the registry show a trend to less severe organ involvement in patients presenting in dermatological centres, whereas rheumatological centres are more often seeing patients with overlap syndromes. This result is supported by the data of the registry demonstrating that patients with prominent musculoskeletal symptoms and gastrointestinal involvement are more common in rheumatological centres. Interestingly, patients had similar lung involvement regarding fibrosis and pulmonary hypertension in dermatological and rheumatological centres, which might reflect the relatively good correlation of skin fibrosis with the extent of lung fibrosis [29].

Comparing the data of this registry with recently published data of the pan-European EUSTAR registry, it is apparent that patients in this nationwide registry on average are less severely affected by the disease and on average have a longer disease duration, also in comparison with previous studies. Although ethnic differences cannot be totally excluded, this presumably reflects more efficient and better recruitment of less severely affected patients.

This cross-sectional nationwide analysis of SSc patients demonstrates that a sizeable number of patients belongs to subsets other than the limited and diffuse cutaneous form of SSc. Continuous analysis of a growing body of data will provide substantial information for improvement of disease classification assessment of prognosis in the different subsets and the development of evidence-based recommendations for diagnosis and treatment.

Rheumatology key messages

- This paper reports data from a nationwide interdisciplinary register for patients with manifestations of SSc.
- More than 20% of patients belong to subsets other than the limited and diffuse form.

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