Performance of the 2013 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Systemic Sclerosis (SSc) in Large, Well-defined Cohorts of SSc and Mixed Connective Tissue Disease

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ABSTRACT. ***Objective.*** To assess the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for Systemic Sclerosis (SSc) on defined subgroups of SSc and in mixed connective tissue disease (MCTD) as an SSc-related disease.

Methods. The 2013 ACR/EULAR criteria were assessed in 425 consecutive patients suspected to have SSc and seen at Oslo University Hospital, and in the nationwide Norwegian MCTD cohort (n = 178). In the SSc group, 239/425 patients had disease duration < 3 years (in 82 of these, duration was < 1 yr). Patients were subgrouped as limited SSc (n = 294), diffuse SSc (n = 97), SSc sine scleroderma (n = 10), and early SSc (prescleroderma; n = 24). Item data were complete, except nailfold capillaroscopy and telangiectasia results, missing in the MCTD cohort.

Results. The 2013 ACR/EULAR SSc criteria were met by 409/425 patients (96%) in the SSc group. For comparison, only 75% (293/391) met the 1980 ACR SSc classification criteria. All the novel items in the 2013 ACR/EULAR criteria were frequent in the SSc cohort. Considering that there were missing data on 2 items, 10% (18/178) of the MCTD cohort met the 2013 ACR/EULAR criteria, giving an estimated specificity of 90% toward this SSc-like disorder.

Conclusion. In our large and representative group of consecutive patients with SSc, the 2013 ACR/EULAR SSc criteria were more sensitive than the ACR 1980 criteria. However, the new criteria did not completely segregate SSc from MCTD, making specificity a potential issue. (First Release Oct 1 2014; J Rheumatol 2015;42:60–3; doi:10.3899/jrheum.140047)

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Systemic sclerosis (SSc) is a heterogeneous disease where the phenotype depends on the disease subtype and on the distribution of organ involvement. In the early disease phase, symptoms can be mild and subtle; and delineation against other connective tissue diseases (CTD), particularly mixed connective tissue disease (MCTD), might be difficult[1,2,3].

When the 1980 American College of Rheumatology (ACR) classification criteria for SSc were designed, the intention was "to be specific rather than sensitive to minimize false positive diagnoses."[4] Because these criteria, by definition, were not applicable to the full spectrum of SSc, alternative classification systems were developed, such as LeRoy and Medsger's modified criteria for early SSc[5].

Very recently, the European League Against Rheumatism (EULAR) and ACR launched unified new classification criteria for SSc. In a multicenter SSc validation cohort, these criteria proved more sensitive than the 1980 ACR criteria for the full spectrum of SSc[6]. The new criteria were also stated to be more specific in differentiating SSc from

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SSc-like diseases. It should, however, be noted that the SSc-like subset in the validation cohort included only 14 MCTD cases[6]. It is evident from the joint ACR/EULAR publication that the new criteria are a significant step forward. However, to confirm their true value, we believe that some important issues need further investigation. Here, we addressed 2 issues we considered important: (1) the performance of the new criteria in consecutive, unselected patients with SSc, and (2) the ability of the criteria to discriminate between SSc and MCTD as the most important and frequent SSc-related disease.

MATERIALS AND METHODS

The SSc study cohort. As part of an ongoing, longitudinal observational study of SSc initiated in 2008, all hospital databases at the Oslo University Hospital (OUH) are regularly screened to identify new eligible patients (i.e., patients with International Classification of Diseases revision 10 diagnoses compatible with SSc: M34.0, M34.1, M34.2, M34.8, or M34.9). This systematic database monitoring (and accompanying chart review by at least 2 SSc experts) allows for early detection of suspected SSc cases. Patients fulfilling the 1980 ACR classification criteria for SSc[4] and/or LeRoy and Medsger's modified criteria for the classification of early SSc[4,5] are enrolled in the longitudinal study and registered in the Norwegian systemic connective tissue disease and vasculitis registry (NOSVAR) at OUH[7]. Patients who do not fulfill the criteria (predominantly SSc sine scleroderma and prescleroderma) are followed up at the OUH outpatient clinic. The current study cohort includes 425 patients: 382 patients enrolled in the longitudinal SSc study and 43 patients from the outpatient clinic. Patients were categorized as (1) early SSc (prescleroderma) defined by Raynaud phenomenon (RP) plus SSc-type nailfold capillaroscopy pattern or SSc-related antibodies, but no skin or organ involvement; (2) SSc sine scleroderma (sine SSc) defined by RP, positive capillaroscopy, or SSc-related antibodies, and typical SSc organ involvement, but no scleroderma; (3) limited cutaneous SSc (lcSSc); or (4) diffuse cutaneous SSc (dcSSc), as described[4,5]. This is a completely independent cohort; there were no Norwegian patients included when the 2013 EULAR/ACR SSc classification criteria were developed and tested.

Disease duration was defined as the time period from onset of the first non-RP symptom to study enrollment. Clinical variables registered were RP[8] skin involvement, digital ulcers (DU) or pitting scars, telangiectasia, nailfold capillaroscopy, and SSc-related antibodies. Interstitial lung disease (ILD) was assessed by high-resolution computed tomography (HRCT) and pulmonary function tests. The presence of ILD was defined by findings of fibrosis on HRCT and a forced vital capacity below 70% of the expected value[9]. Pulmonary hypertension (PH) was defined by right heart catheterization (RHC) at rest according to the European Society of Cardiology criteria[10]. In some patients, missing data were retrieved retrospectively by chart review for this study.

MCTD cohort. The MCTD cohort included 178 patients, 147 patients enrolled in the unselected Norwegian nationwide MCTD cohort from 2005–2008, and 31 included in NOSVAR from 2008–2013[11,12]. Inclusion criteria for the MCTD cohort have been described[13]: (1) age at least 18 years at inclusion, (2) fulfillment of at least 1 of 3 MCTD criteria sets [Sharp, Alarcón-Segovia, and/or Kasukawa (reviewed[14])], and (3) exclusion of other CTD[14]. Data on RP, SSc-related antibodies, skin thickening of the fingers (puffy hands and/or sclerodactyly), DU, ILD, and PH were readily available, while data on telangiectasia were missing. Data on nailfold capillaroscopy were incomplete and therefore excluded.

Classification criteria. The patients were scored by the 2013 EULAR/ACR classification criteria for SSc as described[6]. Briefly, the criteria are based on a scoring system where the first criterion alone [skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal (MCP) joints] gives the 9 points needed to classify the patient as having SSc. If the first criterion is not met, the patient can gain 9 points by 7 other items (listed in Table 3)[6].

Statistics. Descriptive statistics were applied to analyze the number of patients of both cohorts meeting the newly established classification criteria for SSc. Sensitivity and specificity were calculated with confidence limits by using 2×2 tables with chi-square test.

RESULTS

SSc study cohort. The OUH cohort included 425 consecutive SSc patients; 328 who met the Leroy and Medsger criteria for early onset SSc (294 with lcSSc, 24 with prescleroderma, and 10 with sine SSc) and 97 patients diagnosed with dcSSc (Table 1). Because prescleroderma and sine SSc, by definition, would not be tested by the 1980 ACR criteria, only 391 patients would be classifiable by these criteria. Hence, the frequency of patients meeting the ACR 1980 criteria was 75% (293/391), and for Leroy and Medsger criteria, 100% (328/328; Table 1). The mean age at disease onset was 48 years (SD 15.0) and the female-to-male ratio was 4:1. Altogether, in 82 of the consecutive patients with SSc, the time from first non-RP symptom to study inclusion (disease duration) was < 1 year and in 239 the disease had lasted < 3 years (Table 2). Median disease duration of the whole SSc group was 8 years (range 0–44). ILD was identified in 174 patients (41% of the whole group) and 60 (14%) had PH, verified by RHC (Table 3). Serum antinuclear antibodies were present in 407 patients (90%): of these 226 (50%) had anticentromere antibodies, 68 (15%) antitopoisomerase antibody, and 21 (5%) anti-RNA polymerase antibodies. Anti-RNP was identified in 5% of the patients with SSc.

The 2013 EULAR/ACR classification criteria for SSc were met by 409 of the patients with SSc (96%; Table 1); 97 of these (23%) were classified as SSc because of bilateral skin thickening proximal to the MCP joints (Table 3). The remaining 312 patients reached 9 points or more by fulfilling other variables defined by the criteria (Table 3). Percentage frequencies of the individual items in the 2013 criteria did not differ between patient subsets stratified by disease duration, except for telangiectases being present in 62% of the subset with disease duration less than 3 years and 89% of the subset with duration longer than 10 years.

The 16 patients with SSc who did not meet the 2013 EULAR/ACR criteria had complete data on all the variables defined by the criteria. They were classified as lcSSc (2 patients), prescleroderma (6 patients), or sine SSc (8 patients; Table 1).

MCTD cohort. Of the 178 patients in the MCTD cohort, 166 patients (93%) met the Sharp criteria for MCTD, 157 (88%) the Alarcón-Segovia criteria, and 155 (87%) the Kasukawa criteria. Mean age at onset of MCTD was 35 years (SD 15.7), and the female-to-male ratio was 4:1. Puffy fingers were present in 134/178 of the patients with MCTD (75%), 54 (30%) had sclerodactyly, DU were recorded in 12

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Table 1. Frequency of SSc subgroups meeting the 2013 ACR/EULAR SSc criteria in comparison to previous criteria sets.

	SSc Subgroup, n/N Tested (%)				Total
	Prescleroderma	lcSSc	dcSSc	Sine SSc	
ACR 1980 criteria, n/N tested (%)	NA	196/294 (67)	97/97 (100)	NA	293/391 (75)
Medsger & Leroy criteria, n/N tested (%)	24/24 (100)	294/294 (100)	NA	10/10 (100)	328/328 (100)
2013 ACR/EULAR criteria, n/N tested (%)	18/24 (75)	292/294 (99)	97/97 (100)	2/10 (20)	409/425 (96)

SSc: systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; NA: not applicable.

Table 2. Overview of SSc subgroups stratified by disease duration.

	SSc Cohort (N = 425)			
	lcSSc (n = 294)	dcSSc (n = 97)	Sine SSc (n = 10)	Prescleroderma (n = 24)
< 3 years (n = 239)	149	57	9	24
3–10 years (n = 125)	100	24	1	0
> 10 years (n = 61)	45	16	0	0

SSc: systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis.

Table 3. Overview of the 2013 ACR/EULAR classification criteria items in the Oslo University Hospital SSc cohort (N = 425), and in the nationwide MCTD cohort (N = 178).

Items (points)	SSc (N = 425), n/N Tested (%)	MCTD (N = 178), n/N Tested (%)
Bilateral skin thickening proximal to the MCP joints (9)	97/425 (23)	0
Skin thickening of the fingers; whole finger distal to MCP (4), puffy fingers (2)	294/425 (69)	146/178 (82)
Finger tip lesions; digital ulcers (2), or pitting scars (3)	169/419 (40)	12/147 (8)
Telangiectasia (2)	283/408 (69)	NA
Abnormal nailfold capillaries (2)	292/318 (92)	NA
Pulmonary arterial hypertension and/or interstitial lung disease (2)	182/407 (45)	44/178 (25)
Raynaud phenomenon (3)	402/418 (96)	176/178 (99)
Scleroderma-related antibodies (3) (ACA, ATA, or anti-RNAP)	310/407 (76)	4/178 (2)
Total score of 9 or more points	409/425 (96)	18/178 (10)

SSc: systemic sclerosis; MCTD: mixed connective tissue disease; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; MCP: metacarpophalangeal; ACA: anticentromere antibody; ATA: antitopoisomerase antibody; anti-RNAP: anti-RNA polymerase antibodies; NA: not applied; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

patients (7%), and 4 (2%) had SSc-related antibodies. ILD was identified in 44 patients (25%), and 5 (3%) had PH, as verified by RHC (Table 3).

The 2013 ACR/EULAR criteria for SSc were met by 18 patients (10%) in the MCTD cohort (Table 3). All these 18 patients had RP, 17 had sclerodactyly, 4 had DU, and 15 ILD, but none had PH.

Criteria performance. The sensitivity of the new classification criteria was 96% (95% CI 93.39, 97.36) and the specificity was 90% (95% CI 84.85, 94.05) toward MCTD as a scleroderma-like disorder. For comparison, the estimated sensitivity of the ACR 1980 criteria was 75%.

DISCUSSION

Our study demonstrated the applicability of the 2013 EULAR/ACR classification criteria for SSc in a large Scandinavian cohort. The OUH SSc study cohort has characteristics that make it particularly suitable for "real-life" performance testing of the new SSc criteria: (1) the cohort is representative, covering the whole spectrum of SSc, from mild and early disease to cases with severe and life-threatening complications, including a large number of patients with short disease duration; and (2) item data are nearly complete and the data quality is verified by longitudinal patient followup[7,15]. Only 4% of the cohort patients remained unclassifiable. These unclassifiable SSc cases had early disease (here classified as prescleroderma) or sine SSc. This is in line with the data from Alhajeri, *et al* and Jordan, *et al* on early and limited disease[16,17].

In our current study, patients were defined as "true" SSc cases if they fulfilled either the ACR 1980 criteria and/or the Leroy and Medsger criteria. Using this combination of

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criteria as the "gold standard" for SSc has been common for epidemiological purposes[15,18,19]; however, it has never been validated. Hence, it is not known whether this combined criteria approach selects for the same individual patients as the expert opinion gold standard used when the 2013 ACR/EULAR criteria were developed. However, our data do indicate that the combined criteria-based approach selects for patients who actually meet the 2013 ACR/EULAR criteria.

Although the ACR/EULAR criteria were developed for patients with clinically suspected SSc, specificity is an issue, particularly against diseases with overlapping clinical features such as MCTD. Another challenge related to MCTD is the overlap in serology: anti-RNP antibodies, obligatory in MCTD, are also present in around 5% of patients with SSc. Hence, we found it of interest to test the new SSc criteria in our nationwide MCTD cohort, which is the largest unselected MCTD cohort worldwide. In the absence of 2 criteria items (telangiectasia and nailfold capillaroscopy findings), 10% of the patients with MCTD met the new SSc criteria. This high frequency mainly reflects the protean nature of MCTD and the potential evolution of MCTD into a more SSc-predominant phenotype over time. The clinical challenge of discerning MCTD from SSc will continue to require detailed clinical investigations on a case-by-case basis, and in some cases, longitudinal followup data.

Limitations of the current study include partial dependence on chart review for collection of the SSc data and missing data on telangiectasia and capillaroscopy in MCTD. Pathological capillaroscopy is often present in MCTD[20] and telangiectasia has been reported as frequent in 1 study[21]. Hence, it seems likely that the exclusion of these items caused underestimation of patients with MCTD meeting the new SSc criteria. The inclusion of those missing items would probably increase the frequency of false positives and diminish the specificity of the 2013 criteria for SSc.

Our data support the notion that the 2013 ACR/EULAR criteria are a major step forward and that their application should improve the quality of clinical and epidemiological SSc research in the years to come.

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