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A comparison between nailfold capillaroscopy patterns in adulthood in juvenile and adult-onset systemic sclerosis: A EUSTAR exploratory study

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ABSTRACT

Objective: Qualitative capillaroscopy patterns in juvenile- and adult-onset systemic sclerosis (SSc) were studied in adulthood using data from the EULAR Scleroderma Trials and Research (EUSTAR) database.
Methods: Data collected between June 2004 and April 2013 were examined with focus on capillaroscopy. In this retrospective exploratory study, series of patients with juvenile-onset SSc were matched with series of adult-onset SSc having the same gender and autoantibody profile.
Results: 30 of 123 patients with juvenile-onset and 2108 of 7133 with adult-onset SSc had data on capillaroscopy. Juvenile-onset SSc showed scleroderma pattern more frequently than adult-onset SSc (93.3% and 88%). The OR was 2.44 and 95% CI 0.57–10.41. An active scleroderma pattern was present in 58% of juvenile- and 61% of adult-onset SSc. The OR was 0.91 and 95% CI 0.28–2.93. The late scleroderma pattern was present in 61% of juvenile- and 55.5% of adult-onset SSc. The OR was 1.06 and 95% CI 0.34–3.56.
Conclusion: This is the first exploratory study on the comparison of capillaroscopy between juvenile- and adult-onset SSc in adulthood. Juvenile-onset SSc had an increase prevalence of scleroderma pattern, but a similar distribution of the three patterns was suggested. Further studies are needed to define this issue.

Introduction

Nailfold capillaroscopy is a useful investigation tool to differentiate primary from secondary Raynaud's phenomenon as typical capillary changes (i.e. giant loops, widened capillaries or avascular areas) that characterize the transition can be clearly demonstrated in adults as well as in children (Ingegnoli and Herrick, 2013). Although the pathogenesis of systemic sclerosis (SSc) is undoubtedly complex, strong evidence exists in favor of the crucial role of local and systemic vasculopathy (Herrick, 2012). The typical microvascular abnormalities of SSc can be clearly observed as morphological alterations of the nailfold capillaries all along the course of the disease, from the very early onset up to the late organ complications in both juvenile- and adult-onset SSc (Martini et al., 2006). It has been also suggested that capillary changes may be considered a mirror of internal organ involvement progression in adult-onset SSc (Ingegnoli et al., 2013; Smith et al., 2013).

In patients with juvenile-onset SSc, the presence of nailfold capillary abnormalities (i.e. giant capillaries, avascular areas, capillary dilation or tortuosity) is included in the provisional classification criteria for the disease, and in adult-onset SSc, the presence of "scleroderma pattern" or isolated suspicious capillary abnormalities is one of the criteria for classifying patients with early adult-onset SSc and overt adult-onset SSc (Minier et al., 2013; van den Hoogen et al., 2013).

Data from the EULAR Scleroderma Trials and Research (EUSTAR) database showed that patients with juvenile- and adult-onset SSc share similar clinical manifestations and laboratory features, except for the frequency of anticentromere antibodies (Foeldvari et al., 2012b). Although it would be of interest to monitor capillary changes over time, from childhood to adulthood, the EUSTAR database does not allow such a study as it involves only adult patients with capillaroscopy data taken at the time of the visit. A previous study showed that at the time of diagnosis, most of the patients with juvenile-onset SSc had non-specific capillary abnormalities, while during the course of the disease most of them developed a scleroderma pattern (Martini et al., 2006). When a capillaroscopy follow-up was performed, a progressive reduction in the number of giant capillaries and enlarged loops was noted over the years (Russo and Katsicas, 2007). However, in juvenile-onset SSc, the overall capillaroscopic pattern is also called "scleroderma pattern", the classification in "early", "active" and "late" patterns (Cutolo et al., 2004) has never been applied, and differences in microvascular abnormalities between juvenile- and adult-onset SSc have never been explored.

As nailfold capillaroscopy provides the clinician with a unique window into the microcirculation, it is often used in research and clinical trials for monitoring disease progression and treatment response in adult-onset SSc. As microangiopathy is present from the early stages of the disease, it would be important to know if the patient's age at disease onset has to be taken into account in the evaluation of capillaroscopy patterns.

Against this background, we studied the nailfold capillaroscopy patterns of adult patients with juvenile and adult-onset SSc using data from the EUSTAR database. For this purpose, we performed a retrospective exploratory matched study in which series of adult patients with juvenile-onset SSc with available information on capillaroscopy were matched with corresponding series of adult-onset SSc having the same gender and autoantibody profile.

Materials and methods

This is a retrospective exploratory study in which data from patients with SSc were extrapolated from the EUSTAR database. This database covered demographics, clinical, laboratory and therapeutic data of SSc. It started in June 2004 by collecting data of consecutive adult patients referred to SSc medical centers worldwide into this specific database, which was locked for this study in April 2013. The structure and minimal essential dataset (MEDS) as well as the quality and the standardization of the clinical and capillaroscopic assessments of the EUSTAR database have been previously described (Foeldvari et al., 2012a; Ingegnoli et al., 2013; Meier et al., 2012).

To guarantee the quality and the standardization of the clinical and capillaroscopic assessments, EUSTAR and EULAR regularly held courses to coach, update and standardize the assessment of SSc patients. In every course, there is a coaching session specifically devoted to capillaroscopy. Moreover additional coaching materials are available on the EUSTAR website.

In particular, data on capillaroscopy are recorded as scleroderma pattern "present" or "absent"; and in its presence, specification of its type (i.e. early, active or late). Among different data requested in the database, ticking these 2 items on capillaroscopy is not mandatory.

Capillaroscopy examination was performed generally on eight digits (excluded thumbs) using the technical equipment available in each EUSTAR center, ranging from videocapillaroscope to dermatoscope with magnification from 20× to 200×. The use of different instruments has been allowed based on the results of previous studies on the agreement between capillaroscopic methods (Anders et al., 2001; Wildt et al., 1999, 2012), and because data collected in the EUSTAR registry are based on an overall capillaroscopic pattern characterized only by morphological capillary abnormalities easily identifiable with all the tools employed.

All of the patients included in the database gave their informed consent approved by the respective local Ethics Committees, and the study was approved by the clinical research committee of EUSTAR.

As shown in Fig. 1, we extrapolated data from patients with juvenile-onset SSc, defined as SSc onset in children and adolescents younger than 16 years of age, and from patients with adult-onset SSc. All the patients with data on capillaroscopy were included.

For our analysis, we selected the first available visit with data on capillaroscopy. Clinical and laboratory data are referred to the same visit in which capillaroscopy was performed.

Juvenile-onset SSc patients were grouped according to gender and autoantibody profile (i.e. antinuclear antibodies (ANA), anticentromere antibodies (ACA) and anti-Scl-70 antibodies). Then, each series of juvenile-onset SSc was matched with a series of adult-onset SSc with the same gender and autoantibody profile (see Supplementary materials). Anti-RNA pol III antibodies were not included as it was tested only in a very few number of patients. As elderly patients have different clinical features (Manno et al., 2011; Perez-Bocanegra et al., 2010), adult-onset SSc patients have been selected by considering patients with disease onset before 65 years old.

Statistical analysis

After selecting groups of patients as explained above, the analysis was performed by a conditioned logistic regression model.

All available adult-onset SSc patients which could be matched with juvenile-onset SSc patients were used to avoid selection strategies which may potentially influence results. Model results were reported in terms of estimated odds ratio (OR) and 95% confidence intervals (CIs). To facilitate in the interpretation of impact of results, the OR corresponding to a relative differences in the percentage of scleroderma patterns between juvenile- and adult-onset SSc within 5% (calculated taking into account for conditional matching) were reported as can be considered not clinically relevant. No formal statistical tests were reported because of the exploratory nature of the study and the low number of patients with juvenile-onset SSc. Nevertheless, CIs have been reported mainly to provide information on the precision of the estimates.

The comparison of scleroderma pattern in juvenile-onset SSc with respect to adult-onset SSc was performed firstly in univariable model (unadjusted estimates), then the estimates were adjusted for potentially confounding variables (i.e. age of onset of Raynaud's phenomenon, the presence of lung fibrosis, esophageal involvement and the skin

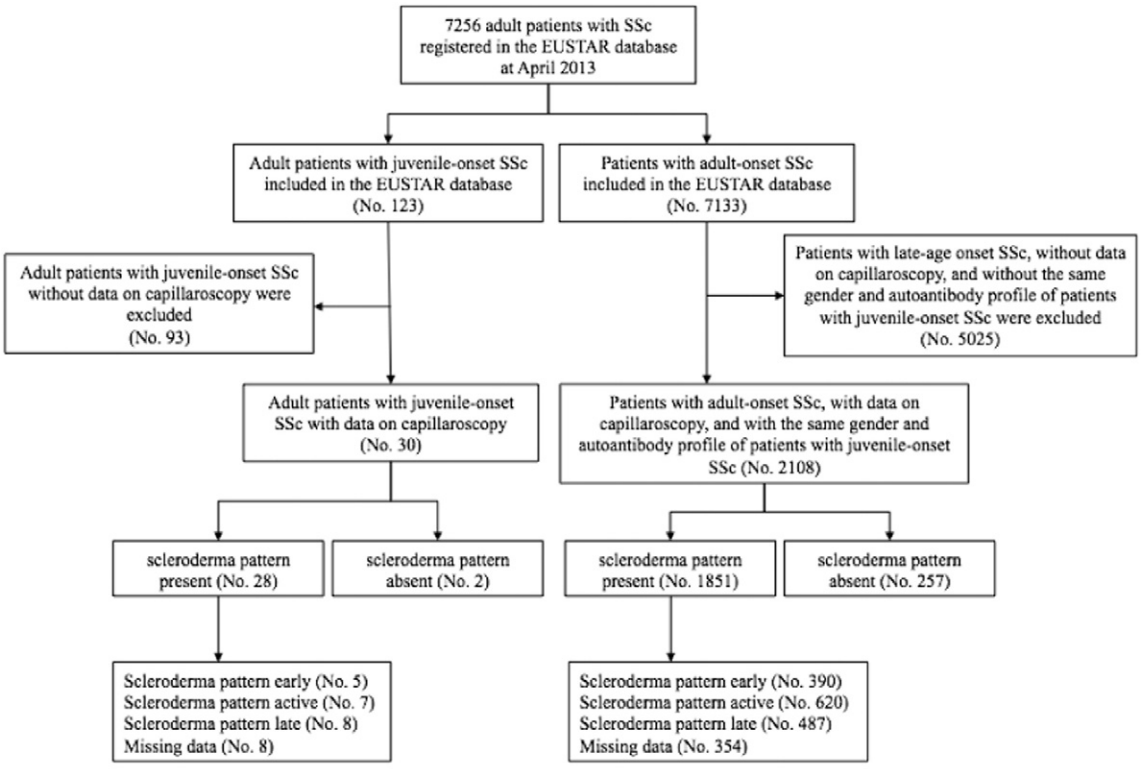

Fig. 1. Selection of patients with juvenile- and adult-onset systemic sclerosis from the EUSTAR database.

score). Nevertheless, because of the low number of juvenile-onset SSc, only multivariable models including only two variables could be considered. To this aim, regression models including scleroderma patterns and each one of the explanatory variables abovementioned have been done.

Results

Among all the 7256 adult patients with SSc included in the EUSTAR database, we identified 123 (1.7%) patients with juvenile-onset SSc. Among these, 30 of 123 (24.4%) patients had data about the presence or absence of scleroderma pattern. 22 of 30 patients with juvenile-onset SSc have complete data on the type of scleroderma pattern. 2108 of 7256 (29%) of patients with adult-onset SSc have data on capillaroscopy (Fig. 1).

By comparing the 30 subjects with juvenile-onset SSc included in the analysis and the 93 patients excluded, no clinically relevant differences were observed.

The demographic, clinical and laboratory data at the visit in which nailfold capillaroscopy was performed of the 22 patients and of 1497 patients with adult-onset SSc included in the analysis are shown in Table 1.

The distribution of the variables within each matched group is reported in Supplementary Table S2. The mean age at the visit of patients with adult- and juvenile-onset SSc was 52.91 ± 12.6 and 29.56 ± 10.71 years old respectively. Mean age at the onset of Raynaud's phenomenon was 38.60 ± 12.23 years old in adult-onset and 11.36 ± 5.12 years old in juvenile-onset SSc. Similar distribution of modified Rodnan skin score between adult- and juvenile-onset SSc was observed. The majority of patients had a scleroderma pattern (28 of 30, 93.3% of juvenile-onset and 1851 of 2108, 87.8% of adult-onset) and, early, active and late patterns were almost equally distributed in juvenile- and adult-onset SSc (see Table 1).

At the time of the visit in which capillaroscopy was performed, the mean age progressively increases from the group of patients with an early scleroderma pattern to those with a late scleroderma pattern (Table 1).

Concerning the disease subset, juvenile-onset SSc patients were mainly equally distributed in diffuse and limited cutaneous SSc. The distribution of juvenile-onset SSc patients was fairly well balanced between the absence and presence of esophageal symptoms, digital ulcers, joint contractures, scleredema and lung fibrosis assessed by HRCT, whereas adult-onset SSc showed more frequently the presence of esophageal symptoms, absence of digital ulcers, joint contractures and lung fibrosis.

The analysis of scleroderma pattern "present" versus "absent" was based on all 30 juvenile-onset SSc patients of whom we have information on capillaroscopy. Patients with juvenile-onset SSc showed scleroderma pattern more frequently than adult-onset SSc (28/30 = 93.3% and 1851/2108 = 87.8% respectively). The estimated OR was 2.44 and 95% CI 0.57–10.41. The OR corresponding to a relative difference within 5% was within 0.73–1.5, thus suggesting that the estimated differences were in agreement with a difference greater than 5%.

For the analysis involving the three scleroderma patterns, 22 juvenile-onset SSc patients have been considered, as 6 patients with missing data were found.

An active versus early scleroderma pattern was present in 7/12 = 58.3% of juvenile-onset SSc and in 620/1010 = 61.4% of adult-onset SSc. The model estimated OR was 0.91 and 95% CI 0.28–2.93. The OR corresponding to a relative difference within 5% was within 0.88–1.13. This result supports that the estimates were in agreement with a difference lesser than 5%.

The late versus early scleroderma pattern was present in 8/13 = 61.5% of juvenile-onset SSc and in 487/877 = 55.5% of adult-onset SSc. The estimated OR was 1.06 and 95% CI 0.34–3.56. The OR corresponding

Table 1
Demographic, clinical data and investigations of the 22 patients with juvenile-onset and of 1754 adult-onset systemic sclerosis with data on capillaroscopy. These groups are subsamples of the whole series of juvenile- and adult-onset SSc that has been selected as explained in the methods about the matching strategy.

	Juvenile-onset SSc				Adult-onset SSc			
	Scleroderma pattern present			Scleroderma pattern absent (no. 2)	Scleroderma pattern present			Scleroderma pattern absent (no. 257)
	Scleroderma pattern early (no. 5)	Scleroderma pattern active (no. 7)	Scleroderma pattern late (no. 8)		Scleroderma pattern early (no. 390)	Scleroderma pattern active (no. 620)	Scleroderma pattern late (no. 487)	
Female	5	6	4	2	370	564	438	229
Age at disease onset, mean (range) yrs	10.8 (4.7–14.2)	13.6 (8.4–15.7)	10.4 (5.2–14.8)	15.1 (15–15.3)	42.7 (16.2–65.0)	42.7 (16.7–65.0)	41.2 (16.8–65.0)	43.3 (16.2–65.0)
Duration of Raynaud's phenomenon, mean yrs	16.21	16.13	24.47	8.88	13.5	13.59	18.29	17.3
Disease subset, no.								
lcSSc	3	4	2	1	230	360	229	148
dcSSc	2	3	6	1	96	189	235	60
Modified Rodnan skin score	7.5	5.7	15.5	11	6.4	9.4	11.8	5.6
History of digital ulcers, no.	1	3	5	1	96	237	242	45
Lung fibrosis by HRCT, no.	2	2	5	1	61	102	91	26
Muscle weakness, no.	1	0	2	0	66	119	131	39
Joint contractures, no.	2	2	6	0	64	185	229	34
Synovitis, no.	1	1	0	0	45	97	95	28
Tendon friction rubs, no.	0	0	2	0	19	64	66	13
Renal crisis, no.	0	0	0	0	0	9	10	5
Conduction blocks, no.	0	0	0	0	29	73	79	33
Esophageal involvement, no.	2	4	4	1	236	406	335	159
Stomach involvement, no.	0	1	2	0	69	150	142	46
Intestinal involvement, no.	0	0	1	0	76	150	128	58
Positive ANA, no.	4	7	7	2	380	604	468	234
Positive Scl-70, no.	0	4	2	1	131	234	260	78
Positive ACA, no.	0	1	0	1	163	249	120	88

HRCT: high resolution computed tomography; ANA: antinuclear antibodies; ACA: anticentromere antibodies; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis.

to a relative difference within 5% was 0.80–1.10. This result indicates that the estimates were in agreement with a difference lesser than 5%.

No relevant changes were observed when the analysis was adjusted for esophageal symptoms, modified Rodnan skin score, lung fibrosis and patient's age at the onset of Raynaud's phenomenon.

Discussion

This is the first exploratory study on the comparison of capillaroscopy between juvenile- and adult-onset SSc in adulthood. We showed that the microvascular involvement documented by capillaroscopy in patients with juvenile-onset SSc was apparently more frequent than in adult-onset SSc as documented by the increase prevalence of the presence of scleroderma pattern. When the scleroderma pattern is present, a similar distribution of the three patterns was suggested.

Nevertheless, despite the EUSTAR cohort gathering a large number of centers, we could examine a low number of adult patients with juvenile-onset SSc with information on capillaroscopy. This could be mainly due to different factors: 1) the EUSTAR database involves only adult patients, thus partially excluding pediatrics centers, 2) thicking information on capillaroscopy is not mandatory, 3) juvenile-onset SSc is a rare disease (Foeldvari, 2015) and, 4) juvenile-onset SSc is a very severe disease with predominance of diffuse skin involvement and high mortality during the first 5 years after disease onset (Foeldvari, 2015).

Nailfold capillaroscopy is still an operator-dependent technique, and the potential heterogeneity in the interpretation of capillaroscopic images may be a limitation of this study. To overcome this issue, continuous EUSTAR/EULAR effort is done to standardize the assessment with different devices (e.g. videocapillaroscope, microscope, or dermatoscope) used to perform this exam. To this end, also recently the EULAR study group on microcirculation in rheumatic diseases has started which has in between other aims standardization of capillaroscopic definitions worldwide. Of note, nailfold capillaroscopy has been also introduced in the new ACR/EULAR classification criteria for SSc with significant improvement of sensitivity and specificity of the criteria (van den Hoogen et al., 2013).

It is known that capillaroscopy is feasible also in children because it is noninvasive, rapid, easy to repeat, and as in adult, a key investigation in the diagnosis of juvenile-onset SSc (Ingegnoli and Herrick, 2013). It has also been suggested to use the pathologic capillary pattern, as a screening method, to recognize early juvenile SSc presenting with Raynaud's phenomenon.

To date, in juvenile-onset SSc, single capillary abnormalities have been described as dilated loops, avascular areas, meandering loops, hemorrhages, giant capillaries, and neoangiogenesis and generally called “scleroderma pattern” (Ingegnoli et al., 2005; Martini et al., 2006; Spencer-Green et al., 1983).

Although at the time of diagnosis most children with juvenile-onset SSc have non specific capillary abnormalities, during the course of the disease a scleroderma pattern is frequently observed (Martini et al., 2006; Russo and Katsicas, 2007). Moreover, in patients with juvenile-onset SSc in whom a thorough capillaroscopy followup was performed, there was a trend toward the progressive reduction in the number of giant capillaries and enlarged loops and an increasing frequency of avascular areas over the years (Martini et al., 2006; Russo and Katsicas, 2007). This is not in contrast with our results showing similar pattern as the adult-onset SSc, because the survival bias should be considered; in fact, there is a higher rate of death in diffuse cutaneous juvenile-onset SSc during the pediatric age.

Despite the differences in anticentromere antibody positivity, esophageal involvement and lung fibrosis, juvenile-onset SSc and adult-onset SSc shared similar organ involvement. These results are similar only in part to the previous study on juvenile-onset SSc in the EUSTAR cohort (Foeldvari et al., 2012a) in which only differences in anticentromere antibodies had been found. This could be explained by the fact that we did not select for the analysis only adult-onset SSc with disease onset between 20 and 40 year-old.

Conclusions

This retrospective exploratory study suggests that in juvenile-onset SSc the presence of scleroderma pattern detected by capillaroscopy is more frequent in juvenile-onset, this result may be related to the longstanding microangiopathy. In contrast, the distribution of different scleroderma patterns (i.e. early, active or late) appears to be similar to those observed in adult-onset SSc. Therefore, the possibility in using the available classification of scleroderma patterns without considering the age of SSc onset may help in the standardization process for this investigation, but this exploratory study is only an effort to define this issue. Because of the low number of patients with juvenile-onset SSc, these results cannot be confirmed by a statistical test procedure. This was an exploratory study and as such it has not been planned to provide definite conclusion, but it can consider a starting point to help clinicians realize further research studies.

Conflict of interest

Francesca Ingegnoli, Patrizia Boracchi, Roberta Gualtierotti, Maurizio Cutolo, and Ivan Foeldvari: none.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.mvr.2015.07.007.

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