Systemic sclerosis, changes in the incidence rates in the Finnish population during years 1999–2018

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Running title: The incidence of systemic sclerosis is increasing

Abstract

Objective: The aim of our study was to examine changes in the incidence of systemic sclerosis (SSc) in Finland using two different classification criteria.

Methods: Medical records of patients who had been registered with the ICD-10 code M34 from 1999 to 2018 in two university hospitals were reviewed retrospectively. This period was divided into 5 -year-periods, 1999–2003, 2004–2008, 2009–2013 and 2014–2018.

Using ACR/EULAR 2013 criteria and clinical findings we reclassified patients into four different groups: diffuse SSc, limited SSc, sine SSc or early SSc. In the same population we also investigated whether the ACR1980 criteria were fulfilled.

Results: In 1999-2018 altogether 246 new patients with SSc and 45 patients with early SSc were identified using ACR/EULAR 2013 criteria. Of these patients, 70 fulfilled the ACR1980 criteria. When ACR/EULAR 2013 criteria were used, the increase in new diagnoses was statistically significant when the fourth period was compared the first period (p=0.0012). The increase was due to a rise in the limited SSc. The mean annual incidence rates in these groups were 0.9, 1.2, 1.9 and 2.8 per 100,000 ≥ 16 years old inhabitants. Increasing trend was also seen when ACR1980 criteria were used, but this was not statistically significant.

Conclusion: Incidence of SSc increased during the periods between 1999–2003 and 2014–2018 using ACR/EULAR2013, but not using the ACR1980 criteria. The increase was detected within a limited SSc subclass, due to more sensitive classification criteria.

Introduction

Systemic sclerosis (SSc) is a rare rheumatic autoimmune disease, characterized by vasculopathy and fibrosis of the skin and internal organs. The severity of the disease varies from mild phenotypes to those with life-threatening complications. Mortality and morbidity of SSc is significant (1). SSc is classified in two subtypes of the disease depending on the extent of the fibrosis, diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). SSc can exist without scleroderma of the skin, sine scleroderma (ssSSc). SSc is more frequent in women than in men (2), the female to male ratio varying from 3:1 to 7–8:1. Incidence rates of SSc varies worldwide (3). The rates are lowest in Asia (4–5) and highest in Northern America (6–9) and Australia (10). These rates vary from 0.8 per 100,000 to 4.6 per 100,000 person-years (4,7). In Europe, there seems to be an incident gradient from north to south, with higher incidence rates in Southern Europe (11–12). A study from northern Italy (11) examining the years between 1999–2007 showed annual incidence rates varying from 3.2 to 4.3 per 100,000 inhabitants depending the use of either ACR 1980-criteria (13) or the LeRoy-Medsger criteria (14). According to some older studies,the incidence of SSc in northern Europe is lower varying from 0.4 to 0.8 per 100,000 inhabitants (15–18). In Finland, the annual incidence in 1990 was 0.4 per 100,000 inhabitants using the doctor´s opinion (17) and 4.4 per 100,000 inhabitants in 2010 using ACR/EULAR 2013 criteria (19, 20). A Swedish study also showed higher incidence rates than previously reported in northern Europe (21). In this study the mean annual incidence rates from 2006 to 2010 were 1.4 per 100,000 inhabitants using ACR 1980-criteria (13) and 1.9 per 100,000 using ACR/EULAR 2013 criteria (20). In another study from Sweden the mean standardized incidence was 11.9 per million person-years during the years 2004–2015 (22).

The classification criteria applied have a significant role in assessing the incidence of the disease. ACR 1980-criteria (13) emphasizes established fibrosis and damage, and these criteria are unable to identify cases with a limited phenotype or the absence of fibrosis. Later, in order to obtain better

sensitivity and to identify early SSc, first LeRoy 1988 (23) and then LeRoy and Medsger 2001 criteria (14) were established. Reformed ACR/EULAR 2013 criteria (20) detects milder cases in which the nailfold capillaroscopy and autoantibodies have a significant role. The sensitivity and specificity of ACR/EULAR 2013 criteria has been shown to be high, 0.91 and 0.92, respectively (20). Two meta-analyses of SSc incidence have been published recently (24,25), the increasing trend has been detected in recent studies.

The aim of our study was to assess the incidence of SSc during a 20-year period between 1999 and 2018 using hospital-based study population in Finland. We evaluated changes in the mean annual incidence rate and the age at diagnosis of SSc patients and the impact of applying the more sensitive ACR/EULAR 2013 criteria to these changes.

Methods

Study population

Patients with a diagnostic code of SSc (ICD-10 codes beginning with M34) that appeared at least once in their medical records either at an outpatient or inpatient visit during the years 1999–2018 were identified from the hospital discharge registers of Turku and Oulu University hospitals in Finland.

In Finland, in recent years, all patients suspected of having secondary Raynaud´s phenomenon (RP) are typically evaluated by a rheumatologist, and a capillaroscopy is performed at a university or central hospital.

The annual numbers of inhabitants over sixteen years of age living in these two hospital districts (Southwest Finland and Northern Ostrobothnia) were obtained from Statistics Finland, in which all residents are registered. The cut-off age of sixteen years was used because patients under sixteen years of age are followed by pediatric rheumatologists in Finland.

All medical records were evaluated using commonly agreed principles by two experienced physicians, i.e. a rheumatologist (S.K.) and a resident of internal medicine (M.K.), both doctoral students. False diagnoses (other rheumatic condition or other diagnosis that better explained the patient's condition) and typing errors (M34 diagnosis without supporting medical data) were excluded. Using ACR/EULAR 2013 criteria and clinical findings, the diagnoses were reclassified and divided into different subsets of the disease (26). For the analyses, we included the two ssSSc cases in the group of lcSSc.

We also evaluated the same population according to the ACR 1980-criteria. Extraction of patients with true SSc is described earlier in an article on the validity of SSc diagnoses (26). To reduce the random annual variation of SSc incidence, we calculated the mean annual incidence of SSc in 5-year intervals, 1999–2003, 2004–2008, 2009–2013 and 2014–2018.

We collected the exact dates of diagnoses of SSc or the dates of first visits of patients with early SSc, who attained less than 9 diagnostic points and did not fulfill ACR/EULAR 2013 criteria, at the rheumatology in- or outpatient clinics. We analyzed the changes in gender distribution and the mean age at diagnosis, as well as the examination of nailfold capillaries and autoantibody positivity, in the different study periods.

In total 19 of the 291 patients, three from Northern Ostrobothnia and 16 from Southwest Finland, did not have all the baseline data available except for the diagnosis year, however their diagnoses were made by a rheumatologist. Four patients had dcSSc and 15 had lcSSc. Four of these diagnoses were made between 1999–2003, three between 2004–2008, four between 2009–2013 and eight between 2014–2018.

The study data were collected and managed using REDCap electronic data capture tools hosted at the University of Turku (27–28).

Statistics

Continuous variables were presented using means and standard deviations (SD) and for categorical variables, percentages and frequencies were used. Differences between time periods and age of diagnosis were tested using two-way analysis of variance (ANOVA). In the main analyses of incidence using ACR 1980- and ACR/EULAR 2013 classification criteria, differences between time periods were tested using one-way ANOVA. If there was a statistically significant difference between time periods then pairwise comparisons with the first period were performed and Dunnett's correction for p-values was used. Additional analyses were performed on incidence rates using ACR/EULAR 2013 classification criteria which included a diagnosis of the model. A two-way ANOVA was used for the additional analyses. With a statistically significant interaction of the diagnosis and period, the effect of the period in each diagnosis group was tested and if the p-value was significant, then pairwise comparisons between other periods with the first one were carried out and the Bonferroni method was used to correct the p-values. The results were quantified using means and 95% confidence intervals (95% CI). The normality of residuals was checked for justification of the analyses. Differences between time periods in the categorical variables (sex, antibodies) were tested using Chi-squared -test or in cases of small frequencies a Fisher's exact test was used. Two-sided tests were used and p-values less than 0.05 were considered statistically significant. Statistical analyses were carried out using the SAS System for Windows, Version 9.4 (SAS Institute Inc., Cary NC; USA).

Ethical considerations and study permissions

This was a non-interventional retrospective study without direct patient contact. According to Finnish legislation, no patient consent or ethical committee approval was needed. Permissions for the study were obtained from the hospital district of Southwest Finland for Turku University Hospital and the hospital district of Northern Ostrobothia for Oulu University Hospital.

Results

Altogether from 291 individuals with M34 diagnoses 246 new patients were reclassified as having SSc using ACR/EULAR 2013 classification criteria at the rheumatology inpatient or outpatient clinics during years the years 1999–2018 (Table 1). At the end of the same time period 743 075 inhabitants over sixteen years of age were living in these two hospital districts. Occurrence of lcSSc was dominating over dcSSc with both criteria. Of these 291 patients 45 patients were classified as early SSc i.e. they did not meet ACR/EULAR 2013 classification criteria of less than 9 points. Among all 291 individuals with M34 diagnoses, 84.5% fulfilled ACR/EULAR2013 and 26.1% fulfilled ACR 1980 classification criteria (Table 1).

The majority of the patients were female especially in the lcSSc and early SSc cases. The typical age of diagnosis was around fifty years of age (Table 2).

The frequency of autoantibody positivity and abnormal findings in nailfold examinations did not change during the whole study period (Table 3). Anti-centromere antibodies (ACA) were detected in 10.8% in dcSSc, 81.1% in lcSSc and 82.2% in the early SSc group ($p<0.0001$). The percentages of antitopoisomerase (ATA) antibodies detected were 32.4% in dcSSc, 6.3% in lcSSc and in none of early patients ($p<0.0001$). Anti-RNApolymerase III -antibodies (RNAPol III) were not tested due to the lack of availability at the local laboratories until the last few years of the study. Only three patients with dcSSc and 1 early SSc patient were found positive for these antibodies.

The mean annual incidence of SSc can be seen to be increasing between these 5-year periods**,** when ACR/EULAR 2013 criteria are used ($p=0.002$)(Figure 1). When comparing incidence rates in these 5-year periods of time, it was significantly higher in the most recent period compared to the first one (p-value 0.0012) (Table 4).

Discussion

The purpose of this retrospective register study of two hospital districts was to investigate changes in SSc incidence in Finland during a 20-year period (1999–2018). The main finding of this study

was that the incidence of SSc can be observed to have increased throughout the whole study period and the main reason for the growing incidence rate is the implementation of more sensitive classification criteria for SSc i.e. ACR/EULAR2013 criteria. Considering the trend towards growing incidence of SSc before 2013 in this study suggests that increasing knowledge about the disease and better diagnostic tools may have contributed to frequencies of new diagnoses as well.

A meta-analysis with 39 individual studies dealing with incidence of SSc was published in 2021 (24). The methodology and inclusion criteria varied using, for example: the doctor's opinion, ICD codes, LeRoy 1988, LeRoy and Medsger 2001, ACR 1980 and ACR/EULAR 2013 classification criteria. Most of these studies were conducted using ACR 1980-criteria or ICD codes. Only a few studies were done using ACR/EULAR 2013 criteria (19, 21, 29) and one study was performed with both criteria ACR 1980 and ACR/EULAR 2013 (21).

Using ACR 1980-criteria, the incidence of SSc in our study is well in line with those previously reported in northern Europe (15-18, 21). When ACR/EULAR 2013 criteria were used, our incidence rates were generally higher than reported in recent years, especially in the most recent period of 2014-2018 (21,29). In the period between 2009–2013, the SSc incidence of 1.9 per 100,000 seen in our study was same which has been reported in Sweden during the years 2006–2010 (21) and close to that (11.9 per million) which has been reported in Sweden during the years 2004-2015 (22).

The earliest study conducted in Finland in 1996 (17) showed a lower incidence of SSc than shown in any period of our study between years 1999-2018 i.e.four cases per million inhabitants. This incidence rate was based on the special reimbursement allowance for the medication in 1990 in five districts. It is obvious that at that time, only the most severe cases of SSc had been diagnosed and treated with DMARDS or glucocorticoids. The incidence rate of the early Finnish study is comparable to the average incidence rate of SSc during the period 1999–2003 using ACR 1980 criteria in our study.

The results of another Finnish study using 1988 LeRoy and ACR/EULAR 2013 criteria for SSc, showed a higher incidence rate, i.e. 44 per million inhabitants in Northern Savo (Eastern Finland) in 2010 (19). In our study, the average incidence rate with ACR/EULAR 2013 criteria during the period 2009–2013 was lower, i.e. 19.5 per million inhabitants in Northern Ostrobothnia and South-West Finland. The difference is possibly to be due to random variation since the incidence in the previous study was only assessed during one year (19).

The nailfold capillaroscopy device that was acquired by Turku and Oulu University hospitals in 2012 and 2010, respectively,and facilitated the screening of early SSc patients. Growing knowledge about the disease and the use of nailfold capillaroscopy have especially enhanced the diagnostics of early SSc and SSc with mild symptoms. The hypothesis of better screening contributing the incidences was not fully supported by our results since the trend towards growing number of early SSc subjects across the study periods was not statistically significant.

The trend towards higher incidence rates can be seen in many countries as more sensitive criteria are applied (21).

The other aim of our study was also to examine if the age at diagnosis was decreased as the criteria became more sensitive. The mean age at diagnosis of dcSSc patients tended to get younger over the whole study period while the mean age at diagnosis of lcSSc remained similar (between fifty to sixty). There were no statistitically significant changes in any of the groups which suggests that the overall diagnostic delay of SSc could not be reduced with the use of ACR/EULAR criteria. Unfortunately, to verify this we could not calculate disease durations due to limited data of the disease onsets (RP and non-RP were known for 122 and 160 of 246 subjects, respectively).

This study has many strengths including the use of medical records to verify proper diagnosis (instead of using register data with simple ICD codes),the location of study subjects in two distinct

hospital regions and a relatively long study period. By counting the average incidence rates in 5-year periods allowed a reduction in random variations between the years.

The data was collected retrospectively which may predispose misclassification in some subjects due to unclear or incomplete recordings. In addition, at the beginning of our follow-up, milder cases were possibly not detected as the more developed diagnostic tools were not in use. In the Swedish study (21), all patients with a diagnosis of RP in their medical records were reviewed retrospectively. Of these only 7 of the 231 fulfilled ACR/EULAR 2013 criteria, and none fulfilled the ACR 1980 criteria. We assume that including all patients with diagnosed RP would not have had a remarkable impact to our results since those patients that had gone through a full rheumatologic assessment most with capillaroscopy and those with RP diagnoses set were excluded as having SSc. On the other hand, the patients with RP diagnoses set at primary health care lacked the data that would be needed to reclassify them as having SSc.

Another limitation of our study was the missing data from a few subjects at the time of diagnosis. The hospital records included a few patients whose diagnosis had been done in another hospital district. In our opinion this has no impact on the main result, because the proper diagnosis could be verified during the follow-up period at the two university hospitals. Nevertheless, we may have missed a few patients diagnosed and followed up for example, in private clinics or the policlinic of rheumatology provided by primary health care. The common practice in recent years is that all patients with suspected secondary RP are referred at least once for a capillaroscopy at a university or central hospital.

The dcSSc is a rare disease in Finland comprising only 15% of SSc cases diagnosed during 1999-2018. The fact that the autoantibodies against RNA Pol III were provided only during the last few years of the study may have affected the number of dcSSc that remained without known autoantibody specificity but not the number of dcSSc cases because they were not diagnosed without skin involvement. The proportion of ATA positive SSc patients and incidence of dcSSc

were also lower than previously reported from the EUSTAR cohort (30), but it must be noted that the latter may be enriched with more severe cases. In a Swedish population-based study the majority (82%) of prevalent SSc patients had a lcSSc subtype of the disease (21) corresponding our study (84% had lcSSc). In a hospital-based cohort of Norwegian SSc patients, 22 percent were diagnosed having dcSSc (31). We don't think we had missed a significant part of the subjects since dcSSc patients are always followed at tertiary centers in Finland to enable multi-professional treatment**.** It is possible that small sample size and random variation have had a small impact on our results. The low portion of dcSSc in Finland can be confirmed in future studies.

A few SSc specific autoantibodies like anti-fibrillarin, anti-PM-Scl, anti-fibrillin and anti-RNA polymerase I and III have been found, and their use in clinical practice has been increasing during our study. It would be interesting to see the impact of the wider use of different autoantibodies in the classification of SSc in the future.

Conclusion

In our study we found that incidence rates of SSc are increasing due to use of more sensitive classification criteria and obviously due to more efficient screening.

Conflict of interest

S.K. is an investigator in clinical PsA drug studies funded by Abbvie, Pfizer and BMS, has received consulting and speaker fees from Boehringer Ingelheim and scientific meeting attendance support from Roche, Jansen-Cilag and Abbvie, which are all unrelated to this work. J.H. has received consulting and speaker fees from Boehringer Ingelheim, Abbvie, Amgen, Novartis and scientific meeting attendance support from Abbvie, Medac, Novartis and Pfizer, which are all unrelated to this work. M.K. and S.H. have declared no conflicts of interest. J.P. is an investigator in clinical PsA drug studies funded by Lilly, Abbvie, Pfizer and BMS, she has received speaker fee from UCB and scientific meeting attendance support from Medac, Jansen-Cilag and UCB, which are all

unrelated to this work. L.P. is an investigator in clinical PsA drug studies funded by Abbvie, Pfizer and BMS, has received consulting and speaker fees from Abbvie , Boehringer Ingelheim, Jansen-Cilag, Novartis Finland, Sandoz, Eli Lilly and Swedish Orphan Biovirtum, and scientific meeting attendance support from Orion and Sanofi, which are all unrelated to this work.

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Data availability

All data collection and analyzation were performed by authorization of two hospital districts. Owing to Finnish legislation to protect data, the register data used in this study cannot be shared without permission from the Health and Social Data Permit Authority of Finland.

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Figure 1. Comparison of mean annual incidence rates (cases per million inhabitants) using two different classification criteria.

*p=0.002. The difference was statistically significant according ACR/EULAR 2013 criteria but not ACR 1980 criteria (p=0.1530) when the groups were compared.

Table 1. Distribution of subjects by hospital districts and clinical diagnosis according ACR/EULAR 2013 and ACR1980 criteria.

	Southwest Finland	Northern Ostrobothnia	Number of subjects fulfilling ACR/EULAR 2013 criteria	Number of subjects fulfilling ACR1980 criteria*
All SSc	139	107	246	70
dcSSc	30	7	37 (15.0)	29 (41.4)
lcSSc	109	98	207 (84.1)	41 (58.6)
ssSSc	0	2	2 (0.8)	0 (0)
early SSc	36	9	0 (0)	0 (0)

From 291 subjects 246 individuals (84.5%) fulfilled ACR/EULAR 2013 criteria, the rest 45 subjects were presenting an early disease. From the same study population only 70 individuals (26.1%) fulfilled ACR1980 criteria. Number of individuals in different subclasses of systemic sclerosis are shown (percentages). * Data for ACR 1980 criteria were available for 268 subjects. In the different subtypes of the disease, this data was available for 33, 189, 2 and 44 in the subtypes dcSSc, lcSSc, ssSSc and early SSc respectively. At the end of 2018, there were 743 075 inhabitants over sixteen years of age in these two hospital districts combined, 419 405 at Southwest Finland and 323 670 at Northern Ostrobothnia.

Table 2. The number of new diagnoses and mean age at diagnoses in the 5 -year periods.

	1999–2003	**2004–2008**	**2009–2013**	**2014–2018**
All SSc*				
females % (n)	87.1 (27/31)	83.7 (36/43)	75.7 (53/70)	82.4 (84/102)
mean age at diagnosis (SD)	56 (12.1)	56 (14.4)	56 (13.3)	56 (15.0)
dcSSc				
females % (n)	80.0 (4/5)	62.5 (5/8)	50 (4/8)	50 (8/16)
mean age at diagnosis (SD)	59 (19.4)	54 (10.2)	47 (14.5)	51 (17.3)
lcSSc				
females % (n)	88.5 (23/26)	88.2 (30/34)	80.3 (49/61)	88.4 (76/86)
mean age at diagnosis (SD)	55 (10.7)	55 (14.8)	57 (12.2)	58 (13.4)
Early SSc				
females % (n)	100 (2/2)	66.7 (6/9)	76.9 (10/13)	85.7 (18/21)
mean age at diagnosis (SD)	65 (12.0)	60 (16.1)	58 (16.6)	52 (18.3)

No statistically significant difference was found in the age of diagnosis. SD=standard deviation. Two patients with ssSSc are included in the group of lcSSc. *Patients fulfilling ACR/EULAR 2013 criteria.

Table 3. Number of SSc patients having positive autoantibodies and abnormal finding in nailfold capillaries

	1999–2003	**2004–2008**	**2009–2013**	**2014–2018**	**p-value***
Antinuclear-antibodies positive % (n)	86.2 (25/29)	87.8 (43/49)	92.4 (73/79)	91.2 (103/113)	0.4437
SSc-specific antibodies positive % (n)	72.6 (21/29)	85.7 (42/49)	88.5 (69/78)	83.6 (92/110)	0.2401
Antitopoisomerase antibodies positive % (n)	13.8 (4/29)	14.3 (7/49)	7.7 (6/78)	7.3 (8/110)	0.3592
Anticentromere antibodies positive % (n)	58.6 (17/29)	73.5 (36/49)	79.5 (62/78)	72.7 (80/110)	0.1052
Anti-RNA-Pol-3-antibodies ** positive	ND	ND	ND	ND	-
Nailfolds examined positive % (n)	92.8 (13/14)	81.0 (17/21)	76.2 (48/63)	86.5 (90/104)	0.2862

The data for antinuclear and SSc-specific antibodies were available for 268 and 264 subjects respectively. *Fisher´s exact test. **Prior to year 2018 Anti-RNA-Pol-3 antibodies were not tested for all subjects. ND= not determined

Table 4. Mean annual incidence rates (cases per million inhabitants) using ACR1980- and ACR/EULAR 2013 classification criteria.

Classification criteria	**1 (1999–2003)**	**2 (2004–2008)**	**3 (2009–2013)**	**4 (2014–2018)**	**p-value of time**	**p-value between time points**
ACR1980 (CI)*	3.3 (0.7 to 5.8)	4.3 (1.7 to 6.9)	5.0 (2.4 to 7.6)	7.3 (4.8 to 9.9)	0.1530	
ACR/EULAR 2013 (CI) *	9.2 (2.9 to 15.5)	12.3 (6.1 to 18.6)	19.5(13.2 to 25.7)	27.7 (21.4 to 34.0)	0.002	** 0.7960 0.0653 0.0012
dcSSc (CI)***	1.5 (-1.8 to 4.7)	2.3 (-1.0 to 5.5)	2.2 (-1.0 to 5.5)	4.3 (1.1 to 7.6)	0.6327	
lcSSc (CI)	7.7 (4.5 to 11.0)	10.0 (6.8 to 13.3)	17.2 (14.0 to 20.5)	23.4 (20.1 to 26.6)	<0.0001	**** 0.9495 0.0003 <0.0001
early ssc (CI)	0.6 (-2.7 to 3.8)	2.6 (-0.7 to 5.8)	3.6 (0.4 to 6.9)	5.7 (2.5 to 9.0)	0.1725	

*One-way ANOVA, only time period in the model.

***Two-way ANOVA for ACR/EULAR 2013. Time period, clinical subtype (including early systemic sclerosis) and interaction of time period and clinical subtype included in the model. P-value <0.001 for interaction of diagnose and time period.

If there was statistically significant difference between time periods, then pairwise comparisons with first period were performed. **Dunnett´s and ****Bonferroni´s correction used to correct p-values.

The two patients with ssSSc are included in the group of lcSSc, these diagnoses were made in years 2006 and 2009. CI= 95% confidence interval.