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Characteristics of Progressive Systemic Sclerosis in a Cohort of Egyptian Patients

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Abstract

Objective: To estimate the frequency of epidemiological, clinical and laboratory characteristics of progressive systemic sclerosis in a cohort of Egyptian patients.

Methods: Fifty systemic sclerosis patients were included. These patients were subjected to detailed history taking, clinical and rheumatological examination, Measuring the dermal skin thickness by the modified Rodnan skin score (mRSS), Nail fold capillaroscpy (NFC) and the relevant radiological, laboratory and immunological investigations.

Results: Our results revealed that the mean age at time of diagnosis was 32.66 ± 13.08 with the disease durations range from 1 to 40 years with a median of five years. Male to female ratio of 1: 5.2 and 20% of patients were smokers. Skin tightness was present in all patients, the mRSS ranges from 4 to 45 with a mean of 17.48 ± 10.44. ANA was detected in 98%, RF was detected 4%, antitopoisomerase I (antitopo I) was detected in 36% and ACA was detected in 8% of patients. 96% of patient had abnormal NFC. There were statistical significant negative correlations between mRSS and both of FEV_1% and FVC%.

There was also a statistical significant positive correlation between mRSS and FEV_1/FVC.

Conclusion: This study has shown that almost our Egyptian SSC patients have ANA seropositivity, abnormal pulmonary function tests and abnormal nailfold capillaroscopy (NFC). The study revealed that anti topo I antibody seropositivity, ILD, abnormal pulmonary function tests, worsening skin score, late pattern of NFC are more common in Diffuse Cutaneous Systemic Sclerosis (DCSSC) than Limited Cutaneous Systemic Sclerosis (LCSSC).

Also ILD in SSC patients is commonly associated with antitopo I antibody seropositivity, abnormal pulmonary function tests, worsening skin score and late pattern of NFC. Therefore ANA, antitopo I, high resolution CT chest, pulmonary function test, mRSS and NFC should be considered for early diagnosis and follow up of SSC patients.

Keywords: Systemic sclerosis; Modified rodnan skin score; Nailfold capillaroscopy; Diffuse cutaneous systemic sclerosis; Limited cutaneous systemic sclerosis

Introduction

Systemic sclerosis (SSC) is a rare multisystemic connective tissue disease characterised by microvascular damage, fibrosis of the skin and internal organs and specific immunologic abnormalities. The clinical recognisable disease is classified on the basis of extent of skin involvement into subsets with diffuse cutaneous involvement (DCSSC) and limited cutaneous involvement (LCSSC) [1].

Systemic sclerosis (scleroderma, SSC) is an autoimmune disease in which fibrosis of the skin and internal organs occur in association with small vessel vasculopathy and autoantibody production. Organ-specific and non-organ specific impairments lead to a spectrum of mild to severe limitations in physical, work and social activities, ultimately influencing health-related quality of life [2].

As with many other autoimmune disorders, scleroderma is approximately 4–5 times more common in women than men. The average age at the time of diagnosis is approximately 50 years [3].

There are 2 primary clinical subsets of the disease: limited cutaneous and diffuse cutaneous SSC. Limited cutaneous SSC is typically manifested by Raynaud's phenomenon, involvement of acral skin (hands, forearms, face, legs, and feet), gastroesophageal reflux symptoms, and, occasionally, pulmonary hypertension with or without interstitial lung disease (ILD). Nailfold capillaroscopy demonstrates dilated capillary loops, usually without capillary dropout [4].

Diffuse cutaneous SSc typically causes widespread and often early involvement of internal organs. Raynaud's phenomenon, proximal and/or truncal as well as acral skin involvement, arthritis, tendon friction rubs, myositis, ILD, malignant hypertension, diffuse gastrointestinal (GI) disease, and/or myocardial involvement may occur. Nailfold capillaroscopy demonstrates capillary dilatation and destruction [4].

However, not all patients with systemic sclerosis fall clearly into one of these two disease subsets, and some can change their subset assignment over time. Furthermore, some individuals present with hallmark clinical and serological features of systemic sclerosis in the absence of detectable skin involvement (systemic sclerosis sine scleroderma); others manifest features of another connective tissue disease, such as rheumatoid arthritis or polymyositis, in overlap with systemic sclerosis (overlap syndrome) [5].

As in other connective tissue disorders such as systemic lupus erythematosus, ethnicity has a role in systemic sclerosis [6].

A striking feature of systemic sclerosis is its patient-to-patient variability, and heterogeneity has been observed in clinical manifestations, autoantibody profiles, tempo of disease progression, response to treatment and survival. On the basis of the extent of their skin involvement, patients are grouped into limited cutaneous systemic sclerosis (LCSSC) and diffuse cutaneous systemic sclerosis (DCSSC) subsets [5].

The aim of this study was to estimate the frequency of epidemiological, clinical and laboratory characteristics of progressive systemic sclerosis (PSS) in a cohort of patients from Egypt to elicit any difference from that of other ethnic group.

Patients and Methods

Study design

This is a cross-sectional cohort study in which 50 adult patients, diagnosed with progressive systemic sclerosis according to the 2013 American College of Rheumatology/ European League Against Rheumatism Systemic Sclerosis classification criteria [7], were recruited from the outpatient clinic and inpatient departments of rheumatology in Ain Shams university and military hospitals in the period between November 2014 to September 2016.

Study protocol

For all patients the followings were done:

Detailed history taking, and clinical and rheumatological examination with special emphasis on age, gender, occupation, family history, smoking, duration of disease, medications and cardiac, pulmonary, renal, gastrointestinal and neuropsychiatric manifestations.

Measuring the dermal skin thickness by the modified Rodnan skin score (mRSS) in 17 evaluated areas. These areas are the face, anterior chest, anterior abdomen, and 7 bilateral sites including the upper arm, forearm, dorsum of the hand, fingers, thigh, lower leg, and dorsum of the foot. The grading of the mRSS is as follows: 0=normal, 1=thickened skin, 2=thickened and unable to pinch, 3=thickened and unable to move [8].

Laboratory and immunological profile: A blood sample was drawn from each patient to measure: CBC,ESR,CRP, AST, complete urine analysis, serum creatinine, calculated creatinine clearance by Cockcroft-Gault Equation, CrCl=(140-age) × weight in Kilogram/(Scr × 72) (× 0.85 for females) [9], RF, ANA, Antitopoisomerase I antibodies and Anticentromere antibodies.

Assessment of internal organ affection according to individual patient presentation by: Plain X-rays of the chest, High resolution CT chest (HRCT) without contrast, ECG and Echocardiography, Pulmonary function tests (PFTs), Abdominal Ultrasonography, Nail fold capillary microscopy.

Ethical consideration

The participating patients gave their written informed consent, and the study protocol was approved by the regional ethics committee at Ain Shams University and military hospitals.

Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 15.0; SPSS, Chicago, IL, USA). All data was expressed as mean and standard deviation (Mean ± SD) for quantitative and parametric data. Mode was used for quantitative non parametric (extreme values) data.

Qualitative (categorical) data was expressed as numbers and percentages. For comparative statistical analysis, Student's t test was performed for quantitative variables in two independent groups; ANOVA (f) test was performed for quantitative variables in more than two independent groups. Mann-Whitny (Z) test was performed for non-parametric quantitative variables in two independent groups.

Kruskal-Wallis (K) test was performed for non-parametric quantitative variables in more than two independent groups. Pearson Correlation coefficient (r value) test was done to correlate between two quantitative data in the same group.

Spearman Correlation coefficient test was done to correlate between two non-parametric quantitative data in the same group. Chi square (X^2) test was done to compare qualitative (categorical) variables between two or more proportions. The significance level was calculated as $P<0.05$=significant.

Results

This study was conducted on 50 adult Egyptian patients diagnosed as progressive systemic sclerosis with a mean age 41.36 ± 12.71 years and a mean age at diagnosis of 32.66 ± 13.08 years. Eight patients (16%) were males and 42 patients

(84%) were female. Disease durations range from 1 to 40 years with a median of five years (Table 1).

Table 1: Demographic and clinical characteristics of patients with SSC (50).

Parameter		Number=50 (or mean ± SD)	Percentage (%)
	Females	42	84
	Males	8	16
	Disease duration	5 Years	1 to 40
	Age (mean ± SD)	41.36 Years	± 12.71
Demographic	Smoking	10	20
	Tightness	50	100
	Puffy fingers	39	78
	Digital tip ulcers	34	68
	Pitting scars	36	72
	Telangiectasia	37	74
	Calcinosis	16	32
Cutaneous	Raynaud's	47	94
	Weight loss	30	60
Constitutional	Fatigue	45	90
	GERD	42	84
	Dysphagia	29	58
	Constipation	14	28
GIT	Diarrhea	13	26
	Arthralgias	43	86
	Muscle weakness	39	78
Musculoskeletal	Tendon friction rub	12	24
	PAH	9	18
	ILD	25	50
Pulmonary	Dyspnea	38	76
	HTN	13	26
Cardiovascular	Palpitation	18	36
Renal manifestations		10	20
	Neuropathic pain	27	54
	Headache	25	50
	Depression	26	52
	Stroke	1	2
	Dementia	19	38
	Seizures	3	6
	TIA	7	14
Neuropsychiatric	Psychosis	1	2

PAH: paulmonary artery hypertension, ILD: interstitial lung disease, HTN: hypertension, TIA: transient ischemic attack

The commonest clinical presentation in our SSC patients (50) was the cutaneous lesions in 100% of cases followed by equal percentages (90%) regarding constitutional, GIT, musculoskeletal, and neuropsychiatric manifestations, followed by pulmonary and cardiovascular manifestations in 88% and 40% of cases respectively, however, renal manifestations were the least common recorded in 20% of cases (Table 1). The mRSS was ranging from 4 to 45 with Mean ± SD of 17.48 ± 10.44. The most common affected site is fingers (100%), then face (78%), hands (70%), feet (56%), forearms (42%), legs (36%), arms (30%), thighs (28%), chest (26%) and the least affected site is the abdomen (20%) (Table 2).

Table 2: Modified rodnan skin score (mRSS) in SSC patients (50).

Parameter	Mean ± SD or No.=50 (%)
mRSS/51	17.48 ± 10.44
Face	39 (78.0%)
Arms	15 (30%)
Forearms	21 (42.0%)
Hands	35 (70.0%)
Fingers	50 (100.0%)
Chest	13 (26.0%)
Abdomen	10 (20.0%)
Thighs	14 (28.0%)
Legs	18 (36.0%)
Feet	28 (56.0%)

The mRSS was ranging from 4 to 45 with Mean ± SD of 17.48 ± 10.44. The most common affected site is fingers (100%), then face (78%), hands (70%), feet (56%), forearms (42%), legs (36%), arms (30%), thighs (28%), chest (26%) and the least affected site is the abdomen (20%) (Table 2). Sixteen patients (32%) were presented with anemia, of them 11 patients (22%) presented with iron deficiency anemia and 5 patients (10%) presented with anemia of chronic illness. ANA was detected in 49 patients (98%), RF was detected in two patients (4%), anti-topoisomerase I was detected in 18 patients (36%) and anti-centromere antibody (ACA) was detected in 4 patients (8%) (Table 3).

Table 3: Laboratory findings in SSC patients (50).

Item	Mean ± SD or No.=50 (%)
RBC'S (millions/cc)	4.25 ± 0.56
Hb (gm/dl)	11.60 ± 1.81
MCV	78.50 ± 7.26
MCH	26.21 ± 3.79
WBCS (thousands/cc)	6.74 ± 2.22
Platelet (thousands/cc)	256.30 ± 90.95
ESR (mm/1st hour)	30 (21 to 45)
CRP (mg/dl)	6 (5 to 10)
AST (u/dl)	25.60 ± 12.60
ALT (u/dl)	17 (15 to 22)
Urea (mg/dl)	32.64 ± 14.27
Creatinine (mg/dl)	0.77 ± 0.35
Calculated Cr. Clearance	120.00 ± 40.81
Albuminuria present (No./%)	5 (10.00%)

Granular cast present (No./%)	1 (2.00%)
Positive ANA (No./%)	49 (98%)
Positive RF (No./%)	2 (4.0%)
Positive Anti topo I (No./%)	18 (36.0%)
Positive Anticentromere (ACA)	4 (8.0%)
RBC: red blood corpuscles, Hb: hemoglobin, MCV: mean cell volume, MCH: mean cell hemoglobin, WBC: white blood cells, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST:aspartate aminotransferase, ALT: alanine aminotransferase, ANA: ant nuclear antibodies, RF: rheumatoid factor, Anti topo I: anti topoisomerase I antibodies.	

Regarding to pulmonary diseases in our study, 44 patients (88%) had abnormal PFTs, of them 42 patients (84%) had restrictive lung disease versus 2 patients (4%) had obstructive lung disease. 25 patients (50%) were presented with pulmonary fibrosis detected by HRCT chest. Regarding PAH, it was recorded in 9 patients (18%) (Tables 4-6).

Table 4: Radiological and ECG findings in SSC patients (50).

Item	Result	Number=50	Percentage (%)
CT chest	Free	24	48.00%
	Basal pulmonary fibrosis	25	50.00%
	Minimal pleural reaction	1	2.00%
ECG	Free	43	86.00%
	Hypertensive strain	1	2.00%
	PVCS	2	4.00%
	Right BBB	1	2.00%
	SVTC	3	6.00%
Echocardiography	Negative	36	72.00%
	MR	5	10.00%
	AR	2	4.00%
	PAH	9	18.00%
	TR	4	8.00%
	Concentric LV hypertrophy	1	2.00%
	Dilated Rt side	1	2.00%
Abdominal US	Free	44	88.00%
	Fatty liver	1	2.00%
	Grade I nephropathy	1	2.00%
	Grade III nephropathy	1	2.00%
	Hepatomegaly	3	6.00%
	Splenomegaly	2	4.00%
	Hepatosplenomegaly	2	4.00%

Table 5: Pulmonary function tests (PFTs) in SSC patients (50).

Item		No.=50 (%)or Mean ± SD
PFT	Mild restriction	15 (30.0%)

	Moderate restriction	13 (26.0%)
	Normal	6 (12.0%)
	Severe obstruction	2 (4.0%)
	Severe restriction	14 (28.0%)
FEV_1%	Mean ± SD	66.12 ± 19.01
FVC	Mean ± SD	63.56 ± 22.18
FEV_1/FVC	Mean ± SD	108.17 ± 22.25

Table 6: Nailfold capillaroscopic finding in SSC patients (50).

Item		No. =50 (%) or Mean ± SD
Abnormal NFC		48 (96.0%)
No. of capillaries (Mean ± SD)		6.90 ± 1.76
Enlarged cap		48 (96.0%)
Mega cap		29 (58.0%)
Hemorrhage		33 (66.0%)
Loss of cap		38 (76.0%)
Cap. Ramification		2 (4.0%)
Tortuous cap		1 (2.0%)
Pattern	Normal	2 (4.0%)
	Early	28 (56.0%)
	Active	13 (26.0%)
	Late	7 (14.0%)
Staging	0	2 (4.0%)
	I	12 (24.0%)
	II	19 (38.0%)
	III	10 (20.0%)
	IV	7 (14.0%)
Scoring	0	2 (4.0%)
	1	18 (36.0%)
	2	20 (40.0%)
	3	9 (18.0%)
	4	1 (2.0%)

The 50 SSC Patients were classified also according to presence of ILD into 2 groups, those with ILD (25 patients) and those without ILD (25 patients), and comparative statistical analysis were done and shown in the following Table 7. The 50 SSC Patients were classified also according to presence of pulmonary hypertension (PAH) into 2 groups, those with PAH (9 patients) and those without PAH (41 patients), and comparative statistical analysis were done and shown in the following table (Tables 8 and 9).

Table 7: Comparison between SSC patients with or without ILD.

Item	No ILD	ILD	P- value

Cardiovascular		5 (20.0%)	15 (60.0%)	0.004
Dysphagia		11 (44.0%)	18 (72.0%)	0.045
Dementia		6 (24.0%)	13 (52.0%)	0.041
Anti-topoisomerase I positivity		5 (20.0%)	13 (52.0%)	0.018
mRSS/51(median ± range)		9 (4 to 34)	20 (8 to 45)	0.002
PFTs(Mean ± SD)	FEV_1%	74.35 ± 20.44	57.88 ± 13.37	0.001
	FVC%	74.65 ± 21.46	52.48 ± 16.96	0
	FEV_1 /FVC	101.72 ± 23.49	114.62 ± 19.30	0.039
NFC Pattern	Normal	0 (0.0%)	2 (8.0%)	0.025
	Early	14 (56.0%)	14 (56.0%)	
	Active	10 (40.0%)	3 (12.0%)	
	late	1 (4.0%)	6 (24.0%)	

Table 8: Comparison between SSC patients with or without PAH.

Item		No PAH	PAH	P-value
Age (Mean ± SD)		39.51 ± 12.41	49.78 ± 11.09	0.027
FEV_1% (Mean ± SD)		70.15 ± 17.50	47.75 ± 14.82	0.001
Renal affection		6 (14.6%)	4 (44.4%)	0.043
Dysphagia		21 (51.2%)	8 (88.9%)	0.038
Sicca complex		16 (40.0%)	7 (77.8%)	0.04
NFC hemorrhage		30 (73.2%)	3 (33.3%)	0.022
NFC Pattern	Normal	2 (4.9%)	0 (0.0%)	0.031
	Early	24 (58.5%)	4 (44.4%)	
	Active	12 (29.3%)	1 (11.1%)	
	Late	3 (7.3%)	4 (44.4%)	

Table 9: Correlation (r) between mRSS and some clinical data.

Item	MRSS/51	
	r	P-value
FEV_1%	- 0.462	0.001
FVC%	- 0.47	0.001
FEV_1 /FVC	0.299	0.035
	median (range)	P-value
Pulmonary affection	17 (6 to 45)	0.025
ILD	20 (10 to 45)	0.002

Discussion

Systemic sclerosis (SSC) is an orphan disease with an annual incidence of 19 per million and prevalence of 19-75 per 100,000 in the western countries. The female:male ratio is 3:1, and it increases in mid to late childbearing years to 8:1. Aside from varying prevalence of internal organ involvement, Raynaud's phenomenon and skin involvement are two major hallmarks clinically characterize SSC [10]. The aim of this study was to estimate the frequency of epidemiological, clinical and laboratory characteristics of progressive systemic sclerosis in a cohort of Egyptian patients to elicit any differences from that of

other ethnic groups. In our study the patients age range from 16 to 67 years with a mean age at diagnosis of 32.66 ± 13.08 years. 84% of the patients were females whereas 16% were males with female to male ratio of 5.2:1. The disease durations range from 1 to 40 years with a median of five years. These findings are comparable to the results of previous large studies [11-13]. Twenty percent of the patients were smokers but we failed to find associated significant relations of smoking to either skin tightness (mRSS), raynaud's, digital tip ulcers, interstitial lung disease (ILD), pulmonary hypertension (PAH), internal organ affection, and nail fold capillaroscopy (NFC).

Similar results were obtained in 2 other studies [14,15]. On the other hand, a large Canadian study (606 SSC patients) focused on cigarette smoking and the disease manifestations of SSC [16], found that cigarette smoking had negative effects on the vascular, gastrointestinal and respiratory outcomes of SSC. Moreover, that study also demonstrated that smoking cessation actually improved vascular complications of SSC like Raynaud's phenomenon.

In our Egyptian cohort study sclerodactly was the commonest cutaneous manifestation present in 100% of patients then puffy fingers in 78%, raynaud's phenomena in 94%, telangiectasia in 74%, pitting scars in 72%, digital tip ulcers in 68%, and the least was calcinosis in 32% of patients. Among the cutaneous manifestations of 46 patients from eastern India; Raynaud's phenomenon was present in 84.8% sclerodactyly in 82.6%, fingertip ulceration and scarring in 63%, telangiectasia in 23.1%, puffy finger in 8.7%, cutaneous calcinosis 2.2% [12]. In another Brazilian study conducted on 32 patients, skin sclerosis and Raynaud's phenomenon present in 100% of patients, digital scars in 65.6%, telangiectasia in 43.7%, and calcinosis in 12.5% [17]. The mean modified rodnan skin score (mRSS) in this study was 17.48 ± 10.44 (4 to 45). It showed significant positive association with pulmonary manifestations, abnormal pulmonary function tests (PFTs), and interstitial lung disease (ILD) and there was significant negative correlation between mRSS and forced vital capacity (FVC%).

Similar results presented by Ooi and colleagues who reported that mRSS was 21.2 ± 9.9 (2 to 46) in a total of 45 Chinese SSC patients. They also found that mRSS had positive relationship with ILD and abnormal PFTs [18]. In agreement, Bhakuni et al. reported that mRSS was 15.5 ± 8.4 in a total of 42 Indian SSC patients and there was significant increase in the mean mRSS score for DCSSC versus LCSSC (22.1 ± 5.6 versus 8.2 ± 2.8) [19]. Regarding ILD (50%), it was significantly associated with higher skin score, cardiac involvement, low FVC%, and anti-topoisomerase I seropositivity.

Similar findings were detected in another study [20]. Also, ILD in our patients was significantly associated with the late pattern of nialfold capillaroscopy (NFC) and the same finding was reported by by other researchers [21]. In our study 88% of patients had inadequate PFTs (The mean FVC% was 63.56 ± 22.18%). 30% of patients had mild restriction, 26% had moderate restriction, 28% had severe restriction, and 4% had severe obstruction while 12% of patients had normal PFTs. Sumphao-Ngern et al. studied the medical records of PFTs in 249 SCC cases, of them 73 (29.3%) patients had inadequate PFTs (The mean FVC% was 69.2 ± 14.7% predicted), 52.7% had mild restrictive lung disease, 21.8% had a moderately restrictive lung disease [22]. It was reported that 40 to 75% of SSC patients have reduction in FVC, with 15% having a severe reduction (FVC ≤ 50% predicted) in another study [23]. Also, it was reported that 16% of 953 SSC patients presented with severe restrictive lung disease (forced vital capacity<55% of predicted) in a different study [24].

In a Spanish study, ILD was detected in 43% of patients, the mean FVC% was 85 ± 22, while FVC<70% was detected in 25% of patients [14]. Concerning the serological finding in our study, ANAs were detected in 98%, Anti-topoisomerase I antibodies were detected in 36%, Anti-centromere (ACA) antibodies were detected in 8%, RF was detected in 4%, of patients. In a large US study (706 SSC patients), ANAs were found in 89.3%, anti-topoisomerase I antibodies were found in 19.6% (18.1% in whites and 22% in blacks) and Anti-centromere antibodies were observed in 22.1% (27% in whites and 9.7% in blacks) of tested patients [13].

In another study done in Malaysian rheumatology center, ANAs were positive in 83.6% and anti-Scl 70 antibodies were positive in 34.4% [25]. A different study reported that antinuclear antibodies were present in 67%, anti-SCL-70 autoantibodies in 28% and RF in 25.9% of tested patients [26]. Tolosa-Vilella et al. observed that ANAs were found in 91%, ACA in 45% and anti-topoisomerase antibodies in 22% of 1326 Spanish SSC patients [14]. The lower percentages of ACA prevalence in our results may be related to the darker skin color in our SSC cases and lower cases with isolated pulmonary hypertension (two cases) where ACA is commonly associated with the white races and isolated pulmonary hypertension. Also similar findings were reported that SSC Patients with combined PAH and ILD were diagnosed at an older age than patients with ILD alone, and had a lower incidence of ACA positivity, a higher incidence of anti-topoisomerase positivity and DCSSC when compared to SSC-PAH alone [27]. In conclusion, this study has shown that almost our Egyptian SSC patients have ANA sero-positivity, abnormal pulmonary function tests and abnormal nail fold capillaroscopy (NFC). Also LCSSC is more common than DCSSC in our SSC patients. Anti-topoisomerase I (anti topo I) antibody sero-positivity, ILD, abnormal pulmonary function tests, worsening skin score, late pattern of NFC are more common in DCSSC. Also ILD in SSC patients is commonly associated with antitopo I antibody sero-positivity, abnormal pulmonary function tests, worsening skin score and late pattern of NFC. Therefore ANA, antitopo I, high resolution CT chest, pulmonary function test, mRSS and NFC should be considered for early diagnosis and follow up of SSC patients.

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