SPECTRUM OF SYSTEMIC SCLEROSIS IN PATIENTS PRESENTING TO A TERTIARY CARE HOSPITAL IN PAKISTAN

Taqdees Khaliq, Wajahat Aziz, Abid Farooqi

Pakistan Institute of Medical Sciences, Islamabad

ABSTRACT

Objective: To examine the clinical and laboratory features in the patients of systemic sclerosis coming to a tertiary care hospital in Islamabad, Pakistan.

Study Design: Observational cross-sectional study.

Place and Duration of Study: Study was conducted at the department of Rheumatology in Pakistan Institute of Medical Science between May 2012 and April 2013.

Subjects and Methods: Both male (n=5) and female (n=40) patients of Systemic sclerosis (SSc) who presented in the Rheumatology outpatient department (OPD) were recruited in the study with informed consent. All the patients enrolled in the study fulfilled the American College of Rheumatology (ACR) criteria for diagnosis of SSc.

Results:: The mean age of the patients was 35.77 ± 13.10 years. Out of 45 patients, 28 (62%) had limited cutaneous systemic sclerosis (LcSS) and 17 (38%) had diffuse cutaneous systemic sclerosis (DcSS). Mean duration of disease was found to be 4.72 ± 4.78 years. Anti-nuclear antibody (ANA) positivity was seen in 80% of the patients. The most common clinical feature of the disease was Raynaud's phenomenon (100%) followed by microstomia (98%), sclerodactyly (91%), digital pitting (89%), digital ulcers (82%) and arthralgias (73%). Among the constitutional symptoms fatigue was the most common one reported by 93% of the patients.

Conclusion: Clinical features of systemic sclerosis examined in this cohort of patients were found to be consistent with the findings from other Asian countries.

Keywords: Anti nuclear antibody (ANA), Diffuse cutaneous systemic sclerosis (DcSS), Limited cutaneous systemic sclerosis (LcSS), Raynaud's phenomenon.

INTRODUCTION

Systemic sclerosis is an autoimmune disease of unknown aetiology, characterized by fibrosis of skin along with various other parts of the body. It is a multisystem disorder affecting almost every organ system like skin, gastrointestinal system, lungs, heart and kidneys. It is a debilitating disease with potentially life threatening consequences[1].

Prevalence of systemic sclerosis is variable in different parts of the world and ranges from 7/million to 489/million. Its incidence ranges from 0.6/million/year to 122/million/year[2]. Systemic sclerosis is more prevalent in America and Australia as compared to European countries[2]. However, figures from Asian countries are not available.

Correspondence: Dr Taqdees Khaliq, PIMS, Islamabad
Email: taqdeeskhaliq@gmail.com
Received: 12 Aug 2013; Accepted: 31 Dec 2013

The diagnosis of SSc is mainly clinical although certain criteria have been proposed to classify patients with scleroderma. The most commonly used ones are American College of Rheumatology criteria for systemic sclerosis[3] proposed in 1980 and LeRoy-Medsger criteria[4]. Clinically this disease can be divided into two main subtypes;

Limited Cutaneous Systemic Sclerosis[5] where there is skin involvement distal to elbows and knees.

Diffuse Cutaneous Systemic Sclerosis[5] involvement of skin of limbs extending proximal to elbows and knees along with involvement of the trunk.

Other than the extent of skin involvement, the frequency of different features of SSc is different in both types. This has been linked to the presence of different antibodies in both these subsets[6]. Many registries have been formed worldwide which keep a record of different

presentations of the disease along with the record of different treatments that these patient are put on[7]. This serves as a basis for research as well as a means to assess patient response to different treatment strategies and in doing so also keeps the medical professionals up-to-date on latest advances in this field. No such database is available from Pakistan and although autoimmune profile of SSc patients has been studied, no studies describing the clinical spectrum of SSc have been done, so, disease kinetics is not known in Pakistan. With this background in mind, this particular study was conducted to see the clinical spectrum of SSc in a tertiary care hospital in Islamabad where mainly patients from the capital city and its neighbouring areas as well as from Khyber Pakhtunkhwa (KPK) and Azad Kashmir present

MATERIAL AND METHODS

The study was conducted at the Department of Rheumatology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. It was a cross-sectional observational study. All new and previously diagnosed patients of SSc, who were being followed in the department, were enrolled in the study. Epidemiological, clinical and laboratory data of each patient was collected on an approved proforma after taking consent from each patient. Only those patients were included in the study who fulfilled the American College of Rheumatology criteria for SSc. Patients with mixed connective tissue disease, overlap syndromes or having localized SSc i.e. morphea were excluded from the study.

Detailed history including age, marital status, duration of disease and different clinical features of the disease was taken from each patient. This was followed by a thorough examination to look for different signs of SSc. Routine blood tests like blood complete picture, erythrocyte sedimentation rate (ESR), liver and renal function tests as well as special tests for SSc like ANA, extractable nuclear antigen (ENA) profile, anti-centromere antibody test and anti-Scl 70 antibody tests were performed. The involvement of lungs in the form of interstitial lung disease (ILD) was investigated by performing X-ray chest and pulmonary function tests. The patients with any abnormality in x-ray or pulmonary function tests but with a clear chest on auscultation were asked to have a high resolution CT (HRCT) scan to rule out presence of early changes of interstitial lung disease. Echocardiography was ordered in all the patients to look for evidence of pulmonary arterial hypertension (PAH) and also for cardiac involvement in the form of diastolic dysfunction. A patient was defined as having PAH if systolic pulmonary arterial pressure was found to be equal to or more than 40 mm Hg. Although right heart catheterization is the gold standard for diagnosis of PAH, studies have shown that right ventricle systolic pressure (RVSP) ≥ 40 mm Hg can also reliably diagnose this condition with a sensitivity of 83% and specificity of 72%, but to monitor the disease activity and treatment response cardiac catheterization should be used[8]. ECG of each patient was also obtained to rule out any conduction defects.

Extent of skin involvement was also checked because it is known that higher skin scores are associated with increased activity of the disease and poorer outcome. Modified Rodnan skin score (mRSS) was calculated to determine the extent of skin involvement in the patient. Joint involvement was described as presence of arthritis or arthralgias of more than one joint. Microstomia (reduction in size of oral aperture) was also looked for in the patients. Oesophageal involvement in the form of dysphagia was based on history only; it could not be confirmed by barium swallow in all the patients.

Scleroderma renal crisis is one of the most dreaded complication of the disease and all the patients were also screened for its presence. A patient was said to have scleroderma renal crisis if he/she presented with abrupt onset of moderate to severe hypertension along with features suggestive of acute renal failure.

Data was entered in Microsoft Office Excel 2007 and was analyzed for descriptive statistics.

RESULTS

Total 45 patients, 5 (11%) males and 40 (89%) females, were enrolled in the study after taking consent. Male to female ratio was 1:8. Out of these, 62 (28%) of the patients had LcSS and 38% (17) had DcSS with an LcSS to DcSS ratio of 1.6:1. Mean duration of disease was 4.72 ± 4.78 years. The mean age of patients was 35.77 ± 13.10 years (range 12-65 years). Frequency of different features of SSc in two subsets of the disease has been shown in table-1. Microstomia was noted in 98% of patients. Scleroderma renal crisis was seen in 7% 0f patients, 2 in DcSS group and 1 in LcSS group. Out of these 3, 1 patient died after presenting to hospital. Proteinuria without florid renal crisis was noted in another 14% of patients. No other cause of proteinuria could be found in these patients. Abortions were also commonly reported by married females. Out of 40 female patients, 32 were married and 9 out of these reported past history of abortion with an incidence of 28%; early abortions were relatively commoner than late abortions. Constitutional symptoms were also reported by the patients with fatigue being the commonest feature reported by 93% of the patients. During the study period, 2 patients became pregnant and 4 patients died (3 because of PAH and 1 from a non SSc related cause). Cardiac involvement in the form of conduction abnormalities was seen in 2 patients, one patient had complete heart block for which a pacemaker had to be implanted while the other one had multifocal atrial tachycardia.

Table-: Frequency of different features of systemic sclerosis.

Clinical features	Patients (% age)		Total
	Limited SSc	Diffuse SSc	
Raynaud's phenomenon	100%	100%	100%
Telengiectasia	43%	35%	40%
Calcinosis	14%	6%	11%
Digital pitting	93%	82%	89%
Digital ulcers	79%	88%	82%
Sclerodactyly	89%	94%	91%
Arthralgias / Arthritis	75%	71%	73%
Joint flexion contractures	50%	70%	58%
Dysphagia	54%	53%	53%
Interstitial lung disease	50%	65%	56%
Pulmonary hypertension	14%	12%	13%
Renal crisis	4%	12%	7%

DISCUSSION

This study was done to examine different clinical and immunological features of systemic sclerosis and to compare them with data available from other countries. So far no studies describing the clinical spectrum of SSc have been done in Pakistan whereas data from many countries is available for literature review including that from many Asian countries like Singapore, Malaysia, Iran, China and India etc.

It is clear from the study that there is a lot of variation in clinical presentations of scleroderma. It was seen that patients with DcSS suffered more from complications of the disease as has already been described in literature[9]. The female to male ratio was 8:1 which is consistent with an Iraqi cohort (8.3:1)[10] and an Indian cohort (8.2:1)[11]. Recently conducted studies in Asian countries show figures of 9.2:1 from Iran and 10.9:1 from a Chinese European Scleroderma Trial and Research Group (EUSTAR) database[12].

Raynaud's phenomenon which is the most common feature of this disease[13] was found in 100% of the patients in this study. Studies conducted on Asian cohorts show slightly lower

frequencies between 80.5% to 94.1%[12,14-16]. Digital pitting and digital ulcers, which develop as a consequence of long standing Raynaud's phenomenon, were seen in 89% and 82% of patients respectively. This frequency is higher than that reported from other Asian countries. Reason probably is higher frequency of Raynaud's phenomenon in this cohort. Almost all the patients (97%) had GI involvement either in the form of dysphagia, gastroesophageal reflux, early satiety, diarrhoea, constipation or alternating diarrhoea and constipation. Most common of all of these was dyspepsia (75%). Dysphagia was reported by 53% of the patient while gastro-oesophageal reflux disease (GERD) was noted in 38% of the study population. Previous studies have shown a frequency of dysphagia between 21.8 – 87%[16].

Lung and heart involvement is also very common in systemic sclerosis patients. These two are in fact the major causes of death in this disease[17]. In our study interstitial lung disease (ILD) was found in 56% of the patients. It was more common in DcSS (65%) than in LcSS (50%). This figure is close to the ones reported from Singapore (51.8%)[14] and Malaysia (52.2%)[15]. Previous studies have also shown that incidence of ILD is higher in diffuse variety of SSc[18]. However, in our study we found that LcSS patients also had quite a high incidence of ILD. The reason for this could be that in LcSS, ILD develops quite late in the course of the disease. And since this cohort of patients was from a tertiary care hospital, the patients referred had had this disease for quite some time and thus had developed most of the complications of the disease. Pulmonary hypertension was seen in 13% of patients and this is similar to figures from two Malaysian studies (11.5% and 13%)[21,15]. Incidence was almost equal in both the groups; DcSS 12% and LcSS 14%.

Renal involvement is also seen in scleroderma patients. Different manifestations of the disease include asymptomatic microalbuminuria to nephrotic range proteinuria, reduced renal functional reserve, isolated reduced glomerular filtration rate and most important of all, scleroderma renal crisis[19]. Before the era of angiotensin converting enzyme (ACE) inhibitors , scleroderma renal crisis used to be the major cause of death in these patients but now the incidence has dropped down to around 5%[20]. In our study population 3 patients (7%) developed renal crisis.

ANA was found to be positive in 80% and this figure is consistent with figures from India (78.2%)[11], Singapore (78.7%)[14] and Malaysia (83.6%)[21]. Other Asian countries report ANA positivity of less than 80%[10,15,22]. On the other hand, literature review from European cohorts shows an ANA positivity of more than 90%, 90.2% from Germany[23], 92.2% from Spain[24] and 93.4% from EUSTAR database[25]. Results for anticentromere antibody were available for 8 patients only and had a 12.5% positivity. Anti-Scl 70 results were available for 30 patients and had a 20% positivity. No significant correlation of these antibodies could be found with any of the disease subset.

Constitutional symptoms in the form of fatigue, malaise, weight loss and anorexia are also commonly reported by SSc patients and those with other rheumatologic diseases[26]. In this cohort, fatigue was the commonest symptom reported by 93% of the patients followed by weight loss (52%) and anorexia (47%). However, this should be noted that weight loss was based on history only; it could not be recorded for all the patients in the clinic. This clearly depicts the high burden of disease on the patients, affecting not only their quality of life but also their psychological well being. It would be worth studying this separately based on quantitative measures so that effective measures can be taken to improve the over all well being of the patients.

A few deficiencies of the study need to be high-lighted. Firstly, the sample size is too small so the results of this study cannot be generalized. Secondly, complete antibody screening of these patients could not be done even though it is known that a few clinical features of scleroderma are influenced by presence or absence of anti

centromere and anti-Scl 70 antibody. We could not find out such associations as complete antibody profile was not available for all the patients. Nevertheless, this study can serve as a pilot study, on the basis of which future studies can be done.

CONCLUSION

It was found that spectrum of systemic sclerosis was quite similar to that observed in other Asian countries. It is recommended that a national registry of systemic sclerosis and other rheumatologic diseases be made for detailed evaluation of these patients and different treatment strategies.

REFERENCES

1. Cossio M, Menon Y, Wilson W, deBoisblanc BP. Life threatening complications of systemic sclerosis. Crit Care Clin. 2002; 18(4): 819-39.
2. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheu. 2008; 37(4): 223-35.
3. Subcommittee for Scleroderma Criteria of American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for classification of systemic sclerosis (scleroderma). Arthritis Rheum. 1980; 23: 581-90.
4. LeRoy EC, Medsger TA Jr. Criteria for the Classification of Early Systemic Sclerosis. J Rheumatol. 2001; 28: 1573-6.
5. Krieg T, Takehare K. Skin disease: a cardinal feature of systemic sclerosis. Rheumatology. 2009; 48 (suppl 3): iii14-iii18.
6. Hamaguchi Y. Antibody profiles in systemic sclerosis: predictive value for clinical evaluation and prognosis. J Dermatol. 2010; 37(1): 42-53.
7. Galluccio F, Walker UA, Nihtyanova S, Moinzadeh P, Hunzelmann N, Kreig T et al. Registries in Systemic sclerosis: a world wide experience. Rheumatology (Oxford). 2011; 50(1): 60-8.
8. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. Heart. 2011; 97(8): 612-22
9. Ostojic P, Damjanov N. Different clinical features in patients with limited and diffuse cutaneous systemic sclerosis. Clin Rheumatol. 2006; 25(4): 453-7.
10. Al-Adhadh RN, Al-Sayed TN. Clinical features of systemic sclerosis. Saudi Med J. 2001; 22(4): 333-6.
11. Ghosh SK, Bandyopadhyay D, Saha I, Barua JK. Mucocutaneous and Demographic features of Systemic Sclerosis: A profile of 46 patients from Eastern India. Indian J Dermatol. 2012; 57 (3): 201-5.
12. Xu D, Li MT, Holi Y, Wang Q, Bai YN, Song N et al. Preliminary analysis of Chinese patients with systemic sclerosis – from Chinese EUSTAR database. Int J Rheu Dis. 2010; 13(suppl.1): 181-91
13. Denton CP, Korn JH. Digital ulceration and critical digital ischemia in scleroderma. Scleroderma Care Res. 2003; 1: 12-6.
14. Low AHL, Teng GG, Law WG, Ng SC, Santosa A, Chan G et al. Disease characteristics of the singapore systemic sclerosis cohort. Proc Singapore Healtc. 2013; 22(1): 8-14.
15. Teh CL, Kuan YC, Wong JS. Systemic Sclerosis in Sarawak: a profile of patients treated in the Sarawak General Hospital. Rheumatol Int. 2009; 29(10): 1243-5.
16. Sharma VK, Trilokrai T, Khaitan BK, Krishna SM. Profile of systemic sclerosis in a tertiary care center in North India. Indian J Dermatol Venereol Leprol. 2006; 72(6): 416-20.
17. Ranque B, Mounthon L. Geoepidemiology of systemic sclerosis. Autoimmum Rev. 2010; 9(5): A311-8.
18. Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. Arthritis Rheum 2009; 60(2): 569-77.
19. Shanmugam VK, Steen VD. Renal manifestations in scleroderma: Evidence for subclinical renal disease as a marker of vasculopathy. Int J Rheumatol. 2010; pii: 538-89.
20. Mouthon L, Berezne A, Bussone G, Noel LH, Villiger PM, Guilleven L et al. Scleroderma renal crisis: a rare but severe complication of systemic sclerosis. Clin Rev Allergy Immunol. 2011; 40(2): 84-91.
21. Pagalavan L, Ong SG. Demogrphy, clinical and laboratory features of systemic sclerosis in a Malaysian Rheumatology Center. Med J Malaysia. 2007; 62(2): 117-21.
22. Krishnamurthy V, Porkodi R, Ramakrishnan S, Ragendran CP, Madhavan R, Achuthan K et al. Progressive systemic sclerosis in South India. J Assoc Physicians India. 1991; 39(3): 254-7.
23. Hunzlemann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M et al. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. Rheumatology (Oxford) 2008; 47(8): 1185-92.
24. Simeon-Aznar CP, Fonollosa-Fla V, Tolosa-Villela C, Espinosa-Garriga G, Ramos-Casals M, Campillo-Grau M et al. Registry of Spanish network for systemic sclerosis: clinical pattern according to cutaneous subsets and immunological status. Semin Arthritis Rheum. 2012; 41(6): 789-800.
25. Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis. 2012; 71(8): 1355-60.
26. Sandusky SB, McGuire L, Smith MT, Wigley FM, Haythornthwaite JA. Fatigue an overlooked determinant of physical function in scleroderma. Rheumatology (Oxford) 2009; 48(2): 165-69.