Profile of systemic sclerosis in a tertiary care center in North India

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ABSTRACT

Aim: To study the clinical and immunological profile in patients of systemic sclerosis from North India and compare it with other ethnic groups. **Methods:** Patients presenting to us between the years 2001 and 2004 and fulfilling the American Rheumatism Association (ARA) criteria for systemic sclerosis were included. There were 84 females and 16 males with the mean age of 32.5 ±11.62 years and a mean duration of 6.49 ± 4.34 years. All patients were admitted to the dermatology ward for detailed history and examination including Rodnan score. Investigations including hemogram, hepatic and renal functions, serum electrolytes, urine for albumin, sugar, microscopy and 24h urinary protein estimation, antinuclear antibody, chest X-ray, barium swallow, pulmonary function test, electrocardiogram and skin biopsy were done. **Results:** The most common presenting symptoms were skin binding-down (98.5%), Raynaud's phenomenon 92.9%, pigmentary changes 91%, contracture of fingers 64.6%, fingertip ulcer 58.6%, restriction of mouth opening 55.5%, dyspnea 51.1%, joint complaints 36.7% and dysphagia in 35.2%. The mean Rodnan score was 25.81 ± 10.04 and the mean mouth opening was 24.6 ± 19.01 mm. The laboratory abnormalities included raised ESR in 87.8%, ANA positive in 89.1%, proteinuria in 6.0%, abnormal chest X-ray in 65.3%, abnormal barium swallow in 70.2% and reduced pulmonary function test in 85.8%. **Conclusion:** The clinical and immunological profile of systemic sclerosis in North India is similar to that of other ethnic groups except that pigmentary changes are commoner and renal involvement is relatively uncommon.

Key Words: Anti-nuclear antibody, Ethnic groups, Pigmentary changes, Systemic sclerosis

INTRODUCTION

Systemic sclerosis (SS) is a multi-system connective tissue disorder characterized by thickening of the skin and involvement of other organs like kidney, lung, gastrointestinal system and heart. It is characterized by excessive accumulation of collagen and other extracellular matrix components and damage to the endothelium of the small vessels resulting in hyperplasia and tissue ischemia and activation of the immune system.[1] SS has been well described from the West[2-7] and recently, ethnic variations in the clinical and immunological profile have been reported. The data from India, especially on cutaneous manifestations of SS is still lacking.[8,9] We studied the clinical and immunological profile in patients of SS from North India and compared it with other ethnic groups.

METHODS

All the patients who were admitted to the

How to cite this article: Sharma VK, Trilokraj T, Khaitan BK, Krishna SM. Profile of systemic sclerosis in a tertiary care center in North India. Indian J Dermatol Venereol Leprol 2006;72:416-20.

Received: January, 2006. **Accepted:** April, 2006. **Source of Support:** Nil. **Conflict of interest:** None declared.

dermatology ward from March 2001 to May 2004, who fulfilled the ARA criteria for the diagnosis of systemic sclerosis were recorded. Patients who had overlap with dermatomyositis, systemic lupus erythematosus, mixed connective tissue disease and other connective tissue diseases were excluded. Patients who were admitted to the dermatology ward were evaluated in detail. This included history and clinical examination and assessment of disease severity by Rodnan skin scoring system and measurement of mouth opening. Baseline investigations included a complete blood count, blood glucose, serum electrolytes, renal function tests, urine examination (albumin, sugar, microscopic examination and 24h protein), ANA, chest and hand X-rays, barium swallow and pulmonary function test (spirometer, PK Morgan Ltd.™, England). All these variables were expressed in mean, standard deviation and frequencies.

RESULTS

One hundred patients (84 females and 16 males) of systemic sclerosis were studied. The age of the patients was between 12 and 72 years with mean age of 32.75±11.62 years. The duration of disease varied from one month to 17 years with a mean duration of 6.49±4.34 years. The clinical and laboratory profiles are summarized in Tables 1 and 2 respectively. The types of pigmentary abnormalities noted were diffuse pigmentation in 88.1%, mottled hypo-depigmentation (salt and pepper-like pigmentation) in 51.2% and depigmentation at the sites of scars in 31.3%. The antinuclear antibody was demonstrated in 89.1% and speckled pattern (62.1%) was most common followed by nucleolar pattern (21.6%) and homogenous pattern (9.4%) [Table 3]. The Rodnan skin scores varied from 7 to 54, the mean score was 25.81±10.04. The restriction of mouth opening scale varied from 10 mm to normal mouth opening, the mean score was 24.6±19.01 mm. The various abnormalities found on the chest X-ray were ground glass appearance in 32 (45.7%), reticular shadows in 28 (40%), honeycombing in seven (10%), nodular opacity and paratracheal lymph nodes in three (4.2%). The X-ray of hands was done in 36 patients and the abnormalities which were detected were as follows: acrosteolysis in 21, osteoporosis in seven and contractures in 10 patients. The abnormalities seen in the barium study were reduced peristalsis in 55 (93.2%), narrowing of lumen in one (1.6%) and dilatation of esophagus in 13 (27.1%). None of these patients had any renal crises or severe hypertension. The renal abnormalities found in these patients were elevated 24h urinary proteins. Skin biopsy showed dermal fibrosis of moderate to severe degree in 68%, pulled up appendages in 65%, flattening of epidermis in 18% and in the rest it was normal.

Table 1: Clinical profile of systemic sclerosis in north India and comparison with different ethnic groups

Clinical features	Present study (n=100)	South Indian study[8] (n=78)	Iraq study[13] (n=75)	Thailand study[11] (n=222)	Whites[12] (n=79)	Hispanics[12] (n=54)	African American[12] (n=28)
Raynaud's phenomenon	92.9	28.2	100	94.1	86	93	96
Skin sclerosis	98.5	100	96.5	100	46	61	62
Restricted mouth opening	55.5	-	-	-	-	-	-
Finger tip ulceration	58.6	47.4	-	53.6	49	61	82
Finger tip resorption	46.6	7.8	-	-	80	87	89
Contracture of fingers	64.6	-	-	-	-	-	-
Gangrene of fingers	6.7	-	-	-	-	-	-
Pigmentation	91.0	73.1	83	-	51	59	82
Diffuse pigmentation	88.1	-	-	-	-	-	-
Mottled pigmentation	51.2	-	-	-	-	-	-
Scar depigmentation	31.3	-	-	-	-	-	-
Telangiectasia	36.8	-	58	9.5	53	61	14
Dyspnea	51.1	19.2	57.4	44.6	-	-	-
Dysphagia	35.2	21.8	87	41.9	52	54	57
Joint complaints	36.7	66.7	96	52.3	-	-	-
Skin rash	3.3	-	-	-	-	-	-
Renal dysfunction	6.0	10.3	9	5.8	23	24	25

All figures in table are in percentages

Table 2: Laboratory profile of systemic sclerosis in north India and comparison with different ethnic groups

Laboratory profile	Present study (n=100)	South Indian study[8] (n=78)	North Indian study[9] (n=87)	Western study[12] (n=727)	White[12] (n=79)	Hispanics[12] (n=54)	African[12] American (n=28)	Thailand study[11] (n=222)
ESR elevation	87.8	70.5	75.3	72	-	-	-	-
Proteinuria	6.0	-	19.5	14.9	-	-	-	-
Chest X-ray abnormalities	65.3	21.8	26.8	33.7	14	22	32	-
Barium swallow abnormalities	70.2	20.4	33.2	44.3	62	63	71	41.9
Abnormal pulmonary function test	85.8	55.0	65.8	-	-	-	-	44.6

All figures in table are in percentages

Table 3: Antinuclear antibody profile of systemic sclerosis in north India and comparison with different ethnic groups

Antinuclear antibodies (indirect immunofluoresence)	Present study (n=83)	North Indian study[9]	Western study[12]	Whites[12] (n=191)	Hispanics[12] (n=77)	African Americans[12] (n=77)	Thailand study[11] (n=222)
Total positivity	89.1	83.7	65.3	79	86	84	85.6
Speckled	62.1	70.9	81.2				45.8
Homogenous	9.4	22.5	15.6				4.7
Nucleolar	21.6	4.8	3.1	23	34	34	7.9
Rim	1.3	-	-				4.7
Anti centromere	1.3	-	-	18	32	4	-
Speckled + nucleolar	1.3	0	0				*

•Speckled +peripheral = 36.8%, all figures in table are in percentages

DISCUSSION

All the 100 patients fulfilled the ARA (1980) criteria for the diagnosis of SS.[10] There was female preponderance, the male to female ratio being 1:5.2, which is well documented in the literature.[1-4,6] Twelve patients (13.3%) were below 20 years and, of these, four patients were males, in contrast to the finding by Medsger *et al* where none of the males were below 25 years.[2] The mean age of our patients was 32.75±11.62 years, similar to the previous series from India[8,9] and Thailand[11] but lower than the Western series.[2-4] The mean duration of the disease was 6.75±4.53 years, which was longer than the previous study (three years) from the same institute,[9] but was similar to the study from Thailand.[11] In another study, It has been reported that Hispanics had longer disease duration (30±20 months) compared to African Americans and whites (24±21 and 21±18 months) respectively.[12] The patients presenting to the dermatology department may have longer duration of disease compared to those presenting to other departments with acute symptoms.

The frequency of Raynaud's phenomenon in our patients was similar to the various studies from other parts of the world, except the study reported from the southern part of India where it was 28.2%, probably due to the hot climate prevalent throughout the year.[8] Binding down of skin was recorded in all the patients, which is similar to previous studies (range 96.5-100%). Fingertip ulceration was noted in 58.6% which was also nearly similar to that of previous studies (range 35-53%).[2-9] In a recent study it was found that fingertip ulcer and scars were higher in African Americans compared to Hispanics and whites.[12] The mean Rodnan score was 25.81±10.04 which was higher compared to a recent study which compared the three ethnic populations. The whites, Hispanics and the African Americans had scores of 14±19, 15±12 and 16±15 respectively.[12] This could be due to longer duration of illness in our patients compared to the above study.

The highlight of this study was the increased pigmentary disturbance observed in 91% of the patients, and which was the third common manifestation of systemic sclerosis, when compared to the previous studies (36.8-83%).[2,3,8,9] It was also one of the complaints at presentation in many patients (43 patients), especially depigmentation as a presenting complaint in 11 of them, the rest of the patients reported on enquiring. Pigmentary disturbances were common among the African Americans compared to the Hispanics and whites.[12] It was also noticed that similar higher pigmentary

disturbances were found in the Iraqi patients.[13] The most common pigmentary disturbance in our study was diffuse hyperpigmentation (88.1%) followed by mottled pigmentation (51.2%) and scar depigmentation (31.3%) which have not been reported in earlier studies. The most common site of telangiectasia was observed in the periungual region (36.8%) which is higher compared to previous North Indian study (8%).[9] A recently conducted study [Table 1] on the three ethnic populations showed a significantly lower proportion of the whites with diffuse skin involvement, digital pits and scars, hypo/hyperpigmentation as compared to the Hispanics and African Americans but a higher proportion of facial telangiectasia.[12]

Dysphagia was seen in 35.2% patients, but one previous study has shown increased incidence of gastrointestinal symptoms (50.5%), probably due to inclusion of other gastrointestinal manifestations like reflux, epigastric pain and eructation. About 51.1% of patients had dyspnea which was similar to the previous study but which was in contrast to a South Indian study (19.2%).[8,9] The joint complaints (36.7%) and renal dysfunction (6%) was similar to previous studies.[8,9]

In the laboratory profile [Table 2], the chest X-ray, barium swallow study and pulmonary function tests showed higher rate of abnormalities compared to previous studies. This could be due to longer duration of illness in our patients compared to the previous studies.[2,3,8,9] The incidence of changes in the X-ray of hands was found to be higher as compared to the previous study.[9]

The frequency of antinuclear antibodies (ANA) in different ethnic groups varied from 65.3 to 85.6 % [Table 3]; our figure of 89.1% was similar to the previous study from India (83.7%)[2] but comparatively higher than the Western studies.[2-4] A recent study from the United States showed ANA to be positive in 86%, 84% and 79% Hispanics, African Americans and Whites respectively.[12] The ANA positivity in Iraqi and Thai patients were 67% and 85.6% respectively.[11,13] The ANA was less frequently positive (77.9%) in limited type than in the diffuse SS (91.3%).[13] The higher rate of diffuse / homogenous pattern (22.5%) and combination of speckled and peripheral pattern of ANA reported in previous studies was not observed.[9,11] But, in contrast we found nucleolar pattern being the second most common pattern (20.5%). In another study of 276 patients from Sweden, nucleolar pattern was associated with pulmonary fibrosis ($p < 0.01$) and cardiomegaly ($p < 0.05$). Anticentomere antibodies were related to organic vasculopathy ($p < 0.05$) and renal involvement ($p < 0.01$), but not to pulmonary fibrosis ($p < 0.01$). A nucleolar pattern and antihistone antibody (AHA) were both associated with a decreased survival [relative risk of death 1.71 ($p < 0.05$) and 2.36 ($p < 0.01$), respectively]. The AHA and a nucleolar HEp-2 cell pattern may indicate critical organ involvement and predict a reduced survival in SS patients.[14] High rate of positivity for the nucleolar pattern in our study could also explain the high rate of pulmonary involvement in our patients. In another study antinucleolar antibodies were more frequent in Thais (71%) compared to the Australians (25%) and anticentromere antibodies were more common in Australians (51%) versus Thais (2%). There was high frequency of diffuse scleroderma in the Thai patients (100%) versus. 15% of the Australian patients.[15] It is becoming evident that several genetic factors participate in modulating the susceptibility to SS and its clinical manifestations. Some genes that specifically affect extracellular matrix protein metabolism and vascular function may be unique to SS and scleroderma-related disorders; others, such as those genes involved in regulating immune tolerance, are likely shared with other autoimmune diseases. This suggests that environmental or genetic factors may influence the expression of scleroderma.[16]

The study also confirms that renal involvement is less frequent in our patients compared to the Western literature. Renal involvement was reported in 23-40% in Western countries in contrast to our figures, which are similar to that of Iraq and Thailand[11,13] and previous Indian studies, emphasizing that racial variation in frequency of renal involvement in systemic sclerosis could occur, although marginal increase in renal involvement reported from the same institute could be because patients with renal

involvement would have directly presented to the medicine or rheumatology departments.

In conclusion, we reiterate that systemic sclerosis follows the same pattern of clinical manifestations as in the western countries, albeit with varying frequency. The pigmentary disturbance was found to be the third most common manifestation of systemic sclerosis. The diffuse pattern of ANA was less frequent than the nucleolar pattern. The renal involvement was relatively less frequent compared to the Western series.

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