Original Article

Antibody profile in systemic sclerosis patients: A cross-sectional study from Kashmir Valley of India

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Abstract

Objective This study aimed to find the prevalence of the most common antibodies in patients of systemic sclerosis and to ascertain their prevalence with the limited and diffuse cutaneous variants of systemic sclerosis.

Methods Thirty-four patients of systemic sclerosis, attending the dermatology department, diagnosed as per the American Rheumatology Association criteria were recruited for this cross-sectional study. They were classified as having limited and diffuse systemic sclerosis. All patients were subjected to serum estimations of antinuclear antibodies, anticentromere antibodies and anti-Scl70 antibodies. The results were tabulated and analyzed for possible association between disease subsets and antibodies.

Results There were 27 patients with limited disease and 7 with diffuse disease. Antinuclear antibodies were seen in 76.5% of all patients. Anticentromere antibodies were seen in 9 (33.3%) limited disease patients and 1 (14.3%) in diffuse variant. The total prevalence of anticentromere antibodies was 29.4%. Anti-Scl70 antibodies were found in 5 (18.6%) and 3 (42.9%) patients of limited and diffuse disease subset, respectively. Overall, these antibodies were seen in 23.5% patients.

Conclusion Anticentromere antibodies are more common in limited systemic sclerosis while anti-Scl70 antibodies are seen more frequently in diffuse systemic sclerosis. Thus, these antibodies can act as a marker of future disease activity, severity of disease and prognosis.

Key words
Anti-centromere antibody, antinuclear antibody, anti-Scl70 antibody, systemic sclerosis.

Introduction

Systemic sclerosis (SSC) is a multisystem autoimmune connective tissue disease with a variable and unpredictable course.[1] The exact etiology remains unknown, but the role of both environmental and genetic factors has been suggested.[2] The disease characteristically shows vasomotor abnormalities, fibrosis and consequent inflammation.[3] It presents with thickening and fibrosis of the skin and various other organs like kidneys, lungs, heart and gastrointestinal tract.[4] SSC has been principally divided into two forms: limited and diffuse SSC. The limited SSC presents as sclerotic changes of the distal extremities and face and features like telangiectasia, calcinosis and late-onset of pulmonary hypertension. Diffuse SSC involves the trunk in addition to the extremities, presents

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with early involvement of various organ systems of the body and tendon friction rubs.[3]

The presence of serum autoantibodies against various nuclear and cytoplasmic antigens has been described as a hallmark of SSC and has been referred to as the most evident expression of humoral dysfunction in these patients.[5,6] Apart from having diagnostic value, these antibodies also help in classification of the disease into one of the two major subtypes and therapeutic response, thus having a prognostic value.[7,8] This study aimed to identify the prevalence of the three major antibodies found in SSC and to correlate it with the limited and diffuse subsets of SSC. The authors couldn't find any such study from this part of the world which inspired them to undertake this cross-sectional study.

Methods

This cross-sectional study was undertaken in the postgraduate department of dermatology, STD's and Leprosy, Government Medical College, Srinagar, Kashmir, India from January 2012 to December 2013 (total 2 years duration). There were 58 patients of systemic sclerosis in total. Eight patients had only one antibody status known; six patients couldn't afford antibody profiling; five patients had two antibodies done; two patients were diagnosed as mixed connective tissue disease, two had overlap with lupus erythematosus and one with overlap with dermatomyositis. Out of these 58, only 34 patients of systemic sclerosis, diagnosed on the basis of the American College of Rheumatology (ACR) classification criteria, were included in this study.[9] Patients were enquired about the social and demographic history of their disease parameters like age, sex, duration of disease and age of onset. SSC patients were divided into limited SSC and diffuse SSC according to Le Roy classification. After this, they underwent laboratory tests to detect the presence or absence

of antinuclear antibody (ANA), anticentromere antibody and anti-Scl70 antibody. These tests were done using the Enzyme Immunoassay method. Patients suspected to have overlap with other connective tissue diseases like lupus erythematosus, or mixed connective tissue disease were excluded from the study. Patients with none, one or two antibodies status known were excluded. Only those patients who were screened for all the three antibodies were included in the study. These parameters were then assessed for any possible correlation between the positivity of tests and clinical parameters of the disease. Appropriate statistical tests were used for analysis. The data were tabulated and mean, standard deviation and percentages of the groups were determined. SPSS software version 20.0 was used for statistical analysis

Results

The general characteristics of the patients in the study have been outlined in **Table 1**. A total of 34 patients presented to us during the study period that satisfied the ACR criteria. Of these, there were 30 (88.2%) female patients and 4 (11.8%) male patients. The mean age of the patients was 43.3 years with a standard deviation of 14.4 years. The mean age of onset of the disease was 35.1 years, with a standard deviation of 13.6 years. The mean duration of the disease was 8.2 years and the standard deviation was 6.1 years.

Table 1 Basic characteristics of the patients in the study (n=34).

Characteristics	Number
Males	4 (11.8%)
Females	30 (88.2%)
Mean age of onset of disease	35.1 ± 13.6 years
Mean duration of disease	8.2 ± 6.1 years
Limited SSC	27 (79.4%)
Diffuse SSC	7 (20.6%)

Table 2 Antibody profile in systemic sclerosis patients (n=34).

Antibody	Limited (n=27)		Diffuse (n=7)		Total (n=34)	
	N	%	N	%	N	%
ANA	19	70.8%	7	100%	26	76.5%
Anticentromere	9	33.3%	1	14.3%	10	29.4%
Anti-Scl 70	5	18.6%	3	42.9%	8	23.5%

The antibody profile of the total number of patients, as well as, the limited and diffuse subset of patients has been tabulated in **Table 2**. ANA was positive in 26 (76.5%) patients, anticentromere antibodies were seen in 10 (29.4%) patients and 8 (23.5%) patients out of the 34 had anti-Scl70 antibodies. Of those 27 patients with limited systemic sclerosis, 19 had ANA positivity. This formed 70.8% of the patients in the limited group. 9 patients had anticentromere antibodies and 5 patients of limited disease had anti-Scl70 antibodies. Thus, anticentromere antibodies were seen in 33.3% of the limited group patients and anti-Scl70 antibodies were seen in 18.6% of the limited group. ANA was positive in all patients of the diffuse form of the disease, i.e. 20.6% of the total number of patients and 100% of the diffuse group. Anticentromere antibody was seen in 1 patient and anti-Scl70 was seen in 3 patients. This makes for 14.3% and 42.9% of the patients with diffuse disease, respectively.

Discussion

The aim of our study was to identify the prevalence of the three main antibodies found in SSC in the regional population and to study these antibodies in the two disease subsets: limited and diffuse SSC. Most of our patients (88.2%) were females. SSC is found predominantly in women and studies have reported female to male ratios as high as 10:1.[10,11] The mean age of onset of disease in our patients was 35.1 years and they presented to us after a mean duration of 8.2 years. These findings are in concordance with other studies that have reported that SSC is a disease with a mean onset in the fourth decade of life.[10-12] It has

been proposed that SSC patients that present to the dermatology outpatient departments have comparatively fewer symptoms and this could be reason for the long duration of symptoms seen in our patients before presenting to us.[13] Of the total 34 patients, 27 (79.4%) patients had limited disease while 7 (20.6%) patients had diffuse systemic sclerosis. Previous studies also indicate that the limited type is the predominant form of the disease.[14,15]

Antibodies in systemic sclerosis have been described in 75% to 96% of patients in different studies.[16,17] In many cases, the antibodies predate the occurrence of the disease manifestations, thus serving as an alarm.[18] Our findings fall in this spectrum as serum antibodies were seen in 26 (76.5%) of our patients. All of these 26 (76.5%) patients tested positive for antinuclear antibodies. Most studies have identified antinuclear antibodies to be present in around 60-90% patients,[13,19,20] with a few case series showing positivity in slightly more than 90% patients.[21,22]

Anticentromere antibodies were seen in a total of 10 (29.4%) patients in the present study. Of these, 9 (33.3%) patients had limited disease while only one (14.3%) had diffuse disease. Thus, the present study showed that anticentromere antibodies are more commonly seen in limited SSC. A similar percentage of 30% patients was found to have this antibody in a Brazilian study.[23] Several studies in the literature have revealed that the prevalence of antibodies in SSC is to the tune of 20-50%.[24-26] The presence of anticentromere antibodies has been found to be around 50-80% in limited disease.[27] However, our study showed a slightly

lower percentage of antibodies in this disease subset than other studies, probably due to ethnic differences.[24] These antibodies are said to be associated with limited cutaneous disease, calcinosis and involvement of peripheral vessels and lesser chances of interstitial fibrosis of the lungs.[26]

The anti-Scl70 antibodies, also referred to as anti topoisomerase antibodies, were seen in 8 (23.5%) patients in the study. These comprised of 5 (18.5%) patients from limited group and 3 (42.9%) patients from the diffuse group. This indicates that anti-Scl70 antibodies are more frequently seen in diffuse systemic sclerosis. An Iranian study evaluated the presence of this antibody by various techniques and found that around 30% patients were positive for these antibodies.[28] A literature search also shows that this number is somewhere between 30-50%.[25,26] The prevalence of anti-Scl70 antibodies in diffuse subset is highly variable and ranges from as low as slightly more than 20% to around 70% of all patients.[24-26] This antibody has been correlated with diffuse skin involvement, greater disease severity, interstitial lung disease, cardiac involvement and a worse prognosis.[29]

Another class of antibodies commonly seen in systemic sclerosis is the anti-RNA polymerase III. It has a variable and lower percentage ranging from 6% to 25% in different regions.[30] It is associated with diffuse disease subset, tendon friction rubs and severe renal involvement.[31] However, due to unavailability this antibody testing was not done in our patients. A unique observation seen in SSC is that the presence of anticentromere antibodies and anti-Scl70 antibodies in a single patient in rare, though the two are not mutually exclusive.[32] This was seen in our study as well, where we found that patients having one of the two antibodies tested negative for the other.

Limitations

There were certain limitations in our study. Only major antibodies like ANA, anticentromere and anti-Scl70 were tested. Other antibodies like anti-RNA polymerase III, anti-endothelial, anti-centriole antibodies, etc. were not screened for because of unavailability and economic restrictions. The clinical correlation between various organ system involvement and antibody positivity could not be studied as the study was designed to investigate mainly the prevalence of antibodies and their relation to the disease subsets.

Conclusion

This study found that a large number of systemic sclerosis patients have circulating antibodies in their blood. The anticentromere antibodies are associated with limited disease subset, which has a comparatively better prognosis. The diffuse subset of patients, who have more severe disease and a poorer prognosis are more likely to test positive for anti-Scl70 antibodies. Thus, the estimation of these antibodies can help in the classification of the disease into limited and diffuse cutaneous subsets and in turn may help to predict likely clinical course and estimate the likely prognosis of systemic sclerosis patients.

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