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AUTONOMIC STATUS IN SYSTEMIC SCLEROSIS IN INDIA

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Abstract : Systemic sclerosis (SSc) is a systemic connective tissue disease characterized by vasomotor disturbances. Autonomic dysfunction has been implicated in the pathogenesis of various symptoms in patients with SSc. In this retrospective study, thirty patients with SSc as cases and thirty age matched healthy subjects were enrolled as controls. The patients as well as controls were subjected to a standard battery of autonomic tests including reactivity and activity (tone) tests. Resting autonomic variables like blood pressure (BP), heart rate (HR) and respiratory rate (RR) were also recorded. In our study, we found significantly higher HR and RR in the patient group (P=0.0001 and 0.012 respectively). We also observed significantly lower parasympathetic tone and parasympathetic reactivity in SSc patients than the controls. This study shows the status of autonomic functions in SSc patients in India, with lower central parasympathetic drive to the heart. The present study may give some insight for better understanding of this multisystem disorder of unknown etiology.

Key words : systemic sclerosis, autonomic reactivity tests, autonomic tone, resting autonomic parameters

INTRODUCTION

Systemic sclerosis (SSc) is a systemic connective tissue disease associated with vasomotor disturbances. Endothelial alterations leading to a cascade of stimulatory changes that involve many cells, including fibroblasts precede the excessive collagen deposition in skin and internal organs. SSc has a worldwide distribution and no racial preponderance exists. Although the disease can occur at any age, the prevalence increases with age and the peak incidence is between third and fifth decade. There is a substantial female predominance, with a female-to-male ratio of 3–6:1; even more often during the mid to late childbearing years (≥8:1). Raynaud's phenomenon, the initial symptom of SSc in the majority of patients, is a clinical expression of the abnormal regulation of blood flow resulting from vascular injury (1).

In a healthy person, the autonomic nervous system regulates blood pressure, heart rate, sleep, bladder and bowel function.

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There is a strong influence of sympathetic nervous system on myocardial contractility and some effect on heart rate control, whereas vagi essentially influence heart rate (2). Autonomic dysfunction has been implicated in the pathogenesis of various symptoms such as Raynaud's phenomenon, digital infarct, dysphagia etc. in patients with SSc (3–6). Parasympathetic dysfunction is known to characterize the early stage of gut wall involvement in SSc (7). Ferri et al showed that SSc is characterized by parasympathetic dysfunction and possibly associated with sympathetic overactivity (8). Sympathetic derangement may occur before SSc manifests and may lead to greater morbidity and mortality from cardiovascular events (9). Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation even in healthy middle-aged and elderly subjects and increased mortality has been reported in these settings (10). An autonomic imbalance in sympathetic system may interact with inflammatory processes in SSc to play an important role in the process of atherosclerosis. Clinical manifestations in our population are slightly different than Western population. In India, an increased incidence of interstitial lung diseases has been reported, but there is a very low incidence of calcinosis, talengiactesis and isolated pulmonary hypertension (11). Since Indian SSc patients behave differently, we felt that autonomic function might also differ. Moreover, to the best of our knowledge, there is no study reported from Indian patients till date. Therefore, this study was planned to study the autonomic status in patients with SSc in India.

METHODS

In this hospital based retrospective study, thirty patients with systemic sclerosis were included as cases who attended the Rheumatology Clinic at the All India Institute of Medical Sciences during Dec. 2003 to July 2005. Patients were diagnosed after a thorough history (nature and duration of symptoms, drug treatment) and physical examination fulfilling the ACR criteria (12). Appropriate laboratory investigations, including autoantibody profile were done in all patients. Patients with diabetes mellitus and scleroderma overlap syndrome were excluded. Thirty sex and age balanced controls comprising doctors, housewives, security guards, lab technicians were included as controls.

Autonomic function testing

The patients as well as controls were subjected to a battery of autonomic reactivity and activity tests. Two-hours fasting was assured prior to testing including all beverages. All the tests were done during the day time between 11 a.m. and 4 p.m.. First, blood pressures (BP), heart rate (HR), respiratory rate (RR) were recorded in each subject after 10–15 minutes rest. The activity test included Heart rate variability (HRV) which was analyzed after recording continuous ECG for 5 minutes in standard test conditions. HRV is a measurement (quantification) of central autonomic drive (activity) to the myocardium. For the HRV recording and analysis Nevrokard software (version 6.4.0), manufactured by Medistar,

Solvenia, was used. The time and frequency domain analysis was done.

The autonomic reactivity tests refer to cardiovascular responses to stimuli. ECG and respiration were recorded continuously on a moving chart. To assess parasympathetic reactivity, HR response to lying to standing test (LST), deep breathing test (DBT) and Valsalva maneuver tests were analyzed. For the assessment of sympathetic reactivity, BP response to LST, hand grip test (HGT), and cold pressor test (CPT) were analyzed. The details of these tests have been described earlier (13).

Statistical analysis

To compare the results, independent sample 't' test and nonparametric tests (Mann-Whitney) were applied as applicable for the analysis of autonomic function tests in the patients and healthy controls. The data are expressed as mean ± SD for normally distributed data and elsewhere the data are expressed as median and range.

RESULTS

There were 30 patients (27 females and 3 males) whose autonomic reactivity was compared with healthy controls (26 females and 4 males). The mean age of patients and control group was not different (32.1 ± 8.6 Vs 29.6 ± 6.3 years, P=0.194). Also the mean BMI (Kg/m^2) of the two groups was comparable. The mean duration of disease before presentation was 4.9 years (6 months – 15 years). Nineteen patients had limited cutaneous scleroderma and 11 patients had diffuse cutaneous variant. Raynaud's phenomenon was present in majority (86%) of the patients but evidence of digital ischemia was found in 15 (50%) patients. No patient had calcinosis cutis. Cutaneous telangiectasias were observed in 5 (16%) patients. Dysphagia was seen in 20 patients and arthralgia was present in 18 patients. Clinical and radiological investigations revealed interstitial lung disease in 78.5% patients. None of these patients had any major coronary artery diseases. Anti nuclear antibody (ANA) was positive in all the patients.

HRV could be analyzed only in 26 patients and compared with age (patients 32.3 ± 8.4; controls 31.9 ± 7.2 years; P=0.565) and sex matched (24 females and 2 males in both groups) healthy controls. The resting HR and RR were significantly higher (Table I) in the patient group. The parasympathetic reactivity (E:I ratio, Valsalva ratio and 30:15 ratio) was significantly lower in the patients with SSc (Table II). Parasympathetic tone was also significantly lower, reflected by low NN50 (Number of R-R interval differences equal or more than 50 milliseconds), HF (power of high frequency band), HF (nu) (high frequency in normalized unit) while sympatho-vagal balance (LF/HF ratio) was high, in the patient group (Table III).

TABLE I: Resting autonomic variables.

Parameters	*Controls*	*Patients*	*P value*
Systolic BP (mm Hg)	110.6±8.7	111.9±16.3	NS
Diastolic BP (mm Hg)	70.7±7.9	72.8±9.9	NS
Heart Rate (per minute)	74.9±9.3	87±14.0	0.0001
Respiratory Rate (per minute)	19.7±4.1	23.4±6.6	0.012

The data are expressed as mean±SD.

TABLE II: Comparison of sympathetic and parasympathetic reactivity of SSc patients with healthy controls.

Parameters	*Controls*	*Patients*	*P value*
DBT (delta HR)	27.73±8.56	23.73±12.0	NS
E:I ratio	1.49±0.33	1.30±0.16	0.009
Valsalva ratio	1.85±0.45	1.59±0.30	0.026
HGT	16±6.56	13.04±5.62	NS
CPT	14.07±7.67	13±6.55	NS
LST (delta SBP)	–5.4±5.23	–5.66±6.12	NS
30:15 ratio	1.34±0.25	1.20±0.13	0.009

The data are expressed as mean±SD.

Abbreviations:
DBT - Deep breathing test.
E:I ratio - expiration: inspiration ratio.
HGT - Hand grip test.
CPT - Cold pressor test.
LST - Lying to standing test.

TABLE III: Autonomic tone: heart rate variability in patients with SSc versus healthy controls.

Parameters	*Controls*	*Patients*	*P value*
NN50	38 0–107	3.5 0–131	0.001
PNN50	11.2 0–32.5	0.8 0–35.8	0.0001
LF	462.5 55.2–1781	157.5 9.8–1473.4	0.0001
LF (nu)	38.8 6–72.5	52.7 10.4–81.5	NS
HF	633.9 29.6–4552.6	83.7 2.2–706.7	0.0001
HF (nu)	49.5 13.3–92.8	20.6 7.9–135.5	0.0001
LF/HF	0.8 0.1–5.5	2.1 0.3–7.3	0.0001
Total power (ms×ms)	1808.7 269.4–7357.6	470.9 35.5–2450.8	0.0001
Total power (nu)	131.5 92.4–444.2	157.1 32.4–316.1	NS

The data are expressed as mean and range.

Abbreviations:
NN50 - Number of R-R interval differences equal or more than 50 milliseconds.
PNN50 - Percentage of NN50.
LF - Power of low frequency band.
LF (nu) - Low frequency in normalized unit.
HF - Power of high frequency band.
HF (nu) - High frequency in normalized unit.
LF/HF - Ratio between LF and HF.

DISCUSSION

Systemic sclerosis is a chronic multisystem disorder of unknown etiology. There are a few studies available which show that the autonomic dysfunction is common in SSc. A study done by Dessein et al has shown autonomic dysfunction, characterized by parasympathetic impairment and marked sympathetic over activity, in 34 patients with SSc particularly in early disease (3). In another study involving 25 patients with SSc, significant sympathetic and parasympathetic dysfunction was found (4). Sonnex et al showed early parasympathetic damage in three out of six patients in their study (6). In our study, we found a lower parasympathetic tone in patients with SSc, (Table III). HF power was lower in the patients when compared with controls [patients 83.7 (2.2–706.7); controls 633.9 (29.6–4552.6); P=0.0001]. Similar results were obtained in the normalized unit for HF [patients 20.6 (7.9–135.5); controls 49.5 (13.3–92.8); P=0.0001]. Values in the normalized unit are considered to be better representative of any parameter. The high LF/HF ratio reconfirmed the lower parasympathetic tone in the patient group. It is known that high frequency (HF) component is attributed to parasympathetic influence of heart and low frequency (LF) component is due to both sympathetic (mainly) and parasympathetic activity (14). By and large a tilt towards vagal (parasympathetic) dominance is beneficial for the cardiovascular system in health as well as for the outcome of some diseases especially after myocardial infarction (15).

While analyzing the resting autonomic variables, we observed significantly higher

HR in the patient group. The RR was higher in both the groups, however, it was significantly higher in the patient group than control group. It reflects a decrease in parasympathetic (vagal) tone and an increase in sympathetic tone in the SSc patients. This autonomic derangement has been reported earlier also (3). A similar study done by Pancera et al has revealed that heart rate variability was reduced and sympathetic output was increased in patients with systemic sclerosis. Subjects with primary Raynaud's phenomenon were characterized by normal heart rate variability and by some degree of sympathetic hyperactivity (16).

In the autonomic reactivity tests, we found that the parasympathetic reactivity was significantly lower in SSc patients than the controls. However, the values were in normal range in both groups (Table II). No significant difference was found in the sympathetic reactivity between the two groups.

One of the limitations of our study was that we could not observe the influence of menstrual cycle on autonomic status. Although different phases of menstrual cycle may influence the autonomic status of a female, this variable was not planned during the active phase of the study. As the study was of retrospective nature, we could not include this variable in our study.

An autonomic imbalance in favor of the sympathetic system (with lower parasympathetic drive) may interact with inflammatory processes to play a more important role in the process of atherosclerosis. Therefore, therapeutic strategies directed towards rectification of this alteration in the autonomic imbalance may trim down the vascular events associated with SSc. As far as we know, this study is first in India to show the status of autonomic functions in SSc patients with lower central parasympathetic drive to heart and lower parasympathetic reactivity. The present study may give some insight for better understanding of this multisystem disorder of unknown etiology.

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