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Original Article

Cardiovascular Autonomic Neuropathy in Systemic Lupus Erythematosus

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Abstract

Purpose: Objective is to evaluate cardiovascular autonomic function in SLE by simple non-invasive tests.

Methods: A case control study was carried out involving 18-50 yrs old previously diagnosed SLE patients and same number of age and sex-matched controls. Parasympathetic function was assessed by heart rate (HR) response to Valsalva maneuver, deep breathing and standing. Sympathetic function was evaluated by blood pressure response to standing and sustained hand-grip test (HGT).

Results: There were 50 female SLE patients. They had significantly higher minimum resting HR and diastolic blood pressure (DBP). HR variation with deep breathing, expiratory inspiratory ratio, 30:15 ratio and DBP change in response to HGT were significantly lower inpatients compared to controls. Thirty patients (60%) had at least one abnormal or two borderline test results indicating autonomic impairment of which 27 had parasympathetic dysfunction and 7 had sympathetic dysfunction.

Conclusion: Autonomic dysfunction is common in SLE with higher prevalence of parasympathetic impairment.

Keywords: Cardiovascular autonomic dysfunction; systemic lupus erythematosus; valsalva maneuver.

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Introduction

Systemic lupus erythematosus is a multi-system autoimmune connective tissue disorder that commonly affects women of child-bearing age. Involvement of central and peripheral nervous system

is well-documented in SLE but literature on prevalence and pattern of autonomic neuropathy are few (1-3). Reported prevalence of autonomic dysfunction varies from 9-90% in different studies (4, 5). Autonomic neuropathy in SLE predisposes to cardiac arrhythmias and sudden cardiac death (6). Women with SLE have been found to have 5-8 fold increased risk of coronary heart disease (7, 8). Autonomic dysfunction in the presence of structural cardiovascular disease is associated with adverse prognosis (9). Further, autonomic symptoms like fainting, dry eyes, Raynaud's phenomenon may not be recognized to be due to autonomic dysfunction (2).

Racial differences in disease manifestation and complications are well-known in SLE (10). To the best of our knowledge, there is only one case control study on autonomic function in SLE in India (11). Considering the important consequences of autonomic impairment in this disease, autonomic function was evaluated in these patients with the help of several cardiovascular reflex autonomic function tests (AFT).

Methods

This case control study was carried out in the Institute of Postgraduate Medical Education & Research from July 2013 to June 2014. The study commenced after approval from the Institutional Ethics Committee. Cases were previously diagnosed 18-50 yr-old consecutively reporting SLE patients attending the Outpatient Department of Rheumatology. The patients were diagnosed on the basis of American College of Rheumatology (ACR) revised criteria, 1997 for the classification of SLE (12). Severely ill and bedridden patients, patients with hypothyroidism, diabetes, heart failure or any form of cardiac arrhythmia, patients receiving any drug affecting heart rate or blood pressure were excluded from the study. Age and sex matched healthy volunteers who did not have any autonomic symptom and did not use any medication served as the control group. An age difference of up to 5 years was the age-matching criterion for each matched pair (13).

Informed consent was obtained from all subjects before their inclusion in the study. Patients were checked for symptoms and signs suggestive of autonomic dysfunction like orthostatic hypotension (lightheadedness, blurred vision, sensation of weakness and unsteadiness, fainting or syncope upon standing), perspiration, palpitation and Raynaud's phenomenon. Laboratory investigations included complete blood count, fasting and post prandial plasma glucose, serum TSH, urea, creatinine, SGOT, SGPT, C3, C4, anti-dsDNA, routine examination of urine, 24-hr urinary protein, albumin-creatinine ratio, X-ray chest, echocardiography and ultrasonography of abdomen. Disease activity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (14).

Each subject underwent the tests of autonomic function in the morning after about 15 minutes of rest in supine position at a temperature of 22-25°C. Tobacco and caffeinated drinks were not allowed for 3 hours and alcohol withheld for 8 hours before tests (15). Electrocardiogram (ECG) and blood pressure were obtained from multi-parameter monitor (BPL Excello). Minimum resting heart rate (RHR) was noted and three readings of blood pressure were recorded at 2 minutes intervals after the period of rest. Resting systolic blood pressure (RSBP) and resting diastolic blood pressure (RDBP) were calculated by averaging those three readings. Tests of autonomic function were performed using battery of cardiovascular reflex tests devised by Ewing (16, 17). Parasympathetic function was assessed by heart rate response to Valsalva maneuver, heart rate response to deep breathing and immediate heart rate response to standing. Sympathetic function was evaluated by blood pressure response to standing and sustained hand-grip test (HGT). The tests were performed in the following order: immediate heart rate and blood pressure response to standing, heart rate response to Valsalva, heart rate response to deep breathing followed by blood pressure response to HGT.

a) Immediate heart rate response to standing: The subjects were asked to stand up within 5 seconds from supine position and to remain still (18). The ratio of the longest R-R interval around the 30th

beat to the shortest R-R interval around the 15th beat was considered as 30:15 ratio.

b) Heart rate response to Valsalva: Each subject in sitting posture blew forcibly into a mouthpiece connected to the open end of an aneroid manometer maintaining a pressure of 40 mm Hg for 15 seconds. The maneuver was performed thrice at intervals of one minute. Valsalva ratio (VR) was calculated as the ratio of longest RR intervals after the maneuver to the shortest RR interval during straining. The mean of the three Valsalva ratios were taken as the final value (16).

c) Heart rate variation during deep breathing: Subjects sat quietly and breathed deeply and regularly at 6 breaths per minute for a period of 1 minute. Heart rate was calculated from the ECG and HR variation during deep breathing (HR var) was calculated as mean of the differences between maximum HR during inspiration and minimum HR during expiration for 6 cycles. Expiratory: Inspiratory (E:I) ratio was also calculated as mean of the maximum HR during inspirations divided by mean of minimum HR during expirations.

d) Blood pressure response to standing: Subjects stood up from supine position and blood pressure was recorded at 30 seconds, 1, 2 and 3 minutes after standing. Difference between RSBP and minimum of four readings of SBP upon standing were expressed as postural change in SBP (dSBP_PT). Similar procedure was used for calculating change of DBP with posture (dDBP_PT).

e) Sustained handgrip test (HGT): Subjects were asked to forcefully compress a handgrip dynamometer (Inco, Ambala, India, 0-60 kg). The maximum force that could be attained during handgrip was noted from the pointer on the scale. Each subject was asked to maintain force at 30% of this value, for three minutes or as long as possible without undue discomfort during which blood pressure was measured at 30 seconds intervals (17, 19). It was observed that 36 cases and 37 controls could maintain the handgrip at the required level beyond 1 minute. Difference between resting BP and maximum of those readings were expressed as handgrip response to change in BP (dSBP_HGT and dDBP_HGT).

To grade the severity of autonomic damage, the five test parameters viz. VR, HR var., 30:15 ratio, dSBP_PT and dDBP_HGT were scored using reference values from Ewing et al giving 0 for a normal result, 0.5 for a borderline result, and 1 for an abnormal result, thus giving a score of 0-5 for each subject who underwent the standard battery of all five tests (17). Autonomic dysfunction was considered to be present if total score for any patient was 1 or more.

GraphPad Prism version 5 (San Diego, CA: GraphPad Software Inc., 2007) was used for statistical analysis. Data were analyzed by Mann Whitney test. Spearman's test was used to determine correlation between two parameters. P value less than 0.05 was considered significant.

Result

Out of 78 SLE patients initially enrolled for the study, 19 were very sick, 3 had diabetes, and 5 had been receiving antihypertensive drugs. Of the remaining 51 patients, 50 were female and included for analysis. Median age of the patients was 27.50 years with an age range of 18-46 years. Median disease duration was 5 years (range 0.5-19 yrs). All of them had normal plasma glucose, serum TSH, urea, creatinine, and SGOT and SGPT. Fourteen patients were anemic; 2 suffered from leucopenia; 3 had thrombocytopenia. Low complement level was found in 5 patients while 3 showed increased antids DNA. X-ray chest showed pleural effusion in one. Echocardiography and ultrasonography of abdomen were normal in all. Two patients had arthritis and two had malar rash. Two patients had untreated hypertension and 3 patients had abnormal albumin creatinine ratio. Thirty five patients were in remission with SLEDAI score being zero. SLEDAI score was 2 in 9 patients; and 4 in 4 patients. Remaining two cases had SLEDAI score more than 7. Mean SLEDAI score was 1.244. None of the patients had any symptom suggestive of autonomic dysfunction.

TABLE I : Autonomic function test (aft) parameters of cases and controls.

Parameters	*Cases (n=50)*	*Controls (n=50)*	*p value*
	Median (IQR)	*Median (IQR)*	
Minimum RHR (bpm)	90 (81-96)	79 (71-88)	0.0006*
RSBP (mmHg)	113.3 (104.9-121.7)	109.0 (104.3-116.9)	0.2398
RDBP (mmHg)	74.17 (68.50-80.92)	69.67 (65.00-76.83)	0.0276*
VR	1.48 (1.25-1.75)	1.49 (1.30-1.67)	0.8442
30:15 ratio	1.12 (1.06-1.20)	1.28 (1.18-1.42)	<0.0001*
HRvar	11.83 (9.00-15.33)	17.67 (14.92-21.75)	<0.0001*
E:I ratio	1.13 (1.10-1.18)	1.24 (1.20-1.29)	<0.0001*
dSBP_PT (mmHg)	–1.00 (-3.33-2.50)	–0.33 (–5.42-2.67)	0.9067
dDBP_PT (mmHg)	–4.00 (-7.75-0.33)	–4.67 (–7.42-1.25)	0.6243
dSBP_HGT (mmHg)	21.33 (16.25-27.08)	20.50 (11.25-24.08)	0.2930
dDBP_HGT (mmHg)	17.17 (13.25-24.67)	20.83 (15.33-26.33)	0.0430*

p value obtained by Mann-Whitney test; negative values indicate increase in BP on standing.

IQR, inter-quartile range; RHR, resting heart rate; RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure; VR, Valsalva ratio; HRvar, heart rate variation with deep breathing; E:I, expiratory: inspiratory ratio; dSBP_PT, change in systolic blood pressure on standing; dDBP_PT, change in diastolic blood pressure on standing; dSBP_HGT, change in systolic blood pressure with sustained handgrip; dDBP_HGT, change in diastolic blood pressure with sustained handgrip.

Controls included 50age-matched female healthy volunteers.

Table I depicts autonomic parameters of cases and controls. The table shows significantly higher minimum RHR and RDBP in SLE patients compared to controls. 30:15 ratio, HR var and E:I ratio and dDBP_HGT were significantly impaired in SLE patients.

Table II shows the number of cases and controls with normal, borderline and abnormal results for five AFT parameters. Abnormality in heart rate variation with deep breathing was most common followed by impairment in DBP response to HGT in SLE patients.

TABLE II : Frequency of impairment of different autonomic function test (aft) parameters in cases and controls.

Parameters		*Normal (%)*	*Borderline (%)*	*Abnormal (%)*
Valsalva ratio	Case	43 (86)	4 (8)	3 (6)
	Control	47 (94)	2 (4)	1 (2)
30:15 ratio	Case	43 (86)	2 (4)	5 (10)
	Control	48 (96)	1 (2)	1 (2)
Heart rate variation with respiration	Case	15 (30)	14 (28)	21 (42)
	Control	42 (84)	5 (10)	3 (6)
SBP response to standing	Case	47 (94)	2 (4)	1 (2)
	Control	50 (100)	0 (0)	0 (0)
DBP response to HGT	Case	27 (54)	17 (34)	6 (12)
	Control	46 (92)	3 (6)	1 (2)

At least one of the three parasympathetic test parameters was abnormal in 27 patients, only one borderline in 13 while remaining 10 patients had normal result for all three parameters. Both the sympathetic function test parameters were normal in 25 patients, only one borderline in 18 and at least one abnormal in seven patients. AFT score was zero in four (8%) patients and 40 (80%) controls while 16 (32%) patients and 6 (12%) controls had AFT score being 0.5. Thirty (60%) patients had autonomic dysfunction with AFT score being 1 or more. Of them, 10 had at least one abnormal parasympathetic test result with normal sympathetic function. Only one had abnormal sympathetic function with normal

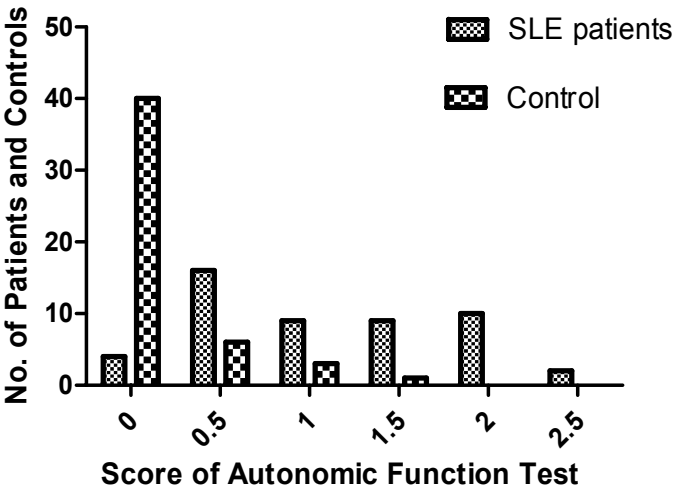

Fig. 1 : Score grading autonomic function in patients and controls.

parasympathetic test parameters. Overall, 27 patients had parasympathetic dysfunction with abnormal value of at least one of the parasympathetic test parameters. Seven had sympathetic dysfunction with at least one of the sympathetic test results being abnormal. Score wise distribution of cases and controls has been shown in Fig. 1. There was no significant correlation between disease duration and AFT score (Spearman's r=0.1158, p=0.4232) as shown in Fig. 2.

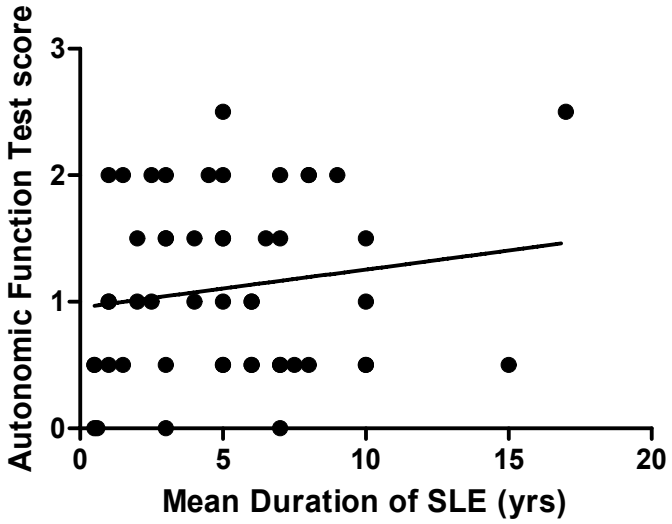

Fig. 2 : Scatter plot of disease duration vs autonomic function test score.

Discussion

In this study, significant decrease in HR variation with deep breathing, E:I ratio and 30:15 ratio in SLE patients compared to controls is suggestive of impaired parasympathetic function . There was also significant decrease in DBP response to HGT indicating sympathetic dysfunction. Overall, autonomic dysfunction was present in 60% of patients.

Abnormalities in heart rate variation during deep breathing and in 30:15 ratio in SLE have been described previously in various studies (11, 19-21). Decrease in DBP response to HGT has also been reported earlier (6). In contrast, some studies have not found any impairment in heart rate or blood pressure response to above tests in cases of SLE (2). We found a higher number of patients with abnormal response to deep breathing in contrast to that reported in an Indian study, which was conducted on a similar number of patients (11). However the frequency of abnormal results for other parameters was similar. Prevalence of autonomic dysfunction has been reported to differ widely in different studies, reflecting lack of standardized criteria for defining autonomic neuropathy (4, 5). Studies which defined autonomic dysfunction on the basis of abnormality in two or more tests reported lower prevalence rates compared to those defining it as abnormality in one or more tests. Absence of autonomic symptoms in this study is possibly due to young age of most of the patients. Earlier some studies have found a correlation between duration of disease and autonomic neuropathy while others did not (3, 4, 19). However, no correlation was observed between disease duration and autonomic dysfunction in this study.

Abnormalities in the autonomic tone increase the propensity for lethal arrhythmias and sudden cardiac death (6, 22). A recent study has shown protective action of vagus nerve against ventricular fibrillation (23). In our study, six out of seven patients with sympathetic dysfunction had also borderline or abnormal heart rate response. Twenty seven out of 30 patients with autonomic dysfunction had at least one abnormal heart rate test reflecting abnormal parasympathetic function. These patients are prone to developing cardiac arrhythmia (6). Coronary heart disease is 5-8 times more likely to occur in women with SLE (7, 8). Autonomic impairment in such cases can blunt the symptoms of ischemia and acute myocardial infarction (24, 25). Besides, they can also suffer from autonomic symptoms which may be misdiagnosed to be due to the disease itself (2).

Case control studies on autonomic function in SLE are scarce. Since autonomic function has been reported to deteriorate with age, we have compared autonomic parameters of SLE patients with those of age and sex-matched healthy controls (26). Ethnic variation in disease manifestation and complication is also well documented in SLE. But report on the prevalence of autonomic neuropathy in Indian SLE patients is hard to find (11). Addressing the need, prevalence of autonomic impairment in these patients

has also been estimated using a scoring system. Since 35 patients (70%) were in remission with SLEDAI score of zero and 47 (94%) had normal albumin: creatinine ratio, relation of autonomic dysfunction with disease activity and renal complications could not be established. In this study, cardiovascular autonomic function was evaluated by non-invasive, simple, inexpensive tests that can be easily carried out in centers with limited resources. In a developing nation, these tests are especially suitable for periodic evaluation of autonomic function that can help in early detection of autonomic impairment and assessment of its severity. This is an essential step for preventing future cardiovascular complications in these patients.

In conclusion, autonomic impairment is common in SLE patients making them prone to silent myocardial ischemia. Reduced vagal activity in most of the patients indicates they are at risk of developing life-threatening arrhythmia. A longitudinal study is needed to elucidate whether there occurs any decline in autonomic function with duration and renal impairment.

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