Autonomic neuropathy in systemic lupus erythematosus: cardiovascular autonomic function assessment

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Abstract

Aim—To assess the prevalence and the nature of autonomic neuropathy (AN) in 17 patients with inactive or mild active systemic lupus erythematosus (SLE).

Methods—Patients were tested using questionnaires related to possible AN symptoms, and four non invasive cardiovascular autonomic function tests at rest, during lying to standing, and sustained handgrip. Eleven age matched normal subjects were also enrolled as a control group.

Results—At least one abnormal cardiovascular autonomic function test was observed in 15 of the 17 patients. The two groups did not differ in deep-breathing (parasympathetic, PS) and handgrip tests (sympathetic, S) although responses in patients with SLE tended towards abnormal values. Statistical differences were found in standing-heart rate ratio (R-R ratio) (PS) with a lower ratio in the group with SLE ($p < 0.01$) and in standing blood pressure with a higher decrease in systolic blood pressure ($p < 0.05$) in patients with SLE. No correlation was found between AN, age, disease duration and presence of Raynaud's phenomenon.

Conclusion—In inactive or mild active SLE, AN could represent residual abnormalities of autonomic nervous system involvement and/or could be related to glucocorticoids.

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sympathetic pathways. We have compared these cardiovascular reflexes in a group of patients with SLE and a group of normal subjects, and found abnormal responses in the SLE group.

Patients and methods

PATIENTS AND CONTROL SUBJECTS

Seventeen consecutive female patients (mean age: 37.1 years, range 24 to 59 years) with SLE satisfying the revised ARA criteria¹³ and 11 control healthy female volunteers with a mean age of 35.5 years (range 23 to 55 years) took part. Informed consent was obtained from all patients and volunteers before entry in the study.

The lupus activity was judged to be mild in all patients. A SLEDAI score of under 7 (of 105) was present for all of them.¹⁴ No active arthritis, pericarditis or nephritis were present in these patients. Relevant clinical features of the patients are presented in table 1. Guillain-Barré syndrome occurred five years before these examinations in patient 3. Patients were normotensive, not on antihypertensive drugs and none was anaemic or in cardiac failure. No other disorders responsible for autonomic neuropathy were associated with SLE.¹

At the time of the study, 13 patients were receiving a maintenance dose of corticosteroids (CS) less than 17.5 mg daily. Three patients (cases 3, 7, 8) were taking no medication. Other concurrent medications are reported in table 1. Patient 2 had stable asthma treated with terbutaline 7.5 mg daily and salbutamol inhalations.

All control subjects were hospital staff who were not taking any medication. The exception was control 10 who was on thyroid hormone treatment for an euthyroid nodule.

METHODS

Normal sinus rhythm was confirmed before cardiovascular tests in all patients and volunteers. Historical clinical data were noted with respect to symptoms compatible with autonomic dysfunction including Raynaud's phenomenon, sweating abnormalities, postural hypotension (fall of 20 mmHg systolic BP) and cardiac arrhythmias. The autonomic responses were assessed by four cardiovascular reflex tests.^{11 12} All tests were performed in standard technique at a set time in relationship to meals.

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The development of a chronic autonomic neuropathy (AN) has been described as a complication of a variety of diseases including primary neurological diseases,¹ diabetes mellitus,² chronic renal failure³ and drug-related manifestations.¹ Recent reports mentioned abnormal autonomic responses in both active⁴ and chronic⁵⁻⁸ phases of autoimmune diseases. CNS involvement and peripheral neuropathy have been extensively studied in systemic lupus erythematosus (SLE), but only few reports of autonomic neuropathy in this disease have been made.^{9 10}

A battery of non invasive tests based on cardiovascular reflexes can be used to given a simple yet accurate assessment of generalised autonomic nerve function.^{11 12} These tests probably reflect both sympathetic and para-

Table 1 Clinical characteristics and existing therapy in 17 female patients with SLE

Patient	Age (Years)	SLE duration (Years)	Raynaud's phenomenon	Neuropathy	Autonomic symptoms	Treatment
1	31	7	—	—	Symptoms of orthostatic hypotension	P (10 mg/d) AVK
2	59	10	+	Lower limbs areflexia	Symptoms of orthostatic hypotension Excess sweating	P (5 mg/d) Thyroid hormone
3	26	13	+	Abnormal deep vibration Areflexia (Guillain-Barré)	—	P (10 mg/d)
4	29	7	—	—	Postural symptoms	P (17.5 mg/d) AZA
5	29	7	+	Right hemiparesis Pupils asymmetry	—	P (15 mg/d)
6	53	14	+	Hyperaesthesia of feet Lower limbs areflexia	—	P (2.5 mg/d) AMD
7	50	3	—	—	—	—
8	32	1	+	—	—	—
9	50	8	—	—	—	—
10	34	12	+	—	Dizziness/postural symptoms	NSAID P (15 mg/d)
11	27	7	—	Hypoaesthesia of feet	—	P (12.5 mg/d)
12	35	2	—	—	—	AMD
13	49	14	—	—	—	P (2 mg/d) AMD
14	28	6	+	—	Orthostatic hypotension	P (5 mg/d)
15	33	7	—	—	—	P (7.5 mg/d), NSAID
16	42	8	+	—	Orthostatic hypotension	P (10 mg/d), NSAID
17	24	2	—	—	—	P (7.5 mg/d)

Key: P: prednisone; AVK: antivitamin K; AZA: azathioprine; AMD: antimalarial drugs; NSAID: non steroidal anti-inflammatory drug.

I—TESTS MAINLY REFLECTING

PARASYMPATHETIC NERVE FUNCTION

1—Heart-rate variation during deep breathing

Respiratory sinus arrhythmia depends on an intact parasympathetic nerve supply. Reduction or complete absence of this heart-rate variation can occur in autonomic neuropathy. A continuous electrocardiographic tracing was recorded during deep-breathing, at a rate of six breaths per minute. The maximum and minimum R-R intervals on the cardiogram during breathing cycles were measured and converted to beats a minute. The result is expressed as the mean of the difference between maximum and minimum heart-rates for the six measured cycles in beats per minute.

2—Heart-rate responses to postural changes

These responses are also mediated by the vagus nerve. Change from horizontal to vertical produces an integrated cardiovascular response which includes variation in heart-rate. There is a characteristic early increase in heart-rate usually within 10 seconds and often maximal at the 15th beat after standing. Subsequently, a relative bradycardia follows by about the 20–60 seconds time interval, often maximal at about the 30th beat. Patients and controls were kept recumbent for 10 minutes, then were asked to stand up unaided. Continuous electrocardiographic recording was taken from 15 seconds before to one minute after standing. The R-R intervals on the cardiogram were measured at beats 15 and 30 after standing and the values were expressed as a ratio (30:15).

II—TESTS REFLECTING SYMPATHETIC NERVE FUNCTION

1—Blood pressure response to standing

When the posture is changed from recumbent to erect, a fall in pressure occurs as a result of gravitational pooling of blood. An intact baroreflex rapidly reverses this effect via a sympathetic nervous system mediated vasoconstriction. In patients with autonomic dys-

function, the blood pressure (BP) falls on standing but correction of this fall is impaired. The patient's blood pressure was measured while resting supine on an examination couch. Blood pressure was subsequently recorded immediately and each minute for 10 minutes after standing. The postural fall in blood pressure is calculated as the difference between the stable systolic blood pressure lying and the lowest systolic blood pressure recorded during the 10 minute period while standing.

2—Blood pressure response to sustained hand grip

During sustained handgrip a sharp rise in blood pressure occurs, due to a heart-rate dependent increase in cardiac output with unchanged peripheral vascular resistance. A maximum voluntary contraction force is first determined using a handgrip dynamometer. In the test, the handgrip is maintained at 30% of that maximum for as long as possible up to three minutes. Blood pressure is measured before the exercise and at one minute intervals during handgrip. The result is expressed as the difference between the highest diastolic blood pressure during handgrip exercise, and the mean of the three diastolic blood pressure measurements made before the procedure was started.

STATISTICAL ANALYSIS

Values are expressed as mean (SD). Comparison between mean values in both groups used 2 tailed unpaired Student's *t* test as parametric test and Mann Whitney test for non parametric values (R-R test). A *p* value <0.05 was considered as statistically significant.

Results

Six of the patients had clinical symptoms suggesting autonomic dysfunction: patient 2 had severe orthostatic symptoms with dizziness and faintness. Previous investigations had ruled out other CNS diseases including

Table 2 Cardiovascular assessment of autonomic neuropathy in patients with SLE and healthy volunteers

	SLE (n = 17)	Controls (n = 11)	P value
Deep-breathing test (PS)*	15.84 (6.01)	18.37 (6.71)	NS§
Standing heart rate (PS)	1.18 (0.60)	1.32 (0.11)	0.01
R-R ratio			
Handgrip test (S)	16.66 (7.98)†	20.63 (8.92)‡	NS§
(Diastolic BP increase)			
Standing PB (S)	10.12 (7.37)	5.66 (4.62)	0.05
(Systolic BP decrease)			

Key: *PS = parasympathetic damage; S = Sympathetic damage; †n = 15; ‡n = 10; §NS = Non significant; Expressed values: mean (SD).

Table 3 Autonomic status in 17 patients with SLE

	Normal response	Parasympathetic nerve dysfunction only	Sympathetic nerve dysfunction only	Parasympathetic and sympathetic nerve dysfunctions
Number of patients (N = 17)	2	4	6	5
Abnormal tests	–	2	4	2
Border line tests	–	2	2	3

The table shows the number of patients with SLE who displayed abnormal and/or borderline values of AN assessment according to Ewing's criteria.¹¹

peripheral neuropathy related to diabetes mellitus, porphyria or amyloid to explain the symptoms. This patient also complained of excess sweating, mainly after meals. In two of the patients the postural symptoms were not accompanied by a fall in systolic blood pressure during the study. No relationship was demonstrated between peripheral neuropathy and AN in our patients with SLE as well as for age of the patients disease duration and the presence of Raynaud's phenomenon.

The results of cardiovascular autonomic function tests in 17 SLE patients and 10 controls are shown in tables 2 and 3. All except two patients had at least one abnormal or borderline test. Forty seven per cent of those with SLE have definite AN abnormalities. The two groups differed significantly in standing heart rate ratio (R-R ratio) ($U = 34$, $U_s = 51$, $p < 0.01$) and in standing BP fall ($p < 0.05$). The systolic BP decrease during lying to standing test was significantly higher ($p < 0.05$) in the SLE group, reflecting a sympathetic involvement. However, there were no significant difference between the mean values for the two groups in deep-breathing test and handgrip test though responses in patients with SLE tended towards abnormal values. Analysis of results of individual tests revealed that both sympathetic and parasympathetic pathways are impaired either singly or together (table 3).

Discussion

In this study we have used non invasive cardiovascular reflex responses to assess autonomic function in 17 patients with quiescent or mild active SLE. All patients except two had at least one abnormal or borderline test. Forty seven per cent of SLE had definite AN abnormalities. The mean scores of the test results for deep breathing test (PS) and handgrip test were not statistically different between the SLE and control group. Conversely, the two groups differed in standing heart rate ratio (R-R ratio) and in standing

blood pressure control, reflecting an involvement of both parasympathetic and sympathetic pathways. A greater number of patients might give more statistical difference in the results. We did not see any relationship between clinical peripheral neuropathy and autonomic neuropathy in patients with SLE. Edmonds *et al*⁷ suggested that such a relationship exists between AN and peripheral neuropathy in rheumatoid arthritis. However, no electromyographic or nerve conduction study was performed in our cases except in patient 1 who had abnormal investigations. No correlation was found between AN and patient's age, disease duration and the presence of Raynaud's phenomenon.

Since SLE was quiescent or in mild clinical activity, autonomic dysfunction may be considered as residual abnormalities. No instance of acute pandysautonomia could be found by history in our patients. The effect of medications can be excluded since none was taking any drug known to induce, for instance, orthostatic hypotension.

The role of steroid has been questioned. Although 13 patients were still taking prednisone, none had abnormal blood glucose level. Recently, prednisone was shown to abolish the nocturnal fall of blood pressure (BP) in patients with SLE compared with the period before glucocorticoid therapy. This suggests that the circadian BP variation is influenced by the adrenal axis through the AN system.

There are few reports of chronic or acute autonomic neuropathy associated with autoimmune diseases. Victor *et al*⁶ reported a patient with rheumatoid arthritis and abnormal tonic pupils to acetylcholine. In 1979, Edmonds *et al*⁷ demonstrated abnormalities of cardiovascular reflexes in 33% of patients with rheumatoid arthritis. Four of nine patients had autonomic symptoms with postural hypotension and/or gustatory sweating. More recently, Hoyle *et al*⁹ reported a patients with SLE with acute autonomic neuropathy that improved with high dose steroid therapy. Another patient with mixed connective tissue disease (MCTD) and acute pandysautonomia failed to respond to corticosteroids and remained with orthostatic hypotension and abnormal cardiovascular responses to Valsalva's manoeuvre.⁴ Two other patients with autonomic dysfunction and sensory polyneuropathy were observed⁵; one with chronic active hepatitis and another with a MCTD who did not respond to steroid therapy. Most of the reported cases have exhibited cardiovascular, gastrointestinal, pupillary, genitourinary and sweating abnormalities and often presented with residual cardiovascular dysfunction. About 50% of our patients gave a history of symptoms that were cautiously interpreted as possibly related to autonomic dysfunction. Recently, AN was found to be extremely common in systemic sclerosis.⁸ In this disease, it is characterised by severe sympathetic overactivity and by parasympathetic impairment, demonstrated by using non invasive cardiovascular tests and plasma catecholamine

concentrations. Moreover, resting plasma adrenaline concentrations correlated inversely with disease duration, suggesting that sympathetic overactivity was present especially in early disease.

The peripheral autonomic nervous system consists of a somatic afferent pathway, a central integrating complex, that is, brain and spinal cord and two distinct efferent systems, parasympathetic and sympathetic nerves.¹ Cardiovascular tests alone cannot define the exact location of the lesion. It would be necessary to reserve judgment on these cardiovascular test results in patients with a past history of pericarditis or myocarditis. The central integrating complex might be considered as the likely primary site of involvement, in view of the frequency of cortical manifestations such as seizures, psychosis or hemiparesis that occurs in SLE.

The association between AN and peripheral neuropathy is well known in diabetics.² A similar relationship has been observed in five of nine patients with rheumatoid arthritis and AN.⁷ Moreover, the three patients mentioned above with CTD and chronic active hepatitis had also abnormal nerve conduction velocities. The single patient (patient 3) with a preceding lupus related Guillain-Barré syndrome showed some autonomic dysfunction similar to that reported in a case of idiopathic Guillain-Barré syndrome.¹⁵

The pathogenesis of AN in SLE still remains unclear. An immunological mechanism may be responsible for these manifestations in the lupus population. Experimental allergic neuritis has been given as a model of both polyneuropathy and autonomic dysfunction by Appenzeller *et al*¹⁶: circulating antibodies to sympathetic tissue antigens were transiently present. In addition, in isolated acute or subacute pandysautonomia, the presence of IgG has been demonstrated by immunofluorescence on the sudomotor ganglionic cholinergic fibres.¹⁷ Recently, no relationship was found between AN and anticardiolipin antibodies in a group of SLE patients.¹⁰ Moreover, the expression of beta-2 adrenergic receptor on mononuclear cells was reduced in

SLE patients and correlated with the extent of the disease activity.¹⁸ This suggests that an involvement of the AN can take part in the pathogenesis of such autoimmune disease.

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