Cardiovascular Autonomic Nervous System Dysfunction in Iraqi Systemic Lupus Erythematosus Patients

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ABSTRACT:

OBJECTIVE:

To assess the incidence, and pattern of autonomic dysfunction in Iraqi systemic lupus erythematosus (SLE) patients and its possible association to patient's age, duration of disease, SLE activity, drugs used &autonomic nervous system symptoms.

PATIENTS AND METHODS:

Fifty Iraqi SLE patients and 50 healthy controls were included in this study. Full history was taken and complete clinical examination was done for all individuals in both groups. Disease characteristics [age, sex, duration, SLE disease activity index (SLEDAI), drugs used, and autonomic nervous system symptoms] were also documented. Laboratory analysis included complete blood count, general urine examination, and anti-double stranded deoxyribonucleic acid. Individuals in both groups were assessed for autonomic dysfunction using 5 non-invasive tests: heart rate response to Valsalva maneuver, heart rate response to deep breathing, and heart rate response to immediate standing (30:15 ratios), systolic blood pressure response to standing and diastolic blood pressure response to sustained handgrip. Autonomic dysfunction was categorized as normal, parasympathetic, sympathetic, and mixed pattern according to criteria proposed by Ewing.

RESULTS:

Forty three (86%) Iraqi SLE patients have autonomic dysfunction compared with 0 % of controls (p=0.00000000001) and the most common autonomic function pattern was the mixed pattern 28(56%) patients. There was no statistical significant association between autonomic function pattern and age group of patients (p=0.536). Also no statistical significant association were observed between autonomic dysfunction; and age, sex, disease duration, disease activity (SLEDAI),autonomic nervous system symptoms or drugs used (chloroquine, prednisolon, azathioprine) (p=0.434, p=0.213, p=0.405, p=0.450, p=0.069, p=0.935, p=0.204, p=0.443 respectively).

CONCLUSION:

The incidence of autonomic dysfunction in Iraqi SLE patients using non-invasive tests is high (86%) and the most common pattern was the mixed pattern (56%). Also there was no statistical significant association observed between autonomic dysfunction and age, sex, duration, SLE disease activity index (SLEDAI), drugs used, and autonomic nervous system symptoms.

KEY WORDS: Cardiovascular autonomic dysfunction, SLE

INTRODUCTION:

Systemic lupus erythematosus (SLE) is the most common multisystemic autoimmune connective tissue disease [1].The incidence of CNS manifestations attributable to SLE is variable but approximately 20% of cases have neuropsychiatric manifestations [2] .

The neurological manifestations include: central manifestations [3], peripheral neuropathy [4], and autonomic neuropathy [4]. Although the involvement of the peripheral nervous system and central nervous system in SLE has been well described in the standard textbooks of rheumatology[5], autonomic nervous system (ANS) involvement has rarely been studied in SLE, and studies have shown conflicting results[6].

Cardiovascular reflex tests have been the most widely, easily, & noninvasive test to assess ANS [7]. The purpose of this study is to assess the incidence, and pattern of autonomic dysfunction in Iraqi systemic lupus erythematosus (SLE) patients and its possible association to patient's age, duration of disease, SLE activity, drugs used &autonomic nervous system symptoms.

PATIENTS AND METHODS:

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A case-control study was conducted on 50 patients with SLE who were seen at the Rheumatology unit, Department of medicine and Neurological department in Baghdad Teaching Hospital from March 2006 to March 2007. The diagnosis of SLE

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was made using the criteria developed by the American College of Rheumatology [8]. For comparative purposes, 50 healthy control individuals were selected from healthy individuals that did not have symptoms of ANS dysfunction and were not taking any medications.

All patients were checked for symptoms and signs of possible ANS dysfunction including: orthostatic hypotension (light headedness, blurred vision, sensation of weakness and unsteadiness, fainting and syncope upon standing), perspiration, palpitation and Raynaud's symptoms in addition to SLE duration, activity index using (SLEDAI: SLE disease activity index) [9] and drugs used in the management of SLE patients.

The patients were divided into 2 groups according to their age, the 1st group was from 13-30 years, and the 2nd was from 31-59 years.

Patients were excluded from the study if they had: hemoglobin<10g/dl, pregnancy, diseases interfering with ANS including diabetes mellitus, chronic renal failure, and liver diseases, cardiovascular diseases including hypertension, ischemic heart disease, congestive heart failure, valvular heart diseases, cardoimyopathies, and arrhythmias, neurological diseases including multiple sclerosis, polyneuropathy or Guillain Barre syndrome. Drugs: antihypertensive (diuretics, adrenergic inhibitors, vasodilators), antiarrhythmics, sedatives, hypnotics and antiepileptic.

METHODS:

Cardiovascular ANS function assessment was performed using the 5 standard techniques described by Ewing et al [10]:

a. Parasympathetic tests (ECG test): heart rate (HR) response to Valsalva maneuver, HR response to deep breathing, and HR response to immediate standing (30:15 ratio).

Sympathetic tests (blood pressure tests): systolic blood pressure response to standing and diastolic blood pressure response to sustained hand grip.

Blood sample was obtained for measurement of hemoglobin, white blood cells, platelets, and anti ds-DNA.

Urine examination was done for measurement of protein, white blood cells, red blood cells, and cellular casts.

A signed consent was taken from individuals in both groups for admission in the study.

Statistical Analysis: All data coded and entered to computer using statistical package for social science (SPSS 10.0). Association between discrete variables measured by Chi-Square test, difference between continuous variables measured by t-test. P-value ≤0.05 was considered significant.

RESULTS:

Fifty patients with SLE, 42 females (84%) & 8 males (16%), their mean age (30.40±11.20) years, and 50 healthy control group, 40 females (80%) & 10 males (20%), their mean age was (31.86±10.05) years were included in this study. The age & sex of patients & control groups are shown in Table 1 (p-value=0.494 and 0.398) respectively indicating no statistical difference between both groups.

Autonomic function (AF) was abnormal in 43 patients (86%), and normal in 7 patients (14%), while it was normal in all 50 healthy individuals of control group (100%) and (p-value= 0.00000000001) which is statistically highly significant as shown in Table 2.

In the 1st patient's age group (13-30years), we have 31 patients, and of those patients, AF pattern showed that 19 patients (61.3%) were of mixed pattern, 6 patients (19.4%) were of parasympathetic pattern, 1 patient (3.2%) was of sympathetic pattern, and 5 patients (16.1%) were normal. While in the 2nd patient's age group (31-59years), we have 19 patients, and of those patients, AF pattern showed that 9 patients (47.4%) have mixed pattern, 7 patients (36.8%) have parasympathetic pattern, 1 patient (5.3%) has sympathetic pattern, and 2 patients (10.5%) have normal pattern. The association between AF pattern and patients age was statistically not significant for both age groups (P-value= 0.536). The commonest AF pattern was the mixed pattern which was reported in 28 patients (56%) as shown in Table 3.

We found that there is no statistical significant association between AF and SLE patient's characteristics (age, sex, duration, activity of disease (SLEDAI), ANS symptoms and medications taken) as shown in Table 4.

Table1: Distribution of studied sample according to demographic characteristic

Variables	Patients=50	Control=50	P-Value
Age (years)	30.40±11.20	31.86±10.05	0.494 [n.s]
Sex Male n. (%)	8 (16.0)	10 (20)	0.398 [n.s]
Female n. (%)	42 (84)	40 (80)	

n.s, not significant.   n., number; %, percentile.

Table 2: Comparison of AF in 50 SLE patients and 50 controls

Group	AF		P-value
	Normal	Abnormal	
Patients n. (%)	7(14)	43(86)	0.00000000001**
Control n. (%)	50(100)	0 (0)	

** P-value is highly significant; AF, Autonomic Function.

Table 3: Distribution of AF pattern according to age groups in 50 SLE patients

Age group(year)	AF Pattern				P-value
	Mixed n(%)	PST n(%)	ST n(%)	Normal n(%)	
13-30(n=31)	19(61.3)	6(19.4)	1(3.2)	5(16.1)	0.536 [n.s]
31-59(n=19)	9(47.4)	7(36.8)	1(5.3)	2(10.5)	
Total(n=50)	28(56)	13(26)	2(4)	7(14)	

n.s, not significant

PST, Parasympathetic; ST, Sympathetic; AF, Autonomic Function.n;number;%;percentile

Table 4: Association of AF with 50 SLE patients' characteristics

Variables	AF		P-value
	Normal	Abnormal	
Age n.(years)	7(27.28±10.01)	43(30.90±11.41)	0.434 [n.s]
Sex Male n.(%)	0(0)	8(100)	0.213 [n.s]
Female n.(%)	7(16.7)	35(83.3)	
Duration n.(months)	7(33.57±37.01)	43(73.02±122.28)	0.405 [n.s]
SLEDAI Active n.(%)	3(10.7)	25(89.3)	0.450 [n.s]
Inactive n.(%)	4(18.2)	18(81.8)	
ANSS Symptomatic n.(%)	6(22.2)	21(77.8)	0.069 [n.s]
Asymptomatic n.(%)	1(4.3)	22(95.7)	
Drugs n.(dosage)			
Chloroquine(mg/d)	5(240±82.15)	8(243.75±77.63)	0.935 [n.s]
Prednisolon (mg/d)	4(12.50±6.45)	29(22.15±14.51)	0.204 [n.s]
Azathioprine (mg/d)	2(100±0.00)	11(86.36±23.35)	0.443 [n.s]
Cyclophosphamide (mg/month)	0	6(500±0)	—
Meloxicam (mg/d)	1(7.5)	3(7.5±0)	—

n.s, not significant ; AF, Autonomic Function; SLEDAI,SLE disease activity index.

DISCUSSION:

The pathogenesis of ANS dysfunction in SLE is not clearly understood: vasculitis of vasanervosum has been proposed, and it may have an immune component which is supported by improvement of acute autonomic neuropathy after treatment with immune suppressive drugs in patients with SLE [11], and the presence of circulating autoantibodies against nerve growth factor, cervical ganglia, and the vagus nerve have been recently demonstrated in SLE patients who had cardiovascular ANS

dysfunction. [12,13] The significance of these autoantibodies in the pathogenesis of ANS dysfunction remains to be determined.

This is the 1st case control study investigating autonomic dysfunction in Iraqi SLE patients.

The study showed that battery of ANS tests could be used in the assessment of ANS abnormalities in SLE patients and the most precise detection of autonomic reflexes can be achieved by using the whole battery of tests.

In this study, the incidence of autonomic dysfunction was 86%. This finding agreed with other studies done by Gledhill et a l [14] and Loite et al [15] but contrasted with the study done by Games-Nava et a l [16] in which the AD was 48% this can be explained by the incomplete ANS tests that were used by that study, and ethnical reasons in which the results of Ewing score that we compare with; might be not applicable to our population.

The most common pattern in our study was mixed pattern 56%. This finding is in agreement with other study done by Games-Nava et al. [16]

In the present study, there was no statistical significant correlation between autonomic dysfunction; and patients' age, disease duration & drugs taken for the disease. This finding goes with other studies done by Lagana et al [17], Laversuch et al [18], and Stein et al. [19]

Also in our study, there was no statistical significant association between autonomic dysfunction; and patients' sex, disease activity, & ANS symptoms. These findings are in agreement with other studies done by Games-Nava et al [16], Lagana et al [17], Laversuch et al [18], and Stein et al [19].

At time of our study, 5 lupus patients had cutaneous vasculitis, and as we didn't do peripheral nerve conduction study, it is difficult to rule out the absence of peripheral neuropathy. Peripheral neuropathy especially sensory, can affect response in some of the tests used in ANS assessment, in particular cold stimulation, however this test was not used in our study.

CONCLUSION:

Autonomic dysfunction is common (86%) among Iraqi SLE patients, and the most common pattern is the mixed pattern (56%).

There is no statistical significant correlation of autonomic dysfunction with patients' age, sex, disease duration, activity of disease, drug used, and autonomic symptoms.

3. Prospective studies are needed to determine the potential effect of AD in the morbidity of SLE patients.

REFERENCES:

1. Matieu AP. *Systemic lupus erythematosus.* In: Cush JJ, Kavanaagh A, stein MC. *Rheumatology Diagnosis and Therapeutics*, 2nd edn. Philadelphia: Lippincott Williams and Wilkins, 2005; 2: 364-73.

2. Manson J. J., Rahman A. Systemic lupus erythematosus. Orphanet encyclopedia, November 2005 http://www.orpha.netldata/patho/GB/uk-SLE.pdf.

3. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions of neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42:599-608.

4. Petri M. *Systemic lupus erythematosus*. In: Imboden JB, Hellmann DB, Stone JH, eds. *Current Rheumatology Diagnosis and Treatment,* 1st edn. New York, Chicago, San Francisco, Libon, London, Madrid, Mexico Sydney, Toronto: Lange Medical Books / McGraw-Hill 2004; 19: 171-78.

5. Wallace DJ, Metzger AL. *Systemic lupus erythematosus*. In: Wallace DJ, Hahn BH, eds. *Dubois lupus erythematosus*, 5th edn. Baltimore: Williams and Wilkins; 1997: 723-54.

6. Stojanovich L, Milovanovich B, de Luka SR, *et al*. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. *Lupus.* 2007;16:181-5.

7. Louthrenoo W, Ruttanaumpawan P, Armantana A, *et al*. Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus. *Q J Med* 1999; 92: 97-102.

8. Tan EM, Cohens AS, Freis JF, *et al*. The 1982 revised criteria for classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7[PMID: 7138600].

9. Gladman DD, Ibanez D, Urowitz MB. SLE disease activity index 2000. *J Rheumatol* 2002; 29: 288-91.

10. Ewing DJ, Clarke BF. Diagnosis and management of autonomic neuropathy. *Br Med J* 1982; 285: 916-18.

11. Holye C, Ewing DL, Parker AC. Acute autonomic neuropathy in association with systemic lupus erythematosus. *Ann Rheum Dis* 1985; 44: 420-4.

12. Maule S, Quadri R, Mirante D, *et al.* Autonomic nervous system dysfunction in systemic lupus erythematosus and rheumatoid arthritis: possible pathogenic role of autoantibodies to nervous system structures. *Clin Exp Immunol* 1997; 110: 423-7.

13. Bannister R, Mathias CK, Mathias C. *Autonomic Failure*. In: Bannister R, Mathias CK, Mathias C, eds. *Textbook of Clinical disorders of autonomic nervous system*, 3rd edn. Oxford: Oxford University Press, 1992.

14. Gledhill RF, Dessein PH. Autonomic neuropathy in systemic lupus erythematosus. *J Neurol Neurosurg Psychiat* 1998; 51: 1238-40.

15. Loite F, Osterland Ck. Autonomic neuropathy in systemic lupus erythematosus: cardiovascular autonomic function assessment. *Ann Rheum Dis* 1994; 54: 671-4.

16. Gamez-Nava JI, Gonzalez-Lopez L, Suarez-Almazor ME, *et al.* Autonomic dysfunction in patients with systemic lupus erythematosus. *J Rheumatol* 1998; 25: 1092-6.

17. Lagana B, Tubanil L, Maffeo N, *et al*. Heart rate variability and cardiac autonomic function in systemic lupus erythematosus. *Lupus* 1996; **5**: 49-55.

18. Laversuch CK, Seo H, Modarres H, *et al*. Reduction in heart rate variability in patients with systemic lupus erythematosus. *J Rheumatol* 1997; 24: 1540-4.

19. Stein KS, McFarlane IC, Ginzler EM, *et al.* Heart rate variability in patients with systemic lupus erythematosus. *Lupus* 1996; 5: 44-48.