Autonomic dysfunction in multiple sclerosis

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ABSTRACT

Objective: Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system. Autonomic dysfunction in MS patients may cause significant morbidity. The aim of this controlled cross sectional study was to investigate the prevalence, pattern and severity of autonomic dysfunction in Iraqi MS patients and to correlate them with patient's age, disease course, duration and severity.

Methods: Fifty-five patients with clinically definite MS according to Poser's criteria attending Baghdad MS clinic at Baghdad Teaching Hospital were studied between July 2000 and August 2001. Each patient was assessed according to a detailed protocol paper. Expanded disability status scale was used to assess the severity of the disease. The severity of autonomic symptoms was classified according to autonomic nervous system disability scale (ANSDS). Five standardized autonomic cardiovascular (Ewing) tests were performed for every patient which included: heart rate responses to deep breathing, Valsalva maneuver and standing, and blood pressure responses to standing and sustained hand grip. Forty matched healthy subjects were studied as a control group who were assessed with the same protocol paper, ANSDS and Ewing tests.

Results: Autonomic symptoms were significantly more prevalent in MS patients than in the controls. Cardiovascular, urinary and gastrointestinal symptoms were highly prevalent. The severity of the different autonomic symptoms as assessed by ANSDS, were higher in the patients than the controls. All 5 Ewing tests in the patients showed highly significant abnormal results as compared to those of the control. Definite parasympathetic derangement was found in 45.5% of the patients while combined sympathetic and parasympathetic derangements were found in 34.5% of the patients. There were significant correlations between the finding of definite autonomic dysfunctions and the age of the patients at the time of assessment and the duration of the disease.

Conclusions: Autonomic dysfunctions as assessed by a formal interview, ANSDS and by Ewing tests were common in Iraqi MS patients. Careful attention to autonomic disturbances should be considered in the routine evaluation of MS patients which might help in improving their quality of life.

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Multiple sclerosis (MS) is an inflammatory disease that affects the myelin sheath of the central nervous system (CNS), especially the brain and the spinal cord. It is characterized by dissemination in space and time. In MS, there are lesions involving separate parts of the CNS, signs and symptoms cannot be ascribed to a single lesion. In addition, exacerbation's and remissions most often characterize its clinical course.[1] The usual age of onset is the third and fourth decade of life causing a major impact not only on the patient but also on careers, family and social life.[2] The etiology of MS remains unresolved, but the popular overarching theory postulates a genetically predisposed individual who develops a viral infection that disrupts the vascular relation in the blood-brain barrier and initiates an immune reaction that continues as a waxing and waning destructive process damaging the myelin, and perhaps more importantly in the long term, the axons.[3] The pathological hallmark of MS is the white matter plaque, denoting an area of demyelination and

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axonal loss. Multiple sclerosis can produce lesions throughout the CNS, but certain sites seem to be especially vulnerable: the optic nerves, brainstem, spinal cord and periventricular regions, involvement is often bilateral and symmetrical.[4] As there is no definitive diagnostic test for MS, diagnosis still relies on clinical criteria supported by proper laboratory tests and neuroimaging. In 1983 Poser and colleagues developed a set of criteria for use in diagnosis which incorporates modern techniques for demonstrating subclinical lesions referred to as paraclinical evidence for dissemination in space, in addition, it accepts evidence of oligoclonal band or increased synthesis of immunoglobulin G (IgG) within the CNS as additional evidence that would allow a classification of a laboratory supported definitive MS.[5] In 2001, new diagnostic criteria for MS "The McDonald Criteria" was reported[6] emphasizing on early diagnosis and on the increasing use of MRI in obtaining objective evidence of dissemination in time and space of lesions typical of MS. The autonomic nervous system (ANS) supplies and influences every organ in the body and closely integrates vital processes, such as blood pressure, temperature and adaptation to environmental change.[7] Accordingly, sensory, motor, visceral and neuroendocrine functions can be modulated by this system.[8] The clinical signs and symptoms that occur in disturbances of the autonomic function are due to interruption of the reflex arc controlling the autonomic response which is influenced by the organ involved, the normal balance of sympathetic (ST)- parasympathetic (PST) innervations, the nature of the underlying illness and the stage of progression of the disease.[9] The many functions governed by this system include the distribution of blood flow and the maintenance of tissue perfusion, the regulation of blood pressure, the regulation of volume and composition of extra cellular fluid, the expenditure of metabolic energy and supplying substrate, and control of visceral smooth muscles and glands.[10,11] Autonomic symptoms rank high in terms of their impact on aspects of daily living and as reminders to patients and their relatives of what it can mean to have MS, almost every female patient is aware of her bladder and very few males eventually escape some impairment of sexual performance. Although these symptoms can be managed and do not impinge on many domestic roles and professional activities, they are nevertheless a significant cause of morbidity.[12] This study was conduced to investigate autonomic functions in a group of Iraqi MS patients attending Baghdad MS clinic and a group of matched controls to find the prevalence, pattern and severity of autonomic dysfunctions and their correlations with the patient's age and disease course, duration and severity.

Methods.

Fifty-five MS patients attending Baghdad MS Clinic at Baghdad Teaching Hospital, College of Medicine, University of Baghdad, Baghdad, Iraq were studied during the period between July 2000 and August 2001. The patients were diagnosed as clinically definite MS according to Poser's criteria.[5] They had either a relapsing remitting or a secondary progressive course. Each patient was interviewed and assessed according to a detailed protocol paper which included basic demographic data, various autonomic symptoms and a detailed neurological assessment. The expanded disability status scale (EDSS) system was used to assess the severity of the disease.[13] Patients with EDSS score of 8 or less were included in the study. The severity of the autonomic dysfunction was classified according to autonomic nervous system disability scale (ANSDS) in which each symptom is classified into class 0 for no symptom, class 1 for mild or transient symptom and class 2 for severe symptom.[14] Five standardized autonomic cardiovascular (Ewing) tests[15] were performed for every patient, these included: 1. Blood pressure response to standing. 2. Blood pressure response to isometric handgrip. 3. Heart rate (R-R interval) variation during deep breathing. 4. Heart rate response to Valsalva maneuver (VM). 5. Immediate heart rate response to standing. The first 2 tests assess the sympathetic functions while the last 3 tests assess the parasympathetic functions. Each test scored (0) for normal, (0.5) for borderline, and (1.0) for abnormal result. The total score of the 5 tests was used for analysis. Patients with a score of 2 or more were regarded as having definite autonomic neuropathy.[16] Forty healthy subjects, matched for age, were studied as a control. Each control was interviewed and assessed using the same protocol paper, ANSDS and Ewing tests. Patients and control were on no medications and had no medical illness known to affect autonomic function.

Statistical analysis was carried out using a computer with the statistical package for social sciences. Data was presented in simple measures of frequency, percentage, mean and standard deviation. The testing of significance of difference was applied using Student's t-test, and that of association using the Chi-square test. A p-value of ≤ 0.05 was considered as the level of significance.

Results.

This study was performed on 55 clinically definite MS patients and 40 healthy subjects as a control group. In the patients group there were 25 males (45.5%) and 30 females (54.5%). In the control group there were 20 males (50%) and 20 females (50%). The mean age of the patients at the time of assessment was 38.0 ± 7.8 years (range 22-53 years) which was not statistically different from that of the control (mean age 33.6 ± 8.4 years). Eleven patients were in the age group of 20-29 years, 20 patients in the 30-39 years, 19 patients in the 40-49 years and 5 patients were in the age group of 50-59 years. There were no significant differences between the mean age of male and female patients when compared to those of the control. The mean age at onset of the disease was 31.1 ± 8.5 years. There were no significant differences between male and

Table 1 - The prevalence of various autonomic symptoms among multiple sclerosis patients and controls (N=95).

Autonomic symptoms	Patients (55) n	(%)	Controls (40) n	(%)
Cardiovascular	***51***	***92.7***	***20***	***50***
Postural dizziness*	37	67.2	13	32.5
Syncope and pre-syncope	10	18.1	-	-
Palpitation*	35	63.6	9	22.5
Peripheral flushing*	36	65.4	3	7.5
Urinary symptoms	***49***	***89.1***	***3***	***7.5***
Urgency	46	83.6	-	-
Hesitancy	34	61.8	-	-
Incontinence	27	49	-	-
Frequency*	21	38.1	2	5
Polyuria*	13	23.6	1	2.5
Nocturia*	12	21.8	2	5
GIT symptoms	***48***	***87.3***	***12***	***30***
Constipation*	42	76.3	2	5
Dyspepsia*	28	50.9	2	5
Dryness of mouth	16	29	6	15
Fecal incontinence	7	12.7	-	-
Nocturnal diarrhea	5	9.1	2	5
Ptyalism	3	5.4	-	-
Sexual dysfunction (males=25)	***19***	***34.5***	***-***	***-***
Impaired erection	15	60	-	-
Impaired ejaculation	12	48	-	-
Loss of early morning erection	11	44	-	-
Loss of libido	9	36	-	-
Others (fatigue and spasticity)	8	32	-	-
Sweating abnormality	***29***	***52.7***	***7***	***17.5***
Excessive sweating*	25	45.4	7	17.5
Decreased sweating	4	7.2	-	-

*statistically significant, GIT - gastrointestinal tract

female patients regarding the age of onset and the duration of the disease. The mean duration of the illness was 6.5±5.1 years (range 1-17 years). Ten patients had duration of illness of one year or less, 20 patients 1-5 years, 14 patients >5-10 years and 11 patients had a duration of more than 10 years. Forty-four (80%) patients had a relapsing-remitting course of illness, while only 11 (20%) patients had a secondary progressive course. The mean EDSS score was 4.8±0.9 and the range was 1.5-8.0. Nineteen (34.5%) patients had an EDSS score of ≤3.5 (Group I), while 36 (65.5%) patients had an EDSS score of ≥4.0 (Group II). The prevalence of the various autonomic symptoms in the patients and controls is shown in **Table 1**. Most autonomic symptoms were either significantly more prevalent in the patients group or present in the patients group and non existent in the controls. Few autonomic symptoms including dryness of the mouth and nocturnal diarrhea showed no significant differences between patients and control. Female patients reported significantly higher prevalence rates of the following autonomic symptoms: peripheral flushing, urinary urgency and urge incontinence, and excessive sweating as compared to male patients. Sexual dysfunction symptoms were commonly reported in male MS patients as shown in **Table 1**, while none of the controls reported these symptoms.

Table 2 - The distribution of severity of different autonomic dysfunctions as assessed by ANSDS for patients and controls.

Autonomic dysfunction	Class 0		Class 1		Class 2		Class 0		Class 1		Class 2	
	Patients (n=55)						Controls (n=40)					
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Postural dizziness	18	32.7	27	49	10	18.1	27	67.5	13	32.5	-	-
Palpitation	20	36.3	34	61.8	1	1.8	31	77.5	9	22.5	-	-
Peripheral flushing	19	34.5	36	65.4	-	-	37	92.5	3	7.5	-	-
Urinary frequency	34	61.8	6	10.9	15	27.2	38	95	2	5	-	-
Nocturia	43	78.1	2	3.6	10	18.1	38	95	2	5	-	-
Polyuria	42	76.3	1	1.8	12	21.8	39	97.5	1	2.5	-	-
Urgency	9	16.3	18	32.7	28	50.9	40	100	-	-	-	-
Hesitancy	21	38.1	16	29	18	32.7	40	100	-	-	-	-
Incontinence	28	50.9	2	3.6	25	45.4	40	100	-	-	-	-
Constipation	13	23.6	30	54.5	12	21.8	38	95	2	5	-	-
Fecal incontinence	48	87.2	-	-	7	12.7	40	100	-	-	-	-
Nocturnal diarrhea	50	90.9	2	3.6	3	5.4	38	95	2	5	-	-
Dyspepsia	27	49	20	36.3	8	14.5	38	95	2	5	-	-
Ptyalism	52	94.5	1	1.8	2	3.6	40	100	-	-	-	-
Dryness of mouth	39	70.9	10	18.1	6	10.9	34	85	6	15	-	-
Impaired erection (males=25)	10	40	2	8	13	52	25	100	-	-	-	-
Impaired ejaculation	13	52	4	16	8	32	25	100	-	-	-	-
Loss of libido	16	64	1	4	8	32	25	100	-	-	-	-
Loss of early morning erection	14	56	3	12	8	32	25	100	-	-	-	-
Others (fatigue and spasticity)	17	68	8	32	-	-	25	100	-	-	-	-
Excessive sweating	30	54.5	24	43.7	1	1.8	33	82.5	17	17.5	-	-
Decreased sweating	51	92.7	4	7.2	-	-	40	100	-	-	-	-

Class 0 - no symptoms or signs
Class 1 - mild or transient symptoms or signs
Class 2 - severe or persistent symptoms or signs
ANSDS - autonomic nervous system disability scale

Table 3 - The results of different symptoms of autonomic dysfunctions in 2 groups of MS patients with variable levels of disability as assessed by EDSS.

Symptom of autonomic dysfunction	Group I (n=19) EDSS ≤ 3.5 n	(%)	Group II (n=36) EDSS ≥ 4 n	(%)
Cardiovascular symptoms	16	84.2	35	97.2
Urinary symptoms	17	89.5	32	88.9
GIT symptoms	16	84.2	32	88.9
Sexual symptoms (males=25)	10/11	90.1	9/14	64.3
Sweating dysfunctions	8	42.1	21	58.3

EDSS - Expanded disability status scale
GIT - gastrointestinal tract, MS - multiple sclerosis

Table 4 - The distribution of the results of Ewing autonomic cardiovascular reflex tests in MS patients and controls.

Cardiovascular reflex test	Patients (n=55)						Controls (n=40)					
	Normal		Borderline		Abnormal		Normal		Borderline		Abnormal	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1. Systolic BP response to standing*	29	52.7	17	30.9	9	16.3	38	95	2	5	0	0
2. Diastolic BP response to isometric sustained handgrip	26	47.2	7	12.7	22	40	37	92.5	3	7.5	0	0
3. R-R ratio variation to deep breathing*	11	20	6	10.9	38	69	28	70	10	25	2	5
4. R-R ratio variation to Valsalva maneuver*	8	14.5	11	20	36	65.4	28	70	9	22.5	3	7.5
5. R-R ratio variation to standing*	27	49	3	5.4	25	45.4	37	92.5	2	5	1	2.5

*Highly significant (p<0.001), R-R - relapsing-remitting, BP - blood pressure, MS - multiple sclerosis
Test 1 and 2 are for sympathetic functions
Tests 3, 4 and 5 are for parasympathetic functions

Table 5 - The results of different parameters in 2 groups of MS patients with different autonomic cardiovascular test scores (Ewing scores).

Parameter	Group A (n=9) Ewing score < 2	Group B (n=46) Ewing score ≥ 2
Age at investigation time*	33.5±8.6	38.9±7.8
Age at onset of illness	30.3±8.0	32.0±8.9
Duration of illness**	3.9±2.8	7.0±5.2
Course of illness		
Relapsing-Remitting	7 (77.8%)	37 (80.4%)
Secondary-Progressive	2 (22.2%)	9 (19.6%)
Severity of disability assessed by EDSS	4.9±2.1	5.4±1.9

*P = 0.009; **P = 0.007; EDSS - Expanded disability status scale
Ewing score <2 = no definite autonomic neuropathy, Ewing score ≥2 = definite autonomic neuropathy, MS - multiple sclerosis

Table 6 - Patterns of autonomic dysfunction as assessed by Ewing autonomic cardiovascular tests.

Patterns of autonomic dysfunction	Total n	(%)
Normal results (G1)	3	5.5
Early PST derangement (G2)	6	10.9
Definite PST derangement (G3)	25	45.4
Combined ST and PST derangement (G4)	21	38.1

G2 - results of one of 3 tests of PST function abnormal; G3 - results of at least 2 tests of PST function abnormal; G4 - in addition to abnormal PST results, finding in one or both ST tests are abnormal
PST - parasympathetic; ST - sympathetic, MS - multiple sclerosis

The distribution of the severity of the different autonomic dysfunctions as assessed by ANSDS is shown in **Table 2**. Almost all autonomic dysfunctions were more prevalent and more severe in the patients than in the controls. None of the controls was found to have a severe autonomic symptom. Autonomic dysfunctions with the highest classes were reported with the urinary symptoms. In male MS patients, 40% reported severe or persistent sexual dysfunction. Only one patient had a mild breathing difficulty, while no patient had pupillary abnormality. Patients were divided according to the severity of the disability of MS as assessed by EDSS into 2 groups; group I with an EDSS $\leq$3.5 (mild disability) and group II with EDSS $\geq$4 (more severe disability), then the different autonomic symptoms were compared in these 2 groups. Cardiovascular symptoms and sweating disturbances were more prevalent in the more disabled patients as shown in **Table 3**. Male patients with milder disability showed more sexual complaints than those with more severe disability. The results of Ewing tests of the patients and the controls are shown in **Table 4**. All 5 tests showed highly significant differences in the patients as compared to those of the control. Several of the controls showed borderline results while only few of the control showed abnormal results with few of the tests as noticed in **Table 4**. Abnormal tests in the controls were observed with the parasympathetic tests but not with the sympathetic ones. The results of Ewing tests showed that there were 9 (16.4%) patients with a total Ewing score of less than 2 (Group A) (normal or borderline results), while 46 (83.6%) patients had definite autonomic neuropathy (Group B) (total score of 2 or more). The effects of age at investigation time, age at onset of the illness, duration of the disease, course and severity of the illness (as assessed by EDSS) on the results of the total Ewing tests scores in both groups are shown in **Table 5**. The age of the patients at investigation time and the duration of the illness showed significant statistical differences between the 2 groups. Looking at the pattern of autonomic dysfunctions as assessed by Ewing tests showed that none of the patients had a pure sympathetic derangement and the majority showed abnormal tests suggesting definite parasympathetic or combined sympathetic and parasympathetic abnormalities as shown in **Table 6**. In addition, abnormalities in parasympathetic tests were more prevalent than those of sympathetic tests (**Table 4**).

Discussion. There are extensive studies on MS in the literature dealing with different aspects of the disease. Autonomic dysfunction in MS has been a major concern to researchers in the past decades.[17-26] It seems that these autonomic disturbances are the result of reflex pathway impairment in the CNS.[27] In individual patients, diverse abnormality patterns of autonomic dysfunction were found. These patterns were attributed to MS plaques scattered on an anatomically wide spread cardiovascular regulatory system within the caudal brainstem and the spinal cord.[20,21] As important autonomic cardiovascular nuclei (namely nucleus tractus solitarii and hypothalamic nuclei) are located in the periventricular region of the fourth ventricle, it is conceivable that these structures are involved in MS.[28] This cross sectional study was designed to investigate carefully and in detail autonomic dysfunction in a reasonable number of Iraqi MS patients attending a specialized MS clinic in Baghdad as compared to a matched control. It included only patients with clinically definite MS with either relapsing remitting or secondary progressive course to reduce the chance of including non MS patients in the study and excluded patients with EDSS score of more than 8, as their disability might interfere with the ability to perform the required tests. This study, as well as others,[20-22,27,29-33] shows that the battery of autonomic tests could be used in assessment of autonomic dysfunction in MS patients. As the results of each test are not consistent with other test results, the most precise detection of autonomic reflex abnormalities can be achieved by use of the whole battery of tests.[27] The present study showed that symptoms related to autonomic disturbances were present in the vast majority of MS patients and their severity as assessed by ANSDS showed a significant statistical difference in comparison to the controls. The high prevalence of autonomic symptoms found in this study and the fact that the routine assessment of disability in MS patients does not cover all the autonomic disturbances should encourage the practicing clinician to look carefully for these abnormalities in the routine evaluation of their patients, as these autonomic disturbances may be disabling. Simple measures to overcome such disturbances may help the patients to improve their quality of life.

Cardiovascular, urinary and gastrointestinal autonomic symptoms affected 9 out of every 10 MS patients and were of great concern. It was noticed that a number of the controls had cardiovascular symptoms, especially postural dizziness and palpitation, but these were usually mild and not disabling. These symptoms should not necessarily be ascribed to autonomic dysfunction in MS patients and the results of the whole cardiovascular autonomic assessment should be evaluated accordingly. Urinary symptoms were common in the patients but not in the controls, especially urgency, hesitancy and incontinence. These symptoms in MS patients are highly specific and deserve careful assessment and management. Three quarters of MS patients complained of constipation, which was the most common gastrointestinal symptom while only a few of the controls had this symptom. Simple measures are usually useful in management. Sexual disturbances among male patients were prevalent and the most common was erectile dysfunction. These disturbances were severe (class 2) in 40% of affected male patients which should encourage proper evaluation and management of these symptoms which are

commonly neglected by medical staff in our society mainly for social reasons. Sexual symptoms in females were not asked for in the current study for the same reasons.

Excessive sweating was a common complaint in MS patients and especially females, but commonly it was mild and not disabling. In a study, which evaluated sweating function tests in MS patients, it was found that the majority of the patients had subclinical dysfunction of sudomotor system.[34] In the current study, cardiovascular symptoms and sweating abnormalities were more prevalent in the more severely disabled group of MS patients as assessed by EDSS.

Not all symptoms suggesting autonomic dysfunctions are necessarily due to ANS involvement, interestingly 16 (29%) patients reported postural dizziness without marked blood pressure alteration in response to standing. It has been suggested that the role of blood volume depletion as a contributing factor might result in postural instability in MS patients.[28] Blood volume measurement was not performed in the current study. The autonomic cardiovascular (Ewing) tests used in this study and in many similar studies are simple and non-invasive tests. They have shown to be valid and reliable in diabetes mellitus.[35] The sensitivity and specificity of these tests are satisfactory for clinical evaluation.[36] Abnormal Ewing tests were highly prevalent in our MS patients and were significantly different as compared to the control; definite autonomic abnormalities were reported in 83.6% of the patients. Published cross sectional studies on cardiovascular reflexes in MS show a large difference in percentages of patients having autonomic function abnormalities varying from 19% to 75%.[18,20-23,30,32,37,38] The differences may be caused by different factors including: number of the patients examined; patients selection criteria; in-study medication; variation in EDSS score; fluctuations in activity of MS and different batteries, with a wide range of normal values, of cardiovascular tests used.[26,30,39] Although all 5 cardiovascular tests showed significant abnormalities as compared to the control, the highest percentages of abnormalities were noticed with the parasympathetic tests while sympathetic tests showed lower percentages of abnormal results, the lowest was with systolic blood pressure response to standing. In individual patients, abnormalities in sympathetic tests were always associated with further abnormalities in the parasympathetic tests, while abnormalities in the parasympathetic tests could be detected alone. A few of the controls showed abnormal result in these tests as reported by others.[28,39] In the current study these abnormalities were noticed with the parasympathetic tests and not with the sympathetic ones which suggests that sympathetic abnormalities, though less prevalent, are highly specific when detected in MS patients. It is interesting to remember that there is ample evidence that the activation of the sympathetic nervous system has an immunosuppressive effect, whereas sympathetic blockade may enhance immune responses.[28,40] Sympathetic dysfunction was recently reported to be associated with the clinical activity of MS.[38] The finding of abnormal sympathetic test in MS patients might have a prognostic implication.

The highest frequency of abnormal test result was detected by heart rate response to deep breathing (69%), which is a parasympathetic test. The same finding was confirmed by other studies.[21,23,30] This might make such a test a useful tool in screening for autonomic dysfunction in MS patients. There were positive correlations between the presence of definite autonomic neuropathy as assessed by Ewing tests score and the age of the patients at the time of assessment and the duration of the disease which suggests that the older the patient and the longer the duration of the illness the more likely the presence of significant autonomic disturbances. The correlation with the disability as assessed by EDSS was not significant which is similar to the observations of others.[22,28,37] The EDSS is well known for being heavily weighted towards locomotion[28,41] and is unlikely to be useful for detecting small lesions within the brain stem or the spinal cord[28] which are thought to be responsible for the autonomic disturbances. However, in a longitudinal study of cardiovagal tests over a one year period, Nasseri et al[30] revealed a significant correlation between the decrease in the heart rate response to active standing and the EDSS score. In a further 2 year period study by the same group,[26] it was proposed that autonomic functional tests should be further investigated as a surrogate marker of disability in MS. In another prospective study, Lanchencker et al concluded that parasympathetic dysfunction was closely related to the progression of disability in MS patients.[38]

Due to the design of the present study, we were unable to follow up the patients and correlate the progression of the disease with the changes in autonomic functions. A prospective study over a reasonable time is needed to settle this issue.

In conclusion, autonomic symptoms were highly prevalent in Iraqi MS patients attending Baghdad MS clinic. The severity of autonomic disturbances as assessed by ANSDS and autonomic cardiovascular disturbances as assessed by Ewing tests were significantly different as compared to a matched control. Careful attention to autonomic disturbances may provide real help to MS patients.

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