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SHORT COMMUNICATION

AUTONOMIC (SYMPATHETIC) NERVOUS SYSTEM INVOLVEMENT IN RHEUMATOID ARTHIRITIS PATIENTS

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Abstract : Fifty Rheumatoid arthritis (RA) patients between the age group of 20 to 60 years were investigated for sympathetic autonomic functions using standard tests. All the patients liable to develop dysautonomia or having a treatment interfering with autonomic nervous system were excluded. Previous studies to evalute sympathetic nervous system involvement used only a single test like sweating response, orthostatic test. In the present study 3 tests of sympathetic nervous system evaluation have been used. The evaluation was done by cardiovascular tests like orthostatic test, sustained hand grip and cold pressor test. A control series of 50 healthy subjects was tested to determine abnormal threshold for each one of the 3 tests. The reference value of Ewing and Clark were used to interpret the results of the tests. Sympathetic dysfuction was found in 26% of rheumatoid arthritis patients.

Key words : autonomic (sympathetic) nervous system
rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting about 0.8% (range 0.3 to 2.1%) of the general population. The inflammation in RA begins and continues in joints and there is little explanation of why extra-articular manifestations develop in some patients of RA. These include haematologic abnormalities, vasculitis, pulmonary disease, cardiac complications, to name a few. In general, the extra-articular features vary with the duration and severity of the disease (1-5). The involvement of the nervous system in RA patients is well known. The peripheral nervous system is the main target and central nervous system (CNS) involvement is rare. Among the cases of nervous system involvement in RA, those of the peripheral nervous system are well documented and especially RA neuritis. A few studies have been done to study autonomic neuropathy in rheumatoid arthritis (6-8). Previous studies to evaluate sympathetic nervous system involvement used only a single test like

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sweating response, orthostatic test. The sweating tests are very difficult to reproduce and to quantify. Bennett et al studied the sweating response after an injection of acetylcholine in areas of anhidrosis. The abnormal responses were found in most cases of RA with neuropathy, thus indicating a relation between autonomic neuropathy and peripheral neuropathy (6). Later, in 1980, there were studies on dysautonomia in RA using cardiovascular tests which were much more reliable to evaluate. Edmonds et al studied 27 patients with RA with these cardiovascular tests (7). The study of ANS is not easy and comprised cardiovascular tests and investigation of specific organs such as skin, pupils and bladder (9-12). Leden et al reported abnormal responses in 7 patients with severe RA (13). The systolic and the diastolic blood pressures were higher in RA patients as compared to controls. Klocke R, Cockcroft JR et al (14) investigated the augmentation index as a measure of arterial stiffness. They concluded that, chronic inflammation in the form of vasculitis leads to an increased arterial stiffness and blood pressure in RA patients. Similar findings were also reported by Samoridova OS, Zharova EA et al (15). Louthrenoo W, Ruttanaupawan P et al performed the handgrip test in 34 RA patients with clinical dysautonomic symptoms (16). In the present study three tests of sympathetic nervous system evaluation have been used. We aimed to examine the frequency of sympathetic dysfunction in a cohort of fifty patients.

MATERIALS AND METHODS

Fifty rheumatoid arthritis patients diagnosed on the basis of American Rheumatism Association (ARA) criteria were selected for this study along with fifty (50) healthy age and sex matched controls. Each patient was subjected to a questionnaire on rheumatoid arthritis history, current treatment and autonomic symptoms (feeling of faintness in orthostatic change of posture, sweating, gastrointestinal, genital or urinary disorders, neurologic signs). Any patients with a history of dysautonomia or following a treatment interfering with the autonomic nervous system were excluded. The exclusion criteria used in the study are shown in Table I. An informed consent was obtained from the patients after explaining the procedure in detail. The procedures were in accordance with the ethical standards of the committee of the institute. The heart rate (HR) was recorded by an electrocardiographic tracing (lead II) and blood pressure (BP) was monitored. BP and HR was recorded at the beginning and then after continuous rest in supine position. The autonomic function tests were commenced when two consecutive readings taken five minutes apart were identical. This meant that in all probability they had reached their basal values. The following non-invasive tests were carried out (19-22).

1. *Orthostatic test :* The patient was standing. At a signal, he lay down and then stood up again. He was instructed to remain motionless for two minutes. The subjects BP were recorded when lying down and again when the subject stands up from supine position.

2. *Sustained handgrip test :* The subject pressed the handgrip dynamometer for five minutes at 30% of the maximal

voluntary effort. The BP was recorded in contralateral arm and rise in diastolic BP was measured.

3. *Cold pressor :* The subject was asked to immerse one hand in iced water for one minute and the BP measured in opposite arm.

Various indirect autonomic parameters obtained from patients and controls were compared by Student's unparied 't' test.

RESULTS AND DISCUSSION

Fifty RA patients and fifty controls in the age group of 20 to 60 years were studied. Tables II and III present the data of the autonomic responses. Symptoms of autonomic dysfunction related to cardiovascular system were present in 10% related to gastrointestinal system in 6% and related to skin in 2% of the RA patients. Autonomic dysfuction may however occur even in asymptomatic RA patients and symptoms suggestive of peripheral neuropathy are commonest (30%) (Table IV). The resting HR and BP were significantly higher in RA patients as compared to controls. The comparative study, between our series of patients and the controls, using Student's t test showed significant difference between control and patients for all the three sympathetic autonomic function tests (Table V). Out of the 50 patients, 8% of the RA patients had significant orthostatic hypotension with fall in BP by more than 30 mmHg on standing from supine position. The BP response to sustained handgrip was abnormal in 20% RA patients and cold pressor test was found to be abnormal in 22% patients. In our patients of RA, autonomic testing indicates involvement of the sympathetic pathways. Symptoms of peripheral neuropathy were present in 30% patients. This suggests that clinical sensory neuropathy in RA is usually accompanied by an autonomic neuropathy also. ANS involvement is not uncommon in RA, however the actual mechanism in not clear. The association of dysautonomia with RA and systemic diseases could be an immunological mechanism (23). A drug induced cause has also been suggested and gold treatment can induce autonomic disturbances (24). Further studies to co-relate etiological mechanisms involved in RA could have therapeutic and prognostic significance.

TABLE I : Exclusion criteria.

History	*Treatment interfering with ANS*
Diabetes mellitus, Adrenal and thyroid disorders, chronic alcoholism, Parkinson's disease, Renal failure, Multiple sclerosis, Anaemia, Porphyria, Polyneuropathy.	Anti-tuberculosis drugs, Nitrofurantoin, Metronidazole, chloramphenicol, Clofibrate, Imipramine, Phenytoin, Barbiturates, Beta adrenergic blocking drugs.

TABLE II : Distribution of symptomatology and autonomic responses in RA patients.

S.No	*Age*	*Sex*	*CVS*	*GIT*	*GUT*	*Skin*	*PNS*	*Heart rate*	*Basal systolic BP*	*Basal diastolic BP*	*Orthostatic fall in systolic BP*	*Rise in diastolic BP (SHG)*	*Rise in diastolic BP (CPT)*
1	40	F	No	No	No	No	No	107	112	80	10	20	12
2	30	F	No	No	No	No	No	94	108	70	10	18	12
3	45	F	No	No	No	No	Yes	88	124	80	8	16	14
4	48	F	No	Yes	No	No	Yes	78	120	80	12	8	6
5	25	F	No	No	No	No	No	105	124	74	6	14	14
6	35	F	Yes	No	No	No	Yes	94	112	80	32	8	6
7	31	F	Yes	No	No	No	No	84	120	80	30	16	12
8	46	F	No	No	No	No	Yes	88	110	80	10	16	14
9	50	F	No	No	No	No	No	100	112	84	4	20	12
10	42	F	No	No	No	No	Yes	79	114	84	8	16	14
11	40	F	No	No	No	No	No	86	116	78	4	18	16
12	33	F	No	No	No	No	Yes	88	108	84	6	16	12
13	52	F	No	Yes	No	No	Yes	102	118	80	6	6	8
14	54	F	No	No	No	No	No	90	110	84	8	10	10
15	34	F	No	No	No	No	No	78	110	80	10	16	12
16	47	F	No	No	No	No	No	94	116	70	10	16	14
17	50	F	No	No	No	No	No	88	120	78	6	20	18
18	40	F	No	No	No	No	No	84	124	80	8	22	14
19	22	F	No	No	No	No	No	90	124	84	4	16	16
20	27	F	No	No	No	No	No	96	114	82	16	10	10
21	35	F	Yes	No	No	No	Yes	106	120	90	16	8	6
22	28	F	No	No	No	No	No	102	112	84	10	18	12
23	38	F	No	No	No	No	Yes	74	116	80	2	24	20
24	39	F	No	No	No	No	No	86	122	86	4	22	18
25	29	F	No	No	No	No	No	80	120	80	8	20	16
26	45	F	No	No	No	No	Yes	82	114	84	10	8	4
27	42	F	No	No	No	No	No	98	120	86	10	16	12
28	35	F	No	No	No	No	No	105	112	84	6	18	14
29	31	F	No	No	No	No	No	88	120	70	8	22	20
30	41	F	No	No	No	No	No	94	112	76	2	20	16
31	60	F	No	No	No	No	Yes	95	120	80	18	4	6
32	38	F	No	No	No	No	No	76	112	86	10	18	12
33	48	F	No	No	No	No	No	80	124	78	8	18	14
34	24	F	No	No	No	No	No	88	110	72	4	24	18
35	40	F	No	No	No	No	No	104	108	76	6	22	14
36	45	F	No	Yes	No	No	Yes	94	120	70	20	6	8
37	45	F	No	No	No	No	No	70	124	70	8	18	12
38	35	F	No	No	No	No	No	84	118	88	10	16	14
39	30	F	Yes	No	No	No	Yes	92	112	80	30	18	12
40	50	F	No	No	No	No	No	100	120	80	8	18	12
41	33	F	No	No	No	No	No	82	108	84	10	16	16
42	25	F	No	No	No	No	No	88	108	78	20	14	10
43	30	F	No	No	Yes	No	No	102	120	90	8	18	14
44	45	F	No	No	No	No	No	86	108	80	4	22	12
45	50	F	No	No	No	No	No	90	120	70	6	24	18
46	29	F	No	No	No	No	No	72	110	82	2	20	16
47	35	M	No	No	No	No	No	94	120	70	4	20	12
48	25	M	No	No	No	No	No	78	112	78	6	20	14
49	50	M	Yes	No	No	No	Yes	84	120	84	30	10	8
50	42	M	No	No	No	No	No	90	124	76	10	16	14

*CVS : Cardiovascular system
**GIT : Gastrointestinal system
***GUT : Genitourinary system
****PNS : Peripheral nervous system
*****SHG : sustained hand grip
******CPT : cold pressor test

TABLE III : Distribution of autonomic responses in control group.

S.No	*Age*	*Sex*	*Heart rate*	*Basal systolic BP*	*Basal diastolic BP*	*Orthostatic fall in systolic BP*	*Rise in diastolic BP (SHG)*	*Rise in diastolic BP (CPT)*
1	48	F	82	120	86	10	16	14
2	42	F	94	120	84	8	22	16
3	35	F	88	118	94	0	18	20
4	42	F	78	120	70	4	20	18
5	32	F	104	116	80	2	16	16
6	45	F	84	116	84	6	22	12
7	41	F	80	108	82	8	20	20
8	39	F	79	124	90	10	16	16
9	52	F	84	112	70	8	16	20
10	25	F	80	110	82	2	24	16
11	55	F	75	120	80	10	18	12
12	27	F	84	104	70	4	20	14
13	29	F	81	100	68	6	28	18
14	40	F	89	112	78	2	22	22
15	23	F	88	124	80	0	26	20
16	37	F	73	100	78	6	20	20
17	49	F	79	124	84	8	24	12
18	52	F	88	120	68	6	15	12
19	33	F	68	110	70	8	20	18
20	22	F	72	106	64	4	22	16
21	45	F	71	122	80	14	20	14
22	32	F	80	110	70	8	26	20
23	50	F	88	116	74	12	18	12
24	45	F	68	100	68	8	16	14
25	38	F	82	120	80	6	18	18
26	35	F	78	124	60	4	22	12
27	29	F	90	100	78	10	20	14
28	33	F	74	106	66	0	24	16
29	42	F	88	122	84	6	16	12
30	37	F	80	108	82	8	18	22
31	43	F	70	106	72	4	22	14
32	35	F	82	112	78	2	16	20
33	32	F	86	100	76	6	24	18
34	23	F	68	110	70	10	18	12
35	33	F	92	118	76	10	26	14
36	48	F	76	120	84	6	16	12
37	34	F	82	108	90	6	20	12
38	21	F	85	116	72	2	22	20
39	40	F	78	106	68	6	16	12
40	47	F	74	122	78	10	20	12
41	26	F	80	102	72	4	24	16
42	50	F	82	124	74	8	18	18
43	30	F	72	110	68	6	16	14
44	45	F	78	112	82	8	18	16
45	23	F	76	110	74	4	24	12
46	49	F	80	114	76	10	18	12
47	25	M	82	120	80	2	24	22
48	45	M	78	120	82	8	16	14
49	36	M	70	116	78	4	20	14
50	48	M	82	118	78	10	16	12

*SHG : sustained hand grip **CPT : cold pressor test

TABLE IV : Distribution of symptomatology in rheumatoid arthritis patients.

Symptoms	*No.*	*Percent*
Cardiovascular system (CVS)	5	10
Gastrointestinal system (GIT)	3	6
Skin	1	2
Genitourinary system (GUT)	0	0
Peripheral nervous system (PNS)	15	30

TABLE V : Comparison of autonomic function tests in rheumatoid arthritis patients and controls.

	Group	*Mean*	*SD*	*Unpaired T-test applied*		
				T-value	*P-value*	*Significant*
Resting heart rate	Patients	89.54	9.38	5.422	4.24E-07	Significant
	Control	80.44	7.27			
Basal systolic BP	Patients	116.12	5.38	1.988	0.05	Significant
	Control	113.52	7.52			
Basal diastolic BP	Patients	79.68	5.35	2.404	0.018	Significant
	Control	76.64	7.16			
Orthostatic test	Patients	10.12	7.33	3.384	0.001	Significant
(Fall in systolic BP)	Control	6.28	3.26			
Sustained handgrip	Patients	16.4	5.05	-4.115	8.06E-05	Significant
test (Rise in diastolic)	Control	19.94	3.4			
Cold pressor test	Patients	12.8	3.66	-4.076	9.33-05	Significant
(Rise in diastolic BP)	Control	15.64	3.3			

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