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ORIGINAL ARTICLE

Autonomic nervous system changes associated with rheumatoid arthritis: Clinical and electrophysiological study

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Abstract *Aim of the work:* The aim of this study was to evaluate clinically and electrophysiologically the autonomic nervous system changes associated with rheumatoid arthritis (RA).

Patients and methods: The present study included 25 patients with RA [22 women (88%)] and 30 apparently healthy control subjects [27 women (90%)]. A thorough clinical examination was carried out. Disease activity and functional disability were assessed. Tests for assessment of autonomic functions include active and passive orthostatic stress tests, and sympathetic skin response (SSR). The presence of abnormality in 2 tests or more was a clue for the presence of autonomic neuropathy (AN). Sural sensory nerve conduction study and posterior tibial motor nerve conduction study were done.

Results: There was a statistically significant decrease in standing systolic and diastolic blood pressure (BP) components of the active orthostatic stress test and SSR amplitude as well as statistically significant prolongation of SSR latency of RA patients when compared to control. Three patients (12%) had clinical symptoms suggestive of AN; increased to 14 patients (56%) when orthostatic stress tests and SSR were utilized. There were no statistically significant differences between patients with different disease activity score 28 with 4 variables grades of RA activity and SSR latency and amplitude. There were no statistically significant differences between patients with different Stanford Health Assessment Questionnaire Disability Index grades of RA functional disability and SSR latency and amplitude.

Conclusions: Autonomic neuropathy is a common extra-articular manifestation of RA affecting sympathetic and parasympathetic fibers.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disorder. It affects principally the joints and is usually accompanied by one or more of extra-articular manifestations as rheumatoid nodules, normochromic normocytic anemia and neuropathy [1,2]. Neuropathies are estimated to be the commonest neurological extra-articular feature. The neuropathic affection among RA patients includes mononeuropathy (entrapment neuropathy e.g. carpal tunnel syndrome), mononeuritis multiplex, peripheral polyneuropathy and autonomic neuropathy (AN) [3–5]. Autonomic neuropathy results from the affection of the sympathetic and/or parasympathetic nerve fibers. Autonomic neuropathy manifests clinically as cold, clammy, cyanotic extremities, peripheral vasospasm, palpitation, orthostatic hypotension, syncopal attacks and sexual dysfunction [6,7].

Autonomic neuropathy can be assessed by clinical and electrophysiological tests. Clinically, AN can be detected by active orthostatic stress test and passive orthostatic stress test (tilt table test) [8]. Sympathetic skin response (SSR) is an electrophysiological test which assesses autonomic dysfunction [7,9].

There are scanty studies that assess autonomic nervous system (ANS) affection electrophysiologically in RA [10]. The aim of this study was to evaluate clinically and electrophysiologically the ANS changes associated with RA.

2. Patients and methods

2.1. Patients

The present cross sectional study included 25 patients with RA diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR–EULAR) classification criteria for RA [which include the presence or absence of rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA)] [11]. The patients were accrued sequentially from those attending the Outpatient Clinic of Physical Medicine, Rheumatology and Rehabilitation Department, Main University Hospital, Alexandria Faculty of Medicine. A control group of 30 apparently healthy volunteers were included. The volunteers consisted of medical staff, their relatives and patients' relatives. The study was explained to the participants and an informed consent was given by each. The study had been approved by the ethics committee of the Faculty of Medicine, Alexandria University, Egypt. Patients with diabetes mellitus, endocrine disorders, metabolic disorders, neurological disorders including sensory motor peripheral neuropathy and carpal tunnel syndrome, patients who had an overlap with other rheumatological illness and patients on medical therapy known to affect ANS as tricyclic antidepressants were excluded.

2.2. Methods

Patients were clinically evaluated. Clinical examination was stressed on the musculoskeletal system and the detection of extra-articular manifestations. Assessment of functional status of RA patients was done using the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) [12]. HAQ-DI score interpretation: HAQ-DI score of 0–1 represents mild disability, score of 1–2 represents moderate disability and score of 2–3 represents severe disability [12]. Assessment of RA disease activity was done using disease activity score 28 with 4 variables (DAS 28 with 4 variables) [13]. DAS 28 with 4 variables score interpretation: DAS28 score <2 represents not active, scores >2 and $\leqslant 3.2$ represent mild activity, scores >3.2 and $\leqslant 5.1$ represent moderately active and score >5.1 represents highly active [13]. Laboratory investigations were done for the patients and included ESR using Westergren's method and complete blood count [14,15].

Assessment of the ANS in both patients and control was done by using the following tests and the presence of abnormality in 2 tests or more was a clue for the presence of AN [4]:

(1) *Active orthostatic stress test*: It was done by measuring the supine and standing blood pressure (BP) and heart rate (HR). It was done by making the subject to lay supine for 30 min then measure the BP and HR. Then the subject stood upright for 10 min. A sustained decrease in the systolic BP ($\geqslant 20$ mmHg) or drop of the diastolic BP ($\geqslant 10$ mmHg) after standing for 5 min (indication for sympathetic dysfunction) that is associated with or without an increase in the HR > 30 beats per minute (indication for parasympathetic dysfunction) suggests autonomic abnormality [8]. The test was done in a calm atmosphere and after allowing the subject to take a rest period of 30 min before starting the test.

(2) *Passive orthostatic stress test (tilt table test)*: It was done by making the subject to lay supine on a tilt table for 30 min then measure the BP and HR. Then the subject was tilted upright for 10 min at an angle of 60–80°. Abnormal response was: (i) orthostatic hypotension: when there was reduction of the systolic BP by $\geqslant 20$ mmHg or reduction of the diastolic BP by $\geqslant 10$ mmHg with or without syncope (indication for sympathetic dysfunction) and/or (ii) postural orthostatic tachycardia: when there was sustained increase of the HR by >30 beats per minute or a sustained HR of 120 beats per minute (indication for parasympathetic dysfunction) [8,16]. The test was done under the same circumstance of the active orthostatic stress test and in the same room. The subject was allowed to take a rest period of 30 min before starting the test.

(3) Sympathetic skin response of the hand was done as a measurement of the sympathetic function. It was conducted on a Nihon Kohden Neuropack MEB-7102 mobile unit with a two channel evoked potential/EMG measuring system (Nihon Kohden Corporation, Tokyo, Japan). Skin temperature at the site of the recording electrode was maintained around 31–32 °C by the mean of hot packs. The SSR was performed by the same examiner. The hand was manually fixed by the examiner to reduce movement artifacts. The ground electrode was placed between the recording electrodes distally and the stimulation site proximally. An active recording surface disc electrode was attached to the palm and the reference surface disc electrode was attached to the dorsum of the hand. The used stimuli were single electrical stimulus at the wrist (over the median nerve) contralateral to the recording side. The stimuli were delivered

unexpectedly and at irregular time intervals to avoid habituation. The bipolar stimulator had a production current ability of 50 mA. The stimulation frequency was 0.1 Hz and pulse duration was 0.2 ms. The sweep speed was 0.5 s/division and the sensitivity was 50–200 uV/division. The filter bandwidth was 1 Hz–3 kHz. Responses were recorded four times and were superimposed to ensure reproducibility. Measurements included the elicitability of the response, latency and amplitude. The latency was measured from the stimulus artifact onset to the onset of initial negative deflection expressed in seconds. The amplitude was measured from the baseline to the negative peak expressed in microvolt. Abnormality of SSR (sympathetic dysfunction) was defined as absent or delayed latency and/or low amplitude exceeding the cut-off point at which highest diagnostic accuracy was reached that was estimated using the mean + 2SD for latency and mean − 2SD for amplitude [17].

Both components of the ANS were assessed as follows:

(a) The sympathetic nervous system was assessed by using the BP changes in response to postural changes (i.e. active and passive orthostatic stress tests) and SSR [18].
(b) The parasympathetic nervous system was assessed by HR changes in response to postural changes (i.e. active and passive orthostatic stress tests) [18].

Sural sensory nerve conduction study and posterior tibial motor nerve conduction study were done to both patients and control for assessment of the peripheral nerve [19].

Statistical analysis of data was done by using the Statistical Package of Social Science (SPSS version 17) software. Descriptive measures [count, frequency, minimum, maximum, median, mean and standard deviation (SD)] as well as analytic measures (qualitative data were analyzed using chi-square for independent groups; quantitative data were analyzed using Mann Whitney test to compare between two independent groups and Kruskel-Wallis test to compare between more than two independent samples and correlation was conducted using Spearman's correlation test) were used. Statistical significance was assigned to any P value at $\leqslant 0.05$. The cut off value of the electrophysiological studies was equal to the mean plus two standard deviations for SSR latency and was equal to the mean minus two standard deviations for SSR amplitude.

3. Results

The present study included 25 patients with RA [22 women (88%) and 3 men (12%)]. Their mean age was 43.96 ± 11.28 years (ranged from 21 to 64 years). The control group consisted of 30 individuals [27 women (90%) and 3 men (10%)]. Their mean age was 40.23 ± 11.14 years (ranged from 22 to 65 years). There were no statistically significant differences between patients and controls as regards gender ($P = 0.813$) and age ($P = 0.181$).

The clinical data of the patients are summarized in Table 1. As regards HAQ-DI, 13 patients (52%) had mild disability, 10 patients (40%) had moderate disability and 2 patients (8%) had severe disability. The patient group covered the 3 grades of disability. Diseases activity assessed by DAS28 with 4 variables showed that there were 9 patients (36%) with mild activity, 13 patients (52%) with moderate activity and 3 patients (12%) with high activity. The patient group covered the 3 grades of RA disease activity. All patients who had extra-articular manifestation [19 patients (76%)] were RF positive. All patients who had ACPA positive [15 patients (60%)] had extra-articular manifestation. There were no statistically significant differences between patients and controls as regards sural nerve amplitude ($P = 0.389$), sural nerve conduction velocity ($P = 0.642$), tibial nerve amplitude ($P = 0.813$) and tibial nerve conduction velocity ($P = 0.116$) which exclude the presence of sensory motor peripheral polyneuropathy among the RA patient group.

Table 1 Clinical features of rheumatoid arthritis patients.

Clinical features of RA patients	Patients ($n = 25$)	
	Mean ± SD	Range
Age of onset (years)	37.16 ± 10.12	20–58
Duration of the disease (years)	6.20 ± 3.92	1–15
HAQ-DI	1.03 ± 0.58	0.16–2.40
28TJC	15.92 ± 7.84	4–28
28SJC	6.48 ± 4.90	1–18
ESR (mm/1st hr)	48.76 ± 18.40	25–110
Patients' global assessment of disease activity	5.64 ± 2.32	1–10
DAS28 with 4 variables	4.04 ± 0. 84	2.7–5.3
	n	(%)
RF positivity	22	88
ACPA positivity	15	60
Patients with extra-articular manifestations	19	76
Keratoconjuctivitis sicaa	17	68
Normochromic normocytic anemia	19	76
Dysautonomic symptoms	3	12
Orthostatic hypotension	3	12
Syncopal attacks	1	4
Rheumatoid nodules	2	8

RA: rheumatoid arthritis; HAQ-DI: Stanford Health Assessment Questionnaire Disability Index; 28SJC: 28 swollen joint count; 28TJC: 28 tender joint count; ESR: erythrocyte sedimentation rate; DAS28: disease activity score 28; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; SD: standard deviation; *n* (%): number of patients (percentage).

All control individuals had normal response to the active and passive orthostatic stress tests. The frequency of abnormalities in both active and passive orthostatic stress tests among RA patients is tabulated in Table 2. The standing systolic BP and standing diastolic BP components of the active orthostatic stress test were significantly decreased among patient group compared to control group (Table 3). The cut-off point of the SSR latency was 1.44 s and that of SSR amplitude was 40.15 μV. SSR was elicited in all patients and control. The frequency of abnormalities in SSR latency and amplitude among RA patients is tabulated in Table 2. SSR latency was significantly prolonged among patient group compared to control group. SSR amplitude was significantly decreased among patient group compared to control group (Table 4).

There were 3 patients (12%) that had symptoms suggestive of AN (Table 1). The dysautonomic symptoms included

Table 2 Frequency of abnormalities in orthostatic stress tests and sympathetic skin response among rheumatoid arthritis patients.

Tests assessing ANS	Frequency of abnormalities [*n* (%)]
Active orthostatic stress test	
Abnormal response	11 (44)
Orthostatic hypotension	11 (44)
Postural orthostatic tachycardia	2 (8)
Passive orthostatic stress test	
Abnormal response	14 (56)
Orthostatic hypotension	14 (56)
Postural orthostatic tachycardia	6 (24)
SSR	
Abnormal SSR	18 (72)
Prolonged SSR latency	15 (60)
Low SSR amplitude	14 (56)

ANS: autonomic nervous system; SSR: sympathetic skin response; *n* (%): number of patients (percentage).

orthostatic hypotension and syncopal attacks. All these patients had 2 or 3 abnormal tests assessing ANS. The number of patients with AN increased to 14 patients (56%) when cardiovascular autonomic function tests (active orthostatic stress test and passive orthostatic stress test) and SSR were utilized [8 patients (32%) had 3 abnormal tests and 6 patients (24%) had 2 abnormal tests respectively]. All of them had sympathetic dysfunction and 24% of patients had parasympathetic dysfunction. All these patients had other extra-articular manifestations and all of them had positive RF and ACPA.

There were no statistically significant differences between patients with different DAS28 grades of RA activity and SSR latency ($P = 0.625$) and amplitude ($P = 0.350$). There were no statistically significant differences between patients with different HAQ-DI grades of RA functional disability and SSR latency ($P = 0.128$) and amplitude ($P = 0.759$).

There was a statistically significant negative correlation between standing systolic BP and standing diastolic BP components of active orthostatic stress test, and patient's global assessment of disease activity ($r = -0.423$, $P = 0.035$; $r = -0.532$, $P = 0.006$ respectively). Otherwise, there was no statistically significant correlation between other different active orthostatic stress test parameters and RA disease duration, DAS28 score, DAS28 components and HAQ-DI (all had $P > 0.05$). There was no statistically significant correlation between SSR latency and amplitude, and RA disease duration, DAS28 score, DAS28 components and HAQ-DI (all had $P > 0.05$).

4. Discussion

The aim of the current study was to assess the ANS changes associated with RA from the clinical and electrophysiological point of view.

In the present study, both components of the ANS were assessed including the sympathetic and the parasympathetic nervous systems. The sympathetic nervous system was assessed by using the BP changes in response to postural changes and SSR. The parasympathetic nervous system was assessed by HR changes in response to postural changes [18].

Table 3 Comparison between rheumatoid arthritis patients and controls as regards the active orthostatic stress test.

Active orthostatic stress test parameters	Patients ($n = 25$)	Control ($n = 30$)	Z	*P*
Supine systolic BP (mmHg)				
Median	120	120	−0.830	0.407
Mean ± SD	117.72 ± 10.50	119.90 ± 9.69		
Range	100–135	100–135		
Supine diastolic BP (mmHg)				
Median	75	79	−1.111	0.267
Mean ± SD	72.72 ± 11.04	75.46 ± 9.47		
Range	55–95	55–90		
Supine HR (beat/min)				
Median	66	72.5	−1.484	0.138
Mean ± SD	67.80 ± 8.64	72.00 ± 9.04		
Range	54–82	58–86		
Standing systolic BP (mmHg)				
Median	100	110	−2.950	0.003*
Mean ± SD	101.40 ± 13.95	111.36 ± 11.38		
Range	80–135	90–135		
Standing diastolic BP (mmHg)				
Median	65	75	−2.355	0.019*
Mean ± SD	66.12 ± 9.94	71.80 ± 7.77		
Range	50–88	55–80		
Standing HR (beat/min)				
Median	82	81.5	−0.779	0.436
Mean ± SD	82.28 ± 11.55	79.83 ± 10.71		
Range	60–105	60–97		

BP: blood pressure; HR: heart rate; SD: standard deviation; *n*: number of individuals; *Z* = value of Mann–Whitney.
* *P* is significant at $\leqslant 0.05$.

Table 4 Comparison between rheumatoid arthritis patients and controls as regards the sympathetic skin response parameters.

SSR parameters	Patients (n = 25)	Control (n = 30)	Z	P
Latency (s)				
Median	1.39	1.09	−3.584	< 0.0001*
Mean ± SD	1.32 ± 0.27	1.06 ± 0.19		
Range	0.75–1.70	0.69–1.46		
Amplitude (μV)				
Median	38.6	128.05	−6.009	< 0.0001*
Mean ± SD	39.58 ± 20.20	125.41 ± 42.63		
Range	12.80–91.90	53.30–199.00		

SSR: sympathetic skin response; SD: standard deviation; n: number of individuals; Z = value of Mann–Whitney.
* P is significant at ⩽0.05.

Orthostatic stress test assesses the BP and HR changes associated postural changes in the body position from supine to standing. These changes are mediated by sympathetic and parasympathetic nerve fibers. During standing from supine position (actively or passively), there is pooling of blood in the veins of the lower limbs and splanchnic circulation results in decrease in the stroke volume. This leads to a slight decrease in the BP and a slight increase in the HR associated with vasoconstriction of the blood vessels of the lower limbs and splanchnic circulation. This is mediated by reflex sympathetic stimulation and parasympathetic inhibition. Passive orthostatic stress test is more sensitive than the active orthostatic stress test. This test is characterized by minimizing the compensatory response of active muscle contraction of the lower limbs which can affect the result of the active orthostatic stress test by reducing lower limb pooling of blood. In autonomic neuropathy, this reflex is abnormal which leads to the abnormal orthostatic stress test (both active and passive) [8].

In the current study, the standing systolic BP and standing diastolic BP components of the active orthostatic stress test were significantly decreased among patient group compared to control group. There was also a statistically significant increase in the SSR latency and a statistically significant decrease in the SSR amplitude among RA patients. This indicates the presence of sympathetic dysfunction among RA patients.

In the present study, there were no statistically significant correlation between SSR latency and amplitude as regards RA disease duration, DAS28 score, DAS28 components and HAQ-DI. This means that the pathogenic mechanism responsible for the development of AN might differ from that of RA joint involvement.

There was a negative correlation between the standing systolic BP and standing diastolic BP components of active orthostatic stress test, and patient's global assessment of disease activity which is a component of DAS 28 with 4 variables. This correlation was unexplained as there was no significant correlation between the standing systolic BP and standing diastolic BP with DAS28 score and HAQ-DI.

There were 56% of patients with AN. All of them had sympathetic dysfunction and 24% of patients had parasympathetic dysfunction. This indicates that AN among RA patients affects both ANS components: sympathetic and parasympathetic nervous systems. This could not be explained by the limited mobility of RA patients as 92% of them had mild or moderate functional disability assessed by HAQ-DI. Their functional disability was not so severe to the degree that can affect the BP and HR assessed by orthostatic stress test.

All these patients had other extra-articular manifestations and all of them had positive RF and ACPA. The presence of RF and ACPA is an indicator of severe RA disease and is associated with extra-articular manifestations including AN [3,20]. The present study is in agreement with Turesson et al. [20] and De Rycke et al. [21]. Turesson et al. [20] reported that RF is strongly associated with extra-articular manifestations in RA patients and they found a statistically significant difference in RF titers between patients with extra-articular manifestations versus those without extra-articular manifestations. De Rycke et al. [21] reported that the presence of extra-articular manifestations in RA is associated with RF.

The current study is in agreement with other studies that assessed the ANS among RA patients [4,22–26]. Jale et al. [22] assessed the ANS among RA patients. Their study showed that there were frequent abnormalities in SSR and R-R interval variation tests in patients with RA whether there was a clinical symptom of autonomic dysfunction or not. Geenen et al. [23] found that there was diminished ANS response secondary to AN in RA of recent onset and mainly in patients with more severe pain. Edmonds et al. [24] reported that 14.8% of RA patients had symptoms suggesting ANS dysfunction. They detected abnormalities in parasympathetic cardiovascular reflexes in 33% of their RA patients including those who had symptoms of autonomic dysfunction. More than 50% of their patients with abnormal tests for ANS had evidence of peripheral neuropathy. Toussirot et al. [4] investigated autonomic dysfunction among RA patients by three cardiovascular tests which were HR variations in deep breathing, valsalva maneuver and orthostatic change in posture. They found that 60% of their 50 RA patients had ANS dysfunction. No patients showed neurological sign or autonomic sign. They reported that there was no obvious correlation between ANS dysfunction in RA and markers of inflammation, presence of RF, duration of disease or degree of joint destructive lesions [4]. Gokoglu et al. [25] reported that all their RA patients were asymptomatic for AN and had normal neurological examination findings. They assessed the sympathetic functions by systolic BP response to standing and diastolic BP response to isometric exercise and SSR. They also assessed parasympathetic functions by HR variation with deep breathing, HR response to standing and R–R interval variation measurements. They reported that all the assessed parameters were significantly lower in RA patients than in control subjects [25]. Yadav et al. [26] reported that HR variability was significantly altered in patients with RA and independently associated with disease activity.

The present study is not in accordance with Bekkelund et al. [27] and Vlcek et al. [28]. Bekkelund et al. [27] found no cardiovascular ANS abnormality in their 43 RA patients who had no ANS symptoms. Vlcek et al. [28] reported normal reactivity of the sympathoneural system during orthostatic challenge in RA patients younger than 40 years. The current study is not in accordance with these two studies due to difference in the inclusion and exclusion criteria of RA patients' selection and differences in the definition of ANS abnormalities.

The pathogenesis of AN in RA has not been determined yet. It was postulated to be due to abnormalities in the sympathetic postganglionic function. This is secondary to the development of circulating autoantibodies directed to nerve growth factor, sympathetic cervical ganglia, vagus nerve and the ganglionic acetylcholine receptors [29–31]. This can be the explanation for loss of sympathetic nerve fibers in the inflamed joints of RA patients as found in some studies [32–34]. Also, it was found that high level of intrathecal IL-1beta and possibly other inflammatory mediators in the CNS are of importance for the reduced vagal function in RA [35]. Autonomic neuropathy can occur with secondary amyloidosis. This was reported in a case of RA with AN resulting in severe and disabling orthostatic hypotension. Extensive amyloid deposits were found throughout the ANS in this case [36].

It is important to take AN into consideration during dealing with RA patients. Autonomic neuropathy is usually subclinical in most cases. It needs specific tests to diagnose it. Some of them are clinical tests as the orthostatic stress test (active and passive types) and others are electrophysiological tests which are available in many electrodiagnosis laboratories. Autonomic neuropathy can be the initial extra-articular manifestation in RA patient so its presence affects the prognosis of RA. The presence of AN affects the management of RA patients with other comorbidities during prescription of drugs that have effects on the cardiovascular ANS which should be taken into consideration [6].

The current study had two limitations. First one was the small number of RA patients. This was secondary to the wide range of exclusion criteria present in this study which limits the number of the patients. Second one was the few number of men participated in the study which might reduce the generalizability of the results.

Autonomic neuropathy is a common extra-articular manifestation of RA which is usually subclinical. Autonomic neuropathy in RA usually affects both the sympathetic and parasympathetic components of the ANS. It needs to be taken into consideration and to be diagnosed by specific tests clinically and electrophysiologically for better management of RA patients.

Conflict of interest

None declared.

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