Autonomic neuropathy in Rheumatoid Arthritis: Relationship with seropositivity of Rheumatoid factor and disease activity

Kawser Jahan\(^1\), Noorzahan Begum\(^2\), Sultana Ferdousi\(^2\)

1. Department of Physiology, Shahid Mansur Ali Medical College, Dhaka
2. Department of Physiology, Bangabandhu Sheikh Mujib Medical University, Dhaka

Abstract

Background: Autonomic neuropathy (AN) has been recognized as a strong predictor of sudden cardiac death in Rheumatoid Arthritis (RA). Autonomic neuropathy may be assessed by five cardiovascular reflex tests. Objective: To find out the prevalence and severity of AN in RA and also to assess the correlation of inflammatory markers, disease severity and serological factor, Rheumatoid factor (RF) with autonomic reflex test parameters. Method: This cross-sectional study was conducted on sixty (60) female RA patients, age range 18-50 years enrolled from the Out-Patient Department of Rheumatology Wing, Department of Medicine, of Bangabandhu Sheikh Mujib Medical University (BSMMU). Age matched 30 apparently healthy females were control. Cardiac autonomic reactivity was assessed by five cardiovascular reflex tests as described by Ewing include heart rate response to standing, deep breathing, valsalva maneuver and blood pressure response to standing and sustained hand grip. Inflammatory activity in RA was assessed by serum rheumatoid factor (RF) level which was estimated by the latex agglutination test, C-reactive protein (CRP) and ESR and marker of disease activity was assessed by Disease activity score (DAS-28 score) value. For statistical analysis, independent sample ‘t’ test chi-square test, Pearson correlation coefficient test, spearman correlation test were used. Results: Among 60 RA patients, 43 (71.6%) patients were RF positive. Frequency of AN
Autonomic neuropathy – Relation with RF in RA

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Introduction

Rheumatoid Arthritis (RA) is a common inflammatory connective tissue disease and its prevalence rate varies among different groups of people. Global prevalence of RA is 1% and it is same in Bangladesh. RA is the 42nd highest contributor to disability, ranking just below malaria.

Being an autoimmune disease RA affects primarily multiple joints, but also involves various organs including heart muscle, heart valves or the blood vessels of the heart. In most patients, presence of RF characterized by IgM has been detected in blood. Though cardiac involvement is silent, cardiovascular mortality is more than 40% in this group of patients.

RA may alter autonomic nerve function and may produce sympatho-vagal imbalance. Though both peripheral and central nervous system involvement has been well recognized in RA but very few studies published report about the involvement of autonomic nervous system in RA.

Tests of cardiovascular reflexes are sensitive, reproducible, simple, non-invasive and allow extensive evaluation of cardiovascular autonomic neuropathy (CAN). In 1992, Ewing et al. proposed 5 cardiovascular reflex tests to assess cardiac autonomic reflex activity. These include heart rate response to standing, deep breathing and valsalva maneuver and blood pressure response to standing and sustained hand grip. In our previous articles the results of Heart Rate Variability in RA and also autonomic reactivity in RA has been published.

Inflammation is one of the prime drivers of the cardiovascular disease in rheumatoid arthritis. Though few studies investigated autonomic function in RA but the relationship between inflammatory markers (CRP, ESR), disease severity (DAS-28) and autoantibody RF and cardiovascular autonomic reactivity were scarcely studied. Hence, the aim of this study was to evaluate the prevalence of autonomic neuropathy in RA and to explore the relationship between the inflammatory markers [CRP, ESR, disease severity score (DAS-28)& auto-antibody RF] and autonomic reflex action to determine the role of these risk factors on cardiovascular autonomic neuropathy in RA patients.

Methods

Setting & study participants

Sixty diagnosed female RA patients with 18 to 50 years of age participated in this cross sectional study carried out by the department of Physiology, BSMMU during 2010. They were...
diagnosed according to American College of Rheumatology (ACR) classification. Among them, 43(71.6%) patients were RF positive. Thirty age and BMI matched apparently healthy females were taken as control.

Exclusion criteria
RA patients with history of hypertension, heart disease, diabetes mellitus, renal diseases and psychic disorders were excluded from the study. Random blood sugar level and serum creatinine level were measured to exclude diabetes mellitus and renal failure.

Procedure
Before recruitment, the aim and objectives of the study were briefed to all the subjects and a written informed consent was taken from each subject. The protocol of this study was approved by the ethical review committee of BSMMU.

Resting pulse rate and supine resting blood pressure of all the subjects were also recorded. The status of the cardiovascular reflex responses were assessed by Ewing’s five non-invasive cardiovascular reflex tests. To assess parasympathetic reactivity, HR response to valsalva, deep breathing, lying to standing was measured by valsalva ratio, difference between maximum and minimum HR during deep breathing and 30th:15th ratio respectively. In addition, BP response to active standing and sustained handgrip was measured by fall of SBP and rise of DBP respectively to assess sympathetic reflex activity. Moreover, grading of CAN was done according to the description by Ewing et al.16 Disease Activity Score at 28 joints (DAS28) and Clinical Disease Activity Index criteria were used to assess their current disease activity.20-22

Statistical analysis
Data expressed as mean±SD & frequent percent. Data was analyzed by Independent sample t test, chi-square test, Spearman’s correlation and Pearson’s correlation coefficient tests by using SPSS-26.

Results
Basal characteristics of the subjects were presented in table I. The mean resting pulse rate (p<0.05) and DBP (p<0.01) were significantly higher but mean SBP was not significantly different (p>0.05) in RA patients compared to control. Patients’ clinical characteristics were shown in Table II. Frequency of autonomic neuropathy at different grade was shown in table III. Grading was done based on outcome of 5 cardiovascular reflex test.16 Among 90 patients, 78.3% of RA patients showed evidence of AN but none with AN was found in control group (0%). No significant correlation of autonomic nerve function test parameters with DAS-28,CRP and ESR were found. Data were not presented. Figure 1 and 2 showed significant (p<0.05) negative correlation of valsalva ratio and difference between maximum and minimum heart rate during deep breathing with RF in RA patients.

Table I : Socio demographic Data of both group (N=90)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=30)</th>
<th>RA patients (n=60)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>36.50±11.50</td>
<td>37.09±11.10</td>
<td>0.803</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>23.88± 2.27</td>
<td>23.94±1.68</td>
<td>0.876</td>
</tr>
<tr>
<td>Pulse (beat/min)</td>
<td>80.29 ± 10.62</td>
<td>85.34 ± 11.22</td>
<td>0.03*</td>
</tr>
<tr>
<td>SBP (mm of Hg)</td>
<td>114.37±11.79</td>
<td>116.19±11.30</td>
<td>0.451</td>
</tr>
<tr>
<td>DBP (mm of Hg)</td>
<td>68.70±7.59</td>
<td>73.77±7.01</td>
<td>0.001***</td>
</tr>
</tbody>
</table>

Data were expressed as mean ±SD. Statistical analysis was done by Independent sample t-test.
BMI=Body Mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure. ***= p<0.01, *=p<0.05, n=number of subjects.
Table II: RA Patients’ clinical characteristics (N=90)

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF no. (%)</td>
<td>43 (71.67%)</td>
</tr>
<tr>
<td>CRP mg/l, median (min-max)</td>
<td>48 (4-130)</td>
</tr>
<tr>
<td>VAS-GH, median (min-max)</td>
<td>80 (10-100)</td>
</tr>
<tr>
<td>ESR (mm/h) median(min-max)</td>
<td>50 (12-130)</td>
</tr>
<tr>
<td>Number of tender joints, median(min-max)</td>
<td>20 (1-28)</td>
</tr>
<tr>
<td>Number of swollen joints, median(min-max)</td>
<td>0 (0-18)</td>
</tr>
<tr>
<td>Deformity, median (min-max)</td>
<td>2.5 (0-8)</td>
</tr>
<tr>
<td>DAS-28, mean± SD(min-max)</td>
<td>6.75±1.80 (3.49-8.17)</td>
</tr>
</tbody>
</table>

RF - rheumatoid factor; min - minimum; max - maximum; VAS - visual analogue scale; GH - global health; ESR - erythrocyte sedimentation rate; CRP - C-reactive protein; DAS28 - Disease Activity Score based on 28 joint count

Table III: Grading of autonomic neuropathy in RA patients (N=90)

<table>
<thead>
<tr>
<th>Grading of Autonomic neuropathy</th>
<th>Control(n= 30)</th>
<th>RA patients (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early involvement</td>
<td>0 (0%)</td>
<td>25 (54.35%)*</td>
</tr>
<tr>
<td>Definite involvement</td>
<td>0 (0%)</td>
<td>6 (13.04%)**</td>
</tr>
<tr>
<td>Severe involvement</td>
<td>0 (0%)</td>
<td>8 (17.39%)</td>
</tr>
<tr>
<td>Atypical pattern</td>
<td>0 (0%)</td>
<td>8 (17.39%)</td>
</tr>
<tr>
<td>Total</td>
<td>0 (0%)</td>
<td>47 (78.33%)</td>
</tr>
</tbody>
</table>

Data was expressed as percentage. Statistically analysed by chi square test. *P<0.05, **P<0.01

Figure 1: Correlation of valsalva ratio with rheumatoid factor. Statistical analysis was done by Spearman’s correlation coefficient (r) test. HRVR: Heart rate response to valsalva maneuver (valsalva ratio). *=p<0.05. Valsalva ratio is negatively correlated to rheumatoid factor

Figure 2: Correlation of ΔHR during deep breathing with rheumatoid factor. Statistical analysis was done by Spearman’s correlation coefficient (r) test. HRDB= Heart Rate Response to Deep Breathing. * = p<0.05. Difference between maximum and minimum HR during deep breathing is correlated to serum rheumatoid factor.
Discussion
In this study, five noninvasive cardiovascular reflex tests were used to detect autonomic neuropathy in RA patients and healthy control at various grade. Our results showed that 47 out of 60 RA patients had evidence of development of autonomic neuropathy at different grade and also high prevalence of AN was observed in RA patients and the healthy volunteers did not have autonomic neuropathy. These results in RA patients agrees well to the previous studies.23 Similar trends for AN in RA patients was noted by Saraswathi et al.24 However, Maule et al.12 found autonomic neuropathy in 15%, Louthrenoo et al.9 in 47% and Toussirot et al.25 in 60% of RA patients and these frequency rates were much lower than that our study.

In contrast, Bekkelund et al.26 found no cardiovascular Autonomic Nervous System (ANS) dysfunction in RA patients whereas Geenen et al.27 found diminished ANS function in RA patients who had the disease for less than 1 year which was related to severity of pain and might had been related to the pathophysiological mechanism in RA.

These variations in different studies may be due to the difference in the way in which controls were selected and the criteria used to determine ANS dysfunction. Here, we considered single abnormal test as evidence of AN while Toussirot et al.25, considered AN present if a minimum of two tests were abnormal.

Little is known about exact mechanisms for autonomic neuropathy in RA patients. According to literature review, vasculitis, amyloid deposition and autoantibodies to ANS structures may be considered as risk factors for this autonomic neuropathy in patients of the present series.12-13 Results from the present study shows significant negative correlation between autonomic nerve function parameters and RF which suggests that severity of RA was correlated to autonomic nerve dysfunction and thus presence of autoantibody titer has an important role for autonomic neuropathy in RA. A tendency of greater cardiac autonomic nerve dysfunction with positive rheumatoid factor status and higher C reactive protein (CRP) levels has also been reported by some researchers.13,28-29 On the other hand we didn’t find any significant correlation of autonomic nerve dysfunction with ESR, CRP and disease severity (DAS-28) in RA patients. This is in agreement with some previous studies.9,14,24 Though a number of studies have reported significant correlation between AN and disease factors, especially disease severity30-31 in RA.

Conclusion
From this study, it may be concluded that prevalence of autonomic neuropathy is very high in RA and autonomic neuropathy may be related to the presence of autoantibody (RF) in RA patients.

Conflict of interest – None

References


27. Geenen R, Godaert GL, Jacobs JW, Peters ML, Bijlsma JW. Diminished autonomic nervous system


