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CASE CONTROL STUDY OF AUTONOMIC FUNCTION TESTS IN RHEUMATOID ARTHRITIS FEMALE PATIENTS

Medical Science

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ABSTRACT

Background – In Rheumatoid Arthritis (RA) patients' involvement of autonomic nervous system has rarely been studied[1].

Objective – Evaluation of cardiovascular autonomic neuropathy (CAN) in RA patients.

Material and methods – 45 RA female patients (age group 35-45 years) along with 45 age and BMI matched female controls were evaluated by: Valsalva ratio and LF/HF ratio recorded by CAN Win analysis system (window based) and Polyrite D based on EKG respectively. Statistical analysis was performed using SPSS software version 20 and Z-test was used to derive the level of significance.

Results – The mean Valsalva ratio was found lower (p value <0.01) whereas mean LF/HF ratio was found higher (p value<0.001) in RA patients as compared to control group.

Conclusion–Cardiovascular autonomic functions are found deranged In RA patients. Early detection of cardiac autonomic neuropathy in RA patients can help in timely management and prevention of morbidity.

KEYWORDS

Rheumatoid Arthritis (RA)

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic multisystem progressive autoimmune inflammatory connective tissue disease of unknown aetiology characterized by persistent inflammatory synovitis, usually involving peripheral joints in symmetric distribution and in some cases, extra articular involvement leading to severe disability and premature mortality[2]. High serum level of auto antibodies like rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) are evident of the role of autoimmunity in RA patients[3].Rheumatoid arthritis can begin at any age, but has its peak between 35 to 55 years of age[4]. The prevalence of RA is around 0.5 -1% worldwide with women suffering 2-3 times more than men[5]. In RA patients' involvement of autonomic nervous system has rarely been studied[1].

Cardiovascular reflex tests proposed by Ewing et al and heart rate variability (HRV) nowadays have become most popular non-invasive tools for the detection of early sympathetic- parasympathetic imbalance in the autonomic nervous system dysfunction[6, 7]. Both Valsalva ratio and LF/HF ratio reflect sympathetic parasympathetic balance throughout the body[7,8]. Sympathetic parasympathetic balance is highly mandatory to efficiently compensate for internal and external environmental changes as inability may predispose RA patients to arrhythmias, thereby increasing cardiovascular morbidity and mortality by up to 50%[9]. The present study is an attempt to an early understanding of the autonomic nervous system dysfunctions in rheumatoid arthritis patients which can help in diagnosis, prevention and treatment.

Material and Methods

The present study was conducted in the Upgraded department of Physiology in collaboration with the Department of Medicine, S.M.S. Medical College and Hospital, Jaipur, Rajasthan from 1st Jan 2016 to 31st Dec 2016 on 45 RA female patients between the age group of 35-45 years taken from the Department of Medicine, S.M.S. Hospital, Jaipur along with 45 age and BMI matched healthy female controls taken from accompanying attendants of the patients.

Ethical Statement: This study was approved by the Institutional Research Review Board of SMS Medical College and Hospital.

All subjects gave informed written consent.

Inclusion Criteria: 35-45 yrs aged newly diagnosed Rheumatoid Arthritis female patients, as per the 2010 ACR-EULAR CLASSIFI CATION CRITERIA[10] and Age and BMI matched healthy female controls subjects in the follicular phase of regular menstrual cycle (28 days) were included in the study.

Exclusion Criteria: Pregnancy, smoker, chronic diseases and drugs affecting autonomic functions were excluded from the study.

All subjects were tested between 11 am to 1.00 pm under similar laboratory conditions and were allowed to adapt themselves to experimental and environmental condition for 30 minutes to make them comfortable, as anxiety and stress can affect autonomic functions. The subjects were asked to avoid coffee, nicotine or alcohol 24 hours prior and food 2 hours prior of autonomic function test. The room ambient temperature was maintained at 24-25°C. A thorough history was taken and general physical examination was done to screen out the subjects.

Valsalva ratio was performed by using CAN Win based on Ewing battery of tests which reflect both sympathetic and parasympathetic function.

Frequency domain heart rate variability parameter LF/HF ratio which also reflect sympatho parasympathetic imbalance was done by recording with Polygraph (RMS Polyrite D, Version 1.0) based on the principle of EKG. The analogue ECG signals were converted to digital signal and stored in the computer for offline Frequency Domain Analysis. In the frequency domain analysis, the power spectrum for HRV was calculated with the Fast Fourier Transformation (FFT) based method.

LF/HF ratio=LF nu (normalized unit) in %/HF nu (normalized unit) in %

Statistical Analysis: Statistical analysis was performed using SPSS software version 20 and Z-test was used to derive the level of significance.

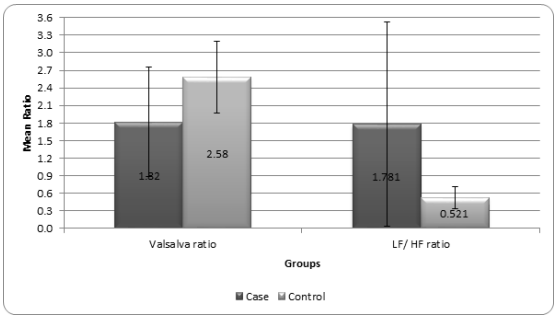
Observations and tables:

Table: 1 Comparison of anthropometric and baseline clinical characteristics of cases and controls

Parameter	Groups (Mean ± SD)		Z-value	p – value	Significance
	Case (n=45)	Control (n=45)			
Age (yrs)	39.82 ± 4.11	38.64 ± 3.06	1.573	>0.05	NS
BMI(Kg/m^2)	24.14 ± 2.42	23.29 ± 1.83	1.89	> 0.05	NS
SBP (mmHg)	119.53 ± 7.78	116.78 ± 8.16	1.637	> 0.05	NS
DBP (mmHg)	81.13 ± 7.16	79.22 ± 7.42	1.242	> 0.05	NS
HR (Beats/min)	79.73 ± 10.43	76.38 ± 12.08	1.408	> 0.05	NS
RR (per min)	11.62 ± 1.68	11.38 ± 1.39	0.738	> 0.05	NS
BMI (Body mass index), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), HR (Heart rate), RR (Respiratory rate) NS (not significant)					

Table: 2 Comparison of Valsalva ratio and LF/HF ratio in Case and Control group subjects

Parameter	Group(Mean ± SD)		Z - value	p –value	Significance
	Case (n=45)	Control (n=45)			
Valsalva ratio	1.82 ± 0.94	2.58 ± 1.74	2.585	< 0.01	HS
LF/HF ratio	1.781 ± 0.61	0.521 ± 0.19	13.263	< 0.001	HS
HS (Highly significant)					



Bar diagram: 1 Comparison of mean Valsalva ratio and LF/HF ratio in Case and Control group subjects

Results:

- The mean of Valsalva ratio in rheumatoid arthritis patients was 1.82 ± 0.94 and of control subjects was 2.58 ± 1.74. (Table 2) (p-value < 0.01) (Bar diagram 1)
- The mean of LF/HF ratio of rheumatoid arthritis patients was 1.78±0.61and of control subjects was 0.52±0.19. (Table 2) (p-value < 0.001) (Bar diagram 1)

Discussion:

In RA patients the morbidity and mortality is attributed more to its cardiovascular complications rather than the disease itself[11].

In our study the mean of Valsalva ratio was found to be significantly lower in Rheumatoid Arthritis patients as compared to control subjects. (p value <0.01) (Table 2, Bar diagram 1) which is similar to the findings of Toussirot E et al.(1993)[12],Milovanović B et al. (2010)[13]. Mean of LF/HF ratio was found significantly higher in Rheumatoid Arthritis patients compared to control subjects (p-value <0.001) (Table 2, Bar diagram 1) which is similar to the findings of Evrengul H et al (2004)[8] and Janse Van Rensburg DC et al (2012)[14].

In this study by using two parameters: Valsalva ratio (cardiovascular reflex test) and LF/HF ratio (frequency domain HRV parameter) we found hyperactive sympathetic system and a hypoactive parasympathetic system hence autonomic imbalance in RA group compared to healthy control group.

The path physiological basis of the development of autonomic nerve dysfunction in RA patients is not clearly known. However contribution of a direct immunological damage to components of neural pathways can be postulated which is supported by the demonstration of circulating complement fixing auto antibodies directed against sympathetic and parasympathetic nervous structures, represented by superior cervical ganglia and vagus nerve, respectively, in patients with SLE and RA[15].

One another mechanism that is presumed that for derangement of autonomic function in RA patients was an increased outflow of the sympathetic nervous system (SNS) and a decreased tone of the hypothalamic pituitary adrenal (HPA) axis so there is increased serum NPY/serum cortisol ratio which is proinflammatory in RA patients because cooperative anti-inflammatory coupling of the two endogenous response axes is missing. In addition, disease related factors such as depression, chronic pain, weight gain, and others may add to the uncoupling phenomenon[16].

Thus regular assessment of autonomic functions can be used as a biomarker for early detection and subsequent management of cardiovascular morbidity and mortality in RA patients.

Conclusion: It is concluded that Rheumatoid Arthritis patients have sympathetic hyperactivity and reduced parasympathetic activity, when compared with the normal subject. Thus, this study signifies the importance of non-invasive and cost effective methods for regular screening of autonomic nerve functions status in RA patients. This early detection of cardiac autonomic impairment is important for timely prevention and management of severe consequences such as arrhythmias and sudden death in RA patients.

Strength, Limitations and Recommendations:

Certainly, the strength of our study is the careful selection of the subjects and an effort to rule out all possible confounding factors which can affect the results.

The study was conducted in a limited time period on a small sample size. Better results may be obtained with a large sample size over a longer time.

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