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ASSOCIATION BETWEEN CARDIOVASCULAR AUTONOMIC NEUROPATHY AND PERIPHERAL SYMPATHETIC NEUROPATHY IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS PATIENTS

Verma Inderjeet [1]. Syngle Ashit[2]. Garg Nidhi[1]. *Krishan Pawan[1].

[1]Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India.
[2]Cardio Rheuma and Healing Touch City Clinic, Chandigarh and Senior Consultant Physician and Rheumatologist Fortis Multi Speciality Hospital, Mohali, India.

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Corresponding author:
*Prof. Pawan Krishan
Department of Pharmaceutical Sciences and Drug research
Punjabi University Patiala-147002, Punjab, India

ABSTRACT

Background and Purpose: The potential association between the cardiovascular autonomic neuropathy (CAN) and peripheral sympathetic neuropathy has not been investigated in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) with the few studies yielding inconsistent results in RA. We evaluated the prevalence and relationship between CAN dysfunction and peripheral sympathetic neuropathy in RA and AS patients

Methods: Autonomic function was assessed in 30 patients of which 15 of RA and 15 patients with AS. 15 age matched healthy subjects. Autonomic function was assessed by applying a battery of non-invasive cardiovascular reflex tests (CRT) and peripheral sympathetic autonomic function was assessed by FDA approved Sudoscan.

Results: Patients with RA and AS had significantly impaired autonomic function as compared with healthy controls. Both parasympathetic and sympathetic neuropathy was prevalent in 53.3% with RA and 60% patients in AS patients. Sudomotor dysfunction was identified in 60% RA patients and 33% AS patients. Lower electrochemical skin conductance (ESC) was associated with higher number of abnormal cardiovascular autonomic neuropathy (CAN) results. Sudomotor function significantly correlated with HR response to standing ($p<0.05$) and BP response to Handgrip ($p<0.05$) in RA and AS patients. Significant correlation was also found between HR response to deep breath and sudomotor dysfunction in RA but not in AS patients.

Conclusion: The present study indicates that CAN and sudomotor dysfunction is prevalent among patients with RA and AS. CAN variables significantly associated with sudomotor function and the incidence of CAN increases with worsening of sudomotor function.

INTRODUCTION

Autonomic neuropathy is the most common type of autonomic nervous system dysfunction in rheumatic diseases occurring in 24-100% of rheumatic patients [1]. Autonomic dysfunction is significant risk predictor for sudden cardiac death in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [2]. There is increased risk for sudden cardiac death in RA & SLE related to severe autonomic dysfunction with sympathetic predominance leading to fatal arrhythmias.[2] Most rheumatic diseases are characterized by excess cardiovascular (CV) morbidity and mortality as compared to the healthy population [3-4].

Autonomic dysfunction in patients with rheumatoid arthritis and ankylosing spondylitis (AS) has been well-documented using a variety of simple, sensitive, reproducible, and noninvasive tests as suggested by Ewing [1]. Peripheral neuropathy has not been studied in RA and AS, but only few studies of peripheral neuropathy in RA have been made [5-6]. However, these studies have not investigated the peripheral sympathetic autonomic dysfunction (sudomotor function) probably because of the cumbersome procedure involved in the absence of diagnostic equipment.

To the best of our knowledge, the potential association between the cardiovascular autonomic neuropathy (CAN) and peripheral sympathetic dysfunction has not been investigated in RA and AS. In the present study we aimed to determine the prevalence of cardiovascular autonomic neuropathy and peripheral sympathetic dysfunction in patients with RA and AS utilizing both traditional cardiovascular reflex tests (CRT) and using the novel sophisticated Sudoscan and also investigates the correlation between cardiovascular autonomic function and peripheral sympathetic function.

MATERIALS AND METHODS

Participants

The study population consisted of 15 patients of RA with mean age 41.87 ± 11.80 (range 21-57 years; 13 female and 2 male), 15 patients of AS with mean age 32.27 ± 10.98 (range 18-59 years; 9 female and 6 male), and 15 age matched control subjects selected from healthy clinic staff with mean age 38.27 ± 8.4 (range 22-54; 10 female and 5 male) years who did not have symptoms of autonomic dysfunction and were not taking medication. Healthy control subjects were recruited as a similar age range as the RA and AS patients, and there was no significant difference in the age of the RA and AS patients and controls.The demographic and clinical features of patients and healthy controls are summarized in table 1.

The diagnoses of RA and AS were according to the ACR 2010 classification criteria and modified New York criteria, 1984 for diagnosis of rheumatoid arthritis and ankylosing spondylitis respectively [7-8]. Patients were excluded from the study if they had any of the following conditions: presence of skin lesions that could affect the ability to assess their neuropathic pain, renal or liver insufficiency, pregnancy, diabetes mellitus, thyroid disorders, patients on antihypertensive drugs, neuroprotective drugs, vitamin B_{12} deficiency, anemia, paraneoplastic neuropathy, alcoholism, cardiac failure, severe cardiac arrhythmia, acute thrombosis, pericarditis or nephritis, smokers and patients on steroid therapy. Patients with disorders responsible for neuropathy and significant neurological disorders other than connective tissue disorders were also excluded. Tobacco, alcohol, caffeine and medications were not allowed before the tests. All patients and control subjects gave their written informed consent before entry in the study.

All participants were found to be in a stable condition. RA disease activity was determined according to the Disease Activity Score of 28 joints (DAS-28) and AS disease activity was determined by the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index).

The study project was approved by the institutional clinical ethics committee and was performed in accordance with the declaration of Helsinki and the code of Good Clinical Practice. All subjects were fully informed about the purpose of the study and gave their informed consent to participate.

Methods

The battery of four cardiovascular autonomic neuropathy tests included two for parasympathetic function [heart rate (HR) responses to deep breathing, and standing] and two for

sympathetic function [blood pressure (BP) responses to standing and to a sustained hand grip] [9]. CAN was considered to exist if at least any two tests were positive out of four [10]. The peripheral sympathetic autonomic function was assessed by a novel FDA approved Sudoscan [11]. Autonomic symptoms were also assessed by using survey of autonomic symptom (SAS) questionnaire [12]. All tests were performed under standardized conditions, in climate-controlled rooms (temperature=23 °C), in the morning.

1. Assessment of Cardiovascular Autonomic Neuropathy

I. Tests Reflecting Parasympathetic Function:-

A. HR response to deep breath: - Participants lay flat. After the pulse had steadied, the pulse rate was recorded during six slow maximal deep breaths. In normal subjects the pulse rate should fall by ≥15 beats, borderline11–14 beats and with autonomic disturbances ≤ 10 beats per minute [9].

B. HR response to standing up (30:15 ratio): The R-R interval on the ECG was recorded and used to determine the instantaneous heart rate, at rest and then on the 15^{th} and 30^{th} beats after standing. The heart rate should normally rise after about 30 seconds as part of the response to return the blood pressure to normal. The normal 30^{th}:15^{th} pulse heart rate ratio is ≥ 1.04, borderline 1.01–1.03 and abnormal ≤ 1.0 [9].

II. Tests Reflecting Sympathetic Function:-

A. BP response to standing: Participants were asked to stand up for 3 minutes after a 10 minute resting period in a supine position. The systolic and diastolic blood pressure (SBP and DBP), just before standing and 3 minutes after active standing were determined to define postural change in blood pressure to evaluate orthostatic intolerance. A fall of SBP < 10 mm normal, 11–29 mm borderline and > 30 mm abnormal [9].

B. BP response to handgrip: Three consecutive (within 5 minute resting periods) handgrip tests were performed by the patients for 2 minutes while beat-to-beat blood pressure was recorded simultaneously. The absolute difference between the highest DBP during handgrip and the basal DBP just before the handgrip is noted. The diastolic pressure should raise ≥16 mm normal, borderline 10–15 mm and abnormal ≤ 10 mm [9].

2. Peripheral sympathetic autonomic function evaluation by sudoscan

Sudoscan is a FDA approved device designed to perform the precise evaluation of sweat gland function based on sweat chloride concentrations through reverse iontophoresis and chronoamperometry [11].

Measurement of sweat function:

The apparatus consists of two sets of large-area nickel electrodes for the hands and feet that are connected to a computer for recording and data-management purposes; the electrodes are alternately used as an anode and cathode, and a direct-current (DC) incremental voltage equal or less than 4 V is applied to the anode. Through reverse iontophoresis, the device generates voltage to the cathode and a current (intensity of around 0.2 mA) between the anode and cathode proportional to chloride concentration. At low voltages (< 10 V), the stratum corneum is electrically insulating and only sweat-gland ducts are conductive. The electrical sweat conductance (ESC), expressed in micro Siemens (μS), is the ratio between the current generated and the constant DC stimulus (≤ 4 V) applied to the electrodes. Sudomotor dysfunction was evaluated according to the ESC measured on the feet: > 60 μS = no dysfunction; 60–40 μS = moderate dysfunction; and < 40 μS = high dysfunction. During the test, patients should require to place their hands and feet on the electrodes, and to stand still for 2 min.

Laboratory investigations included a complete blood count, liver function tests, renal function test, Vitamin B_{12}, Thyroid stimulating hormone, random blood sugar, Erythrocyte sedimentation rate (ESR) was measured by Westergreen method, C-reactive protein (CRP) level was determined using standard commercial kits and urine analysis to detect proteinuria, hematuria and cellular casts. These all investigation were analysed on the same day as the autonomic system analysis was obtained.

Statistical Analyses

Test values are reported as mean ± standard deviation. The analysis of variance (ANOVA) test was used to compare the continuous variables of ANSD for the three groups. Spearman analysis was used to find the correlation between the sudoscan, CAN function and diseases activity. A *P*-value less

than 0.05 were considered statistically significant. Statistical analysis was done using the Prism Graph Pad program for Windows 7.0.

RESULTS

Patients with RA and AS had significantly impaired autonomic function as compared to healthy controls (table 2). Patients with RA and AS had significantly lower HR response to standing, BP response to handgrip and sudomotor function when compared with similar age of healthy controls. HR response to deep breath was significantly lower in AS patients but not in RA patients as compared to healthy controls. However, there was no statistically significant difference between BP responses to standing among the three groups (table 2).

Both parasympathetic and sympathetic cardiovascular autonomic dysfunction was prevalent in 8 patients (53.3%) with RA and 9 (60%) patients in AS patients respectively (table 3). Individually parasympathetic and sympathetic dysfunction was identified in 10 cases and 9 cases respectively in RA patients, while 11 and 9 cases were identified in AS patients respectively. Peripheral sympathetic autonomic dysfunction was identified in 9 (60%) RA patients 5 (33%) and AS patients (table 4). None of healthy volunteers had abnormal ANS dysfunction. Patients had autonomic symptoms like increased constipation, nausea or bloating after eating a small meal and lightheadness. None of the subjects in the control group had autonomic symptoms.

A strong association was found between sudoscan conductance and CRT variables (table 4). Lower ESC was associated with higher number of abnormal CRT results, and patients with ESC<60 µS were approximately 2.5 times likely to have one or more abnormal CRT response compared to patients with ESC>60 µS. AS patients had 100% (n=5) abnormal CRT with moderate lowering of ESC (40- 60 µS) while RA patients had 71% (n=5) abnormal CRT with moderate lowering of ESC (40- 60 µS) and 100% CRT with severe sudomotor dysfunction (<40 µS) (table 4).

Of the four CAN variables in both RA and AS, sudomotor function was individually significantly correlated with HR response to standing ($p<0.05$) and BP response to handgrip test ($p<0.05$). Significant correlation was also found between HR response to deep breath and sudomotor function in RA patients but not in AS patients. HR response to standing statistically significant correlated with age in RA patients ($p<0.03$). There was no statistically significant correlation between autonomic function tests and age, disease duration, body mass index, disease activity and biomarkers of inflammation (ESR and CRP).

Table 1 The demographic and clinical features of the study population

	RA (n=15)	AS (n=15)	CONTROL (n=15)
Patient characteristicS			
Sex (F:M)	12:3	6:9	7:8
Age (years)	41.87 ± 11.8	32.27 ± 10.9	38.27 ± 8.4
Height (cm)	159.4 ± 4.9	170.1 ± 8.5	164.8 ± 7.9
Body weight (Kg)	63.07 ± 12.58	67.67 ± 15.86	64.20 ± 11.16
BMI (kg/m^2)	24.80 ± 5.2	22.87 ± 4.4	24.07 ± 3.96
Disease duration (years)	4.72 ± 0.9	5.32 ± 3.0	-
ESR(mm 1^{st} hr)	29.67 ± 8.8	19.19 ± 10.4	-
CRP (mg/dl)	7.30 ± 6.3	12.46 ± 19.0	-
DAS-28	2.55 ± 1.09	-	-
BASDAI	-	3.83 ± 1.2	-
BASFI	-	2.04 ± 1.97	-

F female, M male, BMI body mass index, ESR erythrocyte sedimentation rate, CRP C-reactive protein, DAS-28 disease activity score in 28 joints, BASDAI Bath ankylosing spondylitis disease activity index, BASFI bath ankylosing spondylitis functional index

Table 2 Results of CAN and Sudomotor function tests in patients with RA, AS and control gro

	RA (n=15)	AS (n=15)	Controls (n=15)
HR response to deep breath (PS)	11.80 ± 5.34	11.7 ± 6.06*	16.07 ± 3.55
HR response to standing (PS) (R-R ratio)	1.0 ± 0.06**	1.02 ± 0.08*	1.11 ± 0.07
BP response to standing (S) (Systolic BP decrease)	6.73 ± 5.35	8.53 ± 6.44	5.40 ± 2.06
BP response to handgrip (S) (Diastolic BP increase)	11.07 ± 5.06*	11.80 ± 5.95*	17.07 ± 4.01
Sudoscan (µs)	56.90 ± 16.33$	66.77 ± 12.11*	74.73 ± 5.55

Key: RA rheumatoid arthritis; AS ankylosing spondylitis; PS= parasympathetic damage; S= sympathetic damage; HR heart rate; BP blood pressure; *p <0.05, **p <0.01, $p=0.001.

Table 3 Cardiovascular autonomic neuropathy status in patients with RA and AS

	Normal Parasympathetic response	Parasympathetic nerve Dysfunction only	Sympathetic nerve dysfunction only	Sympathetic nerve dysfunction
Patients with RA (n=15)	4	2	1	8
Patients with AS (n=15)	4	2	0	9

Table 4 Association between sudoscan conductance measurement and conventional cardiovascular autonomic neuropathy functions.

≥1 abnormal CAN test [n (%)]	ESC > 60 (µS)	ESC 40-60 (µS)	ESC <40 (µS)
RA (n=15)	(n=6) 2 [33%]	(n=7) 5 [71%]	(n=2) 2 [100%]
AS (n=15)	(n=10) 4 [40%]	(n=5) 5 [100%]	(n=0) 0 [0%]

ESC electrochemical skin conductance; CAN cardiovascular autonomic neuropathy; RA rheumatoid arthritis; AS ankylosing spondylitis

DISCUSSION

To the best of our knowledge this is the first study to use Sudoscan for assessing the peripheral sympathetic autonomic function in RA and AS patients. In this study, we have investigated the prevalence and association of cardiovascular autonomic neuropathy and peripheral sympathetic dysfunction in patients with RA and AS.

Despite its massive prevalence, the pathogenesis of the autonomic neuropathy in RA and AS is not clearly understood. It is thought that it could result from vasculitis, amyloidosis and could be related to therapeutic side effect and the presence of circulating auto-antibodies against nerve growth factor and the vagus nerve has been demonstrated in RA patients who had cardiovascular ANS dysfunction [13-14]. In a recent study it was found that the autonomic dysfunction in RA is related to elevated intrathecal proinflammatory cytokine interleukin- 1β and possibly also other inflammatory mechanisms in the CNS which reduces the vagus activity and interferes with the cholinergic neurotransmission [15]. These results are also supported by the observation that heart rate variability, is a marker of vagus nerve tone (that reflects parasympathetic activity) and was inversely related to levels of inflammatory markers (IL-6 and CRP) in the CARDIA (The Coronary Artery Risk

Development in Young Adults) study [16]. Interleukin-6 inhibitor tocilizumab and TNF-α inhibitor infliximab have been shown to improve autonomic dysfunction in RA and AS patients respectively [17-18]. Providing further support to the hypothesis of the role of proinflammatory cytokines in autonomic neuropathy of RA and AS.

Our study results show that autonomic dysfunction is prevalent in patients with RA and AS. Parasympathetic system being more frequently affected (66.6% in RA and 73.3% in AS) than the sympathetic system (60% in both RA and AS) in both RA and AS patients. Previous studies on autoimmune diseases have also found predominance of parasympathetic dysfunction as compared to sympathetic [13, 19-20].

Our findings indicate that the frequency CAN and peripheral sympathetic autonomic dysfunction is almost similar in RA patients, but in AS patients the frequency of peripheral autonomic dysfunction was approximately half of the cardiac autonomic dysfunction. It suggests that peripheral sympathetic dysfunction is less frequent than CAN dysfunction in AS patients. Interestingly, we found no correlation between the duration of disease, age, BMI, severity of the disease and biomarkers of inflammation (ESR and CRP) although RA group in this study shown significant correlation between ages and HR response to standing. Previous reports have documented discrepant results regarding the former relationship. More specifically, certain investigators have found no association between autonomic damage, age, disease duration, BMI, severity of disease and inflammatory markers while Toussirot et al., reported that progress of parasympathetic dysfunction correlated with disease activity (BASDAI) and biomarkers of inflammation (ESR and CRP) in AS patients [19]. It might be due to not adopting more sophisticated method to find a autonomic dysfunction.

The main finding of this study was that patients who had lower ESC reflecting sweat gland dysfunction showed more prevalence of cardiovascular autonomic dysfunction. 71% patients with RA and 100 % patients with AS had CAN dysfunction with respect to moderate ESC (40-60 µS), but RA patients had 100 % CAN dysfunction with severe sudomotor dysfunction (ESC<40 µS). This suggests that prevalence of CAN increases with worsening of ESC and a moderate lowering of ESC correlated with CAN [illegible] of AS patients.

In this study we found a significant correlation of sudomotor function with conventional tests of CAN. Sudomotor function highly correlated with HR response to standing ($p<0.05$) and BP response to hand grip ($p<0.05$) in both RA and AS patients. Sudomotor function also significantly correlated with HR response to deep breath in RA patients but not in AS patients. It suggests that worsening of sudomotor function may be related with increasing incidence of cardiovascular autonomic neuropathy.

Autonomic dysfunction is often asymptomatic or non-specific, autonomic testing is also not a routine part of evaluation and hence it is often missed. Our results suggest that sudoscan could be used as a simple non-invasive test for screening peripheral sympathetic autonomic function. It is not a substitute for conventional neuropathy testing, but would alert the physician to perform more careful testing for different aspects of neuropathy, including autonomic neuropathy.

In conclusion, parasympathetic autonomic dysfunction is more prominent than sympathetic dysfunction. Prevalence of peripheral sympathetic dysfunction is less frequent than CAN in AS patients and equally contributed in RA patients. However, the CRT variables significantly associated with sudomotor function and the incidence of cardiovascular autonomic neuropathy increases with worsening of sudomotor function. There is no correlation of autonomic neuropathy with age, disease duration, disease severity and biomarkers of inflammation in RA and AS patients.

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