Autonomic functions and their relations with disease activity in ankylosing spondylitis

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ABSTRACT

Objectives: To evaluate the autonomic functions in patients with ankylosing spondylitis (AS) by means of clinical and electrophysiological tests, to compare the data with those of healthy individuals and to investigate the relationship with the disease activity.

Patients and methods: 32 asymptomatic AS patients and 30 healthy controls were included in the study. Parasympathetic functions were evaluated clinically with heart rate variability (HRV) and electrophysiologically with R-R interval variation (RRIV). Sympathetic functions were evaluated clinically with diastolic blood pressure response to isometric exercise (DBP) and electrophysiologically with sympathetic skin response (SSR). Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score –C (ASDAS-C) were used to estimate the disease activity.

Results: HRV and RRIV was significantly lower in patients with AS when compared to controls, and in patients with BASDAI≥4 when compared to the patients with BASDAI<4. There was no difference between the AS and the control groups and between the groups with BASDAI≥4 and BASDAI<4 for DBP. Although there was no difference for SSR between AS and the control groups, SSR latency was significantly longer and SSR amplitude was significantly smaller in the group with BASDAI≥4 when compared to the group with BASDAI<4.

Conclusions: Our results indicate a parasympathetic dysfunction in AS patients, however the sympathetic system seems to be affected when the disease activity is increased. Patients with AS even they are asymptomatic must be investigated for autonomic dysfunction.

Keywords: Ankylosing spondylitis; Sympathetic; Parasympathetic; electrophysiology

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that mainly affects the sacroiliac joints and the spine. Neurologic and cardiac involvements are among the extraarticular manifestations of the disease. Neurologic complications of ankylosing spondylitis can be caused by fracture, instability, compression or inflammation. Fractures of the spine, atlantoaxial/atlantooccipital subluxations can occur and can lead to spinal cord injury. Ossification of the posterior longitudinal ligament, destructive intervertebral disc lesions and spinal stenosis may cause compressive neurologic complications. Cauda equina syndrome is another neurologic complication of the disease. The cause of this syndrome may be due to arachnoiditis and arachnoid adhesions.

Manifestations of cardiac involvement include ascending aortitis, aortic valve incompetence, conduction abnormalities, cardiomegaly and pericarditis[1]. Cardiac functions of human body are under the control of autonomic nervous system (ANS). The functions of ANS can be evaluated clinically with some non-invasive, simple tests based on cardiovascular reflexes. The heart rate variation during deep, slow breathing – for the evaluation of parasympathetic system – and the diastolic blood pressure response to sustained handgrip – for the evaluation of sympathetic system – are among them. Sympathetic skin response (SSR) and R-R interval variation (RRIV) are noninvasive electrophysiological tests used in the assessment of sympathetic and parasympathetic nervous system function, respectively.

There is no classical information regarding the autonomic nervous system involvement in patients with AS, and only a few studies have been performed on this issue up to date. Besides the studies showing disturbance of particularly the parasympathetic autonomic nervous system in AS, there is a study with contrary results[2-4].

OBJECTIVES

The aim of this study is to evaluate autonomic functions in patients with AS by means of clinical and electrophysiological tests, to compare the data with those of healthy individuals and to investigate the relationship with the disease activity.

PATIENTS AND METHODS

Thirty-two patients who were diagnosed as AS according to modified New York Criteria, and 30 age and sex-matched healthy controls were included in the study. Ethical approval for the study was obtained from the Committee of Scientific Investigations, Ankara Numune Education and Research Hospital. Informed consents were obtained from all of the participants. They were questioned for their age, gender, disease duration and medication use.

Exclusion criteria were as follows: Patients younger than 18 or older than 65 years of age, patients with diabetes mellitus, hypo / hyperthyroidism, uremia, heart failure, cardiac arrhythmia or other systemic diseases that could affect nervous system or cardiovascular system functions, diseases that could affect electrophysiological tests such as polyneuropathy, peripheral nerve disease, reflex sympathetic dystrophy or entrapment neuropathy, and the patients who use medications that could affect ANS or cardiovascular function.

All subjects were asked to stop caffeine, tea and alcohol intake one day before, and to stop smoking at least 3 hours prior to the study. They were told to avoid activities such as running and jumping that could increase the blood pressure at least two hours before the study. Subjects rested in a quiet room for 30 minutes before the study. All tests were performed in late morning, after a light breakfast.

Symptoms that might be related to ANS dysfunction such as vertigo, vertigo that appeared after standing up suddenly, and vertigo that appeared while standing still were questioned, and a detailed neurological examination was performed. None of the subjects had aforementioned symptoms and their neurological examinations were normal. Laboratory analysis included hemoglobin, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score –C (ASDAS-C) were used to determine the disease activity[5-7]. The patients were divided into two groups according to their BASDAI scores, as patients with BASDAI<4 and patients with BASDAI ≥4.

CLINICAL TESTS

Heart rate variability (HRV) was calculated in order to evaluate parasympathetic nervous system function clinically. The patients were asked to breathe 6 times per minute, each breathing cycle lasting 10 seconds and their electrocardiographies (ECG) were obtained simultaneously for one minute using Nihon Kohden Cardiofax ECG equipment. An ECG ruler was used to calculate the heart rate according to the longest (R-R max) and the shortest (R-R min) R-R intervals during 6 breathing cycles, and the difference between them was determined.

The function of the sympathetic system was evaluated with diastolic blood pressure response to isometric exercise (DBP). For this, the patient's arterial blood pressure (ABP) was measured three times, with one-minute intervals. Then, the patient was asked to grasp the Jamar dynamometer as strong as possible while she/he was sitting up straight, and this value was recorded in kilograms. Later, the patient was asked to grasp the dynamometer with a one-third force of her/his maximal grasp for five minutes, and her/his ABP was measured with one-minute intervals during this time. The difference between the mean of the measurements obtained at rest and the maximum measurement obtained during contraction was calculated[8]. Omron M6 digital sphygmomanometer was used to measure ABP.

ELECTROPHYSIOLOGICAL TESTS

Sympathetic skin response (SSR) and R-R interval variation (RRIV) were performed according to the methods described by Shahani in order to evaluate ANS function electrophysiologically[9]. All measurements were performed by the same physician who was unaware of the identity and clinical information of the patients. The tests were performed at least 2 hours after a light breakfast in a quiet, semi-darkened room in which the temperature was maintained between 23–26°C, and the skin temperature of the patient was at least 31°C. Clinical and electrophysiological tests were performed on the same day.

Parasympathetic functions were evaluated with RRIV. A disk-shaped ground electrode was placed on the right axillary line, over the last rib and disk electrodes were placed over the chest wall, along the car-

diac position. Bandpass filter was set at 20- 1000 Hz with a sensitivity of 0.5 mV and with a screening time of 0.2-1 seconds. Using the triggering mode and adjusting the screening time, two QRS complexes (especially R waves) were displayed on the monitor at the same time. The first QRS complex presented the triggering potential whereas the time-related alterations of the second QRS complex reflected the alterations in R-R interval. Twenty waves were recorded, put together, and a printout was obtained for later measurements. One scanning was performed when the patient was at rest, and the second one was recorded during the forced ventilation, when the patient breathed 6 times per minute. The formula described by Shahani (a/b x 100) was used to calculate RRIV. The R-R interval variation was expressed as percent. In the formula, "a" represented the difference between the earliest and latest R waves and "b" represented the mean of RR intervals. The difference of RRIV% recorded during deep breathing (%RRIV-D) and RRIV% recorded at rest (%RRIV-R) was obtained. Recordings and calculations were performed by the software.

SSR recordings were performed with the disk electrodes attached to the palm and dorsal side of the right hand. For electrical stimulation, single square pulses of 0.1 second duration and 10-20 mA intensity were applied to the volar wrist; dominant median nerve was stimulated first, then nondominant median nerve and dominant tibial nerve were stimulated. When there was no response to 10 consecutive stimuli, it was regarded that there was no response to the stimulus. The latency and the amplitude of the response were analyzed. Peak-to-peak amplitude was measured, and the latency was measured from the onset of the stimulus artifact until the first negative deflection of the signal base.

STATISTICAL ANALYSIS

Statistical analysis of the data was performed using SPSS for Windows 15.0 package program. Shapiro--Wilk test was used to analyze the normal distribution of the continuous variables. Descriptive statistics were presented as mean ± and standard deviation or median (minimum – maximum) whereas categorical variables were presented as number of the patients and (%). The difference of the means between the groups was analyzed with Student's t test while the analysis of the medians of the groups was performed with Mann Whitney U test. The significance of an intergroup difference of one variable was investigated using Kruskal Wallis test. Categorical variables were analyzed with Pearson's Chi square test and Fisher's exact Chi square test. Any significant correlation among the continuous variables was analyzed by using Spearman's correlation test.

RESULTS

The demographic characteristics of the subjects are presented in Table I.

HEART RATE VARIABILITY AND R-R INTERVAL VARIABILITY

HRV was significantly lower in the AS group than controls and was significantly lower in the group with BASDAI≥4 when compared to the group with BASDAI<4. There was less RRIV in AS group when compared to the control group (Table II). This result indicates a parasympathetic dysautonomia in AS group.

DIASTOLIC BLOOD PRESSURE (DBP) AND SYMPATHETIC SKIN RESPONSE

There was no statistically significant difference be-

TABLE I. DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

	AS (n=32)	Control (n=30)	p value
Age (years) (Mean ± SD)	38.8 ± 9.3	37.5 ± 8.9	0.566
Gender M/F	18/14	16/14	0.818
Disease duration (years) (Mean ± SD)	11.7 ± 9	(-)	
Medication used (Number of patients, %)			
NSAID	11 (%34.4)	(-)	
NSAID+SSZ	15 (%46.9)		
NSAID + anti-TNF	6 (%18.7)		

M: Male, F: Female, NSAID: Non-steroidal anti-inflammatory drug, SSZ: Sulfasalazine, TNF: tumour necrozing factor

TABLE II. CLINICAL AND ELECTROPHYSIOLOGICAL TEST RESULTS ACCORDING TO GROUPS

	AS (n=32)	Control (n=30)	p	BASDAI≥4 (n=15)	BASDAI<4 (n=17)	p
HRV (Mean ± SD)	17,3 ± 8,4	28,7 ± 9,5	**0.000†**			
HRV (Mean ± SD)				11.1 ± 2.1	22.8 ± 7.9	**0.000†**
RRIV (Median) (min-max)	22.5 (12.9-104.6)	80.6 (31.7-206.1)	**0.000†**	11 (8-15)	22 (11-40)	**0.000†**
SSR (Median) (min-max)						
D Median lat (ms)	1393 (1180-1765)	1420 (820-2120)	0.657	1525 (1355-1765)	1330 (1180-1585)	**0.000†**
amp (µv)	3.1 (1.2-14.1)	3.16 (0.4-8.6)	0.838	2.5 (1.4-4.4)	3.4(1.2-14.1)	**0.037***
ND Median lat (ms)	1490 (1250-1895)	1500 (1315-1845)	0.592	1615 (1420-1895)	1405 (1250-1620)	**0.000†**
amp (µv)	2.34 (0.813.5)	2.89 (0.5-10)	0.512	2.17(0.8-3.5)	3.7(1.1-13.5)	**0.040***
Tibial lat (ms)	1517 (540-1985)	1512 (985-1890)	0.888	1600 (1385-1985)	1480 (540-1615)	**0.001***
amp (µv)	3.05 (0.8-14.9)	3.1(0.4-8.7)	0.741	2.68(0.9-3.8)	3.87 (1-15)	**0.011***
DBP (Mean ± SD)	16,3 ± 6,8	18,2 ± 5,2	0,239	15,9 ± 4,3	16,6 ± 8,5	0.791

AS: Ankylosing spondylitis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
HRV: Heart rate variability, SD: standard deviation RRIV: R-R interval variation, min: minimum, max: maximum, SSR: Sympathetic skin response D: Dominant, ND: Non-dominant, lat : latency, amp : amplitude, DBP: Diastolic blood pressure to isometric exercise,
*: p<0,05 †: p<0,001

tween AS and the control groups as well as the group with BASDAI ≥4 and the group with BASDAI <4 for sympathetic nervous system functions evaluated clinically with DBP response to isometric exercise. In addition, there was no statistically significant difference between AS group and the control group for sympathetic skin response (SSR) tested electrophysiologically. On the other hand, SSR amplitudes were significantly smaller and the latencies were significantly longer in the group with BASDAI≥4 when compared to the group with BASDAI<4 (Table II). In addition to these, there was a significant positive correlation between BASDAI and ASDAS-C scores and SSR latencies, and there was a significant negative correlation between BASDAI and ASDAS-C scores and SSR amplitudes (Table III).

TABLE III. CORRELATIONS OF SSR WITH BASDAI AND ASDAS-C

	ASDAS-C	BASDAI
Dom. median latency	r = 0,664 **p= 0.000†**	r=0.75 **p= 0.000†**
Dom. median amplitude	r=-0.384 **p= 0.030***	r = -0.392 **p= 0.026***
ND median latency	r=0.611 **p= 0.000†**	r=0.697 **p= 0.000†**
ND median amplitude	r= -0.470 **p= 0.007***	r= -0.434 **p= 0.013***
Tibial latency	r= 0.712 **p= 0.000†**	r= 0.691 **p= 0.000†**
Tibial amplitude	r= -0.521 **p= 0.002***	r= -0.426 **p= 0.015***

SSR: Sympathetic skin response, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS-C: Ankylosing Spondylitis Disease Activity Score–C. Dom: Dominant, ND: Non-dominant
*: p<0,05, †: p<0,001

DISCUSSION

In our study, we found abnormalities in clinical and electrophysiological autonomic tests that evaluates parasympathetic system in patients with AS. These abnormalities were also related with the disease activity. The results of the tests that analyzed the sympathetic system were not different in the AS and the control groups. However, the results of the electrophysiological tests showed a statistically significant difference be-

tween the patients with active and inactive disease. Our results suggest that parasympathetic system is affected in AS whereas sympathetic system is affected when the disease activity increases.

In a review about the autonomic control of immunity, Czura et al. mentioned the effects of the parasympathetic function on the organization of inflammatory response[10]. Cholinergic neurons control TNF synthesis by means of acetylcholine (ACH)[11,12]. ACH is the main neurotransmitter of the parasympathetic system, and it has a property to decrease the activity of the macrophages. This relation between the autonomic nervous system and immune system has been called as "cholinergic anti-inflammatory pathway". Inflammatory stimuli stimulate vagal afferents and then the hypothalamus. Experimental stimulation of the vagus caused decreased TNF synthesis in liver, spleen and heart, and serum TNF levels decreased in endotoxemia, ischemia / reperfusion injury and hemorrhagic shock. After vagotomy, animals showed an exaggerated TNF response to an inflammatory stimulus[11-16]. These results suggest that individuals may develop exaggerated immune response due to dysfunction of cholinergic anti-inflammatory pathway. This concept has been supported in the literature by demonstrating autonomic dysfunction in inflammatory diseases such as diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus and Crohn's disease[17-22]. Other inflammatory conditions such as sepsis have been demonstrated to be related to autonomic dysfunction[23,24].

Initially, this dysfunction was thought to be secondary to inflammation. Recently, as an alternative explanation it has been suggested that excessive cytokine production develops as a result of dysfunction in the cholinergic anti-inflammatory pathway after a harmless stimulus, in other words, inflammation develops as a result of the dysfunction of the parasympathetic system. Treatment of the inflammatory diseases by endogenous neural mechanisms has become a current issue after identification of cholinergic anti-inflammatory pathway. Animal studies previously showed that electrical stimulation of vagus had an anti-inflammatory effect[25]. This method and other similar methods may be treatment options in inflammatory diseases such as rheumatoid arthritis and AS, in the future.

There are a few studies about autonomic nervous system activity in AS patients The first study was performed by Toussirot *et al*. in 1999. They reported that the blood pressure dropped more and there was less spontaneous baroreflex activity in AS patients when they were upright. In addition, when they stood up after a supine position, the heart rate was shown to be higher in the patients with BASDAI score ≥5 when compared to the control group and the ones with BASDAI score <5[2]. Similar to Toussirot *et al.,* our study showed that these results indicating parasympathetic autonomic nervous system dysfunction were more pronounced in the patients with active disease.

Similar to our study Borman *et al*. reported that HRV, RRIV and hearth rate response to standing (HRS, a clinical test that evaluates parasympathetic system functions) were statistically significantly lower in the patient group with AS than the control group. In addition, they reported a significant negative correlation between HRV and BASDAI scores. Although there was no statistically significant difference between the patients and the control groups for SSR, latencies were longer and amplitudes were smaller in patients with active disease[3]. These results indicate that sympathetic dysfunction is only apparent when the disease is active. The disease activity was evaluated with BASDAI in the studies of Toussirot and Borman. Differently, we used ASDAS in addition to BASDAI to investigate disease activity, and found a linear correlation between ASDAS and electrophysiological tests. Another study that investigated this subject was performed by Yildirir *et al*. They investigated heart rate variability in AS patients using power spectral analysis. There was no difference in AS and the control groups for HRV[4]. Mean disease duration was approximately 5 years in the study of Yildirir *et al*. while this duration was 11.7 years in our study, and this difference may be responsible for the dissimilarity of the results of two studies.

It is known that there is increased mortality in patients with AS and cardiovascular diseases are among the causes of death[26]. Parasympathetic nervous system dysfunction may cause mortality in these patients by impairing baroreflex function and causing conduction defects.

CONCLUSIONS

In conclusion, clinicians must be bewared for autonomic dysfunction in patients with AS. Future studies may help us to appreciate its clinical importance and effect on immunity and may aid for the development of new alternative treatment methods for AS and other inflammatory diseases.

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