RESEARCH ARTICLE / *Araştırma Makalesi*

Is Autonomic Dysfunction A Sign of Disease Process in Ankylosing Spondylitis? An Electrophysiological Study

Ankilozan Spondilit'te Otonomik Disfonksiyon Hastalık Sürecinin Bir İşareti midir? Bir Elektrofizyolojik Çalışma

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Geliş Tarihi / Received : **23.09.2019** Kabul Tarihi / Accepted : **27.11.2019**

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(Sakarya Tıp Dergisi / ***Sakarya Med J*** **2019, 9(4):644-651) DOI: 10.31832/smj.623601**

Abstract

Objective — In this study, we aimed to evaluate autonomic nervous system (ANS) functions by using clinical and electrophysiological tests in patients with ankylosing spondylitis (AS), to investigate the relationship with the disease characteristics and to compare the data with healthy individuals.

Materials and Methods — Forty AS patients and 30 healthy controls were included in this case-control study. Clinical measurements including heart rate at rest, systolic blood pressure response to standing were obtained. The electrophysiological assessments of ANS were performed by sympathetic skin response and R–R interval variation measurements. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used to estimate the disease activity. Patients with AS were also subdivided into two groups; BASDAI≥4 and BASDAI<4. The difference between the groups and correlations between ANS variables and clinical entities were determined.

Results — Patients expressed feeling of faintness in orthostatic change, abnormal sweating, disturbed bowel function more than control subjects. The patient's heart rate values at rest were higher than control subjects which indicate parasympathetic dysfunction (p=0,001). No significant difference was found on sympathetic skin response (SSR) latencies and amplitudes between patients and control group or patients with low and high disease activity (p>0,05). A correlation was found between SSR latencies and C-Reactif Protein (CRP) levels and disease durations.

Conclusion — The symptoms of ANS dysfunction were observed more frequently in AS patients than controls but no significant difference of autonomic functions as assessed by R–R interval variation and SSR was found.

Keywords — Ankylosing Spondylitis; Spondyloarthritis; Autonomic Nervous system.

Öz

Amaç — *Bu çalışmada, ankilozan spondilitli (AS) hastalarda klinik ve elektrofizyolojik testler kullanarak otonom sinir sistemi (OSS) fonksiyonlarını değerlendirmeyi, hastalık özellikleriyle ilişkiyi araştırmayı ve verileri sağlıklı bireylerle karşılaştırmayı amaçladık.*

Gereç ve Yöntemler — *Bu vaka-kontrol türü çalışmaya, kırk AS hastası ve otuz sağlıklı kontrol grubu dahil edildi. İstirahatte kalp atışı, ayakta durarak sistolik kan basıncı gibi klinik ölçümler alındı. OSS'nin elektrofizyolojik değerlendirmeleri sempatik cilt yanıtı ve R-R aralık varyasyon ölçümleri ile yapıldı. Hastalık aktivitesini tahmin etmek için Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) kullanıldı. AS'li hastalar da iki gruba ayrıldı; BASDAI≥4 ve BASDAI <4. Gruplar arasındaki fark ve OSS değişkenleri ile klinik özellikler arasında korelasyon belirlendi.*

Bulgular — *Hastalar ortostatik değişimde solgunluk hissi, anormal terleme, bozulmuş bağırsak fonksiyonlarını kontrol grubundan daha fazla olduğunu ifade etmişlerdir. Hastaların istirahatte kalp atış hızı değerleri parasempatik disfonksiyonu gösteren kontrol bireylerinden daha yüksekti (p = 0,001). Hasta ve kontrol grubu veya düşük ve yüksek hastalık aktivitesi olan hastalar arasında sempatik cilt yanıtı (SCY) latans ve amplitüdlerinde anlamlı bir fark bulunmadı (p> 0,05). SCY latansları ile C-Reaktif Protein (CRP) seviyeleri ile hastalık süreleri arasında bir ilişki vardı.*

Sonuç — *OSS disfonksiyonu semptomları AS hastalarında kontrollerden daha sık gözlendi, ancak R–R aralık değişimi ve SCY ile değerlendirilen otonomik fonksiyonlarda anlamlı bir fark bulunmadı.*

Anahtar Kelimeler — *Ankilozan Spondilit; Spondiloartrit; Otonom sinir sistemi.*

INTRODUCTION

Ankylosing Spondylitis (AS) is a chronic inflammatory disease that primarily affects spine and sacroiliac joints and has extraarticular manifestations. Neurologic and cardiovascular manifestations are known to occur in patients with AS.[1] Neurologic involvement in AS is not well defined.

Autonomic nervous system (ANS) is responsible for the regulation of bodily functions. It is comprised of sympathetic and parasympathetic systems whose functions are complementary. Autonomic neuropathy is a kind of neurologic involvement in rheumatic diseases.[2] Imbalance in the ANS has been observed in many established chronic autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriatic arthritis (PsA).[2,3]

Satisfying information is absent regarding ANS involvement in patients with AS. The literature about ANS dysfunction in AS patients revealed conflicting results, some of them showing disturbance of parasympathetic system.[4-6] Cardiovascular autonomic neuropathy (CAN) has been reported in a number of autoimmune rheumatic diseases and severe CAN may result in arrhythmia, myocardial infarction and sudden death.[7]

The symptoms of ANS dysfunction are nonspecific and extremely varied such as dizziness, palpitations, feelings of faintness in orthostatic change of posture, abnormal sweating, gastrointestinal, urinary and sexual disorders. The tests to detect autonomic dysfunction are not routinely employed in clinical practice. Heart rate at rest and during deep breath, blood pressure response to standing or sustained handgrip are some of clinical cardiovascular tests assessing ANS functions. R-R interval variation (RRIV) and sympathetic skin response (SSR) are noninvasive electrophysiological tests used in evaluation of parasympathetic and sympathetic functions. Previous studies have demonstrated that these tests are sensitive for the detection of different part of total ANS dysfunctions in different settings.[8] RRIV is a simple and reliable test used for the evaluation of parasympathetic system functions of the heart. The fluctuations in heart rate exhibit a marked synchrony with respiration (increasing during inspiration and decreasing during expiration), so RRIV increases during deep respiration. Neural control of RRIV by respiration is related to a parasympathetic reflex and is the vagal innervations of the heart. RRIV is other term used for heart rate variability (HRV) in the literature.[9]

SSR is also commonly used for the assessment of ANS function. SSR reflects temporary changes in electrical potential generated in the deep layer of the skin, resulting from internal or external arousal stimuli. The SSR potential wave is originated from synchronized activation of sweat glands in response to efferent sympathetic nerve fibers. The final efferent pathway of the SSR begins within the thoracolumbar cord and is mediated by the unmyelinated postganglionic sympathetic fibers.[10]

The aim of this study was to evaluate ANS functions by using clinical and electrophysiological tests in patients with AS, to compare the data with healthy individuals and to investigate the relationship with the disease activity and disease duration.

MATERIALS AND METHODS

Participants

We included 40 patients with AS from Rheumatology out-patient clinic in this case-control study. All patients fulfilled Modified New York criteria.[11] Thirty age and gender matched healthy control subjects were recruited. Exclusion criteria for patients and controls were systemic diseases that may affect autonomic nervous system such as diabetes mellitus, thyroid disorders, uremia, cardiac failure, arrhythmia. The volunteers using any medications that can affect ANS or cardiovascular functions such as antihypertensive drugs or steroids were also recruited. The study was approved by the local clinical ethics committee. İnfor-

med consents were obtained from all of the participants (protocol number: 2014/12-8). The study was conducted in Bezmialem Vakıf University Medical Faculty Hospital between June and December 2014.

Demographic characteristics including age, sex and body mass index (BMI) were recorded. Disease duration and medications of the patients were also recorded. Detailed neurologic examinations of the volunteers were performed and all of them had normal findings. Laboratory analysis including hemoglobinand C-reactive protein (CRP) levels by turbidimetric method were performed on the same day as autonomic clinical and electrophysiological tests. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score CRP (ASDAS-C) were used to estimate the disease activity. Patients with AS were subdivided into two groups according to disease activity; BASDAI≥4 and BASDAI<4, to investigate whether there is a relationship between autonomic dysfunction and disease activity.

Measurement

Clinical manifestations of autonomic dysfunction were recorded when present. This included dizziness, dizziness during standing, palpitations, feelings of faintness in orthostatic change of posture, abnormal sweating, gastrointestinal, urinary disorders and impotence.

Stopping caffeine, tea and alcohol intake 1 day before and stopping smoking at least 5 hours prior to the study was advised. The subjects were asked to avoid activities that would affect blood pressure like running, jumping, etc. at least 2 hours before the test. Having a restorative sleep, the night before and a light breakfast 2 hours prior the tests were also advised. Subjects rested in a quiet semi-darkened room 30 minutes before the tests.

Clinical measurements including heart rate at rest, systolic and diastolic blood pressure (SBP, DBP) response to standing were performed. For parasympathetic function, heart rate was measured after 10 minutes of rest at supine position. For sympathetic function SBP and DBP was measured with a proper arm sphyngo manometer in supine position after 10 minutes of resting and 3 minutes after standing. Orthostatic intolerance is determined by 20 mmHg decrease in SBP or 10 mmHg decrease in DBP after standing. The electrophysiological assessments of ANS were performed by R–R interval variation (RRIV) and sympathetic skin response (SSR) measurements. All subjects were studied by the same neurologist who was blind to the subjects' clinical data.

1. Heart rate interval variation (RRIV): The patients were studied in the supine position. Recordings were made using two surface electrodes placed on the chest across the cardiac position and a metal electrode strapped around one wrist was used as the ground electrode. Equipment used was from Dantec Keypoint (Medtronic; Dantec, Skovlunde, Denmark); filters were 0.8 to 80Hertz, sensitivity was 500 μV per division, and the sweep rate was 200 ms per division. The normal respiration test was obtained during baseline conditions after a 5-minute rest under standardized conditions. The deep respiration test was performed with six cycles of 5 seconds of deep inspiration followed by 5 seconds of deep expiration. A plot of R-R intervals versus time was displayed online on the computer screen. Positive and negative peaks (maxima and minima) were defined by means of a three-point search algorithm. The normal and deep breathing R-R intervals were analyzed using the following algorithm: the difference between the shortest and the longest R-R intervals given in percent of the mean of all maximal and minimal peaks [(R-R max – R-R min)) 100/R-R mean].

2. Sympathetic skin response (SSR): The SSR was performed according to the Technical Standards of the International Federation of Clinical Neurophysiology.[12] The skin temperature was maintained at 32°C (room temperature stabilized at 25–26°C). A standard active electrode was attached to the palm and sole and the reference electrode to

the dorsum of the hand and foot. The same EMG equipment was used (Dantec, Keypoint, Medtronic).

Electrical stimulation was applied through superficial electrodes over the contralateral median nerve and reference electrode to the dorsum of the hand. Stimuli were delivered unexpectedly and in irregular intervals of more than 1 minute to prevent habituation. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection and expressed in seconds. The amplitude was measured from the baseline to the negative peak and expressed in mV. The response was considered absent if no consistent voltage change maximum stimuli intensity.

Statistical analysis

Statistical analyses were performed using the IBM SPSS for Windows version 22.0 software (IBM Corporation, Armonk, NY, USA). Demographic characteristics of the patients and control subjects were summarized by descriptive statistics. Variables were presented as median (minimum-maximum) or mean± standard deviation, frequency and percentage values were used in the given descriptive statistics of the data. For the sample size, 95% confidence interval (CI) in the G-Power 3.1.9.4 package program (Franz Paul, Germany, 2019) was calculated for the t-test at the beginning of the study. The post-hoc power (n=40, effect size= 0.75, α=0.05) is 0.953. Compliance with the normal distribution of parameters was evaluated by the Shapiro Wilks test. The differences between the groups were assessed by Mann-Whitney U for non-parametric tests and t-test for parametric tests. The mean values of sympathetic (SSR latency and amplitude) and parasympathetic (%D, %R) parameters were also compared with Mann-Whitney U test. Chi-square test was used for the analysis of qualitative data and Fisher's exact test was used when chi-square test conditions were not met. The Spearman correlation analysis was used to evaluate the correlation between ANS parameters and disease characteristics. The statistical significance was determined at p≤0.05.

RESULTS

Forty AS patients (22 males, 18 females) with a mean age of 35,2±10,4 and 30 control subjects (16 males, 14 females) with a mean age of 34,4±11,2 years were included in the study. Demographic characteristics were similar between the groups. Mean disease duration was 7,2±5,3 years. The demographic and clinical characteristics of the groups were summarized in table 1.

Table 1: Demographic, clinical and laboratory characteristics of the Ankylosing Spondylitis patients and controls

	Patients (n:40)		Controls (n:30)		
	n(%)	mean±SD	n(%)	mean±SD	p value
Age (years)		35,2±10,4		34,4±11,2	0,569
Sex					0,890
Female	18(45)		14(47)		
Male	22(55)		16(53)		
BMI (kg/m^2)		25,8±4,8		26,8±4,4	0,238
Disease duration (years)		7,2±5,3			
Hemoglobin (g/dl)		13,26±1,93			
CRP (mg/l)		7,1±7,5			
BASDAI		4,1±2			
ASDAS-C		2,6±0,8			
Treatment					
NSAID	11(28)				
NSAID+SSZ	27(67)				
Anti-TNF	2(5)				

NSAID: Non-steroidal anti-inflammatory drug SSZ: Sulphasalazine
TNF: Tumor necrosis factor med: median min: minimum max: maximum, SD: standard deviation.

Among the symptoms which is related to autonomic dysfunction, feeling of faintness in orthostatic change of posture (p: 0,049), abnormal sweating (p:0,040) and gastrointestinal disorders (p:0,019) were seen more frequently in AS patients than controls (Figure 1).

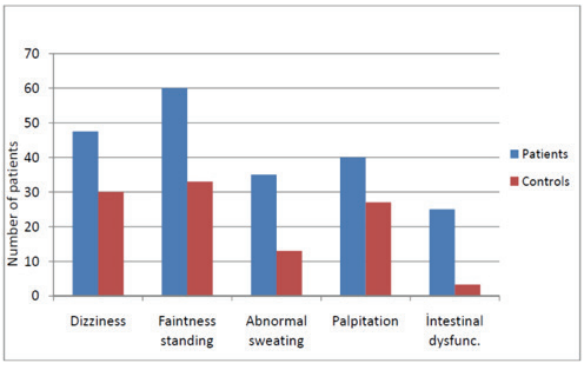

Figure 1: Frequency of the symptoms of autonomic dysfunction in Ankylosing Spondylitis patients and controls.

The clinical measurements of ANS in both groups are shown in table 2. Heart rate at rest was significantly higher in AS patients (p:0,001) which suggest a dysfunction in parasympathetic system. SBP, DBP at rest and blood pressure response to standing were similar in both groups. The electrophysiological findings including RRIV and SSR latencies and amplitudes are shown in table 3. There was no difference between RRIV at rest and deep breath and SSR measurements between patient and control groups.

Table 2: The results of clinical tests of autonomic nervous system in the Ankylosing Spondylitis patients and control subjects

	AS patients (n:40) (mean±SD)	Control group (n:30) (mean±SD)	p value
Heart rate at rest (beats/min)	81,3±9,7	73,3±10	0,001*
SBP supine (mm/Hg)	118±13,5	118±9,5	0,91**
SBP standing (mm/Hg)	116±14,5	112,9±9,7	0,43**
Orthostatic hypotension (n, %)	2 (5)	1 (3,3)	0,73***

*t-test, **Mann-Whitney U, ***Chi-Square test SBP: systolic blood pressure SD: standard deviation AS: Ankylosing Spondylitis

Patients with AS were subdivided into two groups according to disease activity. 19 patients (47,5%) were in high disease activity group with a BASDAI score greater than 4. Electrophysiological tests of ANS were similar in both groups (Table 4).

Table 3: Electrophysiological findings of parasympathetic and sympathetic tests in patients and controls

	AS patients (n:40)			Controls (n:30)			p value
	mean±SD	med	Min-Max	mean±SD	med	Min-Max	
RRIV (rest) (ms)	17,6±7,5			18,4±7,4			0,66*
RRIV (deep breath) (ms)	37±13,5			34,7±15,5			0,50*
SSR latency (median n.) (ms)		1,48	0,9-7,8		1,53	1,2-2,1	0,63**
SSR amplitude (median n.) (mV)		2,57	0,3-9,3		2,92	0,6-9,5	0,16**
SSR latency (tibial n.) (ms)		1,97	1,2-2,9		2,04	0,1-2,5	0,79**
SSR amplitude (tibial n.) (mV)		1,35	0,2-4,7		1,49	0,5-4,5	-0,48**

*t-test, **Mann-Whitney U test, RRIV: R-R interval variation, SSR: sympathetic skin response n: nerve med: median min: minimum max: maximum, SD: standard deviation. AS: Ankylosing Spondylitis

Table 4: The results of electrophysiological tests of autonomic nervous system in patients according to disease activity

	BASDAI>4 (n:21)			BASDAI≤4 (n:19)			p value*
	med	min	max	med	min	max	
RRIV (rest) (ms)	16	7,4	39	17	6,1	27	0,59
RRIV (deep breath) (ms)	36	14	70	31	20	60	0,32
SSR latency (median n.) (ms)	1,41	0,87	2,42	1,53	1,26	7,83	0,21
SSR amplitude (median n.) mV)	2,53	0,3	9,38	2,71	0,45	6,74	0,56
SSR latency (tibial n.) (ms)	1,92	1,19	2,91	2,03	1,22	2,92	0,17
SSR amplitude (tibial n.) (mV)	1,15	0,22	4,78	1,51	0,7	4,59	0,17

*Mann-Whitney U test, RRIV: R-R interval variation, SSR: sympathetic skin response, med: median, min: minimum, max: maximum, SD: standard deviation.

The correlations between electrophysiological parameters of ANS and disease characteristics of the AS patients were analyzed. A negative correlation between disease duration and SSR latency of median nerve (p:0,039) and also between CRP levels and SSR latency of tibial nerve (p:0,015) were found. There was a negative correlation between hemoglobin levels and SSR amplitude of median nerve (p:0,044) (Figure 2).

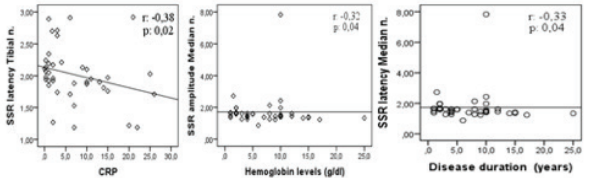

Figure 2: The correlations between electrophysiological parameters of autonomic nervous system and some clinical variables of patients with Ankylosing Spondylitis

DISCUSSION

In this study, we found a correlation between both disease duration and SSR latency of median nerve, and CRP levels and SSR latency of tibial nerve in AS patients. Disease duration, inflammatory markers and levels of hemoglobin may be related to sympathetic functions. Symptoms of ANS dysfunction such as faintness in orthostatic change, abnormal sweating and gastrointestinal dysfunction were more common in AS patients than healthy controls. Resting heart rate of AS patients were significantly higher than healthy controls, which indicate parasympathetic dysfunction.

Interactions between ANS and immune system have been extensively reviewed and there have been a number of studies on the role of sympathetic and parasympathetic system functions on inflammatory response. To the theory of "cholinergic anti-inflammatory pathway", acetylcholine (ACH), the main neurotransmitter of the parasympathetic system, decreases the activity of macrophages and synthesis of Tumor Necrosis Factor (TNF).[13] In a study, experimental stimulation of the vagus caused decreased TNF synthesis in liver, spleen and heart and serum TNF levels decreased in endotoxemia and hemorrhagic shock.[14,15] A recent study by Martelli and colleagues showed splenic sympathetic denervation inhibited and modulated inflammatory responses, but vagotomy did not affect these responses, as a result of this findings Martelli put forward the theory, sympathetic system has more important role in the control of inflammation.[16]

In recent studies by Koopman F.A and colleagues found that stimulation of the cholinergic anti-inflammatory pathway by efferent electrical vagus nerve stimulation VNS or pharmacological activation of the alpha7 subunit of nicotinic acetylcholine receptors improved clinical signs and symptoms of arthritis, reduced cytokine production in RA patients.[17] A study has demonstrated, a cardiac parasympathetic test, heart rate variability may predict anti-TNF therapy response in patients with RA and PsA.[18] Koopman and colleagues also found imbalance in ANS may precede the development of RA. İndividuals at risk of developing arthritis had higher resting heart rate than healthy controls.[19] In this study, similarly, heart rate at rest was significantly higher in AS patients than controls, indicating parasympathetic dysfunction.

Autonomic dysfunctions have previously been well defined in other rheumatic diseases such as RA, SLE, and systemic sclerosis.[2,20] The autonomic neuropathy seen in rheumatic diseases may be due to vasculitis, amyloidosis, side-effects of the immune suppressive drugs or the inflammatory process itself.[20]

The studies about CAN in AS patients are controversial. Yildirir A. et al found no evidence of cardiac autonomic involvement in AS, assessed by HRV.[5] In a recent study Wei C.Y. et al. found significant CAN in AS patients assessed by HRV.[21] Kaya MG. et al found parasympathetic dysfunction in AS patients by impaired heart rate recovery during the first minute following exercise.[22] An earlier study by Toussirot et al has shown decreased parasympat-

hetic activity due to higher resting heart rate and lower cardiac baroreflex slopes and also found a positive correlation between parasympathetic dysfunction and disease activity (BASDAI), CRP and sedimentation levels.[4] RRIV is another term used for heart rate variability (HRV) in the literature.[9] Our study didn't reveal CAN assessed by electrophysiological tests. This may be because of relatively small size of the study and shorter disease duration than previous studies

Our study demonstrated that symptoms of autonomic dysfunction were found more frequently in patients with AS compared to control group such as dizziness, palpitations, feelings of faintness in orthostatic change of posture, abnormal sweating, however no significant difference on electrophysiological tests was found between patients and controls. This may be because of small size of the study. Some potential neurologic mechanisms may have a role at the progression of AS. To our knowledge this is the first study evaluating the presence of ANS dysfunction symptoms in AS patients.

On the contrary to our results, some studies show AS patients with active disease have higher parasympathetic dysfunction than patients with inactive disease on the tests of HRV and RRIV.[6,23] Our study didn't reveal any difference in autonomic electrophysiological tests between patients with high and low disease activity. This may be because of small number of the patients or shorter disease duration than previous studies. Disease duration, inflammatory markers and levels of hemoglobin were found correlated with some electrophysiological parameters of sympathetic system.

Study limitations:

We were able to recruit patients only from single tertiary care hospital. Sample size may not be enough to detect significant differences between patients and control subjects. Large prospective cohort studies are needed to demonstrate autonomic dysfunctions of patients with AS and potential neurologic mechanisms in the pathogenesis of AS.

CONCLUSION

Because cardiac autonomic dysfunctions are related to increased morbidity and mortality, to identify ANS dysfunctions in rheumatic diseases is important. Our study showed parasympathetic dysfunction in AS patients on clinical tests but didn't reveal significant differences between sympathetic and parasympathetic electrophysiological tests between patient and control groups.

Acknowledgement

Authors in this work had no support, including pharmaceutical or industry support.

The authors declare that there are no conflicts of interest
All authors contributed equally in the preparation of this manuscript

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