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Evaluation of Autonomic Nervous System Dysfunction in Fibromyalgia

Fibromyaljide Otonom Sinir Sistemi Disfonksiyonunun Değerlendirilmesi

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Summary

Objective: There have been conflicting results of studies on autonomic nervous system (ANS) dysfunction in fibromyalgia (FM). The aim of this study was to evaluate the sympathetic nervous system dysfunction via sympathetic skin response (SSR) recordings in patients with FM.

Materials and Methods: Twenty-seven female patients with FM and 18 healthy volunteer females as controls were included in the study. All participant were administered the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) and were questioned about chronic symptoms that are characteristic for FM. Right palmar SSRs were evoked by electrical stimulation of the median nerve at the wrist.

Results: The FM patients had higher rates of most of the chronic symptoms of FM. There was no significant difference in SSR latency and amplitude between patients and controls (p>0.05). The patients with FM had no depression and anxiety according to the BDI and BAI mean scores.

Conclusion: We did not find ANS dysfunction in the patients with FM. SSR may be an insufficient way of determining the whole ANS dysfunction as it only evaluates the sudomotor component. ANS dysfunction may be responsible for some of the chronic symptoms of FM and accompanying depression and anxiety (not observed in the present study) rather than taking part in the etiopathogenesis. It can be possible to determine the role of ANS in FM etiopathogenesis by studies evaluating the subsystems of ANS (cardiovascular reflex pathway, sympathetic cholinergic activity etc.) in which chronic symptoms of FM, especially anxiety and depression, are also considered. *Turk J Phys Med Rehab 2011;57:62-5.*

Key Words: Autonomic nervous system, sympathetic nervous system, fibromyalgia, sympathetic skin response

Özet

Amaç: Fibromyaljide (FM) otonom sinir sistemi (OSS) disfonksiyonu hakkındaki çalışmaların farklı sonuçları vardır. Bu çalışmadaki amacımız sempatik deri yanıtı (SDY) cevaplarını kullanarak FM hastalarında sempatik sinir sistemi disfonksiyonunu değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 27 fibromyaljili kadın hasta ve 18 sağlıklı gönüllü kadın kontrol alındı. FM hastaları ve sağlıklı kişiler Beck Depresyon Envanteri (BDE), Beck Anksiyete Envanteri (BAE) ve FM için karakteristik olan kronik semptomlar yönünden sorgulandı. Sağ el palmar SDY, median sinirin bilek hizasında elektriksel olarak uyarılması ile elde edildi.

Bulgular: FM hastalarında kronik semptomların çoğu yüksek orandaydı. Hastaların ve kontrollerin SDY amplitüd ve latansları arasında istatistiksel olarak anlamlı bir fark yoktu (p>0,05). BDE ve BAE ortalama değerlerine göre FM hastalarında anksiyete ve depresyon yoktu.

Sonuç: Bu çalışmada FM'de OSS disfonksiyonu tesbit edilmedi. SDY sadece sudomotor aktiviteyi gösterdiği için OSS'nin tamamını değerlendirmede yetersiz bir yöntem olabilir. OSS disfonksiyonu FM'nin etyopatogenezinden ziyade FM'de gözlenen bazı kronik semptomlardan, eşlik eden depresyon ve anksiyeteden sorumlu olabilir. FM hastalarının kronik semptom, anksiyete ve depresyon durumları da gözönünde bulundurularak, OSS'nin alt sistemlerini (kardiyovasküler refleks yol, sempatik kolinerjik aktivite gibi) inceleyen çalışmalar ile OSS'nin FM etyopatogenezindeki rolünü belirlemek mümkün olabilir. *Türk Fiz Tıp Rehab Derg 2011;57:62-5.*

Anahtar Kelimeler: Otonom sinir sistemi, sempatik sinir sistemi, fibromyalji, sempatik deri yanıtı

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Introduction

Fibromyalgia (FM) is a chronic disorder characterized by widespread pain usually associated with other somatic and psychological symptoms including fatigue, sleep disorders, headache, anxiety, paresthesia, sicca syndrome, Raynaud's phenomenon, irritable bowel syndrome, and dysmenorrhea (1). Despite extensive research, the etiology and pathogenesis of FM remain unclear. Aberrant autonomic nervous system (ANS) function has been shown in many recent studies in patients with FM (2-6). The symptoms observed in FM like fatigue, sleep disorders, anxiety, depression, sicca symptoms, Raynaud's like phenomenon and intestinal irritability may arise due to aberrant ANS function (7,8). The number of tender points in FM can reduced by means of sympathetic blockade, which suggests that sympathetic nerve activity might be responsible for at least part of the pain in patients with FM (9).

ANS abnormalities in FM have been investigated by using various techniques such as sympathetic skin response (SSR), heart rate variability (HRV), and skin blood flow (2-4,6). However, contradictory results have been reported (2-4,10,11). SSR is a simple and easily applicable electrophysiological test (12,13) that measures change in skin surface voltage attributed to sympathetic sudomotor activity (14). Increased activity in cholinergic sympathetic fibers stimulates sweat glands and leads to an increased skin electrical conductance (3). SSR also is named as electrodermal activity, skin conduct level (SCL), electrodermal response, and galvanic skin response (6,15). The response is often recorded from the palm and sole skins by an internal stimulus such as coughing and deep breathing or external electrical stimulation of peripheral nerves (14).

In the present study, we aimed to evaluate the sympathetic nervous system functions by recording SSRs in patients with FM.

Materials and Methods

Twenty-seven female volunteer patients who met the American College of Rheumatology 1990 criteria for the classification of FM (1) were consecutively recruited from the outpatient physical medicine and rehabilitation clinics between January 2007 and April 2007. The control group comprised 18 age and sex-matched healthy female volunteers from the hospital staff. The subjects who were on antidepressant, neuroleptic, cardiovascular, analgesic or muscle relaxant drugs, and who had any neurological, psychiatric or endocrine disease were excluded from the study. All participants were asked questions about distinctive features of FM like symptoms such as chronic fatigue, easy tiring, weakness, sleep disturbances, waking up tired, headache, Raynaud's phenomenon, sicca symptoms, irritable bowel syndrome, functional dyspepsia, severe dysmenorrhea, excessive sweating and dizziness. In the patient group, duration of disease (months) was noted. Spontaneous widespread pain intensity was evaluated by using a 100-mm visual analogue scale (VAS). The Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) were used to evaluate the affective status of the FM patients. The BDI is a 21-item self-report questionnaire on which presence and severity of depressive symptoms are assessed (16). The BDI was adapted into Turkish by Hisli (17) in 1988 and has acceptable reliability and validity. A total score of 0–9 indicates no depression, 10–16 mild, 17–23 moderate and 24–63 severe depression. The BAI is a 21-item inventory designed to assess level of anxiety (18). It measures physical, emotional and cognitive aspects of anxiety and fear of losing control. It was shown to be applicable for the Turkish population by Ulusoy et al. (19). A total score of 0–7 indicates no anxiety, 8–15 mild, 16–25 moderate and 25–63 severe anxiety. This study was approved and reviewed by the Local Ethics Committee. Informed consent was obtained from each subject and the study was performed in accordance with the principles of the Declaration of Helsinki.

SSR Recordings

The experiment was performed with a Nicolet Viking IV channel electromyograph. All of the recordings were done between 15:00 and 17:00 hours. The participants were asked about their menstrual cycles. None of them had menorrhea at the day of recording. They emptied their bladder and bowel before the recording. All of the participants had their lunch at least two hours before the evaluation. The recordings were initiated after an approximately 15 minutes of resting period. The subjects lied in a comfortable supine position in a quiet, brightly lit and an air-conditioned room maintained at 24±1°C. The skin temperature of each participant was over 32°C.

The subjects were instructed to keep their eyes open, not to breathe deeply, not to cough, and not to move during the procedure. SSR recordings were made by standard surface electrodes made of Ag-AgCl (10 mm diameter-Nihon Kohden, NM 312S). The frequency of bandpass was 0.2-100 Hz. The time window for recording was 10 s and the gain was 1000 μV per division.

The electrical stimulation (square pulse with 0.1 ms duration and 25 mA intensity) was applied over the left median nerve at the wrist. The stimuli were delivered at irregular intervals not less than 20 s to avoid habituation. Active and reference recording electrodes were placed on the palm and the dorsum of the right hand, respectively. Ten responses were recorded for each subject. The peak-to-peak amplitude and onset latency were measured for each response. The amplitude and the latency of the highest response were taken into consideration in analyses (20).

Statistical Analysis

In statistical analyses of SSRs, the latency and the amplitude of the highest response were evaluated. Data from patients and control subjects were compared using an independent-samples t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The symptoms of patients and controls were analyzed with chi-square test. The Spearman or the Pearson correlation coefficients were used to assess the relationship between the parameters. A p value of less than 0.05 was considered statistically significant.

Results

The demographic data of patients and controls are given in Table 1. Age, height, and weight of subjects were not significantly different in both patient and control groups (Table 1). Questionnaire of chronic symptoms in the study groups is shown in Table 2. The FM patients had higher rates of chronic fatigue, easy tiring, weakness, waking up tired, sleep disturbances, severe headache, irritable bowel syndrome, sicca symptoms, and dizziness that were statistically significant when compared to those in the healthy subjects ($p<0.001$). The frequency of Raynaud's phenomenon, functional dyspepsia, excessive sweating, and severe dysmenorrhea was similar to that of the controls. The palmar SSRs

were recorded in all patients and control subjects. The means of the amplitudes and the latencies of SSRs are shown in Table 3. There was no significant difference in SSR latency and amplitude between patients and controls (p>0.05). Although BDI and BAI mean scores in patients with FM were higher than those in the controls (p<0.001), they were lower than the border value for diagnosis of depression and anxiety (Table 1). There was no significant correlation between BDI and SSR latency (r=0.021, p=0.91), BDI and SSR amplitude (r=0.015, p=0.94), BAI and SSR latency (r= -0.271, p=0.18), BAI and SSR amplitude (r= -0.038, p=0.85), and VAS and SSR latency (r= -0.006, p=0.97), VAS and SSR amplitude (r=-0.009, p=0.96).

Discussion

We found that SSR amplitudes and latencies were not statistically different in both patients with FM and control subjects.

According to the present study, the cholinergic activity of the sympathetic nervous system against stressor factor was not different in patients with FM and controls. Many studies have suggested sympathetic nervous system involvement in FM, although contradictory results have been reported. Backman et al. (10) showed muscle sympathetic hyperactivity by measuring maximum voluntary handgrip strength after electrical stimulation of ulnar nerve with and without sympathetic blockade in patients with FM. They suggested that increased muscle sympathetic nerve activity is a possible mechanism for FM. Contrary to this finding, Elam et al. (11) recorded muscle sympathetic activity with microneurography in patients with FM. They did not determine exaggerated sympathetic nerve activity against stressor factor. Finally, the authors concluded that muscle sympathetic nerve overactivity does not indicate FM.

Qiao et al. (3) evaluated peripheral sympathetic activity with simultaneous measurements of electrodermal variables and blood flow at palmar skin sites with acoustic stimulation, and cold pressor tests in 27 patients with FM. Compared to the controls, they found a significantly greater increase in the skin electrical conductance level and less vasoconstriction during acoustic stimulation and cold pressor tests in patients with FM. The authors suggested that patients with FM exhibited an increased cholinergic or sudomotor activity and decreased adrenergic activity components of the peripheral sympathetic nervous system during specific stressor stimulus. Vaeroy et al. (5) also observed decreased sympathetic adrenergic response against auditive stimulation and cold pressor test in FM. Thieme et al. (6) recorded SCL in FM during mental and social stress. SCL of patients with FM were found higher than those of the controls. All these studies show that patients with FM exhibit an increased sympathetic cholinergic and decreased sympathetic adrenergic response to the stressor factor. The increased activity in the cholinergic fibers leads to increased sweat secretion and increased skin electrodermal conductance (3). Contradictory to these findings, Unlu et al. (4) notified lower SSR size in patients with FM than in controls, against stressor factors. Furthermore, Ulas et al. (2) reported that the SSR size in patients with FM was not different from that in the controls. In these two studies, whereas Ulas et al. (2) found longer SSR latency in patients with FM, Unlu et al. (4) found similar SSR latency in FM and control groups. Plasma catecholamine levels, an alternative measure of sympathetic activity, were found similar in patients with FM and in controls both at baseline (21) and after prolonged exercise (22). It is obvious that ANS dysfunction in FM is controversial. In the present study, as SSRs in patients with FM were not different from those in controls, we can speculate that patients with FM did not exhibit cholinergic hyperactivity or hypoactivity against stressor factors.

On the other hand, BDI and BAI scores were significantly higher in patients with FM than in controls although patients with FM had no depression or anxiety in the present study. It is known that in some psychiatric disorders, especially related to anxiety and depressive symptoms, exaggerated sympathetic activity at baseline and diminished sympathetic responses to stressor factor were observed (23-25). In a study by Unlu et al. (4), FM patients had moderate depression and severe anxiety scores compared to

Table 1. Demographic data of the patients with FM and control subjects.

	FM group (n=27) Mean±SD	Control group (n=18) Mean±SD	P
Age (years)	29.6±7.2	30.4±5.1	p>0.05
Height (cm)	161.9±5.5	161.6±6.8	p>0.05
Weight (kg)	59.4±9.8	59.6±6.8	p>0.05
VAS (0-100 mm)	72.3±12.9	0	
BDI	5.9±1.2	2.2±0.9	p<0.001
BAI	4.1±0.9	1.7± 0.8	p<0.001
DD (months)	34.3±33.9	0	

FM: Fibromyalgia; P: p value; VAS: Visual analog scale; DD: Duration of the disease; BDI: Beck depression inventory; BAI: Beck anxiety inventory.

Table 2. The chronic symptoms of the study groups.

	FM group (n=27)	Control group (n=18)
Chronic fatigue*	20 (74%)	0 (0%)
Easy tiring*	16 (59%)	1 (6%)
Weakness*	23 (85%)	2 (11%)
Sleep disturbances*	15 (56%)	3 (17%)
Waking up tired*	25 (93%)	3 (17%)
Severe headache*	12 (44%)	0 (0%)
Dizziness*	12 (44%)	0 (0%)
Dry mouth*	19 (70%)	0 (0%)
Dry eye*	15 (56%)	1 (6%)
Irritable bowel syndrome*	15 (56%)	2 (11%)
Functional dyspepsia	14 (52%)	5 (28%)
Severe dysmenorrhea	15 (56%)	7 (39%)
Excessive sweating	4 (15%)	0 (0%)
Raynaud's phenomenon	3 (11%)	0 (0%)

FM: Fibromyalgia; n: number; *: p<0.001

Table 3. The latency and amplitude of SSRs in patients with FM and control subjects.

	FM group (n=27)	Control group (n=18)	p
SSR latency (ms)	1361.1±127.5*	1378.9±138.8*	0.661
SSR amplitude (mV)	3.0 (0.5-11.3)**	3.5 (0.5-12)**	0.378

SSR: Sympathetic skin response; FM: Fibromyalgia; ms: Millisecond; n: Number; mV: Millivolt; *: Parameters were expressed as mean±SD; **: Parameters were expressed as median (minimal-maximal).

controls and exhibited decreased sympathetic cholinergic activity against stressor factors. In another study, in which cardiovascular reflex pathways of ANS dysfunction was evaluated by HRV, it was found that HRV values in patients with FM were lower than those in the controls (26). This result indicated that patients with FM had increased sympathetic activity at baseline. Concurrently, these patients had higher depression and anxiety scores than the controls. The studies (3,6) that observed sympathetic cholinergic hyperactivity against stressor factors, does not provide any information about the levels of depression and anxiety of patients with FM and controls.

Ozgocmen et al. (27) evaluated ANS with simultaneous measurements of HRV and SSR. They found lower HRV values during deep breathing in FM, whereas they did not find any difference in latency of SSR between patients with FM and controls. They left SSR amplitude out of analysis because of habituation. Ulas et al. (2) also measured both HRV and SSR in patients with FM. Though, their HRV results were same as the Ozgocmen et al.'s (27), SSR latency in patients with FM was longer than in controls. Ozgocmen et al. (27) also determined lower HRV values in patients with FM, most of whom concurrently had orthostatic intolerance, sleep disorders and sicca symptoms. Finally, they suggested that ANS dysfunction may be observed in FM and may account for some of the symptoms of this disorder. Cohen et al. (26) also reported that ANS dysfunction may be related to symptomatology, physical and psychological appearances of health status.

In the present study, FM patients had neither depression nor anxiety, nor some of those chronic symptoms related to autonomic nervous system dysfunction. Concurrently, there was no relation between SSRs, BDI, BAI, and VAS. We did not find sympathetic nervous system dysfunction in patients with FM by SSR recording. There may be two possible speculations for that result; first is that SSR may be an insufficient way of determining the whole ANS dysfunction as it only evaluates the sudomotor component and the second explanation is that the ANS dysfunction may be responsible for some of the chronic symptoms of FM and accompanying depression and anxiety (not observed in the present study) rather than taking part in the etiopathogenesis.

In conclusion, we did not find ANS dysfunction in patients with FM. It can be possible to determine the role of ANS in FM etiopathogenesis by studies evaluating the subsystems of ANS (cardiovascular reflex pathway, sympathetic cholinergic and adrenergic system etc.) in which chronic symptoms of FM, especially anxiety and depression, are also considered.

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