Autoimmune rheumatic disease associated symptoms in fibromyalgia patients and their influence on anxiety, depression and somatisation: a comparative study

S. Dönmez[1], Ö.N. Pamuk[1], E.G. Ümit[2], M.Ş. Top[3]

[1]Division of Rheumatology, [2]Department of Internal Medicine, Trakya University Medical Faculty, Edirne; [3]Department of Psychiatry, Edirne State Hospital, Edirne, Turkey.

Salim Dönmez, MD
Ömer Nuri Pamuk, MD, Assoc. Prof.
Elif Gülsüm Ümit, MD
Mehmet Şerif Top, MD

Please address correspondence to:
Dr Ömer Nuri Pamuk,
Eski Yildiz Cad. Park
Apt. no. 22 Daire: 18,
34349, Beşiktaş,
İstanbul, Turkey.
E-mail: omernpamuk@yahoo.com

Received on February 8, 2012; accepted in revised form on September 26, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 74): S65-S69.

Key words: fibromyalgia, systemic lupus erythematosus, anxiety, depression, somatisation

Competing interests: none declared.

ABSTRACT

Objective. *In this study we evaluated the frequency of autoimmune rheumatic disease associated major symptoms in fibromyalgia (FM) patients, and the association between their presence and anxiety, depression and somatisation.*

Methods. *Two hundred and thirty-two FM, 78 systemic lupus erythematosus (SLE) patients and 70 healthy controls were included. All subjects were questioned face-to-face for the presence of autoimmune rheumatic disease-associated symptoms and antinuclear antibody (ANA) was determined. All FM patients were questioned for the severity of pain and symptoms of FM by using a visual analogue scale. In addition, all subjects were interrogated for anxiety, depression, somatic symptoms and neuropathic pain by using different validated questionnaires.*

Results. *FM patients had significantly higher frequency of photosensitivity (27.6% vs. 11.4%) and Raynaud phenomenon (22% vs. 10%) when compared to controls (p-values, 0.005 and 0.026). FM patients had significantly lower frequencies of photosensitivity, oral ulcers, xerostomia, and xerophthalmia than SLE patients (all p-values <0.001). ANA positivity was 11.8% in FM patients and 7.1% in healthy controls. ANA-positive and negative FM patients had similar frequencies of autoimmune rheumatic disease symptoms. FM patients with photosensitivity had higher anxiety (p=0.002), somatic symptoms (p=0.015) and neuropathic pain (p=0.03) scores than others. FM patients with Raynaud had higher anxiety (p=0.004), depression (p=0.001), somatic symptom (p<0.001) and neuropathic pain scores than others.*

Conclusion. *The presence of which findings in FM seems to be associated with anxiety, depression, and somatisation rather than ANA positivity and disease severity.*

Introduction

The prevalence of fibromyalgia (FM) in the general population is nearly 10% and, in addition to its classical findings, it has many interesting symptoms. Some patients may have unexplainable medical symptoms which are usually associated with stress. FM patients are admitted to rheumatology outpatient clinics with these unexplainable symptoms together with widespread pain (1). Sometimes, these symptoms might coexist in autoimmune diseases and this might cause problems in differential diagnosis. In addition, there might be antinuclear antibody (ANA) positivity in some FM patients (2, 3).

Various studies reported that the frequency of ANA positivity varied between 8.8% to 30% in FM patients (2-5). Photosensitivity, Raynaud phenomenon (RP), oral ulcers, xerostomia and xerophthalmia which are frequent complaints in systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and systemic sclerosis (SSc) patients are relatively more common in healthy subjects. In order for these findings to be meaningful for diagnosis, they should be interpreted together with clinical and laboratory data. The differential diagnosis might be especially difficult in patients with relatively milder and unexplainable symptoms.

In this study, we evaluated the presence of anxiety, depression, somatic symptoms, and collagen tissue disease-associated symptoms in FM patients; and tried to determine whether there was any relationship among them. One group consisted of SLE patients and the other included healthy controls.

Methods

Two hundred and-thirty-two consecutive FM patients admitted to the Rheumatology Outpatient Clinics of Trakya University Medical Faculty between

January 2009 to December 2010 were included into the study. The diagnosis of FM was based upon ACR 1990 criteria (6). The control group was composed of 78 consecutive SLE patients who were admitted to our clinics within the same time frame and 70 healthy volunteers matched for age and sex. SLE patients were diagnosed according to previously-mentioned criteria (7). We included only females in this study because FM is most prevalent in women and content analysis scores from females allow a more correct prediction of psychological state than scores from males (8). Patients with a connective tissue disorder and patients who had psychiatric treatment within the last 6 months were not included in the FM group. Patients with a malignancy, chronic liver or chronic renal disease were also excluded. The study protocol was approved by our local ethical committee. All patients were informed about study design and gave verbal consent to take part in the study.

All patients' physical examinations were performed. Their sociodemographic characteristics and clinical findings were recorded down from hospital files. The education level, history of psychiatric disorder, life-style habits (smoking and alcohol intake), medications and marital status of the subjects were questioned. After getting informed consent, blood was obtained from all FM patients (204 cases) and healthy controls (56 cases); and ANA was determined with indirect immunofluorescent method. Titers at or above 1/80 were accepted to be positive. ANA results of SLE patients were obtained from medical charts. All ANA tests were evaluated in the same laboratory with same method by the same laboratory technician.

All patients and the control group were asked face-to-face whether they had photosensitivity, oral ulcer, RP, xerostomia or xerophthalmia. A visual analog scale (VAS) was used to question the severity of chronic widespread pain (CWP) and fatigue (0-100). In order to discriminate between neuropathic and nociceptive pain, the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale was used (9). This scale consists of 5 neuropathic sensory disturbance domains complemented by 2 sensory examination items. As FM causes widespread pain, there was no need for comparative sensory testing and sensory tests were not performed. The validation and reliability of the Turkish version of the LANSS scale was accomplished (10).

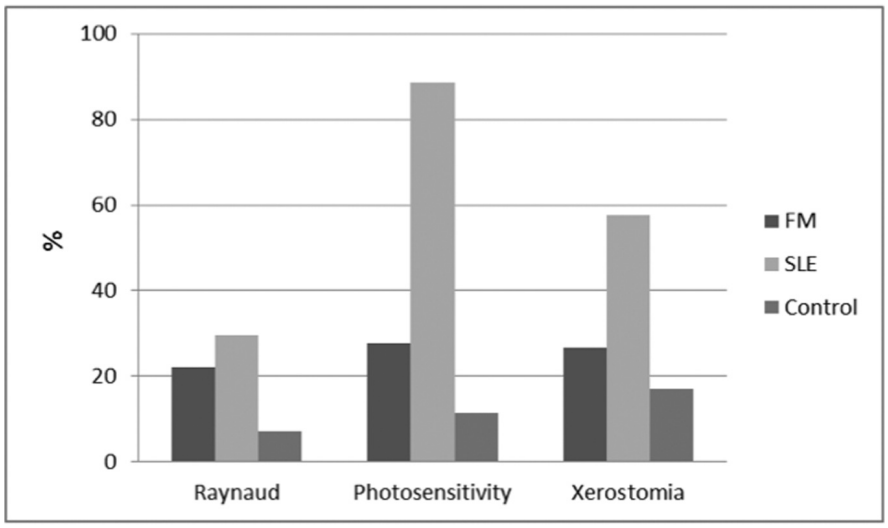

Fig. 1. The frequencies of Raynaud's phenomenon, photosensitivity and xerostomia in FM, SLE and control groups.

The Hospital and Anxiety Depression Scale (HADS) (11) and the physical function items of the FIQ scale (12) were administered to all patients. The HADS consists of two subscales, one assessing anxiety and the other depression, and it was originally developed to rate anxiety and depression in patients with physical illnesses. The reliability and validity of the Turkish version of HADS has been established in Turkish patients (13). The Turkish validation and reliability of the FIQ score was performed by Sarmer et al. (14).

We used the Somatic Symptom Checklist (SSC), consisting of 7 items, to screen for a somatisation disorder (15). The 7 items in SSC are; trouble breathing, frequent vomiting, loss of voice for more than 30 minutes, being unable to remember what you have been doing for hours and days (without any alcohol or drug intake), difficulty in swallowing, frequent pain in the fingers or toes, and frequent trouble with menstrual cramps. SSC was validated as a screening test for somatisation disorders (15) and the American Psychiatric Association uses these symptoms as its criteria for somatisation disorders (16). The total score ranges from 0 to 7.

Chi-square test was used to compare the categorical variables of 3 groups. When comparing the data of 3 groups, one-way variance analysis and *post hoc* Tukey test were used. The unpaired *t*-test was used to compare the quantitative variables of 2 groups.

Results

SLE patients had significantly higher frequencies of photosensitivity, oral ulcer, xerostomia and xerophthalmia when compared to FM patients and control group (all *p*-values <0.001). RP was significantly higher in SLE patients than in controls (p=0.001), however, it was as frequent in FM patients as in SLE patients (22% *vs*. 29.5%, p=0.18) (Fig. 1).

FM patients had significantly higher frequencies of photosensitivity (27.6% vs. 11.4%, p=0.005) and RP (22% vs. 10%, p=0.026) than the control group. The frequencies of oral ulcer, xerostomia, and xerophthalmia were similar in FM patients and in controls (all *p*-values >0.05). The frequencies of different autoimmune rheumatic disease symptoms are seen in Table I.

When compared to FM patients (11.8%) and control group (7.1%), SLE patients (98.7%) had a significantly higher frequency of ANA positivity (*p*-values <0.001). ANA positivity was similar in FM patients and in healthy controls

Table I. The frequencies of autoimmune rheumatic disease-associated symptoms in our groups.

	FM	SLE	Control
n	232	78	70
Age, years	39.4 ± 9.1	39.8 ± 11.2	37.6±7.3
Photosensitivity, n (%)	64 (27.6)	69 (88.5)	8 (11.4)
Raynaud phenomenon, n (%)	51 (22)	23 (29.5)	7 (10)
Oral ulcer, n (%)	64 (27.6)	54 (69.2)	16 (22.9)
Dry mouth, n (%)	62 (26.7)	45 (57.7)	12 (17.1)
Dry eyes, n (%)	71 (30.6)	51 (65.4)	17 (24.3)
ANA positivity, n (%)*	24 (11.8)	77 (98.7)	4 (7.1)

*ANA test was available in 204 FM patients and 56 healthy controls.
FM: fibromyalgia; SLE: systemic lupus erythematosus; ANA: antinuclear antibody.

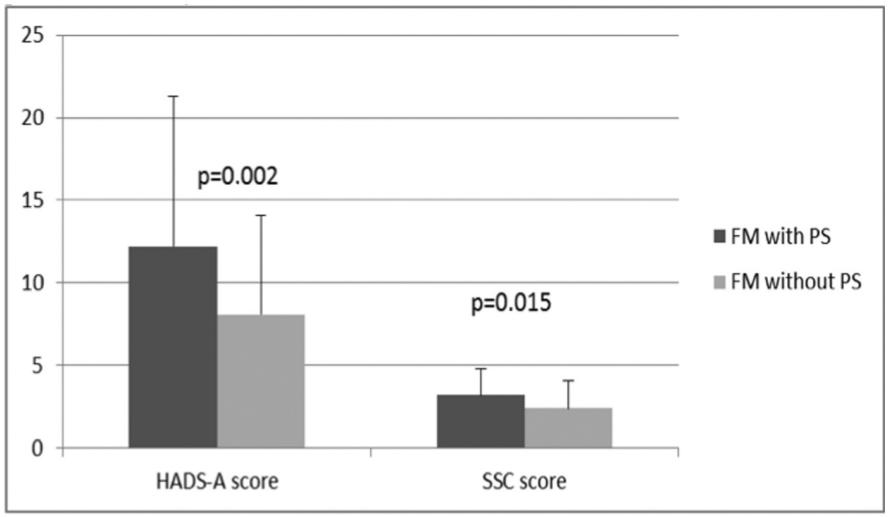

Fig. 2. The mean scores of HADS-A and SSC in FM patients with and photosensitivity. (PS: photosensitivity).

Table II. The comparison of FM patients with and without photosensitivity.

	FM with photosensitivity	FM without photosensitivity	*p*-value
Age, years	40.4 ± 8.8	39.1 ± 9.2	0.3
HADS-Anxiety score	12.2 ± 9.1	8.1 ± 6	0.002
HADS-Depression score	6.5 ± 2.6	6.03 ± 2.4	0.17
FIQ score	1.09 ± 0.69	1.28 ± 0.76	0.15
SSC score	3.23 ± 1.6	2.45 ± 1.7	0.015
Neuropathic pain score	3.8 ± 2.7	2.6 ± 2.3	0.03
Fatigue score (0-100)	50.8 ± 23.9	54.9 ± 25.4	0.37
Pain score (0-100)	53 ± 20.2	56.3 ± 19.7	0.35

FIQ: fibromyalgia impact questionnaire; SSC: somatic symptom checklist.

(p >0.05). The frequencies of connective tissue disease symptoms were not significantly different in ANA-positive and ANA-negative FM patients (p-values >0.05).

FM patients with photosensitivity had significantly higher HADS-A scores (p=0.002), SSC scores (p=0.015) and LANSS neuropathic pain scores (p=0.03) than others; HADS-D, FIQ, pain and fatigue scores were similar (Fig. 2). The comparison of mean scores of different questionnaire in FM patients with and without photosensitivity are seen in Table II.

FM patients with RP had significantly higher HADS-A (p=0.004), HADS-D (p=0.001), SSC (p<0.001), and LANSS neuropathic pain scores (p=0.02); and they were significantly younger (p=0.045) (Fig. 3). The comparison of mean scores of different questionnaire in FM patients with and without RP are seen in Table III.

FM patients with xerostomia had significantly higher HADS-A (13.2±10.4 *vs*. 8±5.1, p=0.001) and SSC (3.3±1.9 *vs*. 2.5±1.6, p=0.01) scores; and they were significantly older (41.4±8.5 *vs*. 38.6±9.2, p=0.03). LANSS neuropathic pain and FIQ scores of the groups were similar.

FM patients with xerophthalmia had significantly higher HADS-A (12±9.7 *vs*. 8.2±5.6, p=0.005) and SSC (3.2±1.8 *vs*. 2.5±1.6, p=0.044) scores than others; and they were significantly older (41.6±8 *vs*. 38.4±9.4, p=0.015). LANSS neuropathic pain and FIQ scores were similar. FM patients with and without oral ulcers were not significantly different from each other (p-values >0.05).

Control subjects who had xerostomia and xerophthalmia were significantly older than other subjects (p-values >0.05). Controls with oral ulcers had significantly higher HADS-A scores (p=0.008). When HADS-A, HADS-D, neuropathic pain and SSC scores of SLE patients with and without symptoms were compared, no significant differences were detected between the groups (p-values >0.05).

Discussion

Our study which aimed to reveal the frequencies of SLE and other connective tissue disease symptoms in FM patients, reported significantly higher frequencies of photosensitivity and RP in FM patients when compared to healthy controls. It is well-known that FM patients with widespread pain are frequently admitted to rheumatology outpatient clinics, and they might pose diagnostic problems with milder forms of connective tissue diseases. Studies reported higher frequencies of unexplained medical complaints in FM; however, there has been no study investigating the association between connective tissue disease symptoms versus distress and somatisation. Our FM patients had more frequent xerostomia, xerophthalmia, and oral ulcers than controls; but, the differences were nonsignificant. In

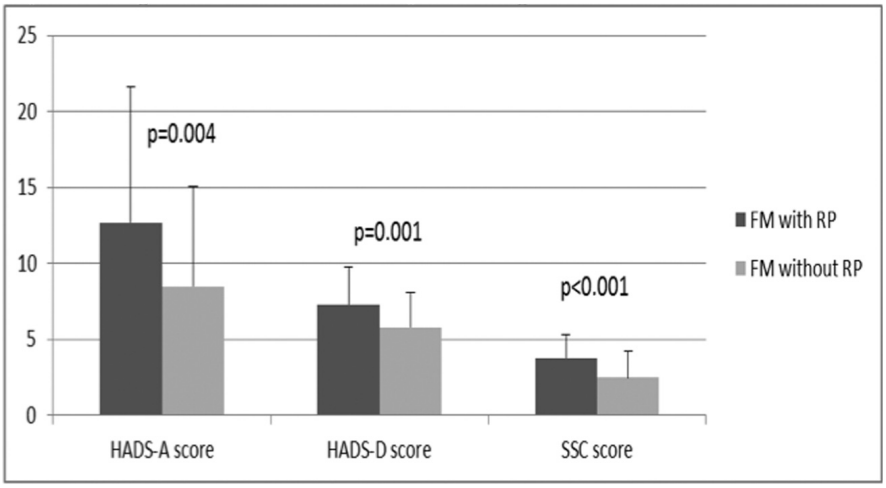

Fig. 3. The mean scores of HADS-A, HADS-D and SSC in FM patients with and without Raynaud's phenomenon (RP: Raynaud's phenomenon).

Table III. The comparison of FM patients with and without Raynaud's phenomenon.

	FM with Raynaud	FM without Raynaud	*p*-value
Age, years	36.9 ± 10.3	40.1 ± 8.6	0.045
HADS-Anxiety score	12.7 ± 8.9	8.5 ± 6.6	0.004
HADS-Depression score	7.3 ± 2.5	5.88 ± 2.3	0.001
FIQ score	13.9 ± 6.7	12 ± 7.6	0.19
SSC score	3.8 ± 1.5	2.5 ± 1.7	<0.001
Neuropathic pain score	4.4 ± 2.5	2.7 ± 2.4	0.02
Fatigue score	60.6 ± 21	52.6 ± 25.7	0.1
Pain score	55.8 ± 19.7	55.5 ± 19.7	0.93

FIQ: fibromyalgia impact questionnaire; SSC: somatic symptom checklist.

SLE patients, as expected, all symptoms – except RP – were more frequent than in FM patients and controls.

In our study, ANA positivity in the FM group (11.8%) was not different from controls. ANA-positive and ANA-negative groups were similar in their autoimmune rheumatic disease symptoms. Various studies investigated ANA frequency and its clinical importance in FM patients. Yunus *et al*. (3) stated that frequencies of ANA positivity (11.5%) and RP (8.8%) in FM patients were similar to controls; however, FM patients had a more frequent xerostomia (12%) when compared to controls. In the study of Dinerman *et al*. (4), the frequencies of ANA positivity, RP, and sicca symptoms were respectively, 14%, 30%, and 18%. In the above-mentioned study, none of the patients developed connective tissue disease. In a study by Smart *et al*. (5), ANA positivity in FM patients was as high as 30%. One recent study, on the other hand, reported ANA positivity to be 8.8% in FM patients which was similar to controls with osteoarthritis (2). The results of all ANA tests were at a low titer. Similar to the results in our study, the above-mentioned study found no significant difference in the frequencies of autoimmune rheumatic disease symptoms between ANA-positive and ANA-negative groups. In the same study, after a follow-up of 2-4 years, one ANA-positive FM patient fulfilled SLE criteria and one ANA-negative patient fulfilled Sjögren's syndrome criteria. None of the patients in our study fulfilled diagnostic criteria for SLE or Sjögren's syndrome and we did not have follow-up data. Calvo-Alen *et al*. (17) observed that 24% of patients who had been referred to a tertiary centre with a prediagnosis of SLE, were found out to have ANA-positive FM.

There is widespread pain in FM and a combination of some symptoms and conditions which make diagnosis and treatment more difficult (18). Although FM is a well-known clinical entity, a recent study stated that differential diagnosis of FM with connective tissue diseases could pose a challenge resulting in misdiagnosis (19). Another problem might be presence of FM in other rheumatic diseases. Kapoor *et al*. (20) reported that FM was common in RA and that FM was caused by low mood instead of joint damage in RA. It is well appreciated that depression, anxiety, stress are associated with FM. A recent study stated that the severity of FM is associated with depression, anxiety and stress (alok3). In this study, we investigated whether the severity of anxiety, depression and somatisation influenced FM patients' reporting of CTD symptoms

We compared our FM patients with significantly higher frequencies of photosensitivity and RP than controls, with the others. Interestingly, we observed that FM-related pain, fatigue, FIQ functional item scores had no association with ANA positivity, photosensitivity or RP. Another remarkable result was that photosensitivity was associated with anxiety and somatisation; RP was associated with anxiety, depression and somatisation. As a result, it might be suggested that the probability of positively responding to connective tissue disease symptoms in FM patients is related with the presence of anxiety, depression, and somatisation which set the stage for FM. Anxiety, depression and somatisation scores of SLE patients with photosensitivity and RP were similar to scores of others. Therefore, although these patients with intensive distress, somatisation responded positively to connective tissue disorder questions, it would not be meaningful to undertake further investigations in these patients.

One limitation of our study might be the absence of longitudinal follow-up data about connective tissue disease-related symptoms. However, our cross-sectional study presents valuable data about SLE and other connective tissue disease symptoms in FM patients. Another limitation was the inclusion of FM patients with widespread pain who

were referred to our hospital. Therefore, we might have diagnosed more frequent depression and somatisation in our FM patients. Results obtained by screening patients with widespread pain in the general population could be reliable. It is anticipated that patients with widespread pain, FM who come to hospital quite frequently would have more frequent depression, anxiety, and somatisation. Nevertheless, it is difficult to reach a patient sample reflecting the whole population. The other limitation of our study was the usage of only a validated questionnaire for a psychiatric diagnosis of anxiety and depression. A structured psychiatric interview (*i.e.* SCID-I) could have been better.

As a result, it should be borne in mind that connective tissue disease symptoms, especially RP and photosensitivity, could exist at a higher frequency in a patient group with widespread pain. The presence of higher frequencies of RP and photosensitivity in a widespread pain patient group who has somatisation, anxiety, and depression might suggest that extreme caution should be exercised in the diagnosis of autoimmune rheumatic disease in patients with primarily psychiatric symptoms.

References

1. CLAUW DJ, CROFFORD LJ: Chronic widespread pain and fibromyalgia: what we know, and what we need to know. *Best Prac Res Clin Rheumatol* 2003; 17: 685-701.
2. AL-ALLAF AW, OTTEWELL L, PULLAR T: The prevalence and significance of positive antinuclear antibodies in patients with fibromyalgiasyndrome: 2-4 years' follow-up. *Clin Rheumatol* 2002; 21: 472-7.
3. YUNUS MB, HUSSEY FX, ALDAG JC: Antinuclear antibodies and autoimmune rheumatic diseasefeatures in fibromyalgia syndrome: a controlled study. *J Rheumatol* 1993; 20: 1557-60.
4. DINERMAN H, GOLDENBERG DL, FELSON DT: A prospective evaluation of 118 patients with the fibromyalgia syndrome: prevalence of Raynaud's phenomenon, sicca symptoms, ANA, low complement, and Ig deposition at the dermal-epidermal junction. *J Rheumatol* 1986; 13: 368-73.
5. SMART PA, WAYLONIS GW, HACKSHAW KV: Immunologic profile of patients with fibromyalgia. *Am J Phys Med Rehabil* 1997; 76: 231-4.
6. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
7. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
8. FREE NK, WINGET CN, WHITMAN RM: Separation anxiety in panic disorder. *Am J Psychiatry* 1993; 150: 595-9.
9. BENNETT M: The LANSS pain scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 2001; 92: 147-57.
10. YUCEL A, SENOCAK M, ORHAN EK, CIMEN A, ERTAS M: Results of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale in Turkey: a validation study. *J Pain* 2004; 5: 427-32.
11. ZIGMOND AS, SNAITH PR: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-70.
12. BURCKHARDT CS, CLARK SR, BENNETT RM: The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 1991; 18: 728-33.
13. AYDEMIR Ö: Hastane anksiyete ve depresyon ölçeği Türkçe formunun geçerlilik ve güvenilirlik çalışması. *Türk Psikiyatri Dergisi* 1997; 8: 280-7.
14. SARMER S, ERGIN S, YAVUZER G: The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. *Rheumatol Int* 2000; 20: 9-12.
15. OTHMER E, DESOUZA C: A screening test for somatization disorder. *Am J Psychiatry* 1985; 142: 1146-9.
16. American Psychiatric Association. American Psychiatric Association diagnostic and statistical manual. Washington DC: American Psychiatric Association, 1980.
17. CALVO-ALÉN J, BASTIAN HM, STRAATON KV, BURGARD SL, MIKHAIL IS, ALARCÓN GS: Identification of patient subsets among those presumptively diagnosed with, referred, and/or followed up for systemic lupus erythematosus at a large tertiary care center. *Arthritis Rheum* 1995; 38: 1475-84.
18. BAZZICHI L, SERNISSI F, CONSENSI A, GIACOMELLI C, SARZI-PUTTINI P: Fibromyalgia: a critical digest of the recent literature. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S1-11.
19. DI FRANCO M, IANNUCCELLI C, BAZZICHI L *et al*.: Misdiagnosis in fibromyalgia: a multicentre study. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S104-8.
20. KAPOOR SR, HIDER SL, BROWNFIELD A, MATTEY DL, PACKHAM JC: Fibromyalgia in patients with rheumatoid arthritis: driven by depression or joint damage? *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S88-91.
21. ALOK R, DAS SK, AGARWAL GG, SALWAHAN L, SRIVASTAVA R: Relationship of severity of depression, anxiety and stress with severity of fibromyalgia. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S70-2.