

CORRELATIONS BETWEEN CLINICAL MANIFESTATION IN PATIENTS WITH PRIMARY AND SECONDARY FIBROMYALGIA

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Abstract

Fibromyalgia (FM) is widespread and covers different age groups, most commonly occurring between 20 and 50 years. Patients with rheumatic diseases – osteoarthritis (OA) and systemic lupus erythematosus (SLE), have an accompanying/secondary FM. The presence of secondary fibromyalgia in SLE and OA has been investigated by various authors and is found in approximately 20% of these patients. The purpose of this clinical trial is to analyze correlations under clinical manifestations of primary vs. secondary FM. The present study is prospective and has been performed at the Clinic of Rheumatology of University Hospital “St. Ivan Rilski” and “Focus 5” Center, Sofia for the period September 2013 – September 2017. Eighty-three patients with primary FM, 39 patients with FM + OA, 23 patients with FM + SLE, 27 patients with SLE and 36 healthy subjects were included. The present study compared chronic pain, depression and anxiety in patients with primary FM, and patients with SLE, OA and secondary FM based on the 2016 criteria for fibromyalgia. The comparison between the patient groups is important for the evaluation of the disease activity and the treatment that will be recommended.

Key words: primary and secondary fibromyalgia, SLE, osteoarthritis

Introduction. Fibromyalgia (FM) is characterized by a chronic widespread pain, general fatigue, anxiety, depression, sleep disturbances, and functional disorders. FM affects both women and men in 9:1 to 20:1 ratio. It affects 7 to 10

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million people in the USA, which accounts for 3 to 6% of the population. There is no definite ethnic predisposition [1].

In 2016, the American College of Rheumatology (ACR) developed new diagnostic criteria based on the presence of chronic widespread pain in more than 7 out of 19 body areas over the past 3 months and accompanying clinical symptoms (severity scale (SS) – fatigue, unrefreshing sleep, cognitive symptoms) [2].

The diagnosis of primary fibromyalgia implied the presence of clinical characteristics of fibromyalgia with no recognizable cause. The diagnosis of secondary fibromyalgia was established when the clinical symptoms of FM were secondary to subjacent rheumatologic diseases, or when it coexisted with another disorder. Osteoarthritis, systemic lupus erythematosus and other diseases have often been and continue to be associated with fibromyalgia.

The association of FM with SLE has been investigated by several authors. The incidence rate of secondary FM in SLE patients is around 20%. This number is much greater than in the general population. According to DE ARAUJO et al. [3], there is a significant difference in the number of chronic pain areas between the FM-only group and the combined FM and SLE group. More tender points (15.05) are found in the FM group, and in the FM and SLE group they are 11.75 ($p = 0.0001$). The severity of chronic pain in the FM group is 87.5 mm on VAS. SLE-only patients rated chronic pain with 35 mm on VAS. Patients with both FM and SLE reported severity of chronic pain of 71.25 mm on VAS. Depressive episodes are more common in patients with FM (80%) and with FM and SLE (60%) than in those with SLE only (15%) [3].

DI FRANCO et al. [4] demonstrated a clear association between chronic pain in fibromyalgia and SLE patients and assessed fatigue and quality of life in SLE patients.

According to MARCHIONE [5], 13% of patients with osteoarthritis suffer from FM. The treatment of FM costs 8453 USD and 11253 USD for OA, including healthcare, absence from work, medication, etc.

Material/patients and methods. We present a prospective study in fibromyalgia patients conducted at the Clinic of Rheumatology of University Hospital “St. Ivan Rilski” and Medical center “Focus 5” in Sofia, between September 2013 and September 2017.

The aim of this clinical trial is to study correlations in clinical manifestations in patients with primary or secondary fibromyalgia (FM) compared with a control group of healthy volunteers.

Objectives:

1. To study the clinical manifestations of primary or secondary FM in patients with systemic lupus erythematosus (SLE) and osteoarthritis (OA) compared with a control group of healthy volunteers.

2. To analyse correlations in clinical manifestations of primary vs. secondary fibromyalgia – pain, chronic fatigue, anxiety, depression.

The history of disease course was investigated in terms of:

- gender distribution;
- mean age of patients;
- age of onset of first symptoms;
- disease duration;
- education level of patients;
- possible etiological factors for disease occurrence.

1. Mean age and gender distribution of patients from all groups and healthy individuals

- » 83 patients, 78 women and 5 men, with primary FM, mean age 40.67 ± 11.15 years;
- » 39 women with fibromyalgia and osteoarthritis, mean age 50.77 ± 10.73 years;
- » 23 patients, 22 women and one man with SLE and fibromyalgia, mean age 47.9 ± 8.86 years, with SLEDAI activity score of 4–6 points, without involvement of vital organs and systems and without neurolupus;
- » 27 patients, 25 women and two men with SLE, mean age 46.96 ± 11.7 years with SLEDAI activity score of 4–6 points without involvement of vital organs and systems and without neurolupus;
- » 36 healthy individuals, 30 women and 6 men, mean age 46.53 ± 9.9 years.

Additional information about patient groups included etiological factors for disease occurrence and duration of FM. Summarized data are presented in Table 1.

Research methods.

Clinical methods:

1. Evaluation of the diagnosis of fibromyalgia according to the 2016 ACR criteria based on presence of chronic widespread pain in more than 7 out of 19 body areas over the past 3 months, and accompanying clinical symptoms (fatigue, unrefreshing sleep, cognitive symptoms) of 7 or higher score from the combined scale (Severity Scale, SS) [2].

2. Assessment of fatigue on the physical, cognitive and psychosocial MFIS subscales. Fatigue in FM patients was assessed by the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS). The scales have physical, cognitive and psychosocial subscales with questions related to change in physical activity, cognitive function and social contacts. Patients answered the scales using scores within a range [6].

3. Assessment of anxiety and depression on the HADS scale for anxiety and depression. HADS focuses on non-physical symptoms so that it can be used to diagnose anxiety and depression in people with significant physical ill-health. The HADS questionnaire has seven items each for depression and anxiety subscales. A total subscale score of > 8 points out of possible 21 denotes considerable symptoms of anxiety or depression [7].

T a b l e 1
Demographic and clinical variables of study population

Patient group	Primary fibromyalgia	Fibromyalgia and osteoarthritis	Fibromyalgia and SLE	SLE	Healthy subjects
Number of patients	83	39	23	27	36
Number /% female	78 / 94%	39 / 100%	22 / 95.7%	25 / 92.6%	30 / 83.3%
Number /% male	5 / 6%	0 / 0%	1 / 4.3%	2 / 7.4%	6 / 16.7%
Patient age (years), mean $\pm$ SD (range)	40.68 $\pm$ 11.15	50.77 $\pm$ 10.73	47.9 $\pm$ 8.86	46.96 $\pm$ 11.7	46.53 $\pm$ 9.9
Duration of FM	4.2 $\pm$ 3.2	7 $\pm$ 4.9	5.17 $\pm$ 3.38	–	–
Mean age in the beginning of FM (years) $\pm$ SD (range)	36.53 $\pm$ 10.32	43.2 $\pm$ 10.0	42.9 $\pm$ 7.58	–	–
Reason for FM					
Mental reason	81.9	69.2	82.6	–	–
Physical reason	15.7	30.8	17.4	–	–
Lack of work	2.4	0	0	–	–
Summary	100	100	100	–	–
Education					
Elementary education	2	3	2	2	2
Average education	36	15	10	14	15
Higher education	42	18	8	8	18
Professional education	3	3	3	0	1

4. Assessment of SLEDAI-2K. The SLEDAI-2K includes evaluation of specific manifestations in nine organ systems. Weighting is used, resulting in individual item scores ranging from 1 to 8, which are simply added to give a global score ranging from 0 to 105. Lupus HDA (high disease activity) has been defined as an SLEDAI-2K score greater than 6. Similarly, lupus LDA (low disease activity) state has been defined as less than or equal to 4, with no activity in major organ systems [8].

Informed consent was obtained from all patients for being included in the study.

This paper received ethics approval by the Ethics Commission of Medical Research at the Medical University of Sofia, No. 237/15.01.2015.

Statistical methods. The data were analyzed using Windows SPSS 16.0 statistical software platform. For all comparisons, a significance level of $p < 0.05$ was chosen at which the null hypothesis was rejected. The quantitative values are presented as arithmetic mean $\pm$ SD.

A non-parametric Kolmogorov–Smirnov test was used to determine the type of distribution. For a correct distribution, parametric methods were used, including Student’s t -test, variance analysis, correlation analysis. In case of incorrect distribution or homogeneity of variables, non-parametric methods were used, including Mann–Whitney test, Kruskal–Wallis test, and Chi-square test.

Results.

Results from multiple correlation analysis of diffuse pain and Modified Fatigue Impact Scale (MFIS) score for chronic fatigue in all patient groups. Figure 1 shows the results from multiple correlation analysis of diffuse pain and MFIS score for chronic fatigue. The analysis shows statistically significant correlation between SLE+FM ($r = -0.2$, $p < 0.05$) and primary FM patient groups ($r = -0.03$, $p < 0.05$), compared with healthy volunteers, i.e. diffuse pain and chronic fatigue are in a strong correlation compared with healthy volunteers. There is no statistically significant correlation between OA+FM, SLE and healthy volunteers groups, and between SLE+FM and SLE patient groups.

Results from multiple correlation analysis of diffuse pain and Hospital Anxiety and Depression Scale (HADS) score for anxiety in all patient groups and healthy volunteers. Figure 2 shows the results from multiple correlation analysis of chronic diffuse pain and HADS score for anxiety in all patient groups. A statistically significant correlation has been shown between OA+FM ($r = 0.26$, $p < 0.05$) and primary FM patient groups ($r = -0.12$, $p < 0.05$) compared with healthy volunteers. The correlation is positive, i.e. lower diffuse pain is associated with lower HADS score for anxiety. A statistically significant correlation has also been shown between OA+FM and primary FM patient groups.

Results from multiple correlation analysis of diffuse pain and HADS score for depression in all patient groups and healthy volunteers. Figure

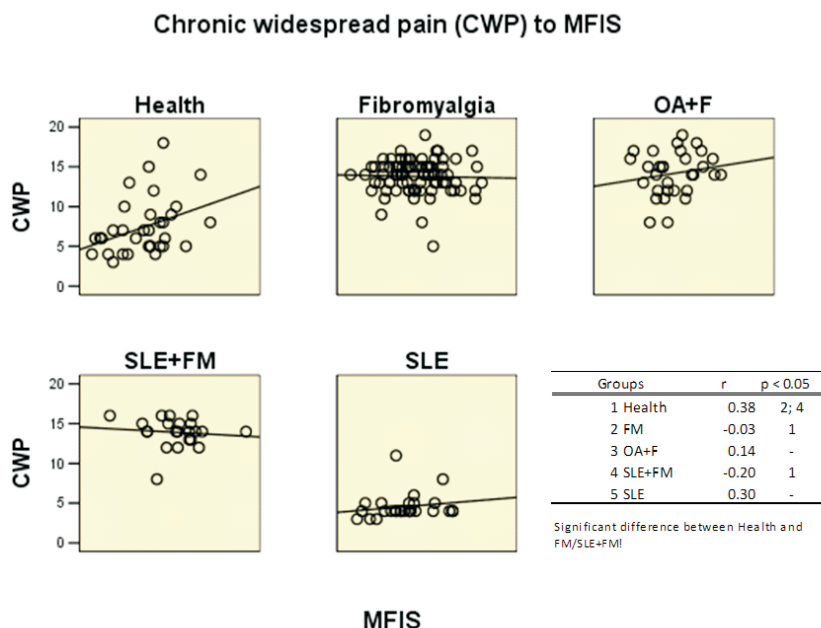


Fig. 1. Multiple correlation analysis of diffuse pain and MFIS score for chronic fatigue in all patient groups and healthy volunteers

3 shows the results from multiple correlation analysis of diffuse pain and HADS score for depression in all patient groups. A statistically significant correlation has been shown between healthy volunteers and primary FM patient group ($r = 0.02$, $p < 0.05$), and the difference is larger between the two groups. All correlations are positive, i.e. higher level of diffuse pain is associated with higher level of HADS score for depression. There is no statistically significant correlation between SLE+FM, SLE, OA+FM and healthy volunteers groups, and between SLE+FM and SLE patient groups.

Results from multiple correlation analysis of MFIS score for chronic fatigue and HADS score for depression in all patient groups and healthy volunteers. A statistically significant correlation has been shown between SLE+FM group and healthy volunteers ($r = 0.03$, $p < 0.05$) and the correlation is positive, i.e. lower MFIS score for chronic fatigue is associated with lower HADS score for depression. A statistically significant correlation has been shown between SLE+FM, OA+FM and SLE patient groups, indicating that FM is the leading cause for higher level of MFIS chronic fatigue and higher level of HADS score for depression. In this case, SLE does not have a strong impact on MFIS chronic pain and HADS depression scores.

Chronic widespread pain (CWP) to HADS - anxiety

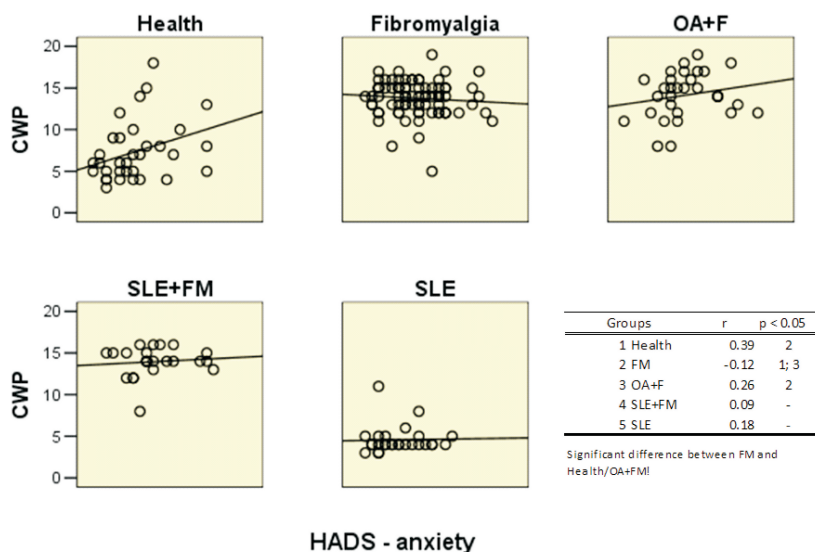


Fig. 2. Multiple correlation analysis of diffuse pain and HADS score for anxiety in all patient groups and healthy volunteers

Results from multiple correlation analysis of HADS score for anxiety and HADS score for depression in all patient groups and healthy volunteers. No significant correlation has been found between patient groups and healthy volunteers' results from multiple correlation analysis of HADS score for anxiety and HADS score for depression in all patient groups and healthy volunteers – correlation is similar in all groups. All correlation coefficients for the correlation between HADS score for anxiety and HADS score for depression are strongly positive, i.e. higher level of anxiety is associated with a higher level of depression.

Discussion. Chronic pain syndromes, such as chronic headache, temporomandibular disorder, fibromyalgia, irritable bowel syndrome, interstitial cystitis/painful bladder, pelvic pain, etc., have similar mechanisms of genesis and development. In patients with visceral pain syndrome, it is not unusual for visceral pain to subside and then symptoms of fibromyalgia to become more noticeable. Chronic pain is combined with other somatic symptoms, including fatigue, poor sleep quality, cognitive impairments and mood swings. The diagnostic characteristics of other clinical symptoms, such as chronic pain syndrome/myalgic encephalomyelitis, include musculoskeletal pain. This often results in many different diagnoses, which may lead to numerous tests that could increase anxiety and have negative impact on patients. [3, 4, 6, 9].

Chronic widespread pain (CWP) to HADS - depression

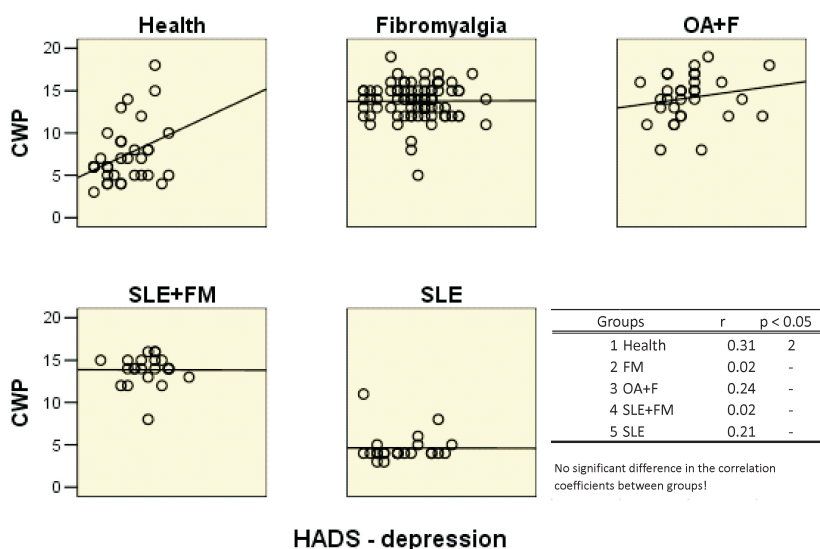


Fig. 3. Multiple correlation analysis of diffuse pain and HADS score for depression in all patient groups and healthy volunteers

Approximately 15–30% of patients with autoimmune rheumatic disease have concomitant fibromyalgia syndrome, also known as secondary FM. This proportion is higher than the incidence rate of FM in the general population (2%). Pain, stress and concomitant chronic rheumatic disease may trigger pathophysiological mechanisms of FM. Fibromyalgia is a confounding factor for diagnosis and assessment of rheumatic disease activity [2].

Results from analysis conducted by ZAUTRA et al. [10] has shown that chronic fatigue and diffuse pain are not associated with pain in a specific joint in OA. Patients with OA report of more consistent fatigue during the course of underlying disease + FM. Patients with FM report of higher peaks of fatigue on different days which is associated with the central regulation of neuropathic pain in FM that is different from the pain regulation mechanism in OA [10]. In our patients with OA+FM, there is a moderate positive correlation with a significant correlation coefficient between HADS score for anxiety and depression, and chronic fatigue.

Depression is a common disorder. One of five people has depression at some time in their life. Depression is twice as common in women as in men. The higher level of depression in women requires medical attention. Depression may worsen during the course of a chronic disease or a chronic disorder. It has been reported that physical impairments can increase during depression. Gonarthrosis, FM and

rheumatoid arthritis are the disorders with the most significant impact [9].

According to our results, moderate positive correlation has been observed in patients with primary FM, with a significant correlation coefficient between depressive episodes assessed using the depression scales HADS ($p < 0.05$) and between chronic diffuse pain and all symptoms in FM and depression.

According to YILMAZ et al. [9] there is no correlation between depression and intensity of pain in gonarthrosis. In patients with primary FM, depression is associated with overall disease activity. The level of depression should be assessed and treated appropriately [9, 11].

Our results from the assessment of FM impact on SLE and OA have also shown that it has the same impact on patient's life both in primary and in secondary FM, with a tendency to worsen daily activities and social life both in patients with a minimum score of 16 and in those with a maximum score of 110. The presence of another rheumatic disease SLE or OA does not change the impact of fibromyalgia on patient's life [12].

An individual approach for patient management and education is required in order to improve other symptoms in FM. Therefore primary care in the family is important for treatment success. Future clinical follow-up must focus to find the most effective treatment for the patient with FM, considering his/her clinical characteristics, and the selection of the most efficient combination therapy for the symptoms. Comprehensive treatment of patients with FM aims to achieve clinical improvement and better quality of life.

Conclusions. 1. Patients with primary fibromyalgia, osteoarthritis and FM, systemic lupus erythematosus and FM, have comparable pain intensity and comparable impact of fibromyalgia on daily activities.

2. Patients with SLE and no fibromyalgia have a higher threshold of pain and lower level of fatigue, comparable to the symptoms of patients with SLE+FM and healthy volunteers.

3. Patients with SLE and fibromyalgia have further symptoms of moderate pain and fatigue which are not associated with SLE and require FM treatment as add-on to SLE therapy.

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