ANXIETY AND DEPRESSION IN PATIENTS WITH PRIMARY AND SECONDARY FIBROMYALGIA IN BULGARIA

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Abstract. Fibromyalgia (FM) is characterized by chronic widespread pain, general fatigue, anxiety, depression, sleep disturbances and functional disorders. FM affects both women and men in a 9:1 to 20:1 ratio. Osteoarthritis, systemic lupus erythematosus and other diseases have often been and continue to be associated with FM. The incidence rate of secondary FM in SLE and OA patients is around 20%. This clinical study aims to analyze anxiety and depression in patients with primary and secondary FM. In the prospective study, eighty-three patients with primary FM, 39 patients with FM and osteoarthritis (OA), 23 patients with FM and systemic lupus erythematosus (SLE), 27 patients with SLE and 36 healthy subjects were included. The present study compared chronic pain, anxiety and depression in patients with primary FM, patients with SLE, FM + OA, FM + SLE and healthy subjects. Based on the HADS clinical parameter, anxiety and depression were at a statistically significant difference in the control group as compared to patients with primary FM, FM + OA, FM + SLE \( (p<0.05) \) and no difference in patients with SLE \( (p = 0.77) \). There was no significant difference in HADS depression scores between the three groups of FM patients. There was no significant difference in terms of the clinical parameter of depression between the SLE and FM + SLE groups. The comparison between the patient groups is important to evaluate the disease activity and the treatment to be recommended.

Key words: fibromyalgia, pain, anxiety, depression

Ethical standards. All procedures followed are in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008.

INTRODUCTION

Fibromyalgia (FM) is characterized by chronic widespread pain, general fatigue, anxiety, depression, sleep disturbances and functional disorders. FM affects both women and men in a 9:1 to 20:1 ratio. It affects 7 to 10 million people in the USA, which accounts for 3 to 6% of the population. There is no definite ethnic predisposition. There are no epidemiological data on the prevalence of FM in Bulgaria [1].

In 1990, a new group of criteria was published under the aegis of ACR. The association of generalized pain and at least 11 tender points sensitive to digital pressure out of 18 possible locations was found to be conclusive in identifying FM patients, with a sensitivity of 88.4%, a specificity of 81.1% and a precision of 84.9% [1].

In 2016, 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, unrefreshed sleep, cognitive symptoms) [1].

The diagnosis of primary FM implied the presence of clinical characteristics of FM with no recognizable cause. The diagnosis of secondary FM 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 FM.

Several authors have investigated the association of FM with SLE. The incidence rate of secondary FM in SLE patients is around 20%. This number is much greater than in the general population.

According to Ana Luiza P. Kasemodel de Araujo, 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 \( (p = 0.0001) \) [2].

According to Marchione V, 13% of patients with osteoarthritis suffer from FM. The treatment of FM costs 8,453 USD and 11,253 USD for OA, including healthcare, absence from work, and medication [6].
Anxiety is one of the symptoms in patients with FM. Anxiety is an unpleasant feeling of worry, apprehension, perception of an imminent threat, or fear of a future event. For the human psyche, normal experiences have two main functions – protective function and a stimulus to study the environment.

Pathological anxiety is a disorder that develops from normal anxiety. However, it is more intense and of longer duration. It leads to distress, disadaptation and disability. Anxiety includes a mental component and a variety of somatic symptoms of various diseases [8].

Anxiety treatment aims to suppress symptoms, prevent complications and preserve the patient’s activity, concentration and normal functioning.

Medications for managing anxiety symptoms in FM include duloxetine, milnacipran, pregabalin, and gabapentin. Stresam, a non-benzodiazepine anxiolytic, is an effective medication for anxiety and FM. Stresam ensures a potent and specific modulating anxiolytic effect due to its original dual mechanism of action. Stresam is a pure anxiolytic used to manage various emotional and autonomic responses (palpitations, tightness in the throat, shortness of breath) and anxiety with depression. In addition, it has neurotrophic, neuroregenerative and analgesic effects [8].

The aim of this prospective study is to examine the main clinical characteristics, including pain, anxiety and depression of patients with primary and secondary FM, compared to a control group of healthy subjects.

**Material/patients and methods**

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 FM and osteoarthritis, mean age 50.77 ± 10.73 years;
   - 23 patients, 22 women and 1 man with SLE and FM at 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 2 men with SLE at 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 is presented in Table 1.

**Research methods:**

*Clinical methods:*

1. Evaluation of the diagnosis of FM according to the 2016 ACR criteria
2. Assessment of anxiety and depression on the HADS scale for anxiety
3. Assessment of anxiety and depression on the HADS scale for 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. Any over-

### Table 1. Demographic and clinical variables of the study population

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Primary fibromyalgia</th>
<th>Fibromyalgia and osteoarthritis</th>
<th>Fibromyalgia and SLE</th>
<th>SLE</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>83</td>
<td>39</td>
<td>23</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td>Number / % female</td>
<td>78/94%</td>
<td>39/100%</td>
<td>22/95.7%</td>
<td>25/92.6%</td>
<td>30/83.3%</td>
</tr>
<tr>
<td>Number / % male</td>
<td>5/6%</td>
<td>0/0%</td>
<td>1/4.3%</td>
<td>2/7.4%</td>
<td>6/16.7%</td>
</tr>
<tr>
<td>Patient age (years), mean ± SD (rang)</td>
<td>40.68 ± 11.15</td>
<td>50.77 ± 10.73</td>
<td>47.9 ± 8.86</td>
<td>46.96 ± 11.7</td>
<td>46.53 ± 9.9</td>
</tr>
<tr>
<td>Duration of FM</td>
<td>4.2 ± 3.2</td>
<td>7 ± 4.9</td>
<td>5.17 ± 3.38</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean age at the beginning of FM (years) ± SD (rang)</td>
<td>36.53 ± 10.32</td>
<td>43.2 ± 10.0</td>
<td>42.9 ± 7.58</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Reason for FM**

<table>
<thead>
<tr>
<th>Mentally reason</th>
<th>81.9</th>
<th>69.2</th>
<th>82.6</th>
<th>-</th>
<th>-</th>
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</thead>
<tbody>
<tr>
<td>Physically reason</td>
<td>15.7</td>
<td>30.8</td>
<td>17.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lack of work</td>
<td>2.4</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Summary</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>-</td>
<td>-</td>
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</table>

**Education**

<table>
<thead>
<tr>
<th>Elementary education</th>
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<th>3</th>
<th>2</th>
<th>2</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average education</td>
<td>36</td>
<td>15</td>
<td>10</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Higher education</td>
<td>42</td>
<td>18</td>
<td>8</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Professional education</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Anxiety and depression in patients with primary... lap, for instance, impaired concentration secondary to
pain rather than depression, is usually easy to sepa-
rate individually. The questionnaire comprises seven
questions for anxiety and seven questions for depres-
sion, and it takes 5-10 min to complete. The Hospital
Anxiety and Depression Scale (HADS) is a self-as-
sessment questionnaire that has been found to be a
reliable instrument for detecting states of anxiety and
depression in the setting of a hospital outpatient clin-
ic. The HADS questionnaire has seven items each for
depression and anxiety subscales. Scoring for each
item ranges from zero to three, with three denoting
the highest anxiety or depression level. A total sub-
scale score of > 8 points out of a possible 21 indicates
considerable symptoms of anxiety or depression.

Statistical methods:
The data was analyzed using the 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 val-
ues are presented as arithmetic mean ± SD.

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

RESULTS

Assessment of the number of chronic
widespread pain areas in the three FM groups
(primary, FM + OA and FM + SLE), healthy
individuals and SLE results

Figure 1 shows a significant difference accord-
ing to the 2016 criteria for diagnosing FM for chronic
widespread pain areas in the arithmetic mean values
of the control group compared to the number of chronic
widespread pain areas in patients with primary FM (p =
0.001), FM + OA (p = 0.001), FM + SLE (p = 0.001), SLE
(p = 0.001). The mean number of chronic widespread
pain areas in all patients of the respective group, com-
pared to healthy individuals and SLE patients, is pre-
sented in Figure 1. The most chronic widespread pain
areas were reported in patients with FM+OA (14.05,
arithmetic mean ± standard deviation: 14.05 ± 2.75),
followed by the FM + SLE group (13.96, 13.96 ± 1.8).
Patients with primary FM had a mean number of chronic
widespread pain areas of 13.8 (13.8 ± 2.1). Healthy
individuals had 7.47 chronic widespread pain areas
(7.47 ± 3.57). In SLE patients, the chronic widespread
pain areas were 4.56 (4.56 ± 1.63) (Figure 1).

Assessment of HADS anxiety results

The HADS anxiety score in patients with FM +
SLE was 10.26 (10.26 ± 4.4), followed by the results
in the FM + OA group (9.87, 9.87 ± 4.25). The mean
value of the HADS anxiety score in FM patients was
9.57 (9.57 ± 4.33). SLE patients had a HADS anxiety
score of 7.04 (7.04 ± 3.68). HADS anxiety score in
healthy individuals was 7.08 (7.08 ± 4.75) (Figure 2).

Table 2 shows the significant difference in anxiety
between the control group and patients with primary
FM (p = 0.01), FM + OA (p = 0.01), FM + SLE (p =
0.01), and no difference in SLE patients (p = 0.77).
There was no difference in anxiety scores between
the three groups of FM patients. Patients with SLE
had similar results for anxiety to those in healthy indi-
viduals, with a statistically significant difference com-
pared to the group of patients with FM + SLE.
Table 2. HADS anxiety scores – comparison between all groups of patients and the groups of healthy controls and SLE patients (*p < 0.05)

<table>
<thead>
<tr>
<th>Group</th>
<th>Group</th>
<th>p &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>2 Fibromyalgia</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>3 Fibromyalgia + OA</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>4 Fibromyalgia + SLE</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>5 SLE</td>
<td>0.77</td>
</tr>
<tr>
<td>FM</td>
<td>1 Healthy controls</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>3 Fibromyalgia + OA</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>4 Fibromyalgia + SLE</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>5 SLE</td>
<td>0.01</td>
</tr>
<tr>
<td>FM + OA</td>
<td>1 Healthy controls</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>2 Fibromyalgia</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>4 Fibromyalgia + SLE</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>5 SLE</td>
<td>0.01</td>
</tr>
<tr>
<td>FM + SLE</td>
<td>1 Healthy controls</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>2 Fibromyalgia</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>3 Fibromyalgia + OA</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>5 SLE</td>
<td>0.01</td>
</tr>
<tr>
<td>SLE</td>
<td>1 Healthy controls</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>2 Fibromyalgia</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>3 Fibromyalgia + OA</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>4 Fibromyalgia + SLE</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The HADS score for anxiety – low, medium or high – was assessed for each group of patients with FM, systemic lupus erythematosus (SLE) and healthy individuals. Results showed normal status in 63% of healthy individuals, 59.3% of patients with SLE, 34% of patients with primary FM, 28.2% of patients with FM + osteoarthritis (OA) and 26.1% of patients with FM + SLE. The remaining patients were divided into groups of low, medium and high anxiety, as shown in fig 3. These results show that more than 2/3 of patients with secondary FM have anxiety of various severity and require treatment for this symptom that accompanies FM.

Assessment of HADS depression results

The HADS depression score in patients with FM + OA was 8.92 (8.92 ± 4.46), followed by the FM group score of 8.71 (8.71 ± 4.17). The mean value of HADS depression scores in patients with FM + SLE was 8.40 (8.40 ± 2.9). SLE patients had HADS scores for depression of 5.63 (5.63 ± 4.06). The HADS depression score in the group of healthy individuals was 5.61 (5.61 ± 3.3) (Figure 2).

A statistically significant difference of p for the HADS clinical parameter depression was found in the arithmetic mean values of the healthy individuals’ group, compared to the values between all FM groups of patients – with primary FM, FM + OA, FM + SLE; in the arithmetic mean values in patients with SLE, compared to the values of all FM groups and the group of patients with FM + OA. There was no significant difference in HADS depression scores between the three groups of FM patients. There was no significant difference in terms of the clinical parameter of depression between the SLE and FM + SLE groups. Patients with SLE had similar rates of depression to those seen in healthy individuals.
**DISCUSSION**

The clinical symptoms of FM develop as a result of complex mechanisms of central nervous and neuroendocrine regulation, which leads to chronic musculoskeletal pain (psychogenic rheumatism, soft tissue rheumatism). The clinical presentation is complex as patients suffer from fatigue, sleep disorders, depression, anxiety and overload. The results of this clinical observation show a statistically significant difference in terms of arithmetic mean values of the number of areas with chronic widespread pain based on the 2016 criteria between the control group and the number of areas with chronic widespread pain in all FM groups of patients with primary FM, FM + OA, FM + SLE, including SLE 1. SLE is an autoimmune disease with multi-organ involvement and joints, skin, kidneys, lungs, heart, blood vessels and brain injuries. The prevalence of the disease is between 14 and 50 patients per 100,000 population. SLE is associated with higher mortality compared to inflammatory joint diseases. An important and objective tool for assessing disease activity is the Systemic Lupus Erythematosus Disease Activity Index (SLE-DAI), which rates the manifestations of damaged organs and systems with a certain number of points [4]. The presence of concomitant FM in patients with SLE has been studied by various authors and was found in 20% of patients with SLE. FM frequency in patients with SLE is higher than in the general population. A study of SLE patients in Brazil provides information on chronic pain and its relationship to SLE disease activity. In patients with SLE-only, disease activity had a more serious impact than in the other two groups. Our results prove this data in terms of the number of tender points, the number of painful areas, and chronic fatigue.

Anxiety is also directly correlated with depression in SLE, according to a study by Grace E. [4]. Depression and anxiety were assessed using the HADS scale. In the study, the depression score was higher compared with the general population but lower compared with the group of patients with mental illness. According to their results, approx. 1/3 of patients with SLE have anxiety, and 13% are on antidepressants. In addition, they found FM in 10% to 70% of patients with SLE. Chronic fatigue can also be interpreted in the course of FM in SLE. The authors concluded that there was a correlation between depression, anxiety and fatigue in the followed-up group of patients with SLE [4].

Anxiety as a separate clinical manifestation was not discussed in published studies. However, it is a symptom assessed using FIQ and SF-36. Therefore, the presence of physical symptoms and distress in patients with FM and SLE was confirmed by Wolfe F [11].

In some studies, it has been noted that the quality of life associated with pain and other clinical symptoms is extremely low in patients with FM. Based on the results of an observational study, a Canadian team of physicians concluded that the combination of FM with SLE is associated with deterioration in the quality of life, overall condition and mental health compared to patients with SLE-only [7]. Conclusions based on a follow-up performed by a Canadian team of physicians show that the presence of FM...
in patients with SLE results in deterioration in their quality of life, general condition and mental health compared to patients with SLE alone. In addition, the results show that pain and emotional disorder are more pronounced in patients with FM alone [7].

Patients need to be informed about their FM and trained on how to communicate and maintain a good quality of life. It is associated with increased pain threshold based on pharmacological and non-pharmacological treatment. An individual program for treatment and education is needed for patients to address all other FM symptoms. Therefore, primary care in the family is important for treatment success. Receiving adequate care from the employer and primary healthcare centers and socializing with these patients is essential for successful treatment [3, 5, 9, 11]. While taking care of FM patients, physicians need to be more persistent in monitoring and treating these patients, have these patients examined or contacted by phone at least once every month, and communicate more with these patients.

A one-hour visit to the rheumatologist has a substantial impact on these patients both to train patients on how to overcome triggers and as a psychotherapy session. It is essential that the physician can take a detailed medical history and reach the deeper problems of the patient. This is essential for both the trust between patient and doctor and for the treatment effect. The complex treatment of FM patients aims at the clinical improvement and higher quality of life for patients.

CONCLUSIONS

1. Patients with primary FM, osteoarthritis and FM, systemic lupus erythematosus and FM have comparable features in terms of pain intensity, anxiety and depression.

2. Patients with SLE without FM have fewer areas with chronic widespread pain and a lower degree of anxiety, depression and fatigue, comparable to these symptoms in patients with SLE + FM and healthy individuals.

3. Patients with SLE and FM have additional symptoms of moderate pain, depression, anxiety and fatigue that are not related to SLE and require treatment for FM, regardless of their current SLE treatment

Conflict of interest. The authors declare that there is no conflict of interest regarding the publication of this article.

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