Inflammatory Markers in the Diagnosis of Fibromyalgia

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ABSTRACT

Background: Fibromyalgia syndrome (FMS) is a chronic disorder characterized by widespread musculoskeletal pain accompanied by various additional symptoms. The prevalence of FMS ranges between 2–8% of the population. The exact pathophysiology of the disease remains unknown, and under certain circumstances it is difficult for the physician to diagnose. Previous studies have shown a correlation between inflammatory biomarkers such as C-reactive protein (CRP) and FMS activity, suggesting that an inflammatory component may play a role in this disease pathogenesis.

Objectives: To investigate the role of certain new inflammatory biomarkers in the diagnosis of patients with FMS.

Methods: In this study data were collected from FMS patients who were admitted to Ziv Medical Center during the period 2013 to 2019 in an attempt to find a connection between inflammatory markers detected by a traditional complete blood count (CBC) tests such as neutrophil-lymphocytes ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet value (MPV), red cell distribution width (RDW), and C-reactive protein (CRP) and FMS.

Results: We found significantly higher CRP levels, MPV, and PLR and lower lymphocyte count in the FMS group compared to the control group.

Conclusions: FMS has certain inflammatory components that may be useful in disease diagnosis.

KEY WORDS: C-reactive protein (CRP), fibromyalgia syndrome (FMS), mean platelet value (MPV), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), red cell distribution width (RDW).

Fibromyalgia syndrome (FMS) is a condition characterized by chronic widespread musculoskeletal pain and discomfort accompanied by fatigue, sleep disruption, cognitive impairment and a variety of other symptoms. Symptoms vary among patients.

The prevalence of FMS is between 2–8% of the population. There is no evidence of variation among countries, cultures, and ethnicities. It is usually present in young women but can affect any sex or age. The exact pathophysiology is not known. Common factors related to FMS are genetic, environmental, and neurohormonal and may include inflammation. Due to an absence of laboratory parameters, the diagnostic process is not accurate and depends on various questionnaires that subjectively assess the patient's symptoms [1,2].

As part of a routine assessment of nearly every patient admitted to any hospital, a complete blood count (CBC) and laboratory tests are performed to reveal inflammation [3]. Many diseases are associated with inflammatory processes and therefore are diagnosed partially by blood test results [4-6]. Several studies have shown that neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet value (MPV), red cell distribution width (RDW), and C-reactive protein (CRP) correlate with inflammatory processes [7-9].

In addition to the inflammation markers, inflammation also correlates with specific cytokine levels [10]. Controversial data have been obtained by numerous studies regarding the levels of the different inflammatory cytokines in FMS patients leading researchers to study cytokine levels such as IL-6, IL-8, and IL-1 and to assess the connection between them and FMS [11,12]. Showing a connection between FMS and these inflammatory cytokines as well as inflammatory markers emphasizes the pathophysiological role of inflammation in FMS. Establishing such a connection could significantly impact on the diagnosis and management of FMS patients and may shed light on the pathophysiology of the disease [13]. Previous studies have shown contradicting findings, making it unclear whether a connection between the two could be made [14,15]. Bote et al. [16] found a connection between reduction of cytokines during physical activity and reduction of pain suggesting that IL-8 may contribute to the pathogenesis [16].

In this study, we accessed a large database of patients with FMS to investigate the role of certain inflammatory biomarkers in the diagnosis of such condition.

PATIENTS AND METHODS

STUDY POPULATION

We performed an observational descriptive retrospective cross-sectional study utilizing the database of the Ziv Medical
Center. The study included all 18 and 90 years old patients who presented with FMS and who were admitted to ZIV medical center or visited the outpatient clinics between the years 2013 and 2019. Patients with severe acute infection, malignancy, rheumatic diseases, decompensated heart failure, acute and chronic kidney injury, or other disease that can alter inflammatory markers were excluded.

The final study population included 151 patients whose baseline demographic and laboratory result were retrieved from their medical files.

The study protocol was approved by the local institutional ethics committee.

LABORATORY FINDINGS

CBCs were analyzed in the hematology unit with a Beckman-Coulter Gen-S system device (Beckman-Coulter Inc., USA). MPV and RDW levels were gathered from patient’s CBC. NLR was calculated as the ratio of absolute number of neutrophil and lymphocyte counts. For each patient two consecutive blood tests were evaluated and checked for consistency of the parameters listed to exclude irregularities.

STATISTICAL ANALYSIS

FMS patients and controls were compared in terms of laboratory findings to detect significant differences. For continuous variables, summary tables show arithmetic mean and standard deviation. Independent sample t-tests were applied to measure the differences between the study groups (FMS vs. control). P < 5% was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

In this study, we compared 75 FMS patients and 76 controls. The majority of patients were female: 67.89% FMS patients and 69.9% controls. The average age was 56.7 years for FMS group and 50.5 years for the control group. There was no statistically significant difference in age or sex between the two groups.

As shown in Table 1 and Figure 1, there is statistical significance regarding higher platelets count in FMS group compared to the control group (265 vs. 231, \(P = 0.003\)) and a slightly lower lymphocyte count (2.06 vs. 2.38, \(P = 0.014\)). There was also statistically significance for higher PLR in the FMS group (143.6 vs. 107.6, \(P < 0.001\)). Interestingly, much higher and positive CRP measurements were found for the FMS group (17.6 vs. 2.7, \(P < 0.001\)). No other parameters that we tested showed significant difference between the groups.

### Table 1. Demographic and clinical characteristic of the study patients according to their group

<table>
<thead>
<tr>
<th>Variables (mean ± standard deviation)</th>
<th>Control (n=76)</th>
<th>Fibromyalgia (n=75)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female (n)</td>
<td>69 (90.3%)</td>
<td>67 (89.3%)</td>
<td>0.765</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>50.5 ± 10.6</td>
<td>56.7 ± 14.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Lymphocytes (10^3 u/l)</td>
<td>2.38 ± 0.79</td>
<td>2.06 ± 0.72</td>
<td>0.014</td>
</tr>
<tr>
<td>Neutrophils (10^3 u/l)</td>
<td>5.16 ± 2.20</td>
<td>5.37 ± 3.12</td>
<td>0.921</td>
</tr>
<tr>
<td>Platelets (10^3 u/l)</td>
<td>231 ± 68</td>
<td>265 ± 81</td>
<td>0.003</td>
</tr>
<tr>
<td>Red cell distribution width (%)</td>
<td>13.83 ± 1.19</td>
<td>13.98 ± 1.01</td>
<td>0.219</td>
</tr>
<tr>
<td>Mean platelet value</td>
<td>8.58 ± 0.96</td>
<td>8.94 ± 1.43</td>
<td>0.316</td>
</tr>
<tr>
<td>Neutrophil-lymphocytes ratio</td>
<td>2.48 ± 1.49</td>
<td>2.99 ± 2.81</td>
<td>0.118</td>
</tr>
<tr>
<td>Platelet-lymphocyte ratio</td>
<td>107.6 ± 45.3</td>
<td>143.6 ± 67.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>2.7 ± 2.3</td>
<td>17.6 ± 33.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Bold indicates significance

DISCUSSION

Our main finding shows statistically significant higher CRP levels, which indicate inflammation, might play a role in the pathogenesis of FMS.

Our results are consistent with the results of previous small studies that showed similar findings showing that FMS is an inflammatory disease [17].

In a cross-sectional study of a large population in the United States, CRP serum levels showed a positive association with FMS, which remained significant after adjustment for multiple variants; however, body mass index (BMI) and co-morbidity substantially attenuated this relationship [17]. We excluded patients with co-morbidities but unfortunately, we did not examine BMI.

Platelets count was higher in the FMS group compared to the control group, but the average number was still not high enough to indicate inflammation due to the slightly lower counts of lymphocytes. PLR a novel inflammatory marker has been suggested to predict the severity of various inflammatory diseases, as was demonstrated in our study. We found that PLR values of the FMS patients were significantly higher than those of the control group. The differences in some inflammatory markers between the groups reinforce the assumption that indicators other than inflammation are involved in the pathogenesis of FMS.

Even though these results assist us in our attempt to determine the pathophysiology of FMS they do not seem to be specific enough to be used as a diagnostic tool to identify FMS patients early in disease presentation. However, an FMS diagnosis should be considered for patients who present with appropriate clinical presentation and elevated CRP but without any obvious inflammation source. To establish a more specific method of diagnosing and
screening for FMS, future studies should focus on testing for levels of markers that are more specific to inflammatory processes such as cytokines and autoantibodies in patients suspected of FMS.

Our study showed that FMS has properties of an inflammatory disease. Although the results were not specific enough to provide a diagnostic tool for diagnosing FMS, the data do suggest the use of inflammatory markers obtained via a simple blood test as a screening tool for patients with appropriate clinical presentation and no other obvious source of inflammation. There is evidence to support the inflammation-driven pathways in the pathogenesis of fibromyalgia.

CONCLUSIONS
Until a more specific marker can be found, FMS diagnosis remains a diagnosis of exclusion. However, further research is required to fully understand the network of inflammation and its possible role in diagnosis and/or treatment of fibromyalgia.

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References
The role that traditional and hybrid in-person schooling modes contribute to the community incidence of SARS-CoV-2 infections relative to fully remote schooling is unknown. Ertem and colleagues conducted an event study using a retrospective nationwide cohort evaluating the effect of school mode on SARS-CoV-2 cases during the 12 weeks after school opening (July–September 2020, before the Delta variant was predominant), stratified by U.S. Census region. After controlling for case rate trends before school start, state-level mitigation measures and community activity level, SARS-CoV-2 incidence rates were not statistically different in counties with in-person learning versus remote school modes in most regions of the United States. In the south, there was a significant and sustained increase in cases per week among counties that opened in a hybrid or traditional mode versus remote, with weekly effects driven by increasing cases among 0–9 year olds and adults. Schools can reopen for in-person learning without substantially increasing community case rates of SARS-CoV-2; however, the impacts are variable. Additional studies are needed to elucidate the underlying reasons for the observed regional differences more fully.

In this ongoing, multicenter, double-blind, phase 3 trial, Gupta et al. randomly assigned, in a 1:1 ratio, non-hospitalized patients with symptomatic COVID-19 (≤5 days after the onset of symptoms) and at least one risk factor for disease progression to receive a single infusion of sotrovimab at a dose of 500 mg or placebo. In this pre-specified interim analysis, which included an intention-to-treat population of 583 patients (291 in the sotrovimab group and 292 in the placebo group), 3 patients (1%) in the sotrovimab group, compared to 21 patients (7%) in the placebo group, had disease progression leading to hospitalization or death (relative risk reduction 85%, 97.24% confidence interval 44–96, P = 0.002). In the placebo group, five patients were admitted to the intensive care unit, including one who died by day 29. Safety was assessed in 888 patients (430 in the sotrovimab group and 438 in the placebo group). Adverse events were reported by 17% of the patients in the sotrovimab group and 19% of those in the placebo group; serious adverse events were less common with sotrovimab than with placebo (in 2% and 6% of the patients, respectively). However, Corley and colleagues, in a similar trial, found that administration of COVID-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of COVID-19 did not prevent disease progression.