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Evaluation of Antiviral Antibodies against Epstein-Barr Virus and Neurotransmitters in Patients with Fibromyalgia

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Abstract

Fibromyalgia (FM) is characterized by chronic widespread pain lasting for a minimum of three months, and pain at mechanical pressure in at least 11 of the 18 tender points. The cause of fibromyalgia is unknown. Several hypotheses have been developed including "central sensitization". This theory proposes that fibromyalgia patients have a lower threshold for pain because of increased reactivity of pain-sensitive neurons in the spinal cord or brain. Some researchers supposed that different neurotransmitters (serotonin, catecholamine) could be involved in the pathophysiology of fibromyalgia-associated symptoms. The connection of FM to different viral infections has been proposed. Epstein Barr Virus (EBV) has been considered a possible cause of FM because of similarity of symptoms, but so far, the connection has not been proven. The objective of this study was to determine the prevalence of antibodies (Abs) IgM and IgG against EBV, and respectively the presence of a viral infection in a group of patients with FM. We also analysed the association between the titter of the antiviral antibodies, some neurotransmitters (serotonin, noradrenaline and adrenaline) and different clinical symptoms. The obtained results revealed that high EBV IgG concentrations in the serum of patients with FM correlated with pain intensity and associated clinical symptoms. This is consistent with the fact that FM is connected to the immune response to certain infectious agents (e.g. EBV, CMV).

Keywords: Antiviral IgM; IgG Abs; EBV; Neurotransmitters

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Introduction

Fibromyalgia (FM) is a disease, characterized by a chronic widespread pain lasting for a minimum of three months, pains at mechanical pressure in at least 11 of the 18 myofascial tender points, general fatigue, sleep disturbances and functional disorders. In 1990 a new group of criteria was published under the American College of Rheumatology (ACR) [1]. The main clinical feature of FM is the decreased pain threshold in sensitive tender points. The myofascial tender points can be activated by chronic muscle bruising and contusions due to frequent microtraumas, poor posture at work, stress, anxiety, impact due to thermal and chemical effects, and much more. The variations in sensitivity and dynamics of tender points still remain poorly developed study area. There are a small number of comparative studies that assess the separate tender points and their response to treatment with different groups of medications [2]. The most important aim is to ameliorate patients' quality of life by adequate treatment of chronic pain, sleep disorders, and depression. Elaboration of proper strategy and individual approach for each patient are needed [3].

The cause of fibromyalgia is unknown. Several hypotheses have been developed including "central sensitization". This theory proposes that fibromyalgia patients have a lower threshold for pain because of increased reactivity of pain-sensitive neurons in the spinal cord or brain. Some researchers supposed that different neurotransmitter (serotonin, catecholamine) could be involved in the pathophysiology of fibromyalgia-associated symptoms [4]. Changed plasma concentrations of different neurotransmitters (serotonin, 5-hydroxyindoleacetic acid, noradrenaline, and adrenaline) were found in patients with FM [5-7]. On the other hand the connection of FM to different viral infections caused

by hepatitis C, Parvovirus B19, human immunodeficiency virus (HIV), and Epstein Barr virus (EBV) has been documented. EBV has been considered a possible cause of FM because of similarity of symptoms, but so far, a connection has not been proven [4]. The treatment of FM patients is carried out with drugs from different groups – antidepressants, antiepileptic, analgesics, muscle relaxants, growth hormone (GH), amino acids [3].

Epstein Barr virus cause or contribute to the symptoms of a large percentage of patients with FM. As stated previously, the presence of active infections correlate with an elevated IgG antibody, despite the lack of IgM antibodies. This infection is generally not acute but rather intracellular reactivation of an old infection; an elevation of IgM antibodies is typically not seen with active infection of EBV. Fatigue, an additional symptom, is likewise common to both FM and viral infections. It is not surprising therefore that early research on both FM and the related syndrome of chronic fatigue attempted to identify evidence of infection with pathogens such as EBV among these patients. One observation by Moldofsky concern the effect of acute viral infection on development of sleep disorders considered to be harbingers of FM. Recent publications have discussed the capacity of early non-structural EBV-encoded protein to cause immune dysregulation as well as instigating clinical symptoms such as fatigue [8].

Fibromyalgia is frequently observable in patients who meet the criteria of chronic fatigue syndrome [4]. The two clinical situations are dissimilar in many ways, in spite of certain manifestations is common (fatigue, paresthesia, myalgia, cephalgia, arthralgia, etc.), suggesting the presence of a subjacent infection; nevertheless, the title of anti-Ebstein Barr virus antibodies in patients suffering from FM is not significantly different from those in other individuals. Fibromyalgia and chronic fatigue syndrome may indeed be intrinsically linked syndromes, but their physiopathological mechanisms are certainly distinct, with FM considered a muscular disease and chronic fatigue syndrome an infectious disease [4].

Patients and Methods

Twenty-one patients (women, men) with fibromyalgia were included in the investigation. The study covered with precision the changes of the pain thresholds measured in kg/cm^2 in all trigger points applying dolorimetric method with a Fisher dolorimeter and assessing with an exact figure the pain scores and changes occurred within 3-months period [2]. The symptom is evaluated on day 0 and after 3 month. The accompanying clinical symptoms in FM patients were evaluated: sleep disturbances, headache, autonomic disturbances, heart palpitations, and presence of diffuse muscle pains. Patients were asked to answer questions on all accompanying symptoms assessing them independently by a 5-point grading system (0–no symptom, 1–slightly expressed, 2-medium, 3–strong, 4–very strong). The symptoms changes were tracked by the 5-point grading system [2].

Inclusion criterias are primary fibromyalgia in the patient from 18 to 65 years measured by Fisher dolorimeter. The patients with other inflammatory or systemic diseases are excluded from study.

Sera and plasmas were collected from all patients. Sera were tested by enzyme linked immunosorbent assay for antibodies (Abs) IgM and IgG against Epstein Barr-virus (EBV)**.** The neurotransmitters serotonin, adrenaline and noradrenaline were tested in the plasma. The normal concentration of adrenaline in the plasma is 30-90 ng/l, of noradrenaline-165-460 ng/l, of serotonin - 50-250 e ng/l.

This examination is worked in LaborLimbach, Heidelberg, Germany with accreditation DAR/ DIN EN ISO/ IEC 17025, ISO 15189 and sertification DAR DAC-ML-0057-98-10-01.

Statistical Methods: The statistical data processing was made by means of SPSS 13.0 for Windows. Parametric (ANOVA and Paired Sample T-Test), as well as nonparametric (Man-Whitley U, Kruskal-Wallis or Wilcoxon) analyses were used. $P<0.05$ was considered as a threshold value of level of statistical significance, unless otherwise specified.

This work is approved by ethics committee in Medical University, Sofia [2].

Results and Discussion

Antiviral antibodies (Abs) IgM, IgG against Epstein Barr-virus (EBV) in the serum and neurotransmitter serotonin, adrenaline and noradrenaline in the plasma of patients with fibromyalgia (FM)

Antiviral IgM Abs against EBV was not found in the patients with fibromyalgia, while IgG Abs were presented in all investigated patients. IgG Abs against EBV in a high titer (5-10 times above normal range) has been reported in 76% of the patients, while we found an increased titter (2-4 times above normal range) of Abs in only 14% [6].

Subsequently we tested the plasma adrenaline, serotonin and noradrenaline concentrations in all patients. We found decreased plasma concentrations of noradrenaline in 71.4% and adrenalin– in 62% of patients with fibromyalgia. Other similar studies [6] have found increased plasma concentrations of noradrenaline and adrenaline in patients with fibromyalgia. The increased noradrenaline levels in FM patients were associated with an anxiety and pain, but not with depression [9]. The results obtained in our study suggest the idea for different pathophysiological mechanism participating in the development of allodynia and hyperalgesia. We further analysed the group of patients with a high titer of IgG EBV Abs, as it was found a low adrenaline concentration (less than normal range) in 62% of patients with high EBV IgG Abs, while other patients were with normal plasma adrenaline levels=

When we tested the plasma serotonin concentrations in the patients, we determined levels below 50 ng/l in 8 of studied patients, in 3 patients–below 25 ng/l or 52.4% of patients were with low plasma serotonin levels (less than normal range). The remaining patients (47,6%) were with normal plasma serotonin levels. Relevant studies have found decreased concentration of serotonin and 5-hydroxyindoleacetic acid in the plasma and the

cerebrospinal fluid of patients with FM [7,10]. The serotonin is involved in central nervous regulation in FM. The reduced levels of serotonin in FM are connected to the reduction of non-REM sleep disorders and decreases pain threshold, somatic complications and depression [10]. Yunus M.B., and colleagues [7] have found statistically insignificant reduction in serum serotonin in patients with FM compared to healthy controls, and a significant reduction of serotonin transport level through the blood-brain barrier in patients with FM [7].

Associations between fibromyalgia clinical manifestations and antiviral IgG Abs against EBV, as well as associations between clinical features and plasma serotonin, adrenaline and noradrenaline concentrations in the patients with FM

We determined a negative correlation between the pain and antiviral IgG Abs. It was observed that the patients with a lower threshold of pain were with higher serum levels of IgG Antibodies. The association was not statistically significant (p=0.65). When we analysed the association between the fatigue and antiviral IgG Abs, it was found a negative correlation or higher serum levels of IgG Abs against EBV were observed in patients with severe fatigue (r=-0.14), as the associations wasn't statistically significant (p=0.55). We determined similar correlations between the IgG Abs and other clinical features. Our data showed that the patients with a lower threshold of pain were with higher serum levels of IgG Abs, as the serum levels of antiviral IgG Abs against EBV were related to pain intensity and were associated with some fibromyalgia clinical features. The results support the idea that the induced immune response to some infection agents (EBV, CMV) can participate in the pathogenesis of FM. It was suggested that the lower titter of antiviral EBV Abs can improve fibromyalgia clinical symptoms.

In our study we found a slightly positive correlation between the pain threshold and the plasma concentrations of adrenaline (r=0.15) and noradrenaline (r=0.13) in FM patients. The patients with a higher pain threshold had higher concentrations of noradrenaline and adrenaline in the plasma. The correlation between the pain threshold and the plasma concentration of serotonin was negative or the studied patients with a lower pain threshold were with higher concentrations of serotonin in the plasma (r=-0.05). The association wasn't statistically significant (p=0.83). Our study showed low plasma serotonin concentration in 52.4% of patients with fibromyalgia, leading us to suggest a correlation between decreased pain threshold and serotonin, but it couldn't explain why people, with normal serotonin concentration, have had a low pain threshold.

Negative correlation dependence was determined between the degree of fatigue and the concentrations of plasma serotonin (r=-0.01), adrenaline (r=-0.19) and noradrenaline (r=-0.43) in the patients with FM. We observed the patients with marked fatigue had lower plasma concentrations of the tested neurotransmitters.

The association between the headache and adrenaline (r=-0.27) and noradrenaline (r=-0.58) plasma concentrations in the patients was negative. The stronger headache in patients was associated with lower concentrations of noradrenaline and adrenaline. The dependence between headaches and the concentration of noradrenaline was statistically significant (p=0.0068).

The correlation between headache and concentration of serotonin in the plasma of patients with FM is very small (r=0.005).

The summary results are presented in **Table 1**.

Conclusion

Some neurotransmitter can be used as potential markers for evaluation the effects of the applied therapy. The investigation of the levels of neurotransmitters and analyse associations with different clinical symptoms can be useful for daily rheumatology practice. Positive antibodies against some viruses in patients with fibromyalgia suggest the role of some viruses in the pathogenesis; through induce of different immune mechanisms.

Table 1 Associations between fibromyalgia clinical manifestations and antiviral IgG Antibodies against EBV, between clinical features and serotonin, adrenaline and noradrenaline plasma concentrations in the patients with FM **(*p<0.05).**

Correlation coefficients*	Pain Threshold	Fatigue Degree	Headache	Autonomous changes
EBV IgG Concentration	-0.11	-0.14	0.19	**-0.46***
Noradrenalin Concentration	0.15	-0.43	**-0.58***	-0.29
Adrenalin Concentration	0.13	-0.19	-0.27	**-0.51***
Serotonin Concentration	-0.05	-0.01	0.005	0.07

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