

Original Article

The prevalence of fibromyalgia among patients with hepatitis B virus infection

Mustafa Ozsahin¹, Ibak Gonen², Fatih Ermis³, Murat Oktay⁴, Fahri Halit Besir⁵, Ali Kutlucan⁶, Ahmet Sahin⁷, Safinaz Ataoglu¹

¹Department of Physical Medicine and Rehabilitation, Medical School of Duzce University, Duzce, Turkey; ²Department of Infectious Diseases, Medical School of Suleyman Demirel University, Isparta, Turkey; ³Department of Gastroenterology, Medical School of Duzce University, Duzce, Turkey; ⁴Department of Pathology, Medical School of Duzce University, Duzce, Turkey; ⁵Department of Radiology, Medical School of Duzce University, Duzce, Turkey; ⁶Department of Internal Medicine, Medical School of Duzce University, Duzce, Turkey; ⁷Department of Infectious Diseases, Medical School of Duzce University, Duzce, Turkey

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Abstract: Fibromyalgia (FM) is a syndrome characterized by widespread and chronic musculoskeletal pain, fatigue, morning stiffness, and sleep disturbance. However, the etiopathogenesis of FM remains unclear. Various etiological factors have been suggested to trigger FM. These include systemic rheumatismal disease, physical trauma, psychological disorders, and chronic infections. We determined the prevalence of FM in patients with chronic active hepatitis B virus (HBV) and inactive hepatitis B carriers, compared with matched healthy controls. Seventy-seven HBV patients (39 HBV carriers and 38 with chronic active hepatitis), were evaluated for FM syndrome. Seventy-seven HBsAg-negative healthy subjects were enrolled as a control group. We found that FM was very prevalent in patients with HBV infections (22% of the total). We found no difference in FM prevalence when patients with chronic active hepatitis B infections (21% FM prevalence) and those who were inactive hepatitis B carriers (23% FM prevalence) were compared. FM was not associated with the levels of HBV-DNA, ALT, or AST. Recognition and management of FM in HBsAg-positive patients will aid in improvement of quality-of-life. We fully accept that our preliminary results require confirmation in studies including larger numbers of patients. More work is needed to allow us to understand the role played by, and the relevance of, infections (including HBV) in FM syndrome pathogenesis.

Keywords: Fibromyalgia, hepatitis B virus, infection, prevalence

Introduction

Fibromyalgia (FM) is a syndrome characterized by widespread and chronic musculoskeletal pain, fatigue, morning stiffness, and sleep disturbance. The condition affects middle-aged women, in particular, and FM prevalence in the general population is thought to be as high as 2% [1]. However, the etiopathogenesis of FM remains unclear. Various etiological factors have been suggested to trigger FM. These include systemic rheumatismal disease, physical trauma, psychological disorders, and chronic infections [2, 3].

It is well-known that the prevalence of FM is higher in patients with Lyme disease, and those with HIV and hepatitis C virus (HCV) infections

[4-6]. Some studies have also suggested that FM may be associated with other chronic infections such as those of human T-cell lymphotropic virus type I, parvovirus B19, and mycoplasmosis [7-9]. FM prevalence was found to be as high as 25% in a single study of hepatitis B virus (HBV) carriers. This study is unique in literature up to our knowledge which is related with FM and HBV infection [10]. We determined the prevalence of FM in patients with chronic active HBV and inactive hepatitis B carriers, compared with matched healthy controls.

Patients and methods

Seventy-seven HBV patients (39 HBV carriers and 38 with chronic active hepatitis), who were referred to infectious disease and gastroen-

Table 1. Demographic data on, and clinical characteristics of, our study group

Variable	Hepatitis B Group (n=77)	Control Group (n=77)	P Value
Gender (female/male)	37/40	34/43	0.747
Mean age (years)	41.70±11.96	39.78±10.14	0.284
Widespread body pain, n (%)	38 (49)	6 (8)	<0.001
Mean number of tender points	5.53±5.08	3.59±3.70	0.008
Fibromyalgia, n (%)	17 (22)	4 (5)	0.004

terohepatology outpatient clinics of the Duzce University Faculty of Medicine, were evaluated for FM syndrome. Seventy-seven HBsAg-negative healthy subjects were enrolled as a control group. The study was approved by the Ethics Committee of our University and written informed consent was obtained from all subjects prior to study commencement.

Patients with any history of other serious chronic systemic diseases, psychological disorders, other rheumatic diseases, chronic infectious diseases (HCV, HDV, and HIV), endocrine diseases, and painful medical conditions, were excluded. Patients who took antidepressants in the 3 months prior to the study were also excluded.

The demographic features of all participants were documented. Routine biochemical tests were performed and HBV DNA levels recorded. All subjects were assessed in terms of FM syndrome by a single physiatrist. Diagnosis of FM was based on the 1990 classification criteria of the American College of Rheumatology (ACR), and required reporting of chronic widespread body pain of at least 3 months in duration and tenderness at a minimum of 11 of 18 specific anatomic sites [11].

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 15.0 (SPSS Inc., Chicago, IL). Parametric values are expressed as means±SDs and nonparametric values as percentages. Student's *t*-test was used to compare parametric values and the Chi-squared test to compare nonparametric values. A difference was considered statistically significant at $p<0.05$.

Results

We studied 77 HBsAg-positive patients (38 had chronic active hepatitis B and 39 were inactive

hepatitis B carriers) and 77 controls (HBsAg-negative healthy subjects). Thirty-seven (48%) of the 77 HBV patients were female. Thirty-four (44%) controls were female. The age of all participants ranged between 18 and 67 years. The mean age was 41.70±11.96 years in the HBV-positive group and 39.78±10.14 years in the control group. No statistically significant

differences with regard to age, gender, BMI, educational level, occupational status, or marital status, were noted between the study and control groups ($p>0.05$). The numbers of patients reporting chronic widespread body pain were 38 (49%) in the HBV group and 6 in the control group (8%). The frequency of chronic widespread body pain was significantly higher in the HBV group than in the control group ($p<0.001$). The mean number of tender points in HBV patients was 5.53±5.08, significantly higher than in the control group (3.59±3.70) ($p=0.008$). FM syndrome was diagnosed in 17 HBV patients (22%) and in 4 (5%) controls. A significant difference was noted in FM prevalence between the two groups ($p=0.004$). In the HBV group, 12 (71%) of 17 FM patients were women, and all 4 FM cases diagnosed in controls were also women. Demographic data and clinical characteristics of the study groups are shown in **Table 1**.

HBsAg-positive patients included both those with chronic active hepatitis and inactive hepatitis B carriers. No statistically significant differences with regard to age, gender, BMI, educational achievement, occupational status, or marital status were evident between these subgroups ($p>0.05$). Seventeen (45%) of 38 chronic active hepatitis B patients and 21 (54%) of 39 inactive hepatitis B carriers reported widespread chronic body pain ($p>0.05$). FM syndrome was diagnosed in 9 (23%) of 39 hepatitis B carriers and 8 (21%) of 38 chronic active hepatitis patients. There was no significant difference between the two subgroups in terms of FM prevalence ($p>0.05$). In patients with chronic active HBV, 6 (67%) of 9 patients diagnosed with FM were women and 6 (75%) of 8 hepatitis B carriers diagnosed with FM were also women. The ratios of patients reporting chronic widespread body pain in those with chronic active hepatitis B and inactive hepatitis B were 0.45

Table 2. Demographic data on, and clinical characteristics of, all HbsAg-positive patients

Variable	Inactive Hepatitis B Carrier Group (n=39)	Chronic Active Hepatitis B Group (n=38)	P Value
Gender (female/male)	16/23	21/17	0.257
Mean age (years)	41.13±12.72	42.29 ±11.27	0.673
Serum ALT level (U/L)	25.10±13.85	40.97±48.60	0.057
Serum AST level (U/L)	24.29±9.29	41.92±50.14	0.036
Widespread body pain, n (%)	21 (54)	17 (45)	0.497
Mean number of tender points	6.21±5.42	4.84±4.67	0.241
Fibromyalgia, n (%)	9 (23)	8 (21)	0.584

(17/38) and 0.54 (21/39), respectively. No significant difference in the numbers of patients with chronic widespread body pain was evident between the two subgroups ($p>0.05$). The mean numbers of tender points in patients with chronic active hepatitis and those who were inactive hepatitis B carriers were 4.84 and 6.21, respectively. No significant difference between the two subgroups was evident ($p>0.05$). Although the aspartate transaminase (AST), alanine transaminase (ALT), and HBV DNA levels in patients with chronic active hepatitis B were significantly higher than in inactive hepatitis B carriers, no significant difference in FM frequency was evident between the two subgroups. The demographic data and clinical characteristics of all HBsAg-positive patients are shown in **Table 2**.

Discussion

In the present study, we found that HBsAg-positive patients had a higher frequency of FM than did either the control group or the general population [1]. The proportions of test and control subjects with FM were 22% and 5%, respectively. The prevalence of FM in inactive hepatitis B carriers were 23%. We also found, for the first time, that the frequency of FM in chronic active hepatitis patients was 21%. These findings are in line with that of a report on the proportion of inactive hepatitis B carriers with FM in a similar, previous study [10]. Thus, a relationship exists between HBV infection status and the presence of FM in patients who either have chronic active hepatitis or who are inactive hepatitis B carriers. FM was not associated with the levels of HBV-DNA, ALT, or AST.

Although environmental and genetic factors may play essential roles in the etiopathology of FM syndrome, the etiopathogenesis of FM

remains incompletely understood. Recently, some authors have suggested that chronic viral infections may trigger FM [12]. Goldenberg et al. found that 60% of FM patients cited a precipitating factor: 33% physical trauma, 18% illness, and 14% emotional distress [12]. To our knowledge, only one prior study has been conducted on HBsAg-positive patients with FM. Adak et al. reported that hepatitis B carriage increased the risk for FM syndrome and development of many typical symptoms. The prevalence of FM syndrome was 26% in inactive hepatitis B carriers and 4% in HBsAg-negative controls when 50 carriers and 50 HBsAg-negative controls were studied [10]. The prevalence of FM syndrome-associated symptoms (fatigue, sleep disorder, diffuse musculoskeletal pain, headache, morning stiffness, anxiety, Raynaud syndrome, rheumatoid factor positivity, paresthesia, menstrual cycle disorders, and irritable bowel syndrome) was significantly higher in inactive hepatitis B carriers. We also found that the frequency of chronic widespread body pain was higher in HBsAg-positive patients than in controls. Also, the mean number of tender points was significantly higher in HBsAg-positive patients.

Clinical studies on the roles played by infectious agents in hepatitis have mostly enrolled patients with HCV. The prevalence of FM in patients with chronic HCV infection ranged from 5-19% in several studies [13-16]; but Mohammad et al. reported a higher prevalence of FM (57%) in subjects with chronic HCV infection [17]. However, although FM prevalence was significantly higher in HCV-positive patients than in controls in all studies, the prevalence of HCV infection in FM patients remains controversial. Although Rivera et al. [6] reported that 15.2% of FM patients had anti-HCV antibodies; other studies found that the prevalence of such

antibodies in FM patients was no higher than in controls [18, 19].

Two pathogenetic mechanisms have been proposed to explain how infection may trigger FM [12]. First, direct infection of host tissues, or inflammatory mediators released during infection, may induce FM. Synthesis of certain inflammatory products or cytokines, such as IFN-alpha, has been associated with development of FM, although no systematic research has yet been performed. Another suggestion is that stress and anxiety caused by the knowledge that a patient has a chronic infectious disease could trigger FM in that patient. Both theories suggest the existence of an association between hepatitis B virus infective status and FM. Hepatitis B virus infection may also trigger FM in other ways. Thompson and Barkhuizen [20] suggested that hepatitis C-mediated alterations in cytokine levels might trigger hyperalgesia and other neural symptoms because cytokine receptors are present on glial cells, and opiate receptors on lymphocytes. Thus, cytokines including interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha, might activate the hypothalamus-pituitary-adrenal axis, whereas interferon-alpha might inhibit axis activity.

Although a higher prevalence of FM might be expected in patients with active hepatitis, we in fact found that the frequencies of FM were similar in patients with chronic active hepatitis and inactive carriers. Patients with inactive hepatitis B infections experience symptomatic complaints including widespread body pain, depression, and anxiety, and are admitted to hospital more frequently than are asymptomatic carriers. This could cause equal rate of FM in both subgroups in HBsAg-positive subjects. Indeed, Mohammed et al. [21] found that rheumatologic symptoms occurred at a higher frequency in chronically infected HCV patients, but no correlation between the extent of liver disease and viral load was apparent. Rivera et al. [6] stated that there were no associations between FM with liver damage or autoimmune markers in active HCV patients, either.

FM syndrome is common and may be associated with much other comorbidity. In the present study, we found that FM was very prevalent in patients with HBV infections (22% of the total). We found no difference in FM prevalence when patients with chronic active hepatitis B infections (21% FM prevalence) and those who

were inactive hepatitis B carriers (23% FM prevalence) were compared. Recognition and management of FM in HBsAg-positive patients will aid in improvement of quality-of-life. We fully accept that our preliminary results require confirmation in studies including larger numbers of patients. More work is needed to allow us to understand the role played by, and the relevance of, infections (including HBV) in FM syndrome pathogenesis.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mustafa Ozsahin or Dr. Safinaz Ataoglu, Department of Physical Medicine and Rehabilitation, Medical School of Duzce University, Duzce, Turkey. Tel: +90 380 542 14 16; Fax: +90 380 542 13 02; E-mail: drozsahin@hotmail.com (MO); safinazataoglu@duzce.edu.tr (SA)

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