Fibromyalgia Frequency in Hepatitis B Carriers

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Background: Fibromyalgia (FM) is characterized by diffuse musculoskeletal pain, fatigue, morning stiffness, and sleep disturbance. Chronic viral infections may trigger FM symptoms.

Objectives: In this study, we aimed to evaluate whether there was an association between HBsAg seropositivity and fibromyalgia syndrome.

Methods: Fifty hepatitis B carriers (HBsAg positivity and anti-HBs negativity in sera for at least 6 months) and 50 age- and sex-matched HbsAg-negative control subjects were enrolled in this study. The hepatitis B carriers with normal or slightly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were recruited from the infectious diseases outpatient clinic and the control group was recruited from the physical medicine and rehabilitation outpatient clinic. The relationship between groups was calculated by independent Student *t* test, chi-squared test, and Fisher exact test for comparing proportions. Alpha criterion for significance was set at $P < 0.05$.

Results: There was no statistically significant difference between the groups according to sex, mean age, body mass index, serum ALT, and AST levels ($P > 0.05$). FM syndrome and FM-associated symptoms were much more prevalent in the hepatitis B group ($P < 0.001$).

Conclusion: The present study suggests that chronic hepatitis B carriage appears to increase the risk of FM and many of the typically associated symptoms. Whether this association is related to altered liver function, viral infection, concerns associated with chronic disease, or other factors, physicians should be aware of this apparent association.

Key Words: fibromyalgia syndrome, hepatitis B infection, hepatitis B carriers

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Fibromyalgia (FM) is characterized by diffuse musculoskeletal pain, fatigue, morning stiffness, and sleep disturbance. The underlying pathogenesis and the cause of this syndrome are still unknown. Its origin can be multifactorial and the factors involved in individual cases may be difficult to identify.[1,2] Infection, neurohormonal disturbances, immunologic factors, systemic diseases like rheumatoid arthritis and systemic lupus erythematosus, physical trauma, and psychologic disorders have coexistent FM symptoms.[3]

Chronic viral infections may trigger FM symptoms. In recent studies, FM has been associated with some chronic infections like Lyme disease, HIV, parvovirus, Epstein-Barr virus, and hepatitis C virus.[4–11] Hepatitis B virus is a small enveloped DNA virus, the replication of which involves reverse transcription of pregenomic RNA. Approximately 300 million people are affected by this virus worldwide. Some rheumatic disorders, especially polyarteritis nodosa, have been associated with hepatitis B virus chronic infection.[12]

In this study, we aimed to evaluate whether there was an association between HBsAg seropositivity and FM syndrome.

MATERIALS AND METHODS

Fifty hepatitis B carriers (with HBsAg positivity and anti-HBs negativity in sera for at least 6 months) and 50 age- and sex-matched HbsAg-negative control subjects were enrolled in this study. Hepatitis B carriers had normal or slightly elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). They were recruited from the infectious diseases outpatient clinic and the control group was recruited from the physical medicine and rehabilitation outpatient clinic.

FM syndrome was diagnosed according to the 1990 American College of Rheumatology fibromyalgia criteria.[2] Patients with secondary FM resulting from any other systemic diseases, history of trauma, or under any other medical treatment were excluded. Tender and control FM points (18 tender and 4 control points) were evaluated by digital palpation. Palpation was performed with the thumb applying pressure approximately equal to a force of 4 kg/cm^2 by the same investigator (MB). A 10-cm visual analog scale was

TABLE 1. Demographic Data of the Patients

	Hepatitis B Group (n = 50)	Control Group (n = 50)	*P* Value
Gender (male/female)	13/37	14/36	>0.05
Mean age (male/female)	32 (28–33)/30.4 (19–38)	33.2 (25–38)/31.4 (18–35)	>0.05
Body mass index (male/female)	27.5/27.8	27.3/28.0	>0.05
Serum alanine aminotransferase–aspartate aminotransferase (ALT-AST) levels	46.1/48.4	44.2/45.6	>0.05
Serum HBsAg positivity (n)	50	0	<0.0001

TABLE 2. Clinical Characteristics of the Patients

	Hepatitis B Group	Control Group	*P* Value
Fibromyalgia syndrome (American College of Rheumatology criteria)	1 M/12 F (26%)	0 M/2 F (4%)	<0.001
Fatigue	5 M/15 F (40%)	2 M/4 F (12%)	<0.001
Sleep disorder	2 M/16 F (36%)	1 M/3 F (8%)	<0.001
Diffuse musculoskeletal pain	6 M/18 F (48%)	1 M/2 F (6%)	<0.001
Headache	3 M/15 F (36%)	2 M/5 F (14%)	<0.001
Morning stiffness (30 min)	1 M/7 F (16%)	0 M/2 F (4%)	<0.001
Anxiety	2 M/9 F (22%)	0 M/1 F (2%)	<0.001
Raynaud syndrome	2 M/10 F (24%)	2 M/2 F (8%)	<0.001
Rheumatoid factor positivity	2 M/9 F (22%)	2 M/3 F (10%)	<0.001
Paresthesia	3 M/7 F (20%)	1 M/2 F (6%)	<0.001
Menstrual cycle disorder	8 F (16%)	3 F (6%)	<0.001
Irritable bowel syndrome	4 M/6 F (20%)	1 M/3 F (8%)	<0.001

used to assess the pain in the last 48 hours. A complete physical examination was carried out in each chronic hepatitis B virus carrier and control subject. Patients were asked about the presence of widespread pain, sleep disturbances, morning stiffness, fatigue, arthritis, and arthralgia.

Laboratory determinations included complete blood count, erythrocyte sedimentation rate, serum creatinine, AST, ALT, alkaline phosphatase, glucose, total serum proteins, albumin, urinalysis, rheumatoid factor (RF), antinuclear antibodies (ANA), serum C3 and C4 levels, serum HbsAg, and anti-HBs titers.

Statistical analysis was performed using SPSS 10.0 package for Windows.

The relationships between groups were calculated by independence Student *t* test, chi-squared test, and Fisher exact test for comparing proportions. Alpha criterion for significance was set at $P < 0.05$.

RESULTS

Demographic data on the patients are presented in Table 1. Between the both groups according to sex, mean age, body mass index, serum ALT and AST level parameters, there was no statistically significant difference ($P > 0.05$). The physical examinations and clinical histories of the patients are summarized in Table 2.

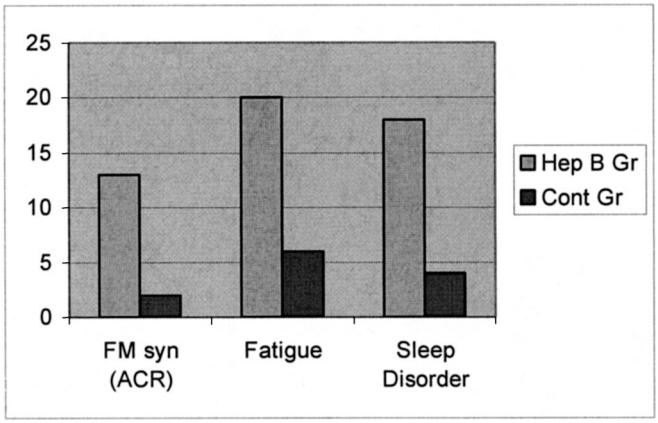

FIGURE 1. Fibromyalgia syndrome and some associated symptom frequency in the 2 groups.

There were statistically significant differences between groups in FM syndrome diagnoses and diffuse musculoskeletal pain parameters ($P < 0.001$). FM-associated symptoms were much more prevalent in hepatitis B carriers ($P < 0.001$).

FM syndrome and some associated symptoms in the 2 groups are presented graphically in Figure 1.

DISCUSSION

FM is a chronic, painful musculoskeletal disorder of unknown etiology. Prevalence studies have shown that 2% of the population has this painful condition.[1]

This study demonstrated that diffuse musculoskeletal pain is present in approximately half of HbsAg-positive patients, and FM syndrome is present in approximately 25% of HbsAg-positive patients. These were significantly more common than in the control group selected. It might also be pointed out as a limitation that the control group from physical medicine may not have been ideal, but they certainly would include some patients with musculoskeletal pain. Of note was that patients with hepatitis B also more frequently had Raynaud phenomena. This is not typical of FM.

The hepatic response to infection with hepatitis B virus has been well characterized consisting of chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. Association with musculoskeletal pain and rheumatologic disorders, especially polyarteritis nodosa, has been known to exist.[12]

The etiology of FM is not understood, and there are many possible variables, including those not yet discovered. Many viruses or antigenic components of those viruses are present in human tissues and can be detected serologically.

Two pathogenetic mechanisms have been proposed for explaining how an infection can trigger FM.[4] First, direct infection of host tissues or inflammatory mediators released during infection could induce FM. At present, some inflammatory products or cytokines, like IFN-alpha, have been related to FM, although no systematic search has been carried out.[4]

Second, another theory proposes that the stress and anxiety produced by the knowledge of a chronic infectious disease could trigger FM as occurs in Lyme disease. In our work, all patients of hepatitis B virus carriers knew that had hepatitis B virus. These data suggested that an association existed between infection by hepatitis B virus and FM in some patients. Age and female sex were important factors in the appearance of FM. Presence of hepatitis B virus could also trigger FM by unknown mechanisms.

Another possible related factor is the finding of low IGF-1 levels in fibromyalgia.[13] The majority of circulating IGF-1 is produced by the liver in response to growth hormone (GH) secreted by the pituitary. Both IGF-1 and circulating GH are important for muscle homeostasis.[14,15] GH deficiency seems to be responsible for the musculoskeletal pain and fatigue in some patients with FM, as evidenced by significant improvement in these symptoms with parenteral GH supplementation.[16] One can thus speculate that the musculoskeletal pain and fatigue reported by hepatitis B virus- and hepatitis C virus-infected patients is the result of the factors common to all liver diseases such as reduced IGF-1 levels, and that the increased frequency of FM of the hepatitis B group is the result of particularly depressed IGF-1 levels or additional factors such as chronically stimulated immune system. We have not measured IGF-1.

In conclusion, according to the present study, chronic hepatitis B infection appears to increase the risk of FM. One possible confounding variable in this study is selection bias, because symptomatic hepatitis B virus-positive patients may be referred to an infectious disease outpatient clinic with greater frequency than asymptomatic patients.

Further studies of hepatitis B virus-positive patients in the community at various stages of disease are required to determine the contribution of hepatitis B virus to FMS.

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