



## Relationship between HBV DNA Positivity and Migraine in Patients with Chronic Hepatitis

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### Authors' contributions

This work was carried out in collaboration between all authors. Author OD designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors SV, EA and TC managed the literature searches, analyses of the study performed the spectroscopy analysis and authors RT and FB managed the experimental process. Author HHO identified the species of plant. All authors read and approved the final manuscript.

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### ABSTRACT

**Purpose:** Migraine headache is one of the oldest diseases known to mankind, affecting thousands of people throughout the world. The objective of this study is to compare the frequency of migraines in the patient group previously diagnosed with chronic hepatitis-B to the migraine frequency in the healthy control group.

**Materials and Methods:** Patients who presented to Dicle University Hospital and who were diagnosed with chronic hepatitis-B were enrolled in the study. The viral hepatitis markers, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hepatitis-b virus DNA (HBV

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DNA), and their levels were included in the evaluation. The control group consisted of healthy individuals with no hepatitis-B detected in the previous screenings. Chronic fatigue observed in the patient group was recorded, and the degree of fatigue was assessed according to the Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F). Approval of the local ethics committee was obtained for this study.

**Results:** The frequency of migraines in patients who tested positive for HBV DNA was significantly higher than in those who tested negative for HBV DNA ( $p < 0.05$ ). Chronic fatigue was also significantly higher in the study group compared to the control group ( $p = 0.01$ ), and their HBV DNA levels were correlated with the VAS-F score ( $r = 0.532$ ;  $p < 0.001$ ).

**Conclusion:** Migraine was found to be correlated with fatigue and the HBV DNA ratio in chronic hepatitis B patients.

*Keywords: Hepatitis B; migraine; HBV DNA positivity; relationship.*

## 1. INTRODUCTION

Migraine-type headache is one of the oldest diseases of mankind, affecting thousands of people the world over. For centuries, remedies have been sought to ease the sufferer's pain. Also known as hemicrania, which means 'half of the head' [1], migraine is ranked 19<sup>th</sup> among diseases causing workforce loss by the World Health Organization (WHO) [2]. A chronic, paroxysmal and neurovascular disease, migraine can start in childhood, although onset is often during adolescence with more than 80% of patients experiencing attacks before the age of 30, although attack frequency diminishes with age [3]. Of those suffering with migraine, disease prevalence among Caucasian females is estimated to be 13-25% and 4-8% in males, with a female / male ratio of 3/1 [3].

Immune mechanisms play a role in the pathogenesis of migraine, and previous studies have demonstrated a relationship between migraine and infectious conditions such as *Helicobacter pylori*, Chlamydia, and HIV [4,5,6]. However, the specific relationship between Hepatitis B virus infection and migraine has not yet been investigated. We have based our study on the assumption that there may be a relationship between migraine and HBV infection, which implicates the immune system. Hepatitis B is a DNA virus and can remain asymptomatic and undiagnosed for years and, if left undetected, can cause a wide spectrum of liver diseases from acute hepatitis to chronic hepatitis (including liver dysfunction due to fulminant hepatitis), cirrhosis, and hepatocellular carcinoma [7]. It is important to note that the individual immune response to these diseases can determine the extent of liver damage [8].

Turkey is a medium endemic level country in terms of HBV frequency, and approximately 3

million people are estimated to be infected with HBV [9]. Carriers of HBV have an increased risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Of the chronic hepatitis B patients, 15-45% may develop serious complications and/or sequels at any point of their lives [10]. And although there is no study as yet on the frequency of migraines among chronic hepatitis B patients, recently a patient who developed migraine attacks during treatment for chronic hepatitis C was presented in a letter to the editor [11]. This study's purpose will be to investigate the frequency of migraines in HBV DNA positive patients as compared with HBV DNA negative patients.

## 2. MATERIALS AND METHODS

The study group consisted of patients who had presented to the Dicle University Hospital Infectious Diseases Clinic between November 2012 and December 2012, were diagnosed with chronic hepatitis B, and were followed up without active treatment. The approval of the Dicle University Medical Faculty Ethics Committee was obtained for this study (Ethical Number 82). Fifty-one patients diagnosed with chronic hepatitis B and fifty-two healthy controls were enrolled. The inclusion criteria for the patient group was: Hepatitis B Surface Antigen- (HBsAg) positive for more than 6 months; normal or high alanine amino transferase (ALT) values; HBV DNA positive or negative; and Hepatitis B e-antigen- (HBeAg) positive or negative.

The control group comprised healthy individuals who were found to be hepatitis B negative during screening. The exclusion criteria for the control group was: diabetes mellitus, liver cirrhosis, hypertension, coronary artery disease, chronic obstructive pulmonary disease, corticosteroid treatment, malignancies, morbid obesity, pregnancy, liver and kidney failure, and previously diagnosed with migraine.

Every participant in the patient and control groups filled out a form containing the 2004 International Headache Association (IHS) diagnostic criteria; migraine diagnoses were based on these criteria. The patient and control groups were evaluated based on information obtained during enrolment, which included symptoms, risk factors, and routine laboratory tests. The participants' age, sex, complaints at presentation, physical examination and laboratory findings, and migraine attacks were assessed. Fatigue level was evaluated by Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F) [12]. Each was tested for a complete blood count (CBC) and biochemical parameters. Viral hepatitis markers, aspartate amino transferase (AST), (ALT), and HBV DNA levels were also evaluated.

For the patient group, in order to analyse migraine frequency, we first tested the relationship between HBV DNA positivity and HBV DNA levels, first isolating the DNA using the COBAS®AmpliPrep Total Nucleic Acid Isolation Kit (Roche Molecular Systems Inc., Branchburg, NJ, USA). After the DNA was isolated, the levels were evaluated with the COBAS®AmpliPrep/COBAS®Taqman® HBV Test v2.0 (Ibid.). The HBV DNA levels of the patients were then recorded in IU/ml. Within the patient group, those who were positive HBV DNA were statistically compared to those who were negative HBV DNA in relation to the percentage of migraine occurrences.

### 2.1 Statistical Analysis

The statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 16.0. The Kolmogorov-Smirnov test was used to confirm the data within the ranges of normal distribution in both groups. A non-parametric test was employed for the variables outside the normal distribution. The comparison of the data between the reciprocal groups was carried out through the Mann Whitney-U and Chi-Square tests. The Chi-Square test with the Yates correction or Fisher's exact test was used for the comparison of

non-parametric values. The independent-samples t-test was used to examine the differences in sleep quality between the patient and control groups. Correlations between sleep disturbance, depression, quality of life, functional status and the SSC-related variables were investigated with the help of Spearman's correlation. Statistical significance was based on a value of  $p < 0.05$  with a 95% confidence interval.

### 3. RESULTS AND DISCUSSION

The clinical and demographic characteristics of the patients and the healthy controls are listed in Table 1. The mean age was  $33.8 \pm 12.09$  years. No statistically significant difference was observed between the patient and control groups in terms of the percentage of the migraine frequency ( $p = 0.113$ ). However, the migraine frequency among those who were HBV DNA positive in the patient group was statistically significantly higher than in those who were HBV DNA negative ( $p = .05$ ). In the patient group, 20 suffered with migraine; of those patients, 13 were HBV DNA positive. Chronic fatigue was more frequently observed among the patient group than in the control group ( $p < .001$ ); and the HBV DNA levels in the patient group correlated with the VAS-F score ( $r = 0.532$ ,  $p < .001$ ) (See Table 2). In sum, increased levels of HBV DNA were reflected by increased chronic fatigue; and chronic fatigue can increase the frequency of migraines.

Migraine is the most commonly observed type of headache and can be relieved through medical treatment. The mistakes made during its diagnosis and the inadequate treatments prescribed lead to workforce losses [13]. Although there are no studies focussing on the relationship between migraine and hepatitis B, there are reports about patients who were diagnosed with migraine subsequent to hepatitis C treatment. A case report published as a letter to the editor emphasized that the migraine attacks that develop during treatment for chronic hepatitis C may affect the success of the treatment.

**Table 1. Clinical and demographic characteristics of the patient and control groups**

	Patient group (n=51)	Control group (n=52)	P
Mean age (years)	33.8±12.09	34.2±10.8	0.85
Gender (female/male) (n)	24/27	26/26	0.85
The existence of migraine	26(51%)	18(34%)	0.11

*Statistical significance was based on a value of  $p < 0.05$*

**Table 2. Evaluation of the HBV DNA levels and the migraine and fatigue rates in the patient group**

	R	P
Correlation between the fatigue score and HBV DNA	0.532	<0.001
Ratio of migraines in among the HBV DNA positive and negative patients in the patient group		<0.001

The report reveals the case of a 38-year old male patient who had chronic hepatitis C was started on a regimen of PEGylated interferon (Peg-IFN) and ribavirin. Twelve weeks into the treatment, the patient developed symptoms that included a throbbing headache, nausea, vomiting, and hypersensitivity to light and noises; he was subsequently diagnosed with migraine according to the IHS criteria. In this patient, the migraine attacks were thought to be associated with the anaemia that developed secondary to the ribavirin treatment [11]. Reports in the literature suggest that the cranial ischemia triggered by the anaemia and the increased prostaglandin E2 levels during treatment for hepatitis C may cause migraine attacks in predisposed patients [14].

In another article published as a letter to the editor out of 452 patients under treatment with interferon (IFN)  $\alpha$ -2band ribavirin, 9 were reported to experience headaches that required the use of opioids as analgesics. After neurological consultation, these patients were diagnosed with migraine. Among the patients diagnosed with migraine, 7 were newly diagnosed, while 2 had a worsening migraine condition. According to this report, especially when oral ribavirin is added to the interferon treatment, 1.6% of the patients experienced a first onset of migraine. It has therefore been recommended that chronic hepatitis C patients should be closely monitored for headaches during treatment with the combination of IFN and ribavirin. The migraine attacks were observed to subside after the treatment with ribavirin was discontinued [15]. In another study, 50 patients with hepatitis B-related cirrhosis and migraine were evaluated, and all patients were *H. pylori* positive. In these patients, the treatment given for the eradication of *H. pylori* seemed to reduce the frequency, intensity, and duration of the migraine attacks. In fact, some have suggested that the relationship between the *H. pylori* infection and migraine should be investigated in order to explain the pathogenesis of migraines [16].

No statistically significant difference in migraine attacks was observed in our study between the hepatitis B patient group and the healthy controls. However, in the patient group when those who were positive for HBV DNA were compared with those who were negative for HBV DNA, the frequency of migraine was found to be statistically significantly higher among those who were HBV DNA positive. Migraines can be triggered by various environmental factors such as stress, changes in sleep and eating patterns, loud noises, stinging smells, and blinking lights [17]. Symptoms of chronic hepatitis B are much less apparent. Some patients may feel severe fatigue and somnolence, or discomfort on the right side of the abdomen. Chronic hepatitis B is a chronic viral disease and this patient population experiences chronic fatigue and accompanying sleep disorders. In our study, we found that the frequency of migraine symptoms was greater in the patients with chronic fatigue; however, our patient population was not large enough to reach a definitive result. However, our findings may be supported by larger-scale studies.

In recent years, the connection of infectious diseases, immune response, and gastrointestinal disorders to migraine-type headaches has been established [4]. It is a known fact in the medical community that immune-related processes play a role in the pathogenesis of HBV infection and that the immune system of the host is pivotal in overcoming the infection [18]. We know that the main mechanism of immunity is the lysis of the infected hepatocytes by the cytotoxic T-cells [19]. We also know that the cytotoxic T-lymphocyte response plays an important role in determining the progression of HBV infection and that the cytotoxic cells are responsible for the clearance of the virus and the destruction of the virus-infected hepatocytes. Secondary mechanisms mediated by inflammatory cytokines such as TNF-alpha and IFN-gamma have also been shown to play a role [20,21].

When we look at the immune pathogenesis of migraines, experimental studies have demonstrated that when the trigeminal ganglion is stimulated, platelet aggregation occurs, degranulation is triggered, and histamine is released from the mast cells [22]. When the mast cells are activated, prostaglandin D2, leukotriene C4, IL 4-13 and TNF alpha are released [23]. In another study focussing on the diseases of the immune system such as HIV, problematic headaches were observed to be common among these patients. The majority of these headaches

are consistent with chronic migraine. It was also emphasized in this study that headaches are strong indicators of the severity of the disease [4].

#### 4. CONCLUSION

Our study found that the frequency of migraines among patients with chronic hepatitis B was not higher than the healthy control group. Still, the frequency of migraines was significantly greater in patients with higher HBV DNA values. This difference was attributed to the correlation of the fatigue score with the HBV DNA value. Therefore, reducing the HBV DNA levels through antiviral therapy may also diminish the frequency of migraines among chronic hepatitis B patients. A major limitation to our study is the relatively small sample size. There is a need for studies conducted on a larger patient group in order to more fully describe the relationship between hepatitis B and migraine.

#### CONSENT

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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