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Relationship between intracellular pathogens Toxoplasma gondii and Borrelia burgdorferi infections and migraine

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ABSTRACT

Aim: In this study, the serological values of our patients followed up with a diagnosis of migraine were compared with the results of healthy controls in terms of possible association with intracellular pathogens, *Toxoplasma gondii* and *Borrelia burgdorferi*.

Methods: Fifty patients with migraine, randomly selected among migraine patients without any additional disease, who applied to Bolu Abant Izzet Baysal Training and Research Hospital between January 1, 2015 and August 31, 2019 were included in the study. Fifty subjects without headache were included as control group. The history of infectious diseases of the patient and control groups (*Toxoplasma gondii, Borrelia burgdorferi*-causing Lyme disease) was determined by serological diagnostic methods.

Results: The study group consisted of 64 women with a mean age of 45.5±13.1 (15-76) years. Migraine and control groups were found to be similar in terms of age (p=0.059) and gender (p=0.211) distributions. The frequency of *Toxoplasma gondii* positivity in the migraine group was 28% (n=14) and 10% (n=5) in the control group. The frequency of Lyme was 19.6% (n=11) in the migraine group and 14.3% (n=8) in the control group. The frequency of *Toxoplasma gondii* positivity was statistically significantly higher in the migraine group (p=0.022), while the frequency of Lyme was found to be similar in the migraine and control groups (p=0.450).

Conclusion: The results of our study suggest that there are statistically significant differences between migraine and control groups only in terms of *Toxoplasma gondii* positivity rates, not Lyme. However, we believe that larger sample studies are needed to determine the detailed relationship between migraine and *Toxoplasma gondii* infection.

Key words: Migraine disorders, Toxoplasma gondii, Borrelia burgdorferi, Lyme, serum immunoglobulins.

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Introduction

Migraine is a form of recurrent headache experienced by approximately 10% of the population, with a 3:1 female-to-male ratio [1]. It is renowned for severely disabling headache attacks which last 4–72 hours, are often unilateral, and are exacerbated by routine physical activity. These attacks can also be associated with nausea, photophobia or phonophobia [2].

Many factors, like foods, psychosocial stress, lifestyle factors and smoking have been suggested to trigger migraine [3]. More interestingly, it has been emphasized that some

infections, such as *Toxoplasma gondii* (causing Toxoplasmosis), can be associated with migraine and it has also been reported that some infections can mimic the clinical features of migraine [4-6]. Therefore, screening patients diagnosed with migraine in terms of these infections may be beneficial for diagnosis and treatment in migraine. Although the relationship between *Toxoplasma gondii* and migraine has been studied relatively more frequently, there are very few studies examining the relationship between migraine and other diseases caused by intracellular pathogens, such as Lyme [5,6]. Lyme disease, usually caused by infection with the spirochete *Borrelia burgdorferi*, is a multisystem disease caused by the body's immune response to infection [7]. These patients may present with physical findings such as headache, meningismus and cranioneuropathy as a sign of aseptic meningitis [7,8].

In this study, the serological values of our patients followed up with a diagnosis of migraine were compared with the results of healthy controls in terms of possible association with intracellular pathogens, *Toxoplasma gondii* and *Borrelia burgdorferi*.

Materials and methods

Patient and control groups

In this study, patients with migraine who had applied to the Neurology Clinic of Bolu Abant Izzet Baysal Training and Research Hospital, between January 1, 2015 and August 31, 2019 were included. A healthy control group comprised of patients who had applied to the clinic in the study period were also included.

Between the specified dates, a total of 50 patients with migraine attended follow-up or were newly diagnosed. Additionally, patients without migraine who had been admitted for other symptoms but were not diagnosed with any neurological condition were included as healthy controls. Among these, patients with any other chronic diseases, history of surgery or malignancy, those with other neurological or psychiatric diagnoses, and individuals who refused to participate in the study were excluded from the analyses. A final total of 50 patients with migraine and 50 controls had undergone serological analyses for Toxoplasmosis and Lyme.

Necessary permissions were obtained from the Clinical Research Ethics Committee of Bolu Abant Izzet Baysal University to conduct the study. (Approval number: 2020/245, Approval date: 13/10/2020) and all the patients were informed about the study and their written informed consents were obtained.

Serological method

The infectious disease history of the patient and control groups (*Toxoplasma gondii*, Lyme) was determined by serological diagnostic methods.

A commercial ELISA kit (Bio-Rad, France) was used for the detection of *Toxoplasma gondii* IgG and IgM antibodies. The presence of Lyme disease serology was assessed via ELISA (Anti-Borrelia IgG and IgM Generic Assay, Germany) in serum samples. All detection procedures were performed according to the manufacturer's instructions. Presence of either or both IgG and IGM antibodies was accepted seropositive

Sample size and statistical analysis

For the sample size, it was determined that at least 50 subjects should be included in each group according to power analysis performed with the following parameters: 5% error margin, 80% power, an expected odds ratio of 3 with a 50% frequency distribution of infection.

The SPSS version 20 program was used for the analysis of all data. The Shapiro-Wilk test was

used to evaluate compliance with normal distribution. For continuous data, median, lowest and highest values (min-max) and/or mean ± standard deviation were preferred for the description of data, with respect to normality of distribution. The Mann Whitney U or Student's t-test was used for the comparison of continuous data between groups in the presence of non-normal and normal distribution, respectively. Pearson Chi-Square test was used for the comparison of categorical data. The $p<0.05$ threshold was defined as the level of significance.

Results

The study group consisted of 64 females and mean age was 45.5±13.1 (min-max: 15–76) years. The migraine and control groups were similar in terms of age (p=0.059) and gender distribution *(p=0.211)*.

Toxoplasma gondii positivity was detected in 14 (28%) patients in the migraine group and in 5 (%10) subjects in the control group. The frequency of *Toxoplasma gondii* positivity was statistically significantly higher in the migraine group compared to the control group *(p=0.022)*.

Lyme positivity was detected in 11 (19.6%) patients in the migraine group and in 8 (14.3%) subjects in the control group. There was again no significant difference between the groups *(p=0.450)* (Table 1).

Discussion

The present study, in which we aimed to determine whether there were relationships between migraine presence and intracellular pathogens, demonstrated that there was no difference between the migraine and control groups in terms of Lyme positivity frequency. However, of note, the frequency of *Toxoplasma gondii* positivity was higher in the migraine group compared to controls.

In previous studies, *Toxoplasma gondii* has been shown to be a neurotrophic pathogen and is associated with neurological and neuropsychiatric symptoms [9-11]. In addition, the relationship between migraine, headache and *Toxoplasma gondii* has also received relatively high interest [5,8,12]. It has been

Table 1. Age and gender characteristics and infection positivity frequencies of the study.

Parameters	**Control group n=50**	**Migraine group n=50**	***p-value***
Age, years, mean ± SD	44.3±15.23	47.5 ± 10.8	*0.059*
Gender, n (%)			
Female	29 (58.0%)	35 (70.0%)	*0.211*
Male	21 (42.0%)	15 (30.0%)	
***Toxoplasma gondii*, n (%)**			
Negative	45 (90.0%)	36 (72.0%)	*0.022*
Positive	5 (10.0%)	14 (28.0%)	
Lyme (*Borrelia burgdorferi*), n (%)			
Negative	44 (88.0%)	40 (80.0%)	*0.275*
Positive	6 (12.0%)	10 (20.0%)	

reported that this infection affects the levels of specific cytokines, causing edema in the brain, which may manifest as headaches [13,14]. In addition, in a study by Koseoglu et al., it was reported that *Toxoplasma gondii* was associated with migraine and was concluded that this infection may cause a neuroinflammatory process in the brain, thereby triggering migraine [8]. In a study comparing 105 patients with headache and 105 non-headache subjects, it was reported that the case and control group were similar in terms of Toxoplasma seropositivity [15]; however, interestingly, the level of IgG for *Toxoplasma gondii* was suggested to be associated with headache –even when the patient group included other types of headaches in addition to migraine (39 patients with migraine in the 105 subjects). Since this infection is very prevalent among humans, has a chronic characteristic in an estimated 30% of individuals [16] and the fact that the infection may persist in the brain [17], have supported the rationale of studies aiming to determine a relationship (if any) between headache and *Toxoplasma gondii* infection. One such study even suggested the introduction of serological testing for *Toxoplasma gondii*, after demonstrating that 11% of children with recurrent headaches had IgG positivity [12]. In a study from Brazil, wherein 261 cases with acute toxoplasmosis were investigated, headache frequency was reported to be the second most frequent symptom (after fever), and perhaps more interestingly, the distribution among sexes demonstrated a female-to-male ratio of 2.1 to 1 [18]. In the current study, to support the information in the literature, the frequency of *Toxoplasma gondii* positivity was significantly higher in patients with a diagnosis of migraine. We believe that these results indicate that the relationship between migraine and toxoplasmosis warrants further investigation, preferably in population-based studies.

When *Borrelia burgdorferi*, the cause of Lyme disease, reaches the cerebral or spinal vessels, it attaches to endothelial cells. It has been reported that the direct and indirect effects of *B.burgdorferi* on the nervous system play a role in the formation of neuroborreliosis [19]. In a previous study, it was reported that *B. burgdorferi* invaded human neuronal and glial cells, remained alive and had no cytopathic effect on the host cell for up to seven days. It has been reported that this situation can lead to the escape of bacteria from the immune system and to long-term infections [20]. Various mechanisms have been reported in the literature regarding the transmission and action mechanisms of bacteria to the nervous system. Grab et al. reported that with the in vitro blood brain barrier model containing microvascular endothelial cells of the human brain, the passage of bacteria through the barrier depends on the ability of the bacteria to affect the Ca ++ signaling system in endothelial cells [21]. Cepok et al. reported that the early stage of *B. burgdorferi* meningoradiculitis is characterized by a well-coordinated immune response involving specific cytokine release and plasma cell uptake, followed by a prolonged, antigen-specific B cell response in the central nervous system [22]. In the study of Rupprecht et al, it has been reported that chemokines (CXCL13) play a key role in attracting other immune cells to the inflammatory focus in Lyme neuroborreliosis, B cell migration to infection sites [23]. In the animal study of Pachner et al., Cytokines such as IL-6 have been reported to be important amplification molecules for cerebrospinal fluid inflammation in Lyme neuroborreliosis [24]. In Lyme disease, as a result of these changes in the central nervous system, it is expected that Lyme positivity in

migraine patients is higher than in the control group. It has been reported that Lyme disease causes various neurological symptoms such as headache and 15% of patients have neurological involvement [25,26]. Chronic headache associated with Lyme disease is difficult to diagnose and can be confused with primary or analgesic overuse headaches. However, it is important to make the correct diagnosis because when this symptom is associated with borreliosis, it tends to regress with antibiotic therapy [27-30]. In the study of Scelsa et al., it was reported that the incidence of new-onset headache was 53.06% and the incidence of migraine was 18.37% among patients hospitalized for recurrent neurological Lyme disease. In addition, it has been reported that all patients with meningitis or encephalitis requiring intravenous antibiotics have not only headache but also focal neurological findings or cognitive abnormalities [28]. In the current study, the migraine and control groups were similar in terms of Lyme disease frequency. However, few studies have investigated the possible relationship between Lyme disease and migraine. We believe it is very important to point out that the initial design and strength of the study may not be sufficient for such a post-hoc analysis, and therefore we suggest that future studies should consider this possibility.

The research has several limitations. One of its limitations is that the research is not community-based and has a single center. On the other hand, questioning the chronology of the onset of migraine and the positivity of these pathogens (*Toxoplasma gondii*, *Borrelia burgdorferi*) could enable us to see the relationship between migraine and the positivity of these pathogens more clearly. Despite these, this study is valuable because it is one of the few studies evaluating the relationship between migraine and Lyme disease and it shares results that support the relationship between *Toxoplasma gondii* and migraine.

Conclusion

In terms of the infections studied in the study group, there was statistically significant difference was found between patients with migraine and controls. However, further studies that enable comparisons by ensuring an infection distribution similar to that of the population are required.

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Ethical statement: *The study was approved by the Local Ethics Committee of University (D*ate: 13/10/2020, approval number: 2020/245), *and written informed consent was obtained from each subject.*

Open Access Statement

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