

Is Helicobacter Pylori Infection a risk factor for Migraine ? A Case-Control Study

Ayşe TUNCA¹, Cansel TÜRKAY², Oğuz TEKİN³, Ayşe Kargılı⁴ and Mustafa ERBAYRAK²

¹Department of Neurology, ²Department of Gastroenterology, ³Department of family medicine, ⁴Internal Medicine Department, Fatih University Medical School, Ankara, Turkey

Abstract

Background : The relation between *Helicobacter pylori* and Migraine and usefulness of the eradication treatment on headache is controversial. The aim of this study was to determine whether *Helicobacter pylori* infection is a risk factor for migraine and whether the eradication of the bacterium can reduce frequency, duration and severity of clinical attacks of the disease.

Methods : A total 70 consecutive patients with migraine with aura and without aura who came to Gastroenterology polyclinic with various complaints were enrolled in the study and compared with a group of 60 matched controls. *Helicobacter pylori* infection was diagnosed by histopathological biopsies, which was taken by endoscopy (Olympus-GIFXQ240 endoscope). The diagnosis and classification of migraine was made according to the International Headache Society (IHS) criteria. We assessed the frequency, duration and severity of clinical attacks of migraine before and after eradication treatment. The eradication control of *Helicobacter Pylori* was made by *Helicobacter pylori* fecal antigen test by PCR after 2 months.

Results : *Helicobacter pylori* positiveness is more relevant in the migranous patients compared with controls. 84.6% of patients with eradication treatment and 75% of classically treated patients informed to get benefit from the treatment.

Conclusion : *Helicobacter pylori* should be examined in migranous patients and eradication of the infection may be helpful for the treatment of the disease.

Key words : *Helicobacter pylori* infection ; migraine.

Introduction

Primary headache is a common, discomfort clinical event, which has been associated with vascular instability (12). Some authors have explained this phenomenon by hypoxia, neurogenic, vascular and endothelial events, but the pathogenesis is still obscure (1).

It is known that *Helicobacter Pylori* (HP) is a gram-negative organism that causes chronic active gastric inflammation. HP infects approximately half of the world population and the prevalence of

the disease in asymptomatic patients appears to be age-related (2).

In the past few years an association between HP and various extraintestinal pathologies such as coronary heart disease and Raynaud phenomenon have been described (6, 7, 13). Recently a relation between HP chronic infection and migraine and the pathogenic role of the infection has been studied but the results of these studies are controversial (2, 3, 8, 9, 15, 16).

In this study, we aimed to observe the presence of HP in the migrainous patients and the benefits of eradication treatment in the management of disease.

Methods and materials

This is an analytical, observational and case-controlled study. From the same geographical district (Turkish- Ankara population), 70 consecutive patients with migraine with and without aura (57 women, 13 men, mean age 36.8 ± 9 years) who applied to our university hospital gastroenterology outpatient clinic and who had normal laboratory results (blood sugar, liver and renal functions, whole blood count, sedimentation rate and computerised brain tomography) were involved in the study. A neurologist examined all the patients and the diagnosis of migraine was made according to the International Headache Society (IHS) criteria (10). Fourteen of the 70 patients (20%) had diagnosed migraine with aura (13 women and 1 man ; mean age 37.1 ± 10 years) and 56 of 70 patients (80%) had diagnosed migraine without aura (44 women and 12 men ; mean age 36.7 ± 9 years). All the patients were given a headache diary which was including the questions : "Date/time headache started ; How long did the pain last (hour) ; headache severity : 1 = mild, 2 = moderate, 3 = severe (throbbing and accompanied nausea and vomiting) ; what did the patient do to relieve the pain". The severity and the duration (hour) of patients' headache decided for the diary and the frequency (per month) of clinical headache attacks were calculated.

A group of 60 patients without migraine who came to the gastroenterology polyclinic with different complaints and also had normal laboratory results (blood sugar, liver and renal functions, whole blood count, sedimentation rate) (46 women, 14 men, mean age 36.9 ± 7 years) served as controls. The patients of control group were also interrogated by the neurologist using IHS criteria (10) for excluding the diagnosis of migraine and neurological examination was done to all of them for excluding a probable neurological disease.

All the patients with migraine and control group were examined for their gastrointestinal symptoms (such as pyrosis, epigastric pain, belching, bloating). A specialist of Gastroenterology department studied all the study and control group patients using an endoscope. They were given midazolone for premeditation and then were examined by Olympus-GIFXQ240 endoscope. Findings of endoscopy were documented; two different biopsies from antrum and corpus were taken. Materials were fixed with 10% formal and blocked with Parafine by a pathologist. Cross-sections, which were taken from this material, were stained with Hemotoxylene-eosin (HES). Giemsa stain was applied to determine the presence of HP on gland lumens and graded relatively from 1 to 3.

Triple therapy consisting of amoxicillin (1 g; bid), clarithromycin (500 mg; bid) and omeprazol (20 mg/d) were given to all the hystopathologically HP positive patients for 14 days for eradication. HP negative migranous patients were treated with Flunarizine. All the patients were asked to continue to put notes on their diary and were invited for controlling the success of eradication treatment after 2 months. Control was made by HP fecal antigen test by PCR. Again, all the patients were asked for the severity, duration (hour) and frequency of clinical headache attacks (attacks per month) of all the patients were investigated according to their dairy.

All analyses were performed to the intention-to-treat principle. Categorical comparison HP was performed by Binary Logistic regression analysis. Differences in the means of continuous measurements were tested by the Student's t-test and checked by Mann-Whitney-U test. P value of < 0.05 was considered to indicate statistical significance; all tests were two-tailed.

Results

GENERAL FEATURES OF SUBJECTS

Clinical characteristics of migrainous patients and control groups were summarised in the Table 1.

We observed HP positiveness within the 40 cases of migraine group (57.1%) and 20 cases of control group (33.3%). HP infection was more frequent in the migraine group. Statistically difference was

Table 1

Clinical characteristics of Migraine and Control groups

Parameter	Migraine (n = 70)	Control (n = 60)	p
Age (Y : Mean \pm SD)	36.8 \pm 9.5	36.9 \pm 7.8	0.94
Women / men ratio	57 / 13	46 / 14	0.65
HP infection	40 (57%)	20 (33.3%)	0.007**

found with chi -square test and with Binary Logistic regression analysis (see : Table 1 and 2).

Clinical characteristics of HP positive and negative migrainous patients were not statistically different (see : Table 3).

COMPARISON OF ERADICATION TREATMENT AND CLASSIC MIGRAINE TREATMENT

HP positive migrainous patients were given eradication treatment and HP negative migrainous patients were given classic migraine treatment. A total 25 of 70 (36%) migrainous patients [13 from eradicated group (32.5%) and 12 from classically treated group (40%)] came to control after 2 months of treatment.

We cross-examined the benefits of treatment for each group. 11 of 13 eradicated patients (84.6%) and 9 of 12 classically treated patients (75%) informed getting benefit from the treatment such as shortening the duration of pain, reducing the frequency and severity of pain. Headache attacks were completely disappeared in 2 patients of eradicated group (18%) and 1 of classically treated group (11%).

Discussion

This study showed that HP infection is a significant risk factor for migraine with no observational difference between two types (migraine with and without aura). Eradication treatment was helpful on the clinical improvement of pain. HP infected and eradicated patients got much better benefit from that patients who were HP negative and migraine treatment were taken.

There are a few previous studies, which examined the relation of HP infection and migraine with contradictory results. Distinct from these studies, we used endoscopy and pathology for the diagnosis of HP infection.

Gasbarrini *et al.* (8) studied a total of 200 patients affected by primary headache (tension type headache, cluster headache, and migraine with or without aura). They reported that 40% of patients diagnosed as having primary headache were positive for HP infection with 13C-urea breath test. Furthermore, eradication of the bacterium resulted in a significant decrease in intensity, duration and frequency of headache. In another similar study,

Table 2

Logistic Regression outputs for the association between Migraine and Helicobacter Pylori infection

	Coefficient	s.e.	Wald	p	OR 95% CI for OR
Migraine	0.981	0.365	7.215	0.007**	2.667 (1.304 to 5.455)
Constant	- 0.288	0.242	1.419	0.234	0.750

Table 3

Clinical characteristics of HP positive and negative Migrainous patients

	HP positive (n = 40)	HP negative (n = 30)	p
Age (Mean ± SD)	36.8 ± 9.4	36.9 ± 9.8	0.97
Duration of disease (y, mean ± SD)	8.15 ± 6.2	7.9 ± 7	0.88
Frequency of pain (No/month, Mean ± SD)	5.5 ± 5.2	6.1 ± 4.6	0.61
Duration of pain (h, mean ± SD)	22.45 ± 21.6	33.9 ± 26.75	0.06
Women / men ratio	35 / 5	22 / 8	0.21
Aura (n, percent)	9 (22.5)	5 (16.7)	0.547
Without Aura (n, percent)	31 (77.5)	25 (83.3)	0.06
Photophobia (n, percent)	23 (57.5)	19 (63.3)	0.622
Phonophobia (n, percent)	21 (52.5)	18 (60)	0.532
Nausea (n, percent)	33 (82.5)	28 (93.3)	0.196
Vomitus (n, percent)	26 (65)	16 (53.3)	0.325
Severe pain (n, percent)	31 (77.5)	26 (86.7)	0.334

Gasbarrini *et al.* (9) studied 225 patients ; HP was detected in 40% of the patients with 13C-urea breath test. With eradication of the bacterium ; intensity, duration and frequency of migraine attacks were significantly reduced. In our study, we detected HP in 57.1% of our patients and got similar benefit from eradication treatment.

However, contradictory results are present in the English language literatures. Pinessi L. *et al.* (15) examined 98 migrainous patients without aura and 5 patients with aura. HP was diagnosed with 13C-urea breath test and the presence of antibodies (IgG) against the bacterium in serum. The results of that study showed that chronic HP infection is as frequent in patients with migraine as in controls and that this infection is not associated with any significant variation in the clinical features of the disease. In a different study, Savi L. *et al.* (16)

searched the effects of eradication therapy in patients with HP migraine in a small study group and found no significant variation in the frequency, duration, intensity and associated symptoms of migraine attacks.

In another study Caselli M. *et al.* (3) researched the relation of HP in migrenous children with 13 C-Urea breath test. They studied the infection prevalence in 36 children suffering from migraine without aura. They found no relation between HP infection and migraine in children.

Recently it has been suggested that the probable pathogenic role of the HP chronic infection in migraine, based on a relationship between the host immune response against the bacterium and the chronic release of vasoactive substances. The reduction of the vasoactive substances determined by bacterium eradication may be one of the physiopathogenetic mechanisms underlying these observations (8).

During the infection, the bacterium releases in the infected tissue toxins and hydrolytic enzymes promoting the peculiar cascade of events associated to the host immune response alterations of vascular permeability, as a result of released vasoactive substances (4, 5, 11). Superoxide radicals and nitric oxide are also produced (14, 17). As a consequence, lipids, proteins and other cellular components undergo oxidative modifications. The resulting oxidative damage may be assessed as an accumulation of lipid peroxidation by products in the blood. Therefore, the prolonged oxidative injury caused by the persistent infection and the release of vasoactive substances might be involved in regional cerebral blood flow changes during migraine (2).

However we found only one study in the English language literatures for searching the relationship between the host immune response against the HP infection and the chronic release of vasoactive substances. The results of these study found no specific link between the infection and migraine (2).

In conclusion ; the findings of our study correlated well with previous opinions that HP can play a pathogenic role in migraine and the probable relationship might be host immune response against the bacterium. So, according to us, HP might be examined in migranous patients. In HP infected patients eradication treatment will be benefit for relief of clinical attacks.

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Ayşe TUNCA, M.D.,
 Fatih Üniversitesi Tıp Fakültesi,
 Çiftlik Caddesi No : 57,
 06510 Emek-Ankara (Turkey).
 E-mail : etunca@e-kolay.net.