

## *Helicobacter pylori* Infection and Migraine

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### Abstract

**Objective:** To determine whether *Helicobacter pylori* (*H. pylori*) is associated with migraine headache.

**Design:** Case-control study.

**Settings:** Local tertiary Hospitals in Cairo, Egypt and in Hafer Albaten, Saudi Arabia.

**Participants:** A total of 70 patients with migraine who were 7 to 17 years old and who fulfilled the International Headache Society criteria for migraine and a total of 50 controls without migraine who were matched by the country of origin, age, sex, ethnicity, and socioeconomic status to the 70 migraine cases.

**Main outcome Measures:** Antibody levels to *H. pylori* (IgG) and *H. pylori* stool antigens were compared between the two groups.

**Results:** Significant association was found between *H. pylori* and migraine and of the total of 70 migraineur cases, 55.7% were positive for *H. pylori* stool antigen testing compared to 20% in control group (*P* value = 0.0002). Joint pain was reported in 44.3% and 18.0% of cases and controls respectively (*P* value = 0.0034).

**Conclusion:** *H. pylori* is associated with migraine without aura and may be a causative factor. Moreover, *H. pylori* may induce joint pain in the migraineur patients

**Keywords:** *Helicobacter pylori*; Migraine; Headache

### Background

*Helicobacter pylori* (*H. p*) is a gram-negative bacillus responsible for one of the most common infections found in humans worldwide, with more than 50% of the world's population infected, especially in developing countries where those chronically infected can reach up to 90% by adulthood [1]. Children differ from adults with respect to *H. pylori* infection in terms of the prevalence of infection, the complication rate, the near-absence of gastric malignancies, age-specific problems with diagnostic tests and drugs, and a higher rate of antibiotic resistance. These and other differences explain why some of the recommendations for adults may not apply to children [2]. Unless treated, colonization usually persists lifelong and *H. pylori* infection represents a key factor in the etiology of various gastrointestinal diseases [3]. Since *H. pylori* is non-invasive and the infection is accompanied by an exuberant humoral response, one might predict that T helper cell 2 (Th2) response would be predominant within *H. pylori*-colonized gastric mucosa. Paradoxically, most of *H. pylori* antigen specific T-cell clones isolated from infected gastric mucosa produce higher levels of IFN- $\gamma$  than IL-4, which is reflective of a T helper (Th1)-type response [4]. *H. pylori* also stimulates production of IL-12 *in vitro*, a cytokine that promotes Th1 differentiation. These findings raise the hypothesis that an aberrant host response (Th1) to an organism predicted to induce secretory (Th2) immune responses may influence and perpetuate gastric inflammation [5].

Urease and motility using flagella are essential factors for its colonization. Urease of *H. pylori* exists both on the surface and in the cytoplasm, and is involved in neutralizing gastric acid and in chemotactic motility [6]. *H. pylori* infection has been clearly linked to peptic ulcer disease and some gastrointestinal malignancies. Increasing evidence demonstrates possible associations to disease states in other organ systems, known as the extra intestinal manifestations of *H. pylori* [7].

In the recent years, the role of infections and the impact of digestive system disorders on migraine have gained more attention. However, in the last few years, researches have focused on the role of *Helicobacter pylori* activity in the pathogenesis of migraine.

Frequent or severe headaches, including migraine, have been reported in 17% of children and adolescents, and the prevalence of headache in general increases from childhood to adolescence, with an increase in the proportion of tension-type headaches from the early teen years [8]. Migraine is divided into two main categories: migraine with aura, in which patients experience transient visual or sensory symptoms (including flickering lights, spots, or pins that develop 5-20 minutes before attacks), and migraine without aura [9,10].

*H. pylori* infection causes a persistent activation of the immune system, which results in local and systemic release of a variety of vasoactive substances. Recent evidence suggest that infection with *H. pylori* may also be associated with migraine [11]. Several mechanisms such as inflammation, pain mediators such as calcitonin-gene-related peptide (CGRP), and neurotransmitters such as serotonin [11,12] are currently discussed; indeed, serotonin agonists such as triptans can relieve migraine, and selective serotonin-reuptake inhibitors and tricyclic antidepressants have been used successfully as prophylactic treatments [12]. A research explained that gastrointestinal neuroendocrine cells such as enterochromaffin cells (EC cells) can synthesize and secrete serotonin (5-hydroxytryptamine; 5-HT) and some factors that motivate the cell to secrete 5-HT can cause central nervous system (CNS) perturbation via the brain-gut axis, which can demonstrate that most patients with migraine assaults are associated with gastrointestinal (GI) symptoms [13]. Inflammation motivates the cell to secrete 5-HT e.g., when *H. pylori* infect a cell. Eradication of *H. pylori* infection has helpful outcomes to improve clinical attacks [14-17]. This was attributed to the effect of eradication therapy on the inflammation induced high levels of 5-HT [17,18].

Among patients with migraines, different studies have shown increased prevalence of *H. pylori* infection as determined by positive urea breath test [19,20]. Similarly, using serology, *H. pylori* IgG positivity was found to be higher in those with migraines compared to matched controls [21].

### Methods

Approval of this study was received from the administrations of the Hospitals in which the study was conducted in. The routine consents for laboratory diagnosis were implemented for all cases according to Hospital regulations, and the study protocol conforms to the Ethical Guidelines of the 1975 Declaration of Helsinki. Children were recruited through primary care physician offices and Neurological Clinics and Nor-khan General Hospital (Hafer Al Batin, Saudi Arabia) as well as Al-Azhar University Hospitals Cairo, Egypt. All participants between 7 years and 17 were investigated for *H. pylori* using two laboratory tests. (*H. pylori* IgG and *H. pylori* stool antigen).

The present case-control study contains information of 70 patients of migraine without aura whose severity was assessed by experienced neurologist and according to the International Headache Society criteria [Headache Classification Committee of the International Headache Society] [22].

The inclusion criteria for the patients were age between 7 and 17 years, without gastrointestinal symptoms (such as epigastric pain, belching, bloating) or receiving any nonstandard medication or any treatment for *H. pylori*, and physical and mental ability to give written consent form.

Controls were 50 randomly selected from companions of non-migraines patients referring to the Hospitals at the about same time as cases. Group matching was done according to age, sex, educational level, geographical origin, and socio-economic status. Required information including age, sex, gastro-intestinal (GI) disorder, history of infant colic, history of migraine in family, degree of headache and

sleep disorder was obtained from all the people in the case and control groups by interviewing and completing a questionnaire. The antibody (immunoglobulin G – IgG) titer of all individuals in the case and control groups (against *H. pylori*) was assessed by Enzyme Linked Immunosorbent Assay (ELISA). It is noteworthy that the geographic distributions of eligible participating children add more strength to the design of the study.

Additionally, the *H. pylori* stool antigen testing was done for all participants. This one-step test is a chromatographic immune assay for the qualitative detection of *H. pylori* infections (Alcon Laboratories Inc.). It is a relatively simple, reliable, more applicable, and noninvasive test of *H. pylori* infections in children. *H. pylori* fecal antigen has shown a high degree of sensitivity, specificity, and positive and negative predictive values [23] IgG is much more specific in children than adults, affirming the fact that adults are more likely to have been exposed to *H. pylori* in the past [24,25]. IgM was not implemented for investigation as it has been found to have little diagnostic utility for *H. pylori* infections and is elevated only acutely after infection, whereas *H. pylori* infections are generally chronic [26].

Statistical software SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA) was used for all statistical calculations. The comparison of clinical characteristics of study groups with regarding measured variables was achieved by t-tests. Associations between *H. pylori* antibodies and severity of headache were estimated using Pearson correlation coefficient.  $P \leq 0.050$  was considered in all tests as a significant level. The demographic characteristics of cases and controls were compared using the Fisher exact test, and odds Ratio.

**Results**

Among the 120 enrolled participants, there was homogeneous distribution in both groups regarding to age, sex, race, family size, insurance status, and education. In migraine cases, there were 37 girls (52.9%) and 33 boys (47.1). In control, the enrolled girls and boys were 54% and 46% respectively. The mean age was  $(10.6 \pm 5.3)$  and  $(10 \pm 8.7)$  years for case and control groups respectively. *H. pylori* IgG was  $31.08 \pm 7.8$  and  $18.82 \pm 6.2$  in case and control groups respectively, 95% CI = -14.90 to -9.63, P value < 0.0001 (Table 1). Of the total 70 migraine cases, 39 cases (55.7%) tested positive *H. pylori* stool antigen compared to 10 controls (20%). OR = 5.03, 95% CI = 2.18 to 11.64, P value = 0.0002. History of infant colic was reported in 58.6% of cases compared to 24.0% in control (OR = 4.48, 95%CI = 2.00 - 10.00, P value = 0.0003). Joint pain was 44.3% compared to 18.0% in control (OR = 3.62, 95%CI = 1.53 to 8.57, P value = 0.0034).

Variables	Healthy control (n = 50) Mean ± SD	Migraine (n = 70) Mean ± SD	P Value
Age (years)	10 ± 8.7	10.6 ± 5.3	0.64
IgG(units/ml)	18.82 ± 6.2	31.08 ± 7.8	< 0.0001
HIT6	--	59.4 ± 5.3	< 0.001

**Table 1:** Baseline characteristic of migraine patients and healthy control regarding age, H pylori IgG and Headache Impact Test (HIT6) questionnaire

IgG: Immunoglobulin G; HIT6: Headache Impact Test Questionnaire.

Highly significant difference between the groups regarding H pylori IgG and HIT6.

Variables	Healthy control, Number (%)	Migraine, Number (%)	OR	95%CI	P value
<i>H. pylori</i> stool antigen test	10(20.0)	39 (55.7)	5.03	2.18 - 11.64	0.0002
History of infant colic	12(24.0)	41(58.6)	4.48	2.00 - 10.00	0.0003
Joint pain	9(18.0)	31(44.3)	3.62	1.53 - 8.57	0.0034

**Table 2:** Comparison of H pylori stool antigen test, infant colic and joint pain in control and migraine groups.

OR: Odds Ratio; CI: Confidence Interval

Highly significant difference between the groups recorded in all variables.

## Discussion

There has been a recent surge of research evaluating the increased evidence of possible associations of *H. pylori* to disease states in other organ systems, known as the extra intestinal manifestations of *H. pylori*. Different conditions associated with *H. pylori* infection include those from hematologic, cardiopulmonary, metabolic, neurologic, and dermatologic systems. The aim of this study is to provide a concise evidence that supports the associations of *H. pylori* and migraine headache. There is a complex interplay between certain unique players that is the complex combination of environmental, host, and bacterial factors which ultimately determines the susceptibility and severity of outcome of *H. pylori* infection and related pathology. Based on the literature review, this is the first study attempting to find a correlation between the severity of headache (in terms of HIT6) in one side and *H. pylori* antibody levels and *H. pylori* antigens in migraineur's children without aura in the other side. As there is a prominent variation in the prevalence of *H. pylori* infection, also there is parallel variation in the prevalence of migraine. The connection between the brain and the gastrointestinal system is imperative to the regulation of the digestive tract and maintenance of the gut immune system.

The results of this study suggest that the relationship between migraine and *H. pylori* infection is a complex one, at least in this clinical sample of children referred for *H. pylori* testing. The genetic diversity of *H. pylori* and the variations in human host response to the microorganism underlie the complex host-pathogen relationship that determines the natural history of infection. Our study results concord with a recent meta-analysis study reported that a total of five case-control studies, showed that *H. pylori* infection is indeed a risk factor for migraine [27]. These studies recruited patients who mainly suffered from migraine without aura because this subtype of migraine seems to be caused by a combination of genetic and environmental factors, whereas migraine with aura is probably determined largely, or exclusively, by genetic factors [28,29]. It has been suggested that the pathogenic role of the *H. pylori* infection in migraine, is based on a relationship between the host immune response against the bacterium and the chronic release of vasoactive substances. Postulated factors of the relationship between migraine and *H. pylori* infection included inflammation, oxidative stress, and nitric oxide imbalance [16,30,31]. During the infection, the bacterium releases toxins in the infected tissue, thus promoting the special cascade of events related to the host immune response alterations of vascular permeability [16,31-34]. Therefore, the prolonged oxidative injury caused by the persistent infection and the release of vasoactive substances might be involved in local cerebral blood circulation changes during migraine attacks [35].

The results show that the level of *H. pylori* IgG is correlated with the migraine severity and this could be explained by the study of Asghar et al, that reported relationship between the host immune response against the *H. pylori* infection and the chronic release of vasoactive substances [36]. This is logically interpreted if considering the chronic inflammation that is perpetuated by *H. pylori* infection. It has recently been demonstrated that only microbial stimuli characterized by the induction of TLR (toll-like Receptor) activation and Th1 responses can activate natural killer cells, which then assist in the initiation of this type-1 response [37]. As a result, the extent of bacterial infection coincides with the severity and progression of the migraine headache. It is the level of stimulation which induces T helper cells differentiation into cells expressing either Th1 cytokine or Th2 cytokine phenotype [38]. Consequently, Development of migraine in subset of individuals is characterized by the Th1 induced high level of microbial stimulation.

Our results reveal correlation between migraine and history of infant colic. This correlation might be explained by the studies of Silanpaa [39] and Romanelli, *et al* [40]. The authors postulated a molecular link between these two conditions in the form of CGRP, which is released during migraine attacks and is potentially also involved in the pathogenesis of abdominal pain by causing inflammation of sensory GI neurons. Additionally, our results recovered relationship between migraine and joint pains, this could be interpreted in the light of the CGRP induced synovitis, where it was found that CGRP contributes to transition from normal to persistent synovitis, and the progression from nociception to sensitization [41]. Also, CGRP may play a role in pain transmission in somatic pain conditions such as joint and muscular chronic pain [42].

## Conclusion

*H. pylori* is associated with migraine without aura and may be a causative factor. Moreover, *H. pylori* may be the pathogenetic mechanism of joint pain in susceptible migraineur patients.

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