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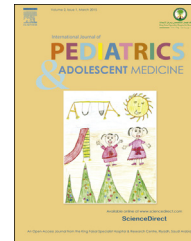


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ORIGINAL RESEARCH ARTICLE

Is *Helicobacter pylori* infection a risk factor for childhood periodic syndromes?



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Abstract *Background and objectives:* *Helicobacter pylori* (*H. pylori*) infection has been assumed to have roles in various extra-digestive diseases. The current study was designed to evaluate the incidence of *H. pylori* infection in patients with cyclic vomiting syndrome and its possible role in the etiology of this disease.

Design and setting: In this case-control study, 120 cases with diagnoses of cyclic vomiting or abdominal migraine who were registered at the Gastroenterology Clinic at Shiraz University of Medical Sciences from 2010 to 2013 were enrolled.

Materials and methods: Primarily information regarding the patients' diseases were collected with a data gathering sheet, and fresh morning stool samples were collected from the patients and examined for *H. pylori* stool antigen with the *H. pylori* Ag EIA test kit. The results were compared with those of healthy children from the control group.

Results: A total of 120 patients with cyclic vomiting (47.5%) and abdominal migraine (52.5%) with a mean age of 7.1 ± 3.4 (range 2–16 years) and a male-to-female ratio of 1.6 were included. The HPs Ag tests were positive in only 7 (5.8%) patients in our case group, and the HPs Ag tests were positive in 13 (13%) of the children in the control group; this difference was statistically insignificant.

Conclusion: Our study did not support *H. pylori* infection as an etiological factor in CV or AM. Copyright © 2015, King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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1. Introduction

Within several years of its discovery in approximately 1982, the association of *Helicobacter pylori* (*H. pylori*) infection with antral gastritis was completely accepted [1]. However, in recent years, in addition to its gastrointestinal functions, the roles of *H. pylori* infection have been assumed to extend to various extra-digestive diseases [2].

The pathogenesis of these extra-intestinal manifestations seem to be related to the chronic nature of the infection and the persistent inflammation it causes. It has been proposed that this chronic inflammation can have direct (i.e., the effects of the infectious agent on the vascular wall) and indirect (i.e., the production of inflammatory mediators) effects, which likely explain the association of these extra digestive diseases with *H. pylori* infection [3].

Different studies have revealed the involvement of this infection within vascular [4–7], autoimmune [8,9], and skin diseases [10]. Lately, many studies have implicated the relationship between *H. pylori* infection and migraine headaches in both children and adults [11–14]. The basis of these studies is related to the fact that migraine headaches seem to have a vascular pathogenesis [15]; moreover, previous investigations have revealed the relation of *H. pylori* infection with diseases of vascular origin, such as atherosclerosis and the Raynaud phenomena [16,17]. As previously explained, the probable pathogenic role of chronic *H. pylori* infection in these cases is based on the relationship between the host immune response against the bacterium and the chronic release of vasoactive substances [13].

The link between cyclic vomiting (CV) and migraine headaches was first expressed in 1904 [18]. Due to similarity of the stereotypical clinical presentations, the progression of CV to migraine headaches, and the frequent occurrence of CV in children with family histories of migraine, later in 1933, Wyllie and Schlesinger described a term called childhood periodic syndrome that included abdominal migraine (AM), cyclic vomiting syndrome, and

benign paroxysmal vertigo that persists into adult life as migraine attacks [19]. In the recent years, this syndrome has been accepted as a migraine variant in children [20]. The cause of CV is still unknown; however, due to the resemblance of their clinical presentations, it has been speculated that migraine headaches and CV share similar mechanisms [21]. Other hypotheses that have been described for the pathogenesis of these diseases include autonomic instability, disturbances in the hypothalamic-pituitary-adrenal axis, mitochondrial disorders, and abnormalities in ion channels [22].

Based on these facts, the current study was designed to evaluate the incidence of *H. pylori* infection in patients with CV as a possible etiologic factor in the pathogenesis of the disease that has not previously been proposed elsewhere.

2. Materials and methods

One hundred twenty cases with diagnoses of CV or AM according to the IHC_ Classification ICHD_II (Table 1) [23] who were registered at the Gastroenterology Clinic at Shiraz University of Medical Sciences from 2010 to 2013 were enrolled in this study. Moreover, a control group consisting of healthy children who were referred to the out-patient clinic affiliated with the Shiraz University of Medical Sciences for routine health care visits was considered. These children were matched to the case group in terms of age and sex.

All patients and their parents were informed of the aims of the study, and written consent was attained. This study was approved by the ethical committee of our institution.

Prophylactic treatment with propranolol (1 mg/kg/day) had been initiated for all of the patients following the diagnoses of CV or AM, and this treatment had been gradually tapered in the patients group (50.8%) who had been symptom free for at least 6 months on prophylactic medication.

Primarily information regarding the patients' diseases was collected on data-gathering sheets and included

Table 1 Diagnostic criteria for abdominal migraine and Cyclic vomiting.^a

Abdominal migraine	Cyclic vomiting
A- At least 5 attacks fulfilling criteria B-D	A- At least 5 attacks fulfilling criteria B and C
B- Attacks of abdominal pain lasting 1–72 h (untreated or successfully treated)	B- Episodic attacks that are stereotypical in the individual patient and include intense nausea and vomiting lasting from 1 h to 5 days
C- Abdominal pain with all of the following characteristics:	C- Vomiting during attacks occurs at least 4 times/hour for at least 1 h
1. Midline location, periumbilical or poorly localized	D- Symptom-free between attacks
2. A dull or only sore quality	E- Not attributable to any other disorder
3. Moderate or severe intensity	
D- During abdominal pain at least 2 of the following occur:	
1. Anorexia	
2. Nausea	
3. Vomiting	
4. Pallor	
E- Not attributable to any other disorder	

^a IHC_ Classification-ICHHD_I.

following: the final diagnosis, the duration of illness, the frequency of attacks per year, the duration of each attack, the associated symptoms, the drugs received, and positive family histories of migraine headaches.

Furthermore, fresh morning stool samples were collected from each child for the evaluation of the *H. pylori* antigen. At the time of sampling, the patients were on no medications, such as antibiotics or proton pump inhibitors. The patients were educated regarding how to avoid contaminating the stool samples with urine or water as such contamination could lead to false laboratory results. The collected samples were stored at 2–8 °C and immediately delivered to the laboratory within 24 h of collection. *H. pylori* stool antigens were examined using the *H. pylori* Ag EIA test kit.

Cases in which *H. pylori* infections had previously been diagnosed and that had received proton pump inhibitors (PPI) or regimes for the eradication of *H. pylori* infection were excluded from our study.

The data gathered from each patient were recorded, coded, and entered into the computer using the SPSS program version 16.0 (SPSS software version 16.0 manufactured by IBM, United states of America). The statistical analyses were performed using chi-square or Fisher's exact tests for evaluation and comparison.

3. Results

A total of 120 patients with CV (47.5%) and AM (52.5%) with a mean age of 7.1 ± 3.4 (range 2–16 years) and a male-to-female ratio of 1.6 were included. Additionally 100 healthy children with a mean age of 6.9 ± 3.1 and a male-to-female ratio of 1.4 were included as the control group. None of the children has previously been diagnosed with *H. pylori* infection or had received drugs such as PPIs or bismuth salts.

The HPs Ag tests were positive in only 7 (5.8%) of patients (3 with CV and 4 with AM) in our case group. The HPs Ag tests were positive in 13 (13%) of the children of the control group. This difference between the case and control groups was not significant. However, there was a significant positive relationship between HPs Ag positivity and age in our control group ($P < .05$).

There were significant relationships of HPS Ag positivity in the case group with the duration of each attack and the consumption of propranolol. The HPs Ag-positive group exhibited greater attack durations (2.4 ± 1.9 days) compared to the HPs Ag-negative group (1.4 ± 1.5 ; $P = .02$); moreover, the HPs Ag-positive group exhibited lower propranolol consumption levels than the HPs Ag-negative group (14.3% vs. 51.3%; $P = .05$). Regarding the associations between the HPs Ag results and the other aspects of the patients' illnesses, there were no significant relationships ($PV > 0.05$; Table 2).

4. Discussion

H. pylori infection is considered to be the most common chronic infection in the world [24]. This infection is typically acquired in early childhood and persists into adult life [25]. In recent years, there seems to have been a decline in

Table 2 Comparison of the HPs Ag results and the characteristics of the patients' diseases.

Disease characteristic	HPs Ag results	
	HPS AG ^a +	HPS Ag–
Age (mean year \pm SD)	7.2 ± 3.8	7.1 ± 3.4
Male to female ratio	2.5	1.6
Duration of illness (mean year \pm SD)	3.3 ± 2.7	1.3 ± 1.2
Frequency of attacks per year (mean episodes \pm SD)	2.7 ± 2.7	1.4 ± 1.3
Duration of attacks (mean days \pm SD)	2.4 ± 1.9	1.4 ± 1.5
Positive family history of migraine %	57.1	52.2
Consumption of Propranolol at the present time %	14.3	51.3

^a HPS Ag: *helicobacter pylori* stool antigen.

the prevalence of *H. pylori* in Western countries; results have shown that the incidence is less than 10% in North America and Europe; however, the infection is highly prevalent in many developing countries [26,27]. For example, in a study from the Czech Republic that was performed by Sykora et al, in 2009 a prevalence of *H. pylori* infections in healthy children of 7% was reported based on the stool antigen method [28]; moreover, a from South Africa that used the same screening method for the detection of the infection revealed a prevalence of 87% in healthy children [29]. In the current study, we have reported a prevalence of *H. pylori* infection of 13% in healthy Iranian children at our geographical region of Southern Iran. This contrasts with a report from years ago by Malekzade et al that reported a much greater prevalence (82%) of infection in the same area [30].

In 1996, Crabtree proposed that the direct and indirect release of vasoactive substances is the pathogenic mechanism associated with *H. pylori* infection and functional vascular disorders, such as atherosclerosis and the Raynaud phenomenon [31]. Considering that migraine headache is believed to have a functional vascular pathogenesis, many recent studies have implicated the role of *H. pylori* infection in this disease [6,14,31–33]. The results of these studies showed that the intensity, duration, and frequency of attacks of migraine were significantly reduced in patients in whom *H. pylori* had been eradicated.

With the knowledge that migraine headaches and childhood periodic syndromes seem to share pathogenic resemblances, in the present study, we investigated the role of *H. pylori* infection in the pathogenesis of CV and AM for the first time. *H. pylori* colonization was found in only 7 cases (5.8%) of our patients who were suffering from CV or AM, and no influences of age or sex were found. *H. pylori* infection was significantly higher among patients with longer disease durations (in days) but not among those with more frequent of attacks.

Worldwide, many studies have implied that *H. pylori* infection is transmitted within the family and primarily from the parents to the child [34–36]. Here, we did not observe any significant relationship between a positive

family history of migraine headache in the first-degree relatives of our patients and the incidence of *H. pylori* infection.

Despite the controversies regarding treatment (i.e., abortive, supportive, and prophylactic) and the durations of therapy for CV and AM, the majority of studies have recommended antimigraine drugs such as pizotifen, propranolol and cyproheptadine as effective prophylactic regimens for these conditions [37–39]. In 2007 our gastroenterology center at Shiraz University of Medical Sciences reported an experience on 181 CV cases in which propranolol was recommended as the first drug of choice for prophylaxis in children with CV. Moreover, in this study, propranolol was discontinued in approximately half of the patients who had been asymptomatic for at least 5 months, and only a few recurrences were observed at a one-year follow up [39].

Considering the previous experiences of our center, we began propranolol for all of our patients following the diagnoses of CV or AM and gradually discontinued this medication in those without any symptoms after at least six months of therapy.

In this study, we showed a lower incidence of *H. pylori* infection in the patients who were on prophylactic treatment with propranolol. At the present time, we have no specific explanation for this finding; furthermore, whether propranolol might have caused false negative results in the *H. pylori* stool antigen tests remains a question that will require further investigation.

5. Conclusions

Our study did not support the *H. pylori* infection as an etiological factor of either CV or AM. Furthermore, we reported a significantly lower prevalence of *H. pylori* in the healthy population of children in southern Iran, which might have been due to the decrease in family sizes and the improvement in living styles that have occurred in recent years. Therefore, this low prevalence does not exclude the role of *H. pylori* in these childhood periodic syndromes. The question remains regarding the possibility that the cure of *H. pylori* might lead to the relief of symptoms in our patients.

Conflicts of Interest

The authors have no conflicts of interest to report.

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