

Helicobacter pylori and Infantile Colic

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Objective: To determine whether *Helicobacter pylori* is associated with infantile colic.

Design: Case-control study.

Settings: Local tertiary hospital in rural Gizan, Saudi Arabia.

Participants: A total of 55 patients with infantile colic who were 2 weeks to 4 months of age and who fulfilled modified Wessel criteria (ie, crying and fussy behavior) and a total of 30 healthy controls with no history of colic who were matched by country of origin, age, sex, and ethnicity to the 55 colicky infants.

Main Outcome Measure: *Helicobacter pylori* infection determined by *H pylori* stool antigen testing.

Results: Of the 55 patients presenting with infantile colic, 45 (81.8%) tested positive for *H pylori*; of the 30 healthy controls, 7 (23.3%) tested positive for *H pylori* (odds ratio, 15.3 [95% CI, 17.9-29.8]).

Conclusion: *H pylori* infection is associated with infantile colic and may be a causative factor.

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SINCE THE DISCOVERY OF *Helicobacter pylori* by Marshall and Warren¹ in 1983, a new era of discovery and understanding of gastroduodenal pathology has begun. *H pylori* infection is a common bacterial infection in humans, and the organism is the most prevalent gastric microbial pathogen. The outcome of chronic *H pylori* infection varies from asymptomatic gastritis to peptic ulcerations to gastric malignancies.² It is currently estimated that half of the world's human population is infected with the gastric pathogen *H pylori*. However, the prevalence of *H pylori* is not homogenous worldwide; it varies and is dependent on the patient's age, country of origin, ethnic background, and socioeconomic conditions during childhood.³ The virulence factors of *H pylori* and the host genetic factors are both considered important determinants of disease.⁴ In an attempt to search for the pathogenesis of some infantile disorders that have an unclear etiology, we investigated the potential role of *H pylori* infection in infantile colic. The cause remains enigmatic, despite its long history and its relatively frequent occurrence. Its prevalence ranged from 5% to 40% depending on the definition and

methods used.⁵⁻⁷ Possible explanations were suggested: painful gut contractions, lactose intolerance, social factors,^{8,9} or high levels of motilin hormone secreted by the small intestinal cells.¹⁰ Colic is similar in both breast-fed and bottle-fed infants. The prevalence of colic among exclusively breast-fed infants, among exclusively formula-fed infants, and among both breast-fed and formula-fed infants was 22%, 20%, and 18%, respectively. There was no significant relationship between the source of early infant nutrition and the development of colic.⁹ Infantile colic has no clear treatment, and its management varies among physicians.¹¹

METHODS

Approval of the present study was received from the administration of Alemeis National Hospital in Sabia, Saudi Arabia. Cases were recruited from the local tertiary hospital in rural Gizan, Saudi Arabia, from May to September 2009. Cases admitted for routine outpatient clinical care, for vaccination, or for medical services were selected. A questionnaire was administered to the mothers of infants 2 weeks to 4 months of age and included questions about maternal health behaviors, demographic characteristics, and the current source of infant nutrition (whether the infant was ex-

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clusively breast fed, exclusively formula fed, or fed both breast milk and formula). Standardized measures (the 6-item state scale of the Spielberger State-Trait Anxiety Inventory, the Support Behaviors Inventory, and Anticipatory Guidance) that assessed maternal anxiety, postnatal depression, and social support were incorporated into the first questionnaire because these constructs have been suspected to play a role in the development of colic.⁹ Mothers were also asked to complete a short questionnaire based on the Ames cry score, which is composed of 3 questions, each with its own 4 response categories that are scored from 0 to 3. This short questionnaire asks about the frequency and the average and maximum duration of an infant's cries during the past week. Overall scores, calculated by summing the scores of individual items, range from 0 to 9, with a score of 3 or greater indicating colic.¹²

Ninety-two participants were categorized into 2 groups (ie, case and control groups), and allocations were concealed from the participants' parents until after pretesting was complete. Of the 92 participants, 85 completed the study. There were no statistically significant differences in baseline sociodemographics between the 7 participants who dropped out of the study and the 85 participants who completed the study. There were 55 case infants aged 2 weeks to 4 months who fulfilled modified Wessel criteria for infantile colic, which criteria meant that a well, thriving infant cried for 3 hours daily for more than 3 days every week for more than 3 weeks,^{4,12-14} excluding other causes of crying. The results of a detailed examination of the infant were recorded to rule out any underlying causes of excessive crying (eg, central nervous system abnormalities, infections, trauma, foreign body in the eye, fractured bone, or other gastrointestinal dysfunctions).⁴ Eligible controls were selected from the same population and matched to case infants by country of origin, age, sex, and race. The study controls were identified as having no colic or no history of colic, and no severe distressing illness or abnormalities.

The case and control groups were investigated for *H pylori* using a stool antigen test. This one-step test is a chromatographic immunoassay 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.^{15,16} *Helicobacter pylori* fecal antigen has shown a high degree of sensitivity, specificity, and positive and negative predictive values.¹⁶

All analyses were performed using SPSS (SPSS Inc). The demographic characteristics of cases and controls were compared using the Fisher exact test, and odds ratios and 95% CIs were calculated.

RESULTS

There were 28 boys and 27 girls enrolled in the case group and 17 boys and 13 girls enrolled in the control group. The 2 groups were similar in terms of age, sex, race, prematurity, insurance status, maternal education, and maternal depression (**Table**). Of the 55 case infants, 45 (81.8%) tested positive for *H pylori*, and 10 (18.2%) tested negative. Of the 30 controls, only 7 (23.3%) tested positive for *H pylori*, and 23 (76.7%) tested negative (odds ratio, 15.3 [95% CI, 7.9-29.8]).

COMMENT

Numerous studies have elucidated the pathogenesis, immunology, and *H pylori* gastrointestinal-related disorders (in addition to the extraintestinal manifestations)

Table. Demographic Characteristics of 85 Participants With or Without Infantile Colic^a

Characteristic	Infants, No. (%)	
	Case Group (n = 55)	Control Group (n = 30)
Infant age, mo		
<2	13 (23.6)	7 (23.3)
2-3	27 (49.1)	14 (46.7)
4	15 (27.3)	9 (30.0)
Male infant	33 (60.0)	17 (56.7)
Infant race		
Saudi Arabian	48 (87.3)	27 (90.0)
Non-Saudi Arabian	7 (12.7)	3 (10.0)
Insurance		
Medicaid	37 (67.3)	20 (66.7)
Private, cash	18 (32.7)	10 (33.3)
<High school education for caregiver	34 (61.8)	19 (63.3)
Maternal depression	7 (12.7)	3 (10)
Prematurity (<36 wks' gestation)		
No	47 (85.5)	27 (90)
Yes	8 (14.6)	3 (10)
Total annual outcome, \$		
<30 000	33 (60.0)	17 (56.7)
30 000-50 000	10 (18.2)	6 (20.0)
51 000-100 000	7 (12.7)	4 (13.3)
>100 000	5 (9.1)	3 (10)

^aSocioeconomic status is based on parental occupation, and education was nearly balanced among participants' parents, particularly when considering the rural nature of this community.

associated with *H pylori* infection, but, to my knowledge, none of these studies have investigated the role of *H pylori* in infantile colic. The present study found a strong association between *H pylori* infection and infantile colic.

Other studies have suggested that this association might be causal. Recently, strains of lactic acid bacteria, selected for their capability of promoting the production of interleukin 10 (IL-10) and, consequently, the proliferation of CD4⁺CD25⁺ T-cell receptors have been used for the treatment of infantile colic.¹⁷⁻¹⁹ A recent study by Savino et al²⁰ has found that a daily dose of a probiotic helps improve colic symptoms. The more recent research conducted by Zhou et al²¹ demonstrated the role of lactobacilli in treating *H pylori*-related diseases, and the results indicated that viable lactobacilli prevented the development of *H pylori* Sydney strain 1 (SS1) lipopolysaccharide (LPS)-activated Toll-like receptor 4 (TLR4) pathways in SGC-7901 cells, leading to the inhibitory effects of lactobacilli on IL-8 production stimulated by *H pylori* SS1 LPSs.²¹

Some studies have demonstrated that *H pylori* stimulates the release of IL-8 from gastric epithelia, which initiates inflammatory damage to gastric mucosa as the basis of the pathogenesis of *H pylori* infections. *H pylori* LPS is the major initiator in *H pylori*-induced IL-8 production. Considering the novel finding that *H pylori* is an indigenous biota in gastric microflora, including lactobacilli, and the hypothesis that the disturbance of the microecosystem plays a more important role in the pathogenesis of *H pylori*, the restoration of the gastric

microecosystem by the therapeutic effects of lactobacilli on *H pylori*-associated diseases has been demonstrated.²²

Christensen et al²² suggested that different species of lactobacillus exert very different dendritic cell activation patterns, and at least one species may be capable of inhibiting the activities of other species. Thus, there is potential for T_H1/T_H2/T_H3-driving capacities of the gut dendritic cell to be modulated according to the composition of gut microflora. Moreover, Kao et al²³ suggested that dendritic cells participate in the host immune response against *H pylori* and that their suppression by *H pylori*-secreted factors may explain why infected hosts fail to prevent bacterial colonization.

In a recent study,²¹ 2 soluble proteins with molecular sizes of 75 and 40 kDa were purified from supernatant of *Lactobacillus rhamnosus* and named P75 and P40, respectively, which ameliorated apoptosis of intestinal epithelia treated with tumor necrosis factor, interferon γ , or IL-1 α and promoted cell growth. Similarly, it could intervene in *H pylori* SS1-LPS-activated TLR4 signaling through modulating other pathways in SGC-7901 cells.²¹ In short, the interaction between the host immune factors and the *H pylori* virulence factors determines the outcome of *H pylori* infection (ie, the development of infant colic after the second week of life). Gradually, the microecosystem and other gastrointestinal flora did come into action to dominate and modulate (*H pylori* vs host) immune responses in order to drive the interactive pathways toward the relief of colic symptoms after 3 to 4 months of age.

I did not find any significant difference between severity of infantile colic and concentration of *H pylori* stool antigen that was compatible with the findings in Madani et al²⁴ and Bahú et al²⁵; both of those studies^{24,25} found no correlation between severe gastritis and marked bacterial colonization. *Helicobacter pylori* infections may be considered the etiologic pathogenic organism of infantile colic.

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