# Interrelation between *Helicobacter Pylori* Infection, Infantile Colic, and Irritable Bowel Syndrome in Pediatric Patients

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## ABSTRACT

**To determine whether irritable bowel syndrome is associated with *Helicobacter pylori* infection and infantile colic .A retrospective case controlled study was conducted in Abha hospital (Saudi Arabia), Abo Hariz Hospital, (Sharkia, Egypt), and Al Hussein University Hospital (Cairo, Egypt). 450 cases of irritable bowel syndrome (IBS) that met the Rome III criteria and 100 controls (IBS-negative), aged 7 to 17 years old, were involved in this study. Complete stool analysis including *H. pylori* stool antigen test and occult blood in addition to urea breath test, were carried out for all participants.Of the total 450 IBS cases, 212 (47.1%) had reported infantile colic at age 0 to 4 months compared to 7 (7.0%) in control group, and family history of IBS was evident in case group (n = 315; 70.0%) versus control group (n = 10; 10.0%). Furthermore, *H. pylori* was present in 192 (42.7%) of IBS cases compared to only 8 (8.0%) in control group. Our findings provide a new correlations between childhood IBS and infantile colic as well as *H. pylori* infection. Moreover, a significant association was found between IBS and family history of IBS. 1-the relationship between *H pylori* and infantile colic and 2-H pylori and adult IBS are the known while what is new is 1- Correlation between childhood IBS and infantile colic, 2- Correlation between childhood IBS and *H. pylori* infection and 3- A significant association between childhood IBS and family history of IBS.**

**Key words:** *Helicobacter pylori*, Rome III Criteria, Stool Antigen Test and Colic.

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## INTRODUCTION

Irritable bowel syndrome (IBS) is a common disorder that may affect over 15% of the general population. It is sometimes referred to as spastic colon, mucous colitis or nervous stomach. IBS should not be confused with other diseases of the bowel such as ulcerative colitis or Crohn's disease. IBS is a functional disorder where the function of the bowels may be abnormal but no structural abnormalities exist. (American Society of Colon and Rectal Surgeons, 2014). IBS is defined as chronic or recurrent abdominal pain, altered bowel habits, and

bloating, with the absence of structural or biochemical abnormalities to explain these symptoms. It is part of a broader group of disorders known as functional GI disorders. It is the most common GI diagnosis among gastroenterology practices in the United States and is one of the top 10 reasons for visits to primary care physicians. Irritable bowel syndrome is recognized in children, and many patients trace the onset of their symptoms to childhood. Children who have a history of recurrent abdominal pain are at increased risk of irritable bowel syndrome during adolescence and young adulthood (El-Baba and Carmen, 2014). Onset of IBS is more likely to occur after an infection (post-infectious), (Spiller and Garsed, 2009) or a stressful life event (Chang, 2011) but its symptoms may slightly vary with age (Rosa, 2014).

In some individuals, abnormalities in the gut flora occur, and it has been theorized that these abnormalities result in inflammation and altered bowel function (Khanna et al., 2014). Although there is no cure for IBS, there are treatments that attempt to relieve symptoms, including dietary, medication and psychological interventions (Mayer, 2008). IBS is diagnosed when a child who is growing as expected has abdominal pain or discomfort once per week for at least 2 months without other disease or injury that could explain the pain. The pain or discomfort of IBS may occur with a change in stool frequency or consistency or may be relieved by a bowel movement (Di Lorenzo et al., 2006). The most common theory is that IBS represents a pathological disorder resulting from complex interaction between brain and gastrointestinal tract, and other abnormalities in the gut flora or the immune system may also participate in its etiology (Stark et al., 2007). Although a direct cause may not be identified, visceral hypersensitivity and colon motility seem to play a role in its etiology (Yu and Rao, 2014). IBS occurs in both children as well as adults and almost 14% of high school students and 6% of middle school students complain of IBS-like symptoms. There is no known gene that causes IBS, but the disorder seems to occur more often in some families (Torpy and Golub, 2011). IBS has no direct effect on life expectancy but, it represents a source of chronic pain, fatigue, and other symptoms (Maxion-Bergemann et al., 2006). Several intestinal disorders have symptoms that are similar to IBS (Bellini et al., 2014).

## Infantile Colic

Infantile colic is defined as episodes of crying for at least three hours per day, for more than three days a week within at least three weeks duration in an otherwise healthy child between the ages of two weeks and four months (Lucassen et al., 2001). By contrast, infants normally cry an average of just over two hours a day, with the duration peaking at six weeks (Roberts et al., 2004). Other time criteria that have been used are: severe crying for several hours per day, crying for more than two hours per day, unexplained crying, crying with which parents felt they could no longer cope or the presence of symptoms of gastrointestinal origin such as flatulence, and difficulties with the passage of stools (Lucassen et al., 2001). Associated symptoms may include legs pulled up to the stomach, a flushed face, clenched hands, wrinkled brows, and often high pitched or piercing cry(Roberts et al., 2004). Recently, potential associations between H. pylori infection and other gastric diseases such as gastro esophageal reflux disease (GERD) as well as several extra-gastric pathologies (for example, asthma, growth retardation, and chronic idiopathic thrombocytopenic purpura) have been postulated (Pellicano et al., 2009). The purpose of this study was to investigate the interrelation between IBS, H. pylori infection, and infantile colic in pediatric patients from various localities.

## Helicobacter Pylori

Helicobacter pylori; is a gram-negative bacillus responsible for one of the most common infections found in humans worldwide. Warren and Marshall first cultured and identified the organism as Campylobacter pylori in 1982. By 1989, it was renamed and recognized to be associated closely with antral gastritis (gastric and duodenal ulcers in adults and children). By the early-to-mid 1990s, further evidence supported a link between chronic gastritis of H pylori infection in adults and malignancy, specifically gastric lymphoma and adenocarcinoma (Mutaz and Carmen, 2015). H pylori infections occur at a low rate in children in the United States, but may infect more than 75% of children in developing countries. Although infections increase in frequency as people get older, most children and adults with H pylori will never develop an infection (American Academy of Pediatrics. Helicobacter pylori infections, 2015).               It is Gram                negative, microaerophilic bacterium found in the stomach, and may be present in other parts of the body, such as the eye (Wikipedia Helicobacter pylori, 2015). It was found that it was present in patients with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and stomach cancer. However, over 80% of individuals infected with the bacterium are asymptomatic and it may play an important role in the natural stomach ecology (Blaser, 2006).

## METHODS, INCLUSION AND EXCLUSION CRITERIA OF PATIENTS

Between April, 2010 and June, 2012; 450 patients were

**Table 1.** Rome III criteria for the diagnosis of IBS.

| Basic Criterion | Symptoms began at least 6 months ago, had abdominal pain or discomfort at least 3 days each month in the last 3 months |
| --- | --- |
| Plus at least,2 of the following criteria | (1) The pain was relieved by having a bowel movement<br>(2) Onset was associated with a change in frequency of stool, and/or<br>(3) Onset was accompanied by a change in the appearance of stool. |

IBS could be defined by presence of the basic Criterion plus at least, 2 other Criteria.

**Table 2.** Modified Wessel Criteria for Infantile Colic.

| Crying of a well thriving infant | Duration |
| --- | --- |
| Every day | 3 h |
| Every week | 3 days |
| Total | >3weeks |

eligible for inclusion (IBS-positive) and 100 for control (IBS-negative) according to the Rome III criteria for the diagnosis of IBS. Cases and controls were matched for any potential confounders. This retrospective study included patients younger than 18 years with mean age (Mean $\pm$ SD) of 11.7 $\pm$ 1.7 who had symptoms that met Rome III criteria. Exclusion criteria included those had no symptoms that met Rome III criteria, had taken antibiotics, or gut cleansing medications. Potential participants were identified and recruited from local tertiary hospitals in Abha (Saudi Arabia), Abo Hariz Rural area in Sharkia Governorate (Sharkia, Egypt) and Al Hussein University Hospitals (Cairo, Egypt) from April 2010 to June 2012. Eligible cases were enrolled from outpatient clinics as well as inpatient admissions after informed consent obtained from a parent or guardian. The study was approved by the medical ethical review boards of the medical centers. Printed records were collected to verify inclusion criteria, medications given, clinical review, family and past histories as well as test results. Participants met the Rome III criteria for IBS (Table 1), Rome III criteria (David and Lola, 2007).

In addition to the above criteria, no evidence of structural, inflammatory, parasitic (Giardia), anatomic, metabolic, or neoplastic alterations that may explain the subject's symptoms (Eric and Samuel, 2010). The more recent Rome III Process was published in 2007 and pediatricians implemented these guidelines in the IBS diagnosis. Medical history questions focus on bowel habits, diet, exercise, and stress. Family history of IBS in Parents was easily confirmed depending on Parent symptoms and physician consultation. Physical examination looks for other causes of GIT problems, as well as systemic diseases. Complete blood count and blood chemistries may be ordered to look for anemia or other abnormalities such as an allergy to gluten. Testing

for blood in the stool, endoscopy of the gastrointestinal tract and biopsy may be taken to exclude the possibility of celiac disease (Grazioli et al., 2006). In the current study, the history of infantile colic was identified and defined according to modified Wessel criteria for infantile colic, such criteria implement a well thriving infant cried for 3 h daily for more than 3 days every week for more than 3 weeks (Ali, 2012). Eligible controls, with mean age $\pm$ SD of 12.1 $\pm$ 1.2, were selected from the same population and matched to cases by country of origin, age, sex, and race. The study controls were identified as having neither IBS nor history of IBS (that is, not fulfill Rome III criteria of IBS), and no severe distressing illness or abnormalities.
Modified Wessel Criteria (Ali, 2012). Table 2.

**Detection of *H. pylori* Infection**
The case and control groups were investigated for *H. pylori* using *H. pylori* stool antigen test or the urea breath test (UBT).

**_H. pylori_ Stool Antigen Test**

Fecal specimens were examined using the stool antigen test (One step *H. pylori* antigen test device; ACON Laboratories Inc., San Diego, CA, USA) according to the manufacturer's directions. *H. pylori* stool antigen test is considered as a flow Immunoassay reaction. In brief, collected stool samples were transferred to vials with the extraction fluid, vigorously agitated, and left for two minutes for settling of suspended particulates. Two to three drops were then transferred into the circular port hole of the test cassette and results were recorded after 10 min of incubation at room temperature. Depending on the development of colored lines across the cassette, simultaneous appearance of two lines (control and test)

**Table 3.** Demographic characteristics of pediatric participants (n = 550) categorized as irritable bowel syndrome- positive (Case; n = 450) and irritable bowel syndrome-negative (Control; n = 100) groups.

| Control Group (n = 100) | Irritable Bowel Syndrome Group (n = 450) | Characteristics |
|---|---|---|
| Nationality | | |
| Egyptian | 210 (46.7%) | 48 (48.0%) |
| Saudian | 240 (53.3%) | 52 (52.0%) |
| Mean Age (±SD) | 11.7 (±1.7) | 12.1 (±1.2) |
| | | |
| Gender | | |
| Male | 198 (44.0%) | 45 (45.0%) |
| Female | 252 (56.0%) | 55 (55.0%) |
| | | |
| Socioeconomic status | | |
| Low | 121 (26.9%) | 29 (29.0%) |
| Average | 279 (62.0%) | 58 (58.0%) |
| High | 50 (11.1) | 13 (13.0%) |
| | | |
| Hospitalization | | |
| Hospitalized | 53 (11.8%) | 9 (9.0%) |
| Non-hospitalized | 397(88.2%) | 91 (91.0%) |
| | | |
| Family history of IBS[*] | | |
| Present | 192 (42.7%) | 10 (10.0%) |
| Absent | 135 (30%) | 90 (90.0%) |
| | | |
| *H. pylori* infection | | |
| Present | 192 (42.7%) | 8 (8.0%) |
| Absent | 258 (57.3%) | 92 (92.0%) |

[*]IBS = Irritable bowel syndrome.

indicates positive *H. pylori* infection. On the other hand, appearance of only one line in the control section indicates negative *H. pylori* infection (Silva et al., 2010; Sabbi et al., 2005).

**Urea Breath Test (UBT)**

Conventionally the $^{13}$C-urea breath test (UBT) with its high diagnostic accuracy (> 95%) a simple, non-invasive, practical, highly accurate, and reproducible test of choice for the confirmation of *H. pylori* infection (Kato et al., 2000). The participants should be fasting at least 1 h before administering the Breath Tek$^®$ UBT (Meretek Diagnostics Inc., Rockville, MD, USA) and should not have taken antimicrobials, proton pump inhibitors, or bismuth preparations within two weeks prior to the test. The diagnostic component of Breath Tek$^®$ UBT kit is $^{13}$C-urea, contained in a granulated powder for oral administration. Urea in the body is referred to as natural isotopic abundance urea (98.9% $^{12}$C-urea and 1.1% $^{13}$C-urea).

Pranactin-Citric product is a component of the Breath Tek$^®$ UBT Kit **(**Meretek Diagnostics Inc.). In the presence of gastric *H. pylori* urease, $^{13}$C-urea decomposes to $^{13}$CO$_2$ and NH$_4$. The $^{13}$CO$_2$ is absorbed in the blood, and then exhaled in the breath. The breath samples were collected

and analyzed by UBiT®-IR300 Infrared spectrophotometer (Photal Otsuka Electronics Co., Japan). The positive results showed an increase in the ratio of $^{13}$CO$_2$ to $^{12}$CO$_2$ in a post-dose breath sample as compared to a baseline sample taken before the $^{13}$C-urea solution was consumed. Delta over baseline (DOB) value of ≥ 2.4 is interpreted as diagnostically positive indicating the presence of urease which is associated with *H. pylori* infection. A DOB value of < 2.4 is interpreted as diagnostically negative sample (Kato et al., 2000).

**Statistical Analysis**

All analyses were performed using SPSS, version 18.0 (SPSS Inc., Armonk, NY, USA).The demographic characteristics of cases and controls were compared using the Fisher exact test, adjusted Odds Ratios, and 95% Confidence Intervals (CIs) calculation.

**RESULTS AND DISCUSSION**

Characteristics of the study population are presented in Table 3. The socio demographic variables such as age (mean and standard deviation), gender, ethnicity, hospitalization, socioeconomic status, family history of

**Table 4.** Distribution of the study population according to the reported infantile colic.

| Reported Infantile colic | Cases with Irritable Bowel Syndrome No. (%) | Cases without Irritable Bowel Syndrome No. (%) |
|---|---|---|
| Present | 212 (47.1%) | 7 (7.0%) |
| Absent | 238 (52.9%) | 93 (93.0%) |
| Total Number (%) | 450 (100%) | 100 (100%) |

Odds ratio= 11.83, that is, the odd of having infantile colic is more than eleven-fold greater for patients who had irritable bowel syndrome than those who had no irritable bowel syndrome (95% confidence interval=5.37 to 26.08, Z statistic =6.129, and P value <0.0001).

**Table 5.** Distribution of the study population according to *H.pylori* infection.

| *H. pylori* Infection | Reported Infantile Colic | Irritable Bowel Cases | Control |
|---|---|---|---|
| + | 170(80.2%) | 192 (42.7%) | 8% |
| _ | 42(19.8) | 258(57.3) | 92% |
| Total | 212 (100%) | 450(100%) | 100% |
| Odds ratio | 46.5476 | 8.5581 | |
| 95% CI | 20.9674 to 103.3359 | 4.0579 to 18.0494 | |
| Z statistic | 9.439 | 5.639 | |
| Significance level | P < 0.0001 | P < 0.0001 | |

colic or IBS, reported infantile colic, and laboratory documentation of *H. pylori* infection were included. The case and control groups were investigated for *H. pylori* using *H. pylori* stool antigen test or the UBT (UBT was advocated to certain patients who can easily swallow medication). Education was not included because it had no significant difference among the study groups due to approximate similarity of education and the relatively similar nature of the communities. The potential confounders are generally limited because of; (1) lack of association between IBS and many commonly known socio demographic factors, and (2) the small number of known risk factors (Eric and Samuel, 2010). *H. pylori* documentation was relatively increased to 192 (42.7%) in the IBS cases and markedly decreased to 8 (8.0%) in the control.

Furthermore, family history of IBS was evident in case group (n = 315; 70.0%) versus control group (n = 10; 10.0%).Table 4 shows that of the total 450 IBS cases, 212 (47.1%) had infantile colic at age 0 to 4 months compared to 7 (7.0%) in the control group. A significant association between IBS and infantile colic as well as family history of IBS are statistically significant. Moreover, Odds ratio of 11.83  indicate that the Odds of having reported infantile colic is more than eleven-fold greater for pediatric patients who had IBS than those who had no IBS (95% confidence interval = 5.37 to 26.08, and *P* value <0.0001). Table 5 shows distribution of the study population according to *H pylori* infection. A significant correlation between both reported infantile colic and IBS in one side and *H. pylori* infection on the other side. Distributions of *H. pylori* infection, family history of IBS, and infantile colic in IBS-positive (Case) and IBS-negative (Control) groups are summarized in Figure 1.

To our knowledge, this is the first study to assess the direct interrelation between irritable bowel syndrome, *H. pylori* infection, and infantile colic. IBS and infantile colic are closely similar disorders in various aspects including (a) functional disorder, (b) presence of family history, (c) showing nocturnal nature, and (d) demonstrating repeated bouts (Ali, 2012; Caroline et al., 2014; Abdelrazak and Samir, 2002). Recent studies indicated that IBS was associated with low-grade inflammation and had demonstrated noticeable distribution of *H. pylori* cytotoxin-associated gene A (*cagA*), and vacuolating cytotoxin A (*vacA*) alleles in patients with diarrhea-dominant IBS as the latter gene causes vacuolation in colonic epithelial cells *in vitro* (Yakoob et al., 2012). Distribution of IBS significantly varies between different countries and its worldwide prevalence ranges between 3 to 22% in different communities (Caroline et al., 2014; Abdelrazak and Samir, 2002).Revising the community prevalence and distribution patterns of *H. pylori* and infantile colic revealed similarity with that of irritable bowel syndrome (Abdelrazak and Samir, 2002; Hungin et al., 2003). Taken together our study findings and the aforementioned information (Ali, 2012; Hungin et al., 2003), revealed an association between *H. pylori* infection and the functional dyspepsia in patients with IBS, we can build up a convincing evidence that both infantile colic and IBS are closely related functional disorder, and commonly associated with *H. pylori* infection in pediatric patients.

Results of the current study demonstrated a significant correlation between colic in infancy and IBS in childhood-adolescence age, and family history is substantially significant in both. Furthermore, these results may explain recent studies which recommended   usage of
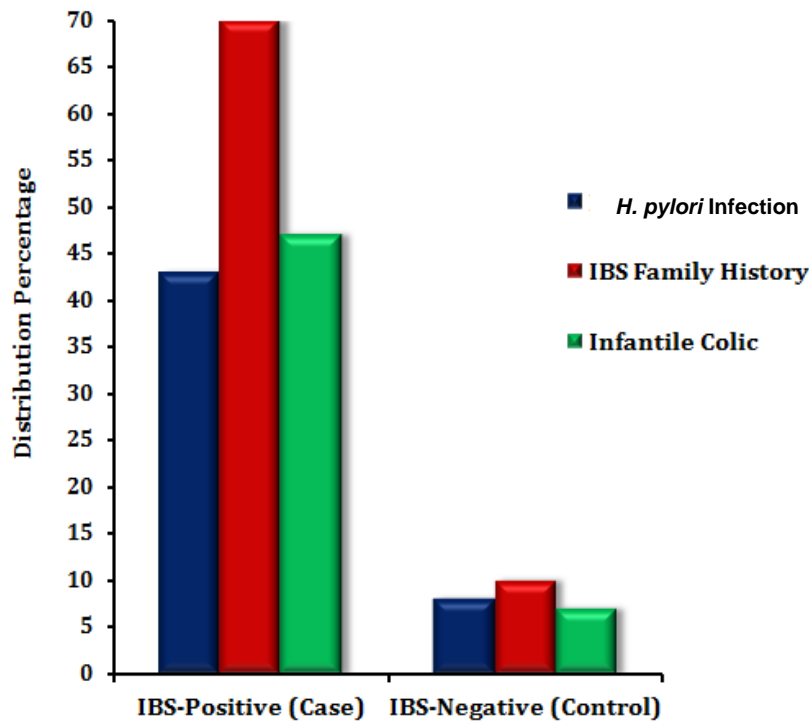
**Figure 1.** Diagrammatic representation of *H. pylori* infection, family history of irritable bowel syndrome (IBS), and infantile colic as distributed in IBS-positive (Case) and IBS-negative (Control) groups.

*Lactobacillus* and *Bifidobacterium* probiotics to treat and alleviate symptoms of infantile colic, irritable bowel, and other inflammatory gastrointestinal disorders. These therapeutic responses were associated with (a) Normalization of the ratio of an anti-inflammatory to a pro inflammatory cytokines, (Su et al., 2000; Liam et al., 2005). (b) Competition for receptors on endothelial cells, (c) Production of antimicrobial compounds, (d) Modifications of the receptors for bacterial toxins, and (e) Promoting production of IL-10 with consequent proliferation of CD4+ CD25 T-cell receptors, suggesting an immune-modulating role for these probiotic organisms (Kajander et al., 2008; Jolanta et al., 2013; Smits et al., 2005; Sarowska et al., 2013). On the other hand, symptoms of IBS were correlated with *H. pylori* infection, female gender, and perceived stress (Su et al., 2000), but the small sample size of that study may compromise its strength.

The current study has several methodological strengths that enhanced the validity of the obtained results including; (a) its design substantially reduces the likelihood of potential bias associated with the participants and assessment of outcomes, and (b) both the exposure risk (*H. pylori* infection) and the clinical outcome (infant colic and IBS) were measured objectively without the knowledge of each other, thus reducing the concern of recall bias associated with the ascertainment of exposure and outcome variables.(c) infantile colic in infants and parental history of IBS are dramatically distressing to the parents, so easily reported and documented, due to the instant recall by the parents. It is clear that IBS and other GIT functional disorders may potentially influence genetically susceptible individuals with an exaggerated response to a variety of physiological and non-physiological gastrointestinal stimuli that may include *H. pylori* infection and probably other infectious agents.

Basically, the results of the current study are in agreement with the recently reported finding that, *H. pylori* represented the main etiologic pathogenic agent of infantile colic (Ali, 2012). While some investigators mentioned that IBS may be related to an undiscovered agent, others believe that IBS patients suffer from overgrowth of intestinal flora, and the antibiotics represent an effective antimicrobial chemotherapy in reducing such microbial overgrowth (Posserud et al., 2007). Other researchers have focused on a possible unrecognized protozoa infection such as blastocystosis as a cause of IBS (Yakoob et al., 2004). *Dientameba fragilis* has also been considered a possible organism to study, though it is also found in people without IBS (Windsor and Macfarlane, 2005). In short, the functional GIT disorders (IBS and infantile colic), could be simplified and virtually formulated in the form of four-

sided square, with the following sides: (a) Genetic susceptibility, (b) Gut microfloral system, (c) Host immune system, and (d) *H. pylori* infection or probably other organisms to be identified.

## CONCLUSION

Our findings provide a new correlations between childhood IBS and *H. pylori* infection as well as infantile colic. Moreover, a significant association was established between childhood IBS and family history of IBS.

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