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Website: www.afrjpaedsurg.org
DOI: 10.4103/0189-6725.86056
PMID: 22005359
Quick Response Code:

Role of *Helicobacter pylori* in the pathogenesis of infantile hypertrophic pyloric stenosis

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ABSTRACT

Objectives: To investigate the possible correlation between infantile hypertrophic pyloric stenosis (IHPS) and *Helicobacter pylori* infection. **Materials and Methods:** In a case-control study, 20 infants with confirmed IHPS (Group 1) and 30 age-matched healthy infants (Group 2) were enrolled for the assessment of *H. pylori* infection. Serological testing of anti-*H. pylori* antibody (IgG) was performed preoperatively on all infants and their mothers. Also, *H. pylori* stool antigen test (HpSA) was carried out preoperatively on all infants in both groups. Statistical analyses were performed with Chi-square test, Fisher's exact test, Mann-Whitney U test, and Independent-Samples T test. **Results:** There were 20 patients in group 1 (18 boys, 2 girls) and 30 infants in group 2 (30 boys). The mean age in groups 1 and 2 were 42.40±18.09 days and 44.67±12.65 days, respectively. The numbers of positive HpSA and positive anti-*H. pylori* antibody both in infants and mothers were comparable between the two groups (P>0.05). The median titres of *H. pylori* stool antigen were not comparable between the two groups (0.20 ng/dL in group 1 vs 0.57 ng/dL in group 2; P=0.02). **Conclusions:** *H. pylori* does not seem to be in a causative linkage with IHPS.

Key words: Aetiology, *Helicobacter pylori*, infantile hypertrophic pyloric stenosis

INTRODUCTION

Infantile hypertrophic pyloric stenosis (IHPS) is characterised by smooth muscle hypertrophy of the pylorus and subsequent obstruction of the gastric outlet.[1,2] It classically presents in a male infant of age 4-6 weeks, with projectile non-bilious vomiting after feeding.[1,3] Pyloromyotomy along with improvements in paediatric anaesthesia and electrolyte correction has dramatically reduced the mortality of IHPS.[4] Despite the unknown aetiology, there is still a debate whether IHPS is congenital or acquired after birth.[3] Nevertheless, structurally normal pylorus at birth in infants with IHPS might support the acquired nature of this condition.[5,6]

First isolated from the human stomach in early 1980, *Helicobacter pylori* has been found in pathogenesis of numerous conditions involving the upper gastrointestinal (GI) tract in both adolescents and children.[2,7,8] Infection with *H. pylori* has been reported in neonates and infants whose infected mothers are the main source of their *H. pylori* infection.[9] Interestingly, Moon *et al*, first assessed the plausible connection between *H. pylori* and IHPS.[10] Later, Paulozzi highlighted that infection with *H. pylori* might cause IHPS in children, on the basis of epidemiological, clinical, and endoscopic evidences.[6] Nevertheless, successive studies have failed to confirm the presence of *H. pylori* infection in infants diagnosed with IHPS.[2,7] Besides these reports, owing to the high prevalence rate of *H. pylori* infection among infants living in developing countries,[9,11] we performed the study to investigate the possible correlation between IHPS and *H. pylori* infection.

MATERIALS AND METHODS

This was a case-control study conducted from August 2007 to February 2009 at a university-affiliated Children's Hospital. This study enrolled 20 infants with confirmed IHPS (Group 1) and 30 age-matched healthy infants admitted to the hospital for circumcision (Group 2) to be assessed for *H. pylori*

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infection. The diagnosis of IHPS was confirmed clinically and by ultrasound and/or upper GI barium study. The exclusion criteria were other acquired or congenital GI anomalies or malformations as well as antibiotic administration within two weeks prior to the study. Serological tests were performed preoperatively on all infants and their mothers for detection of anti-*H. pylori* antibodies (IgG). In addition, to enhance the diagnostic accuracy of *H. pylori* infection, *H. pylori* stool antigen test (HpSA) by using an enzyme immunoassay polyclonal antibody (Equipar HpSA test, Saronno, Italy) was carried out preoperatively on all infants in both groups. The research deputy and ethics committee of the institute approved this study. An informed consent was obtained from the parents before initiating the study.

Data were presented as mean ± SD or as median (interquartile range). Statistical analysis was performed with SPSS for windows version 16.0 (Chicago, IL, USA) by using Chi-square test, Fisher's exact test, Mann-Whitney U test, and Independent-Samples T test wherever appropriate. $P<0.05$ was considered statistically significant.

RESULTS

Group 1 included 20 patients (18 boys, 2 girls) and group 2, 30 infants (30 boys). The mean ages in IHPS (group 1) and controls (group 2) were 42.40±18.09 days (range, 24-90) and 44.67±12.65 days (range, 21-80), respectively. The HpSA test gave positive result in three patients from group 1 and 10 from group 2 ($P=0.127$; Table 1). The median titres of HpSA were not comparable between groups, with 0.20 ng/dL (interquartile range, 0.13-0.40) in group 1 vs 0.57 ng/dL (interquartile range, 0.28-0.85) in group 2 ($P=0.02$; Mann-Whitney U test). The mean titres of anti-*H. pylori* antibody (IgG) in infants were 14.21±8.18 ng/dL in group 1 and 11.79±9.07 in group 2 ($P=0.342$).

DISCUSSION

The results of this study showed that infants with positive HpSA, positive anti-*H. pylori* antibody, and seropositive mothers did not have a tendency to develop IHPS. These results are in agreement with the findings of Dahshan *et al.*, that failed to detect *H. pylori* in biopsies obtained through upper GI endoscopy in infants with IHPS.[7] However, they identified *H. pylori*-like organisms in the gastric mucosa as well as chronic active gastritis in biopsies, thus disclosing the likelihood of infectious aetiology for IHPS.[7] In contrast, Moon *et al*, indicated a significant difference between a group of infants with IHPS and a group of infants without any upper GI symptoms for the *H. pylori*-specific IgG antibody titres.[10] Furthermore, Sherwood *et al*, found no positive results for the presence of HpSA in either infants with IHPS or those in the control group.[2] Likewise, our study confirmed that HpSA titre among the control group was significantly higher than that of infants diagnosed with IHPS. It is postulated that the inflammatory process in the GI tract of children with IHPS as well as the risk factor of IHPS (eg, bottle feeding) might be in favour of the infectious cause for the aetiology of IHPS.[6] Following the study by Moon *et al*,[10] Paulozzi conceptualised a causative link between *H. pylori*, as an infectious agent, and IHPS in the light of some epidemiologic evidences (eg, sex ratio), similarity of clinical findings between *H. pylori* infection and IHPS, and compatible endoscopic findings of IHPS and *H. pylori* infection.[6] In addition, elevated gastrin levels have been denoted both in IHPS and *H. pylori* infection, indicating the probable contribution of *H. pylori* infection to the development of IHPS.[6,12,13] Furthermore, antibiotic treatment to annihilate the *H. pylori* infection in adults has been found to alleviate the pyloric stenosis, in some cases.[6,14]

There is a plethora of possible aetiological factors of IHPS. The recent progresses in the pathogenesis

Table 1: Characteristics of infants and *Helicobacter pylori* diagnostic tests in this study

	Group 1 (with IHPS, n = 20)	Group 2 (healthy infants, n = 30)	*P* value
Gender (male:female)	18:2	30:0	0.556†
Age (days)	42.40±19.09	44.67±12.65	0.615‡
HpSA in infants (ng/dL)	0.20 (0.13-0.40)	0.57 (0.28-0.85)	0.020§*
Anti-*H. pylori* antibody in infants (IgG) (ng/dL)	14.21±8.18	11.79±9.07	0.342‡
Anti-*H. pylori* antibody in mothers (IgG) (ng/dL)	24.10 (19.92-33.47)	19.50 (12.87-38.11)	0.227§
Positive HpSA in infants	3 (15%)	10 (33.3%)	0.127‖
Positive anti *H. pylori* antibody in infants	13 (65%)	11 (36.7%)	0.136‖
Positive anti *H. pylori* antibody in mothers	19 (95%)	23 (76.7%)	0.123†

IHPS = Infantile hypertrophic pyloric stenosis, *H. pylori* = *Helicobacter pylori,* HpSA = *H. pylori* stool antigen, IgG = Immunoglobulin G; *Statistically significant ($P < 0.05$), †Fisher's exact test, ‡Independent-Samples T test, §Mann-Whitney U test, ‖Chi-square test

of IHPS indicate that the abnormalities of hormonal control and the intestinal pacemaker system, abnormal amounts of extracellular matrix proteins, as well as increased expression of growth factors may play plausible roles in this regard.[15,16] Nonetheless, on the basis of a defect in pyloric relaxation in IHPS, the recent investigations have been orchestrated to assess the pyloric innervation in IHPS.[15,16] Impairment in neuromuscular junction including reduced synaptic vesicles and presynaptic terminals and absent neural cell adhesion molecule immunoreactivity in hypertrophied pyloric muscle layers has been denoted.[17,18] Moreover, studies have revealed marked reduction in both peptidergic (non-cholinergic and non-adrenergic nerve fibres)[15,19,20] and nitrergic (cholinergic and adrenergic nerve fibres)[15,20] in muscular layers at the pyloric region in IHPS. Interestingly, among all components of pyloric innervation, solid evidences support the role of nitric oxide (NO) in IHPS.[16] Vanderwinden *et al*,[21] and Kobayashi *et al*,[18] found absent or markedly reduced NADPH diaphorase, an enzyme identical to NO synthase, in hypertrophic pyloric muscles. Later, Huang *et al*, observed low plasma nitrite levels in patients with IHPS, but which normalised following pyloromyotomy.[22] Diminished neuronal NO synthase expression both at the protein[22,23] and mRNA levels[24,25] has further highlighted the plausible role of NO in the pathogenesis of IHPS.

Among the non-invasive diagnostic methods for the diagnosis of *H. pylori* infection, serology-based tests are of least importance due to their low accuracy in young children.[9,26] Maternal antibodies (IgG) from a seropositive mother may remain in the newborn for a maximum of 6 months, revealing the inefficacy of serological testing in this period.[2] Although there is a broad consensus on the urea breath test (UBT) as the best available non-invasive diagnostic test in children, monoclonal versus polyclonal HpSA test has also been shown to be highly accurate and reliable as much as UBT.[2,9,27] Similarly, we have previously found that the sensitivity and specificity of polyclonal HpSA test was low compared to those of gastric biopsies (gold standard of *H. pylori* diagnosis).[26] In the present study, the applied polyclonal HpSA test on stool samples may under-report the true cases of *H. pylori* infection.

The present study has certain limitations. It was a single centre study with a small sample size (n=20). A multicentre study that recruits a large number of patients may give more concrete results. Furthermore, the applied polyclonal HpSA test on stool samples may under-report the true cases of *H. pylori* infection in the present study. Therefore, further investigations on the link between *H. pylori* infection and IHPS based on more reliable diagnostic tests are recommended. Moreover, no attempt was made to reduce the effect of feeding type, breast- or bottle-feeding, on *H. pylori* infection. Reports reveal that bottle-feeding is a risk factor of *H. pylori* infection and breast-feeding may protect against this infection in infancy.[28-30] Further similar studies are required excluding the bottle/formula milk fed infants. On the other hand, some advantages of the current study including the exclusion of infants who received antibiotic within two weeks prior to the study might be highlighted.

In conclusion, *H. pylori* does not seem to be in a causative linkage with IHPS. However, further studies are recommended with larger sample sizes and with the help of more reliable diagnostic tests, particularly in developing countries where *H. pylori* infection among infants is highly prevalent.

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Cite this article as: Aslanabadi S, Rafeey M, Diaz D, Pourhossein D, Ghabili K, Shoja MM, *et al*. Role of Helicobacter pylori in the pathogenesis of infantile hypertrophic pyloric stenosis. Afr J Paediatr Surg 2011;8:172-5.

Source of Support: Nil. **Conflict of Interest:** None declared.

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