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H. *Pylori* Infection and Iron Deficiency Anemia in Children

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Abstract: Iron Deficiency Anemia (IDA) in childhood is public health problem in developing countries. The aim of this study was to determine the relation between H. *pylori* infection and iron deficiency anemia in children of this region which has a high prevalence of H. *pylori* infection. We investigated consecutive children (3-12 y/o) who underwent upper gastrointestinal endoscopy without an obvious bleeding during November 2005 to 2006 in Pediatric Hospital of Tabriz, Iran. H. *pylori* positively was defined as a positive RUT plus positive specimens. Thirty HP infected patients and thirty age and gender matched HP negative subjects where enrolled. Gastritis was graded according to the updated syndey histologic scoring system in both groups. Serum iron, total iron binding capacity and ferritin level and complete blood count were determined in all patients. The presence of IDA was found to be significantly common among patients infected with H. *pylori*. The mean serum hemoglobin, serum ferritin and iron levels were significantly lower in H.P positive patients. Additionally there was a trend toward higher serum TIBC in H.P positive patients. Gastritis was more prevalent between cases with H.P infection. Refractory and recurrent iron deficiency anemia in children is still a problem in Iran. The growing body of evidence suggests that H. *pylori* infection plays an important role in developing anemia, it necessitates further investigations to reveal possible mechanisms.

Key words: Iron Deficiency Anemia (IDA), *Helicobacter pylori* (HP), gastritis, infection, children

INTRODUCTION

Iron deficiency anemia which is a major public health problem in developing countries may contribute abnormalities of immune function, potentially motor and mental deficits and poor growth significantly in infants and children (Sarker *et al*., 2004).

Low dietary intake of iron (believed to be the principle cause in developing countries) chronic blood loss, conditions affecting gastric acid secretion and malabsorption syndromes are the well established causes leading to Iron Deficiency Anemia (IDA) (Bini, 2001).

The prevalence of H. *pylori* infection is very high in developing countries. Additionally, individuals are believed to be infected early in life. H. *pylori* infection is believed to be a major reason for chronic gastritis and peptic ulcer disease in children (Seo *et al*., 2002), which may develop consequences like chronic gastrointestinal bleeding due to the lesions or low gastric acid to gastric atrophy (Sarker *et al*., 2004). The role of this common infection in the development of extra gastrointestinal diseases, including iron deficiency anemia, has been the focus of attention during the last decade.

Oral iron supplements (Ferrous sulfate drop) has been established as a public health program by ministry of health in Iran and the drop is given free to all of the children under tow years old. On the other hand, iron deficiency anemia in children still remains a common condition in clinics, especially in referral clinics and hospital which refractory IDA and difficulties in treatment may encounter (Kadivar *et al*., 2003).

The aim of this study was to evaluate H. *pylori* infection as a predisposing factor or probable cause of iron deficiency anemia in the absence of bleeding, regarding to the fact that our region has a high prevalence of H. *pylori* infection (Rafeey *et al*., 2004).

MATERIALS AND METHODS

We investigated consecutive children who under-went upper gastrointestinal endoscopy for chronic abdominal pain during November 2005- 2006 in Pediatric Hospital of Tabriz, Northwestern Iran. Patients with an obvious bleeding like epistaxis or GI bleeding, systemic or hematological disorders, motor-mental retardation, celiac disease, recent antibiotic or antacid consumption

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and treated with blood products (e.g., packed cell) or iron supplements were excluded. Duodenal biopsies and stool examination were evaluated for Giardia Lambelia or other intestinal parasites as well and infected patients were excluded. Parents of these children were asked to complete a structured questionnaire about their socioeconomic level and dietary intake and written informed consent was obtained. A same dietitian reviewed the questionnaire with the parents, confirmed the accuracy and calculated the mean intake of iron as milligram per day (mg day^{-1}).

Thirty H. *pylori* infected patients were enrolled in the study while thirty H. *pylori* negative children were selected as controls who were matched in respect to age and gender. Hematological tests were performed in study subjects.

Approval for the study was obtained from the ethical committee of Tabriz university of medical sciences, which is in compliance with the Helsinki declaration.

Endoscopic examinations were performed by a same experienced endoscopist under intravenous sedation, using an Olympus GIF xp-20. Several biopsy specimens were obtained; three from antrum, fundus and body, two from duodenum. Specimens were stained (Hematoxylin, Eosin and Gimsa) and were examined for the presence of H. *pylori*. Rapid ureas test was also performed. Subjects with both positive urea test and positive histology were diagnosed as H. *pylori* infected. Gastritis was graded according to the updated Sydney histologic scoring system and 2 groups were compared (Dixon *et al*., 1996).

Blood was collected by venipuncture, placed in EDTA contain and plain tubes and various hematological studies were achieved including measurement of hemoglobin, serum iron, total iron binding capacity and serum ferritin level. The hemoglobin concentration was measured using a coulter S-Plus IV. Serum was separated and stored at -20°C for analysis of iron deficiency. Serum iron and total iron binding were determined spectrophotomtrically. The serum ferritin assay was performed using radioimmunoassay. Iron deficiency anemia was defined as a low serum ferritin concentration (<12 μg mL^{-1}), low serum iron level (<50 μg dL^{-1}) and a low serum hemoglobin concentration (<120 g L^{-1}).

All statistical analysis were performed using SPSS 11 for Windows. Chi-square or fishers exact tests were used to evaluate the association between H. *pylori* infection and presence or absent of IDA. Student's t test was used to compare the means. Data were expressed as mean (±SD). A p value <0.05 was considered as significant.

RESULTS

The age of participants ranged from 3-12 years and the mean (±SD) age for HP positive and HP negative patients was 7.7 (±3.4) and 7.2 (±3.2), respectively. The mean age and the gender of groups were not significantly different. Iron deficiency anemia was found in 33% of the study population, which included 16 of 20 (80%) H.*Pylori* positive and only 4 (20%) H. *pylori* negative, patients. The presence of IDA was found to be significantly common among patients infected with H. *pylori* ($p<0.005$). The mean serum hemoglobin, serum ferritin and iron levels were significantly lower in H. *pylori* positive patients (Table 1). Additionally there was a trend toward higher serum TIBC in H.P positive patients.

Table 1: Characteristics of the study population

	HP positive	HP negative	P*
Serum Hgb	10.9±2.2 †	12.2±1.4	<0.05
Serum ferritin	19.3±15.4	32.9±17.2	<0.05
Serum iron	47.4±30.4	66.0±37.5	<0.05
TIBC‡	391.9±111.2	371.0±61.9	NS

† mean±SD (all such values), ‡ TIBC: Total Iron Binding Capacity,* $p<0.05$ was considered as significant

Patients were categorized into four groups according to the score of gastritis: mild, moderate, sever and no gastritis. The status of gastritis was commonly of a mild (40%) or moderate (40%) type in HP positive children, while most of HP negative children had no gastritis (73%). Hence gastritis was more prevalent between cases with H.P infection ($p = 0.03$)

Moderate gastritis was dominant (43.7%) among H.P positive patients who had IDA. However the difference of the severity of gastritis between subjects with anemia and subjects without anemia was not statistically significant.

DISCUSSION

The problem of anemia and H. *pylori* infection in developing countries is overwhelming. The adverse effect of H. *pylori* infection on Fe absorption makes it more difficult to design an adequate controlling strategy in population with a high rate of asymptomatic H. *Pylori* infection. H. *pylori* infection has been a matter of interest as probable cause of iron deficiency anemia, while the underlying mechanism is poorly defined. Several cross-sectional serologic surveys have been carried out to evaluate the possible association between H. *pylori* infection and iron deficiency anemia (Hacihanefioglu *et al*., 2003; Choe *et al*., 2003; Baggett *et al*., 2006). Furthermore, only few of these used endoscopy to exclude other gastrointestinal causes of iron deficiency. The present study is an age and gender matched report (including children aged between 3-12 years old) acted upon endoscopy and biopsies. Our results as the first study in Iran show that H. *pylori* infection was associated with iron deficiency anemia in our population, which is compatible with previous studies and from other regions. The difference

between the serum ferritin levels of HP positive and negative children with IDA was found to be significant in a Turkish population (Baycoy *et al*., 2004; Hacihanefioglu *et al*., 2003).

In another large scale study, an association was detected between HP seropositive subjects and iron deficiency in Korea (Choe *et al*., 2003) as well as studies Alaska natives (Baggett *et al*., 2006; Yip *et al*., 1997) but the diagnostic accuracy of ELISA may vary with multiple factors such as geographic differences, age and antigens used in the serologic tests.

The association Refractory iron deficiency anemia and infection with H. *pylori* has been reported which was followed by improvement after H. *pylori* eradication (Pavithran *et al*., 2003; Choe *et al*., 2000). Several possible mechanisms for this association have been suggested in the literature including poor iron absorption due to H.P induced gastric hypoacidity and an increase in iron demand because of bacterial competition for iron (Bini, 2001).

Most people which are infected with HP have a form of chronic gastritis which is not associated with gastrointestinal bleeding Studies do not support gastrointestinal loss of blood as a reason for H.P related IDA (Yip *et al*., 1997). However, in the present study, the subjects with GI bleeding were excluded.

Gastritis was more common in HP positive patients with IDA in the present study. Despite improvement in gastric acid secretion after H.P eradication therapy, no significant improvement in iron absorption of (either water-soluble or non-water-soluble) iron compounds has been reported while improvement in hemoglobin was performed (Sarker *et al*., 2004).

It has also been shown that the concentration of ascorbic acid in gastric juice was decreased in H.P positive cases (Bini, 2001; Choe *et al*., 2001). Hence H.P gastritis can result in impaired iron absorption due to reduced gastric juice ascorbic acid levels.

H. *pylori* is known to use human transferrin a source for iron (Gutierrez *et al*., 1997). According to the fact that iron an essential growth factor for H.P, Human lactoferrin and heme fully support the growth of H.P in media that is lacking of other sources for iron (Seo *et al*., 2002)

Additionally infection with Cag A- positive strains, which has a high prevalence in our region due to a recent study (still in progress), was associated with a greater decrease in gastric juice levels (Baycoy *et al*., 2004).

The findings of this study are subject to some limitations; small sample size may make it difficult to detect differences and reliance on a cross-sectional design limits inferences about the directionality of associations and causality.

CONCLUSION

Our data suggests that H. *pylori* infection may be an important contributor in this region, when endemic iron deficiency persists despite apparent adequate nutritional intake and lack of parasitosis. Additional study is required to determine whether treating H. *pylori* infection facilitates resolution of iron deficiency anemia and whether the benefits of the therapy outweigh the risks.

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