ORIGINAL REPORT

Relationship between *Helicobacter pylori* Infection and Serum Ferritin Level in Primary School Children in Tehran-Iran

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Abstract- Iron deficiency can cause cognitive and functional learning disorders in children. Some studies have reported a relationship between low serum ferritin levels in patients with anemia and *Helicobacter pylori (H. pylori*) infection. Therefore, we aimed to determine the relationship between these two common diseases. This descriptive analytical cross-sectional study was performed to assess serum ferritin levels and *H. pylori* antibody titers (IgG) among 6-12 year old healthy primary school children in Tehran during the academic year 2005-2006. Specimen collection was done by cluster and randomization methods (multistage sampling). Personal information and laboratory results were compiled in questionnaires and data were analyzed by descriptive and analytical statistics via SPSS software. 165 primary school children (43% boys, 57% girls) with mean age 9.2 ± 1.5 years were enrolled in the study. *H. pylori* IgG antibody titer was positive in 26% of cases with mean values of 0.79 ± 0.42 units in boys and 0.75 ± 0.39 units in girls, which showed a significant statistical difference (*P*=0.004). *H. pylori* infection was more common among children of large families or those with low economic status (*P*=0.002). 29% of children had low serum ferritin levels. Out of the children with low serum ferritin levels, 71% and 28% had negative and positive anti *H. pylori* antibody titers (IgG levels), respectively. Also, 296 children (25%) with normal ferritin levels had *H. pylori* infection. We did not find a significant relationship between *H. pylori* infection and low serum ferritin levels or iron deficiency anemia.

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Introduction

Iron deficiency anemia is the most common cause of nutritional anemia throughout the world .The prevalence of iron deficiency anemia in developing countries has been reported to be more than 50% in children, which is mainly due to poor nutrition in most cases. In the U.S its prevalence has been reported (1). Numerous studies have shown that iron deficiency anemia is associated with cognitive disorders, poor learning ability, and lack of concentration, poor memory, educational failure, and behavioral or physical problems (2). Prevention or treatment of iron deficiency anemia requires knowledge about factors affecting this disease. Of course, unknown factors are involved in the etiology of anemia in a considerable percentage of patients (3). One of the factors affecting iron deficiency anemia is *Helibacter pylori (H. pylor)i* infection, which has a high prevalence in developing countries and some believe that resistant iron deficiency anemia, for which a cause has not been found, can be corrected with *H. pylori* eradication regimen (4,5). Some study showed that *H. pylori* seropositive patients are 40% at higher risk of reduced iron reserves (4). A study on Korean adults showed that *H. pylori* infection increases the rate of hypoferritinemia and iron deficiency anemia (5). Resistant iron deficiency anemia can be associated with *H. pylori* infection without any bleeding cause (6). Treatment of *H. pylori* produces a more rapid response to oral iron therapy (7). Although this relationship is not significant in some studies (8), but considering the rising rate of *H. pylori* infection in developing countries as well as the results of some studies which showed a significant relationship between *H. pylori* infection and iron deficiency anemia and low serum ferritin levels (9-11), we aimed to find the relationship between these two diseases among primary school children in Tehran.

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Patients and Methods

This descriptive cross-sectional analytical study was performed on primary school children in the 19 educational sectors of Tehran during the academic year 2005-2006. Exclusion criteria included: history of epigastric pain, vague abdominal pain, and prolonged diarrhea, girls who had passed menarche, chronic or hemorrhagic diseases, and children without written paternal consent or incomplete questionnaires. Using a multistage sampling specimen collection method, two girls and two boys primary schools were randomly chosen from each of the educational sectors of Tehran, without the intervention of the executive researcher, and the study was conducted on 1779 healthy school children. 114 subjects were excluded from the study due to inadequate hemolyzed blood samples or absence of consent forms, and finally 1665 subjects were enrolled into the study. After making the necessary arrangements with related higher authorities of the Ministry of Health, the Health officials of each educational sector, and with the school health officials, blood samples were taken from all children with the inclusion criteria, inside the school by an expert laboratory technician. At the same time as blood sample collection, a questionnaire comprising of personal health information and place of education of school children were completed for all subjects. After transferring the samples to the laboratory and after serum separation, the samples were stored of $^{-}$ 20º C and anti *H. pylori* IgG level was measured using ELISA (Trinity Biotic, Ireland, Capita. TMH *Pylori* 2326400-96 test). The results of this test were reported according to ISR value (Immune status Ratio), such that IgG levels ≤ 0.9, 0.91-1, and ≥ 1.1 were considered as negative, borderline, and positive, respectively. ELISA has a relative specificity of 96% for the diagnosis of anti *H. pylori* IgG (24,25). Serum ferritin levels were also measured using CLIA method (chemiluminescent Immunoassay Technology, Liasion, Italy, REF 313, 551). Serum ferritin $\geq$ 12 mg/dL was considered as normal and values below this were considered as abnormal. After compiling the test results of all patients, data were entered in a SPSS version II computer software data bank and later analyzed by descriptive and analytical statistics using chi-square and t-test.

Results

Samples were taken from 1779 students, of whom 114 subjects were excluded from the study due to various reasons. Thus 1665 subjects; 945 (56.77%) and 720 (43.23%) were girls and boys, respectively and mean age was 9.2±1.5 years. Anti *H. pylori* antibody titers were positive in 429 (26%) of subjects, of whom 220 (23.4%) were girls with mean ISR 0.75 ± 0.39 and 209 (29.1%) were boys with mean ISR 0.79 ± 0.42. In other words, *H. pylori* infection was significantly more common among boys than girls (*P*=0.029) (Table 1). A significant difference was seen between age groups (*P*=0.0001) and anti *H. pylori* antibody titer increased with advancing age, such that maximum infection rate occurred in 12 year olds (43%). Infection rate was highest in South Tehran (33%) with a statistically significant difference between boys (39.4%) and girls (27.9%) (*P*=0.002). *H. pylori* infection rate was higher in highly populated areas and in low socio-economic status areas, and was related to poor personal hygiene such as failure to wash hands with soap after using the toilet (*P*=0.004).

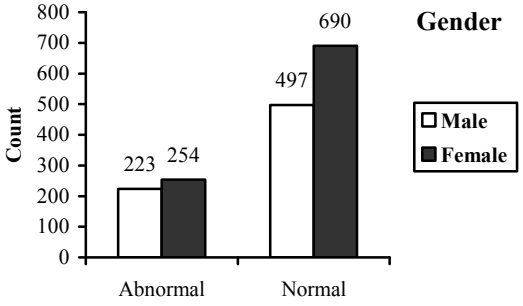

Figure 1. Ferritin level in both sexes

Table 1. *H. pylori* Antibody according to ferritin level

H. pylori -Ab ferritin	Negative N (%)	Borderline N (%)	Positive N (%)	Total N (%)
Abnormal	334(132)	11(2,3)	132 (27,7)	477(100)
Normal	857(72,7)	34(2,9)	296(24,9)	1187(100)
Total	1191(71,6)	45(2,7)	428(25,7)	1664(100)

H. pylori infection was also related to type of nutrition; use of tinned food (*P*=0.015), sandwiches (*P*=0.002) and sausages (*P*=0.07), but there was no such relationship with water or other foodstuff. Mean serum ferritin level was 33.63 ± 22.22 mg/dL, among whom 1187 (71.3%) had normal (≥12 mg/dL) and 477(28.7%) had subnormal ferritin levels (=12 mg/dL), which was more common among boys (Figure 1).

A significant statistical difference was not found between serum ferritin level and gender (*P*=0.078). Low serum ferritin levels were most common among< 9 year old boys (36.6%) and significantly least common among> 12 year olds. But mean serum ferritin level was not statistically different between different age groups (*P*=0.203). A significant difference was not found between different geographical regions (*P*=0.141) and low serum ferritin levels. There was no relationship between low serum ferritin levels, nutritional and health status. Among the 477 children with low ferritin levels, 334 (70.7%), 11 (2.3%) and 132 (27.7%) had negative, borderline, and positive anti *H. pylori* antibody (IgG) levels, respectively. *H. pylori* infection was found in 296 (24.9%) children with normal serum ferritin levels (Table 3).

Discussion

H. pylori is one of the factors effecting iron deficiency anemia and hypoferritinemia, which has a higher prevalence in developing than developed countries and has been reported in 50% of 10 year old children (13). The relationships between *H. pylori* infection and diseases outside the gastrointestinal system have been considered by researchers. One of these is the association of *H. pylori* and iron metabolism (3). Some researchers consider this relationship as significant (1,9,10). *H. pylori* is the main factor involved in peptic ulcer and chronic gastritis. Some studies have reported the relationship between this disease, low serum ferritin levels and iron deficiency anemia, especially with the resistant type (5). Other reports show that resistant iron deficiency anemia, of unknown cause, improves after *H. pylori* treatment (4,5). Some ferrokinetic iron mechanism problems have been associated with *H. pylori* , including the secretion of Hyatosine by hepatocytes which cause decreased iron absorption (3). Also, some believe that presence of *H. pylori* in the gastric antrum can cause lactoferrin production, which causes the iron derived from transferrin to attach to the *H. pylori* bacteria, and to be subsequently lost in the feces after the bacteria is destroyed. Another form of association is the increased iron absorption by 19K Da iron binding protein surface receptors and as a result of erosive gastritis and low iron absorption secondary to the hypochlorite conditions which results in occult blood loss (3,13). For this purpose, in order to detect *H. pylori* , ELISA serology (sensitivity=100%, specificity=96 %) was used to detect *H. pylori* IgG (12). One of the most accurate tests used to determine body iron stores, is serum ferritin level, which is an index for the condition of iron stores and iron deficiency anemia (14). This test was performed by the CLIA method. The current study showed that 26% of school students had *H. pylori* infection (positive IgG), which as compared to Karachi (40%) (11) is lower than neighboring countries. Our study showed that boys are at higher risk of developing *H. pylori* infection than girls, which was statistically significant (*P*=0.004). This is similar to the findings of some studies (13) while others report equal proportions (15). Also, a J-shaped relationship was found between the child's age and IgG antibody level (*P*=0.001), such that it was higher among 6 year old than 7 or 8 year old children. Serum IgG levels were higher in 9-12 year old children, and they were even higher than that of 6 year olds. On the whole, the rate of *H. pylori* infection rises with advancing age. Such findings have also been reported in the studies performed by Bagget *et al.* in Alaska (9), Suogla *et al.* in Turkey (10), Zubier *et al.* in Pakistan (11), Jais (15) and Hveem (13) (Table 1). In our study 29% of children had low serum ferritin levels, which did not show a significant statistical relationship between boys and girls (*P*=0.051) (fig. 1). Serum ferritin level was lower in boys, even though lowest values were seen in 11 year old girls. It seems that the reduced serum ferritin levels in this age group is most probably due to the rapid growth of girls and the loss of blood through menstruation as well as inadequate dietary iron intake in this age . We did not find a significant relationship between low serum ferritin levels, highly populated families, low socio-economic status, and type of diet, level of personal hygiene or geographical area. Another study also showed no difference to exist between serum ferritin levels of poor and wealthy children [(16)]. Correlation coefficient shows the relationship between serum ferritin and *H. pylori* serum IgG titer to be 86%. In our study, in 28% of children with ferritin levels <12mg/dL, had positive *H. pylori* antibody (IgG). Also, 25% of children with normal ferritin levels had *H. pylori* infection (IgG positive).A widespread study showed that *H. pylori* seropositive individuals are 40% at higher risk of developing low iron reserves (4). Another study showed that *H. pylori* infection causes a 17% reduction

in serum ferritin levels (17), whereas in our study, 28% of the children had normal ferritin levels. Our study shows that there is no significant relationship between low serum ferritin levels in school children in Tehran and positive *H. pylori* IgG titers and that there is no significant relationship between mean serum ferritin levels in IgG seropositive and *H. pylori* seronegative individuals, which is in accordance to the findings of Gasbarrini *et al.* (18), who did not agree with this relationship. Our results are different from those of Cardenas *et al.* (1) and Baget *et al.* (9), who have found a significant relationship between iron deficiency anemia with low serum ferritin levels and *H. pylori* infection. Also, in a study performed on 6-12 year old Korean children, low serum ferritin levels were found in IgG *H. pylori* seropositive subjects. This study showed a clear increase in iron deficiency among seropositive (13.9%) as compared to seronegative individuals (2.8%) (5). It seems that a part of those results are due to the fact that Different species of *H. pylori* may be involved. The species which may be associated with peptic ulcer and gastrointestinal symptoms are those bacteria with Cag (Cagpal) genes but Baysoy *et al.* showed that some *H. pylori* species are associated with gastric ulcer or iron deficiency anemia (19).

Epidemiologic studies, which have ruled out the relationship between iron reverses and *H. pylori* , mostly used serum ferritin level estimation, which is an acute phase reactor and its level depends on various factors. Therefore, considering the different factors involved in serum ferritin level, failure to find a significant relationship does not rule out the association between iron deficiency anemia and *H. pylori* infection. Along with other complementary studies, this preliminary study can be a good means of diagnosing and treating iron deficiency anemia resistant to therapy. In conclusion, regarding the overall results of our study as well as those of others, it seems that controversy still exists about the relationship between low serum ferritin levels, iron deficiency anemia and *H. pylori* infection. Based on these findings, we suggest the following in order to reach the goals of our study: The design and availability of iron-fortified food stuff with the help of the Ministry of Health and the Ministry of Education; Identification of the *H. pylori* bacteria species in Iranian patients. Performance of studies to determine the relationship between *H. pylori* infection and iron deficiency anemia according to the type of *H. pylori* bacteria species and Performance of widespread epidemiologic studies on different age groups of asymptomatic healthy children as well as on symptomatic subjects and comparison between the two groups.

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