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Increasing Prevalence of Iron Deficiency Anemia in the Paediatric Population: Is Helicobacter pylori Infection to Blame?

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Abstract

The increase in the prevalence of iron deficiency anemia (IDA) in the paediatric population, who otherwise have an adequate nutritional intake, is of great concern. Helicobacter pylori (H. pylori) is a major cause of gastritis, peptic ulcer disease, and iron deficiency anemia secondary to gastrointestinal bleeding in adult patients. However, studies done on the paediatric population are few regarding H. pylori infection. A systematic literature review was undertaken for evidence of H. pylori infection and IDA in the paediatric population to determine whether eradication of H. pylori improved symptoms of IDA in paediatric patients. Relevant paediatric studies were reviewed, including case reports, observational epidemiologic studies, peer-reviewed articles, and randomized clinical trials. Most studies reported a positive correlation between *H. pylori* infection and IDA in paediatric patients. Moreover, some studies reported that the elimination of H. pylori infection improved laboratory values as well as symptoms of IDA in children. There is substantial evidence that supports the association of H. pylori infection and IDA in paediatric patients. Thus, H. pylori infection should be evaluated in all cases of recurrent IDA as both conditions may commonly coexist. Correct diagnosis and treatment for H. pylori should help reduce morbidity and mortality associated with recurrent or refractory IDA. Further research is needed to determine the exact mode of infection and transmission of H. pylori in paediatric patients.

Keywords: Iron Deficiency Anemia; Microcytic Hypochromic Anemia; Helicobacter Pylori Infection; Paediatric Patients

Abbreviations

IDA: Iron Deficiency Anemia; H. pylori: Helicobacter Pylori; RBC: Red Blood Cell; WHO: World Health Organization; Hgb: Hemoglobin; UBT: Urea Breath Test

Introduction

The increasing prevalence of iron deficiency anemia (IDA) is a global public health problem, concern, and challenge. According to the World Health Organization (WHO), more than twenty-five percent of the world`s population have IDA, being more common in young children [1]. IDA is characterized by a decrease in total red blood cells (RBCs) or hemoglobin (Hgb), resulting in inadequate oxygen supply to tissues and hypoxia [1,2]. IDA results in impairments in immune, cognitive, and reproductive functions, as well as decreased work

performance [3]. The high prevalence of iron deficiency has been strongly linked to the adverse effect of Helicobacter pylori (H. pylori) infection [3].

It has been known for more than a century that bacteria are present in the human gut [3]. These bacteria, however, were thought to be contaminants from the digested food rather than actual gastric colonizers [3]. In 1982, Marshall and Warren successfully isolated and cultured a spiral bacterial species from the human gut, later known as Helicobacter pylori [4]. Various experiments described and performed by Morris demonstrated that these bacteria could colonize the human gut, thereby inducing inflammation of the gastric mucosa [4]. Marshal developed transient gastritis after ingestion of H. pylori; the case described by Morris developed into a more persistent gastritis [5]. These experiments suggested that blood loss from chronic gastritis, and bleeding from duodenal or gastric ulcers related to H. pylori infection, may play a role in the development of iron deficiency [4,5]. These findings resulted in further investigations regarding the link between H. pylori and IDA. In the United States, most studies involved Alaska Natives [5].

The high prevalence of IDA has been observed among Alaska Natives dating to the 1950s, despite adequate intake of nutrients offering optimum iron nutrition [4-8]. Therefore, gastrointestinal blood loss was suggested as the cause of anemia [6]. These findings led to the discovery that 99% percent of people with increased fecal blood loss had chronic active gastritis caused by H. pylori [7]. In determining the prevalence of H. pylori in Alaska Natives, over 2000 serum samples were collected in the 1980s in Alaska Native communities, which were assessed for H. pylori IgG antibodies [7]. Over 75% of the samples were positive for H. pylori. Rates increased from 32% among the age group 0–4 years to 86% among age 20 years and older [7]. There were differences in the rates by region of the state, which was most pronounced among the youngest children (0–4 years), where rates ranged from 5% in south-central (Anchorage vicinity) to 65% in interior Alaska [7]. Ferritin values from the same samples supported an association between H. pylori infection and iron deficiency, especially in those under 20 years of age [7].

In 1996, the H. Pylori Village Impact Survey was undertaken in persons equal to or greater than seven years of age. Residents of five rural villages (467 persons) and Anchorage (243 persons) participated. Serology and urea breath test (UBT) were performed, in addition to completing a questionnaire for risk factors [6,7]. For Anchorage residents, 60% of participants had a positive UBT and 73% positive for all participants, with a lower proportion among Anchorage residents. Evidence of H. pylori infection among non-Natives was less common; 17% had positive UBT, and 23% had antibodies to H. pylori [7]. Gastrointestinal symptoms seemed at similar levels among persons with H. pylori infection compared with uninfected persons [7]. Evidence of H. pylori infection—by the presence of antibodies or by a positive UBT—were more common among rural participants, among those who reported sharing chewing gum, went hunting, or who had a child in the household less than two years of age [7]. These data indicate that H. pylori infections are more common among Alaska Natives than non-Natives and more common among rural Alaska Native residents compared with urban Alaska Native residents, which corresponds to regions with higher prevalence of IDA [4,7,8].

Aim of the Study

The goal of this study was to investigate—based on previous studies—the link between H. pylori infection and IDA in the paediatric population and to determine if eradication of H. pylori improved symptoms of IDA in paediatric patients.

Methods

A systematic electronic search was performed on Google Scholar, PubMed, Springer, Elsevier BV, Wiley Online Library, MEDLINE, and other relevant online databases. Data collected focused on paediatric studies, including case reports, observational epidemiologic studies, peer-reviewed articles, and randomized clinical trials, published in the English language. The search strategies for MEDLINE and PubMed Central are shown as follows: Helicobacter pylori, Helicobacter pylori infection, anemia, iron deficiency, iron, nutritional anemia, microcytic hypochromic anemia, hemoglobin level, hematocrit, serum iron, serum ferritin, and or total iron-binding capacity. Fourteen publications were reviewed.

Results and Discussion

Several studies have linked H. pylori infection to low iron levels in paediatric patients. Parkinson., et al. (2000) showed a correlation between H. pylori infection and decreased iron storage in the study population [4]. In the study, 7462 participants, ages 15–18 years, were surveyed [4]. Multinomial logistic regression analyses indicated that H. pylori infection was associated with the prevalence of IDA: prevalence odds rate (POR) = 2.6, 95% CI: 1.5, 4.6; and, to a lesser degree, other types of anemia: POR = 1.3, 95% CI 1.0, 1.7. H. pylori infection was associated with a 40% increase in the prevalence of iron deficiency (POR = 1.4, 95% CI: 0.9. 2.0) after controlling for relevant covariates [4].

"Severe iron deficiency anemia in adolescents: consider Helicobacter pylori infection", stated Cardamone., *et al*. (2008), who reported on three subjects, 14–16 years of age, who had symptomatic iron deficiency anemia with no apparent clinical cause and refractory to iron replacement therapy [5]. The three subjects underwent diagnostic endoscopies and were found to have H. pylori gastritis [5]. The researchers further reported that histopathology confirmed inflammatory changes, consisting of dense bands of clusters of plasma cells within the lamina propria. Two of the subjects were noted to have numerous H. pylori in gastric crypts and glands [5]; two of the subjects had positive urease tests [5]. Iron deficiency was corrected following antibiotic eradication of the subjects' H. pylori infections [5]. Other studies also reported improvement of iron deficiency anemia after eradication of H. pylori [9–14]. This case series highlighted the significance of considering H. pylori infection as a cause of refractory iron deficiency anemia in adolescents, even in the absence of gastrointestinal symptoms.

Another case study, conducted in Rome, Italy, clearly demonstrated an association between Helicobacter pylori infection and iron deficiency. This study involved thirty patients who had refractory iron deficiency anemia. All patients had undergone a thorough gastrointestinal evaluation. The only abnormality discovered was the presence of H. pylori-associated gastritis. The patients were treated with different medications. At the three-month check-up, all patients reported the complete resolution of anemia-related symptoms, such as fatigue, pallor, and decreased exercise capacity. Endoscopic evaluations at six months showed H. pylori had been eradicated in 89.3% of the patients and 75% of the patients had completely recovered from the anemia. The recovery rate rose to 91.7% after twelve months. Also, average ferritin levels increased by more than 300% over the 12-month follow-up period, from 5.7micrograms/L to 24.1 micrograms/L, despite the discontinuation of iron supplements [2].

Summary

Alaska Native studies were used to lay a foundation regarding the connection between H. pylori infection and IDA, particularly in the paediatric population. Furthermore, a total of fourteen studies related to iron deficiency anemia and H. pylori infection and or gastric colonization were reviewed. The studies involved sample sizes ranging from 3 samples [5] to 7,462 samples [4]. In each of the studies, iron deficiency anemia was strongly linked to H. pylori infection or gastric colonization. Thus, it appeared that the sample size does not preclude the accuracy of the studies. Some of the studies specifically implicated H. pylori infection as the cause of iron deficiency anemia refractory to oral iron treatment [2-6,10-14].

The exact mechanism of H. pylori interference with iron metabolism remains unclear. Some studies suggested that the growth and proliferation of H. pylori require iron from the host and that some H. pylori strains have a specific ability to interfere with iron metabolism leading to low serum iron levels in infected individuals [2,4,14]. Other studies reported that most dietary iron is in the nonheme form, and an acidic intragastric pH is needed to reduce it to ferrous form for absorption. Patients with H. pylori gastritis have altered gastric pH, thereby impairing the process of iron absorption [3,5]. Further studies indicated that iron deficiency anemia may have been due to fecal loss rather than inadequate intake [6,10] or that H. pylori may have contributed to iron deficiency anemia by increasing the demand for iron [11,12].

Conclusion

The data-analysis review of prior studies implicates H. pylori infection as having a role in iron deficiency anemia in the paediatric population. Thus, H. pylori infection should be considered and tested in all cases of recurrent iron deficiency anemia, as both conditions may coexistent. Correct diagnosis and eradication therapy for H. pylori should help in reducing the morbidity and mortality associated with recurrent, refractory iron deficiency anemia.

The prevalence of H. pylori infection in iron deficiency anemia is elevated in specific groups, such as non-breastfed children, female adolescents, and children aged 1–4 years. Further studies are needed to determine the mode of infection and transmission of H. pylori in the paediatric population. More public health programs should be established to foster awareness and education and provide preventive measures to achieve long-term recovery from H. pylori infection and prevent iron deficiency anemia in the paediatric population.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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