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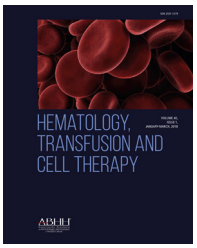

Original article

Helicobacter pylori associated to unexplained or refractory iron deficiency anemia: an Egyptian single-center experience

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ABSTRACT

Background: Refractory or unexplained iron deficiency anemia accounts for about 15% of all cases. The endoscopic gastrointestinal workup sometimes fails to establish the cause of iron deficiency anemia and a considerable proportion of patients regardless of risk category fail to respond to oral iron. The aim of the present study was to assess the etiological role of *Helicobacter pylori* infection in adult Egyptian patients with unexplained or refractory iron deficiency anemia.

Methods: A case controlled study was composed of 104 iron deficiency anemia cases and 70 age- and gender-matched healthy controls. Patients were diagnosed with iron deficiency anemia according to hemoglobin, mean corpuscular volume, serum ferritin, and Transferrin saturation. Upper and lower endoscopies were performed and active *H. pylori* infection was investigated by testing for the *H. pylori* antigen in stool specimens. Hematological response to *H. pylori* treatment with triple therapy together with iron therapy ($n = 32$) or only iron therapy ($n = 32$) were assessed in patients with *H. pylori* infection.

Results: *H. pylori* infection was more prevalent in patients with unexplained or refractory iron deficiency anemia (61.5%). Of the different hematological parameters investigated, there was a significant correlation only between *H. pylori* infection and mean corpuscular volume (p-value 0.046). Moreover, there was a significant correlation between receiving triple therapy together with iron supplementation and improvements in the hematological parameters [hemoglobin (p-value < 0.001), mean corpuscular volume (p-value < 0.001), Iron (p-value < 0.001) and serum ferritin (p-value < 0.001)] compared to receiving iron supplementation alone.

Conclusions: Failing to test for *H. pylori* infection could lead to a failure to identify a treatable cause of anemia and could lead to additional and potentially unnecessary investigations. Furthermore, treatment of *H. pylori* infection together with iron supplementation gives a more rapid and satisfactory response.

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Introduction

Iron deficiency anemia (IDA) is a worldwide nutritional problem; it accounts for about half of the world's anemia burden with most IDA patients living in developing countries.[1]

Refractory or unexplained IDA accounts for about 15% of all cases.[2] It is a diagnostic and evaluation challenge that employs a list of exams from stool testing for parasitic infestations to full gastroenterology endoscopies.[3] The term 'unexplained IDA' can be applied when the endoscopic gastrointestinal workup fails to establish the cause of IDA.[4] On the other hand, the term 'refractory IDA' is applied to a considerable proportion of patients when they fail to respond to iron supplementation at a dose of at least 100 mg of elemental iron per day over 4–6 weeks.[2]

It is estimated that *Helicobacter pylori* infects the stomachs of 50% of the global population. There are variations in infection rates from one country to another with the rates being inversely correlated with the human development index.[5]

Without eradication treatment, *H. pylori* is likely to persist in its human host for a lifetime with a proportion of infected individuals developing peptic ulcers, gastric adenocarcinomas and/or mucosa associated lymphomas (MALT). Beyond the stomach, more than 50 extra-gastric manifestations of *H. pylori* have been reported involving a wide list of medical disorders.[6]

The relationship between *H. pylori* and iron deficiency was first described in 1991 as a 15-year-old boy with IDA had improved hematological parameters after *H. pylori* eradication.[7] The mechanisms underlying the association between *H. pylori* infection and iron deficiency are not fully understood yet. The most obvious mechanism for *H. pylori* to cause IDA is by competing for dietary iron. *H. pylori* requires higher concentrations of inorganic iron and zinc than other pathogens for *in vitro* growth, yet there is no evidence that *H. pylori* has more iron- or zinc-dependent enzymes than other bacteria.[8]

Data on the effect of *H. pylori* eradication on adult Egyptian patients with refractory IDA or IDA of unknown origin, a population with a high prevalence of *H. pylori*, are scarce. The objectives of this study are to evaluate the prevalence of *H. pylori* infection among a cohort of Egyptian patients with unexplained iron deficiency anemia and to investigate the relationship between *H. pylori* infection and hematological parameters of these patients. Furthermore, this study aimed to assess the patients' response to combined *H. pylori* triple therapy with iron therapy compared to iron therapy alone.

Methods

A total of 104 Egyptian subjects who were diagnosed with IDA of unknown cause or who were refractory to oral iron therapy (60 women and 44 men with a mean age of 39.6 ± 10.84 years) and 70 age- and gender-matched healthy controls were enrolled in this study. All subjects were consecutively recruited in the Clinical Hematology Unit of the Kasr Al-Ainy Teaching Hospital, Cairo University where they were diagnosed and followed-up prospectively between October 2014 and June 2017. The study complied with good clinical practice protocols and with the ethical norms stated in the Declaration of Helsinki (as revised in Tokyo 2004). The study was approved by the local Ethics Committee and all patients gave their written informed consent prior to recruitment.

All subjects with unexplained or refractory iron deficiency anemia as well as healthy controls were subjected to full history taking (especially nutritional, menstrual, drugs taken, bleeding or gastrointestinal history as well as compliance to iron therapy), a thorough physical examination, and laboratory tests. The laboratory investigations included a complete blood count (CBC) and blood film, reticulocyte count, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and liver and kidney function as well as upper and lower endoscopies. Patients with malignancies, chronic diseases, dimorphic anemia, obvious causes of IDA and acute infections were excluded from the study.

Diagnosis of iron deficiency anemia

All patients had hemoglobin levels less than reference values for age and gender with a blood film that showed microcytic hypochromic anemia. The mean corpuscular volume (MCV) was less than 80 fl, serum ferritin was below 20 ng/dL; iron was below 50 g/dL and total iron binding capacity (TIBC) was more than 350 g/dL. The transferrin saturation was below 15%. Ferritin was measured using the Elecsys 2010 system using a Roche diagnostics kit by the electro-chemiluminescence immunoassay (ECLIA) method. Serum levels of iron were measured by the colorimetric method with a Roche modular analyzer. TIBC was measured with the Roche modular analyzer.

Diagnosis of H. pylori infection

Stool specimens were collected from participants (patients as well as healthy controls) and tested for the *H. pylori* antigen using the *H. pylori* Ag test (CTK Biotech, Inc. San Diego, CA 92121, USA. Cat # R0192C). This is a sandwich lateral flow chromatographic immunoassay that uses a colloidal gold conjugated monoclonal anti-*H. pylori* antibody and a second monoclonal anti-*H. pylori* antibody to specifically detect the *H. pylori* antigen present in fecal specimens. The detection limit for the spectrum *H. pylori* Ag test device is a 5 ng/mL *H. pylori* lysate.

Therapy response assessment

Patients who were discovered to have *H. pylori* infection were randomly subdivided into two groups:

Group A: received triple therapy for *H. pylori* eradication (omeprazole 20 mg b.i.d., amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d.) for 14 days combined with oral iron therapy (ferrous sulphate 325 mg OD) for three months.

Group B: received only oral iron therapy (ferrous sulphate 325 mg OD) for three months.

After three months of therapy, Group A and Group B were both reassessed regarding hemoglobin, MCV, mean corpuscular hemoglobin (MCH), serum iron, and ferritin levels with *H.*

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