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RESEARCH ARTICLE

STUDY OF RECURRENT ABDOMINAL PAIN IN BETA THALASSEMIA MAJOR PATIENTS: POSSIBLE RELATION WITH HELICOBACTER PYLORI INFECTION

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ABSTRACT

Objective: To determine the frequency of HP seroprevalence and infection in ß-TM patients both symptomatic and asymptomatic for RAP and to compare between ß-TM patients and controls presenting with RAP.
Materials and Methods: The study included 2 groups group I consists of forty ß-TM patients Aged (3 – 18) years. They were subdivided into Group Ia (symptomatic for RAP) and Group Ib (asymptomatic for RAP) each group consists of 20patients. Group II (control group) consists of 20 children complaining of recurrent abdominal pain with no chronic illness whose ages and gender were compatible. Serum samples were examined for anti-HP antibody using HpIgG ELISA test. Stool antigen test (qualitative immunochromatographic assay containing momoclonal antibodies) was applied to seropositive patients to assess the rate of associated active infection.
Results: The overall prevalence of HPIgG (+ve) was equal in ß-TM and controls (45%). compared to stool results which was higher in thalassemia (37.5%) than controls (30%) but not statistically significant. Withstool antigen test, statistically significant difference regarding pain site, splenectomy and serum ferritin.
Conclusion: HP seroprevalence was similar in thalassemic and controls. active infection was higher in thalassemic than controls and affected with splenectomy and high serum ferritin.

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INTRODUCTION

Beta thalassemia syndromes are a group of hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. In ß-thalassemia major, the production of beta-globin chains is severely impaired because both beta-globin genes are mutated. This imbalance of globin-chain synthesis results in ineffective erythropoiesis and severe hypochromic microcytic anemia (Cunningham *et al*., 2009). Children born with thalassemia major (Cooley's anemia) are normal at birth, but develop severe anemia during the first year of life (Galanello and Origa, 2010). So, regular blood transfusion is required with concomitant iron overload because each unit of blood delivers about 200 mg of iron to tissue that cannot be excreted by physiologic means (Lanzkowsky, 2011).

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Thalassemia major patients frequently present with several gastrointestinal tract manifestations including recurrent abdominal pain (Giardina and Forget, 2008). Recurrent abdominal pain (RAP) in children is a common disorder that has been estimated repeatedly over the last 4 decades to affect 10% to 20% of all school-aged children, with a slight increase in females after 9 years of age (Huertas-ceballos *et al*., 2014). Recurrent abdominal pain is defined as at least three episodic attacks of abdominal pain over at least three months that are severe enough to affect the usual activity of the child (Cuvellier and Lepine., 2009). Helicobacter pylori, is a gram-negative curved bacillus that colonizes gastric mucosa in humans. Its prevalence is 70% in developing countries (Spee *et al*., 2011). Risk factors for H. pylori infection are related to living conditions in the childhood, such as living in crowded conditions, living without a reliable supply of hot water, living with someone who has an H. pylori infection (Ruggiero, 2012). Over 80% of people infected with H. pylori show no symptoms. Acute infection may appear as an acute gastritis with abdominal pain (stomach ache) or nausea (Ryan and

keinneth., 2010). Where this develops into chronic gastritis, the symptoms, if present, are often those of non-ulcer dyspepsia: stomach pains, nausea, bloating, belching and sometimes vomiting (Boyanova, 2011). However it is not proven that Helicobacter pylori infection is one of the causes for recurrent abdominal pain in β- thalassemia major patients. There are very limited number of studies about this subject (Christoforidis *et al*., 2008).

MATERIALS AND METHODS

In this study, 40 β TM patients aged 3-18 year, were observed at hematology and oncology unit, pediatric department, Faculty of Medicine, Menofeya University, Egypt during the period of Mars 2013 to Mars2014 .they were subdivided into 2 groups 20 β- thalassemia major with RAP (group Ia) and the other 20 β- TM patients who do not have RAP (group Ib). They all had proved β-thalassemia major on the basis of the usual hematological confirmation (complete blood count and hemoglobin electrophoresis). 20 patients, whose ages and genders were compatible and who had RAP, but not a chronic illness, were included as a control group in the study. All participants or their parents gave written informed consent. RAP is defined by at least three discrete episodes of abdominal pain over a period of three or more consecutive months, and of sufficient severity to impair normal activities. this is as defined by Apley's criteria (Apley and Naish, 1958). Detailed history was obtained from patients and the place and duration of pain was questioned. Abdominal pain was asked mothers and/or children. Detailed physical examination of patients were done. Complete blood count, liver function (ALT and AST), serum creatinine, complete urine and stool analysis, ESR, C-reactive protein, serum ferritin were carried out in all patients as part of the evaluation.

All the patients underwent abdominal ultrasonography. Cases with urinary tract infection, gastroenteritis, parasitic infestation, Previous administration of helicobacter pylori treatment or proton pump inhibitors during last 3 months and complicated thalassemia major patient as gall bladder stones are excluded. All the patients and controls were subjected to serum samples examination for anti-HP antibody using HPIgG ELISA (PISHTAZTEB Diagnostics, Schulweg, Germany). Samples were considered positive for HP infection when antibody levels were >10 U/ml they considered negative when they were equal to or less than10 U/ml. Stool antigen test was applied to patients with positive HPIgG by using (CERTEST Biotic S.L, San Mateo de Gallego, Zaragoza, Spain). It is a qualitative immune-chromatographic assay for detection of H. pylori in the stool samples using monoclonal antibodies on the test line.

Statistical Analysis

Data was tabulated and subjected to analysis using Microsoft Excel version 5.0 and the Statistical Package for Social Science (SPSS) version 11.0. The following methods were employed: frequency and percentage distributions; mean, standard deviation and range of numerical data; comparison of means using the Student t test; testing differences between means for statistical significance; and non-numerical data were compared using the chi-square test. In general, p values less than 0.05 were considered significant, and those below 0.001 highly significant.

RESULTS

Twenty TM patients with RAP, whose average age was (9.80 ± 5.26) and Ranged (3-17) year, 10 females (50%) and 10 males (50%), the other 20 TM patients without RAP, whose average age was (10.75 ± 3.87) Ranged (3-17),13 male(65%) and 7 females(35%) and control group 20 healthy children with RAP with average age (10.75 ± 3.98) Ranged (4-17), 11 females (55%) and 9 males (45%). The overall prevalence of HPIgG in β TM patients was 45% which was equal to that of the control group. However, the overall prevalence of stool antigen positive test was 37.5% in β TM patients compared to 30% in controls. HP IgG was found positive in 8(40%) in TM patients with RAP, 10(50%) in TM patients without RAP and 9(45%) in the control group with no statistical significant difference. The stool antigen test applied to seropositive cases revealed in 8(40%) in TM patients with RAP, 7(35%) in TM patients without RAP, 6(30%) in the control group and again no significant difference. Results of positive HP IgG test, as well as, stool antigen positive test showed no significant difference regarding sex , residence, height, weight and BMI among the studied groups. However, regarding age, significant difference between thalassemia patients without RAP and controls with HP IgG test but no significant difference with stool antigen test.

Table 1. The features of RAP in TM patients and control group

	Thalassemia (GIa) (N=20)		Controls GII (N=20)		Test	P value
	no	%	no	%		
Pain Site						
Epigastric	9	45.0	11	55.0	χ^2 0.21	0.716
Para-umbilical	11	55.0	9	45.0		
Pain Duration						
≤ 6 months	15	75.0	16	80.0	χ^2 0.14	1.0
> 6 months	5	25.0	4	20.0		
Associated Symptoms						
Nausea	3	15.0	3	15.0		
Vomiting	2	10.0	3	15.0		
Diarrhea	1	5.0	3	15.0	χ^2 1.59	0.810
Constipation	1	5.0	1	5.0		
Free	13	65.0	10	50.0		

In β TM patients, results of positive HP IgG test, as well as, stool antigen positive test showed no significant difference regarding chelation type and course, blood transfusion units and frequency per month between both groups of thalassemia. However regarding splenectomy, significant relation with stool antigen test (active infection) but no significant relation with HP IgG test.

Table 2. Comparison between β-TM patients regarding positive HP IgG and stool antigen test results

	+ve HP IgG	+ve stool antigen test
splenectomy	0.180	0.043(S)
chelation type	0.671	0.669
chelation course	0.444	1.0
blood transfusion units\ month	0.588	0.569
blood transfusion frequency \month	1.0	1.0

Regarding hemoglobin, Significant difference was found between both thalassemia groups and controls with positive HP IgG test, but no significant difference among the studied groups with stool antigen positive test.

Table 3. Results of H.pylori stool antigen test among the studied groups

	Thalassemic GIa (N=20)		Thalassemic GIb (N=20)		Controls GII (N=20)		Test	P value
	no	%	no	%	no	%		
Stool							χ^2	
Negative	12	60.0	13	65.0	14	70.0	0.10	P_1=0.744
Positive	8	40.0	7	35.0	6	30.0	0.44	P_2=0.507
							0.11	P_3=0.736

P_1: between GIa and GIb P_2: between GIa and GII P_3: between GIb and GII

Regarding serum ferritin, Significant difference was found between both thalassemia groups and controls with positive HP IgGtest, as well as, stool antigen positive test. Regarding ALT, Significant difference was found between thalassemia patients without RAP and controls with positive HP IgG test. But, no significant difference among the studied groups with stool antigen positive test.

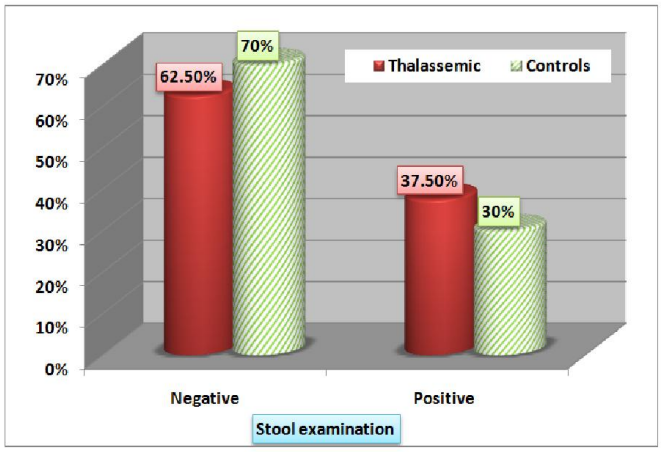

Fig. 1. Results of stool antigen test in thalassemia patients and controls

Regarding AST, Significant difference was found between thalassemia patients without RAP and controls with positive HP IgG test, as well as, stool antigen positive. Regarding viral markers for HBV and HCV, Significant difference was found between thalassemia patients without RAP and controls with positive HP IgG test. But, Significant difference between thalassemia patients with RAP and controls with stool antigen positive test.

In conclusion of the results, our study showed

In terms of the H. pylori IgG positive patients, significant difference between each group of thalassemia and control group regarding hemoglobin and serum ferritin ($p<0.05$), significant difference between thalassemia patients without RAP and control group regarding ALT, AST and viral markers ($p<0.05$). In terms of the positive stool antigen patients, significant difference between each group of thalassemia and control group regarding pain site, splenectomy and serum ferritin ($p<0.05$), significant difference between thalassemia patients without RAP and control group regarding AST ($p<0.05$) and significant difference between thalassemia patients with RAP and control group regarding viral markers ($p<0.05$).

Table 4. Results of the positive H pylori antibody test against positive stool antigen test

	Positive Helicobacter pylori IgG (GIa) (N=8)		GIb (N=10)		GII (N=9)		Fisher's exact Test	P value
	no	%	no	%	no	%		
Stool antigen							0.05	P_1=1.0
Negative	2	25.0	3	30.0	3	33.3	0.14	P_2=1.0
Positive	6	75.0	7	70.0	6	66.7	0.02	P_3=1.0

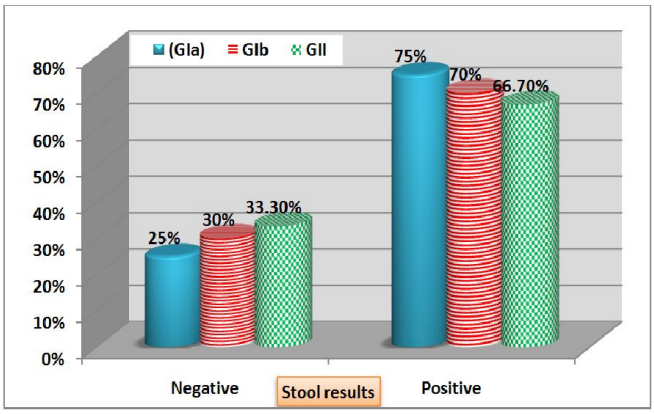

Fig. 2. Results of the serum positive Helicobacter pylori IgG against stool antigen positive results

Table 5. Results of the serum H.pylori IgG among the studied groups

	Thalassemic GIa(N=20)		Thalassemic GIb(N=20)		Controls GII(N=20)		Test	P value
	no	%	no	%	no	%		
IgG							χ^2	
Negative	12	60.0	10	50.0	11	55.0	0.40	P_1=0.525
Positive	8	40.0	10	50.0	9	45.0	0.10	P_2=0.749
							0.10	P_3=0.752

P_1: between GIa and GIb P_2: between GIa and GII P_3: between GIb and GII

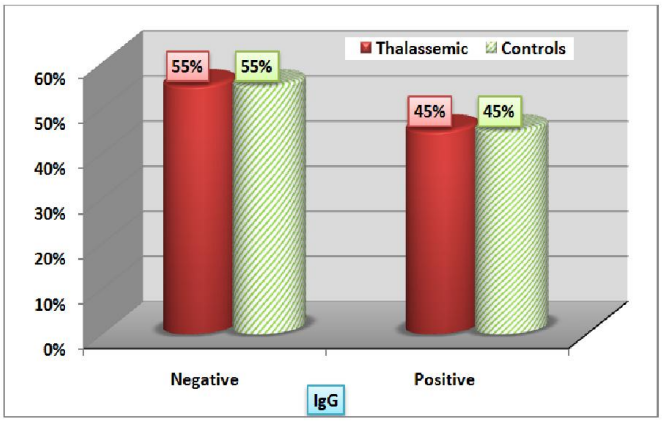

Fig. 3. Reults of HPIgG in thalassemia patients and the controls

DISCUSSION

Recurrent abdominal pain is one of the most frequent reasons of consulting to pediatric clinic. The role of HP was disputable in etiology of RAP in children (Malaty *et al*., 2006). While some studies have reported the significant association between H. pylori infection and RAP (Das *et al*., 2003 and Telmesani, 2009). others have considered no role for H. pylori in this case (Bode *et al*., 2003 and Wewer *et al*., 2001 and Masoodpoor *et al*., 2008). The overall prevalence of HPIgG in β TM patients was 45% which was equal to that of the control group. however, the overall prevalence of stool antigen positive test was 37.5% in β TM patients compared to 30% in controls. We did not observe any significant rise in the frequency of H. pylori seroprevelance (HP IgG) in patients with β-thalassemia major symptomatic and asymptomatic for RAP (40%, 50% respectively) compared with controls (45%). This high frequency of H. pylori infection reflects that H. pylori infection is a common health problem in persons presenting with RAP (Karimi *et al*., 2005). Our results are in accordance with Balci *et al*., 2011 who reported that HP IgG (+) was stated in the rate of 58.1% in TM patients with RAP and 48.8% in healthy children with RAP with no significant difference. In a study, HP IgG antibody scan was done in TM patients and no difference was found between healthy (20%) children and those (15%) (Christoforidis *et al*., 2008).

On the other hand, our study revealed that the frequency of stool antigen positive patients was higher in thalassemia patients with RAP (40%) than thalassemia patients without RAP (35%) and control group (30%) but also no significant difference was found. Similar to our results Karimi *et al*., 2005 mentioned that prevalence of 68% of H. pylori infection was recorded among thalassemia patients with recurrent abdominal pain; however, not significantly increased compared to controls (60%) with same symptomatology. And also, H .pylori infection in higher ratio (48.4%) was stated in TM patients in comparison with healthy children (39%) with no significant difference as mentioned by Balci *et al*., 2011.

In our study we found that there was no significant difference in the incidence of H. pylori sero-prevelance (IgG) and active infection (antigen in the stool) between the studied groups symptomatic and asymptomatic for recurrent abdominal pain (RAP) which means that no relation between RAP and H. pylori infection. And also no significant difference between thalassemia and controls, As a result, HP in our developing country may be one of the causes of RAP in TM patients as well as healthy children. There was no significant difference in distribution of HPIgG (+) against active infection (stool antigen) Results in TM and Healthy Children. This was also stated by Balci *et al*. H. pylori IgG, as well as, stool antigen results showed higher prevalence in school aged children (6-18 year) than pre- school children (3-6 years). This was in accordance with Marie *et al*., 2008 and Ndip *et al*., 2004. This may be caused by the fact that the initial infection probably occurs at an early age and prevalence increases with age. In our study we found that there was no significant difference in H. pylori IgG and stool antigen results regarding sex among the studied groups. This comes in accordance with Martigne *et al*., 2007 and Balci *et al*., 2011. We found no significant relationship between splenectomy and seroprevelance (IgG positive) ($p>0.05$) while there was significant relationship between splenectomy and active infection (stool antigen positive ($p<0.05$). In accordance with our study Balci *et al*., 2011 and Karimi *et al*., 2005 stated the same results. This result makes us think that immune response, which can change after splenectomy, affects active HP infection. In our study, regarding pain site, there was no significant difference among the positive Helicobacter pylori antibody patients ($P>0.05$), but there was significant difference among the stool antigen positive patients ($p<0.05$), Pain was higher localized to the epigastrium in controls and thalassemia this may be attributed to H. pylori induced gastritis which was The most common endoscopy abnormality observed in (72%) of the patients in the study done by Karimi *et al*., 2005 This comes in agreement with Balci *et al*., 2011.

In our study we found that there was no significant difference in distribution of HP Ig G as well as stool antigen results among the studied groups regarding pain duration and symptoms as nausea ,vomiting ,diarrhea and constipation ($P>0.05$).We could not identify a particular symptom associated with H. pylori infection. Regarding hemoglobin, H. pylori IgG positive thalassemic patients were seen more frequently in patients with lower hemoglobin level. However in control group, nearly equal between low (<11 g\dl) and normal hemoglobin level with significant relationship between both thalassemia groups and controls ($p<0.05$). Regarding hemoglobin in stool antigen positive patients no significant difference between both thalassemia groups and controls ($P>0.05$) and nearly similar distribution asIgG positive patients. Higher H. pylori positive patients were observed in thalassemia patients with serum ferritin >1000ng/ml. The relatively high serum iron levels may favor bacterial growth (Weatherall, 2006).

Balci *et al* and Karimi *et al* stated no significant difference between positive and negative patients regarding serum ferritin. In contrast, Christoforidis *et al* found serum ferritin concentrations were significantly lower in seropositive to H. pylori patients compared to seronegative ones. It seems that there is a significant interaction between H. pylori and iron metabolism, not fully elucidated yet (Christoforidis *et al*., 2008). And although it is not difficult to associate H. pylori-induced gastric achlorhydria and gastritis to impaired absorption of food iron and periodic bleeding (Cohen *et al*., 2004)respectively the unresponsiveness of anemia to iron supplementation and its reversal only after bacterial eradication needs additional thinking (Dubois *et al*., 2005). Beutler, 2007 hypothesized that H. pylori subvert the human iron regulatory mechanism by producing hepsidin mimics in a manner that is useful to the micro-organism and deleterious to the host. However, particular for patients with β-thalassaemia this iron sequestration may be proven beneficial. With respect to the limited numbers of our patients, our preliminary data need additional confirmation and further investigation. Our study revealed significant difference between thalassemia patients with recurrent abdominal pain and controls regarding viral markers for HBV and HCV ($p<0.05$) which in agreement with Christoforidis *et al*, Balci *et al* and Karimi *et al*. In conclusion, we recommend that H. pylori infection should be

included in the differential diagnosis of RAP in β thalassemia major patients as well as healthy children in developing countries where H. pylori has a great incidence. HP seroprevalence was similar in thalassemic and controls. Active infection was higher in thalassemic than controls and affected with splenectomy and high serum ferritin.

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