DÜZCE TIP DERGİSİ
DUZCE MEDICAL JOURNAL

ORİJİNAL MAKALE / ORIGINAL ARTICLE

Is Helicobacter Pylori Infection One of the Actual Causes of Vitamin B12 Deficiency?

Helikobakter Pylori Enfeksiyonu B12 Eksikliğinin Gerçekten Bir Nedeni midir?

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Submitted/Başvuru tarihi: 02.11.2010
Accepted/Kabul tarihi: 06.10.2011
Registration/Kayıt no: 10 11 162

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e-ISSN 1307- 671X
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ABSTRACT

Aim: Aim of this study is to determine *Helicobacter pylori* infection rate in Vitamin B12 deficiency and determine whether H.pylori infection is really actual cause of Vitamin B12 deficiency.

Material and Methods: We evaluated 40 vitamin B12 deficient patients and 25 healthy subjects. Those patients did not have known cause of vitamin B12 deficiency. We performed endoscopic evaluation and pathological examination for H.pylori. We determined 50% atrophic gastritis in vitamin B12 deficient group, but we did not observe any atrophic gastritis in the control group endoscopically.

Results: There were H.pylori positivity in 11/40 (27.5%) in the patients group but 16/25 (64) in the control group in pathological examination ($p<0.01$). Pathological examination of patient group also illustrated that 11 patients had mild atrophy in 11 (27.5%), 5 had moderate atrophy (12.5%) and 3 patient (7.5%) had severe atrophy. In contrast, 3 patients had only mild atrophy (12%) in the control group. We also found that H.pylori (-) 17/29 (58.6%) patients and H.pylori (+) 3/11 (27.3%) patients had atrophic gastritis in gastroscopic evaluation.

Conclusion: Patients who have vitamin B12 deficiency had lower ratio of H.pylori in gastric mucosa. On the other hand, the patient group had higher ratio of atrophic gastritis in pathological and gastroscopic examination. H.pylori positivity had been decreased progressively with aging in patients group. H.pylori has disappeared in following years as a result of atrophy in gastric mucosa. We conluded that atrophic mucosa is not suitable for colonization of H.pylori infection.

Key Words: Vitamin B12 deficiency, H.pylori, gastric atrophy

ÖZET

Amaç: Bu çalışmanın amacı vitamin B12 eksikliğindeki H. pylori enfeksiyonu oranını ve h. pylori enfeksiyonunun gerçekten vitamin B12 eksikliğinin asıl sebebi olup olmadığını belirlemektir.

Materyal ve Metod: 40 vitamin B12 eksikliği olan hastayı ve 25 sağlıklı kişiyi değerlendirdik. Bu hastaların B12 eksikliği sebebi bilinmiyordu. H. pylori için endoskopik değerlendirme ve patolojik inceleme uyguladık. Vitamin B12 eksikliği olan grupta %50 atrofik gastrit belirledik, fakat kontrol grubunda endoskopik olarak hiçbir atrofik gastrit gözlemlemedik.

Bulgular: Patolojik incelemelere göre hasta grubunda 40 hastadan 11'inde (%27,5), kontrol grubunda ise 25 hastadan 16'sında (%64) H. pylori pozitifliği vardı ($p<0,01$). Hasta grubunun patolojik incelemesi ayrıca 11 hastanın hafif (%27,5), 5 hastanın orta (%12,5), 3 hastanın ise ağır (%7,5) atrofisi olduğunu ortaya koydu. Zıt olarak kontrol grubunda, 3 hastanın sadece hafif (%12) atrofisi vardı. Gastroskopik değerlendirmede ayrıca H. pylori (-) 29 hastadan 17'sinde (%58,6) ve H. pylori (+) 11 hastadan 3'ünde (%27.3) atrofik gastrit olduğunu bulduk.

Sonuç: Vitamin B12 eksikliği olan hastaların gastrik mukozasında daha düşük H. pylori oranı vardı. Diğer yandan, gastroskopik ve patolojik incelemeye göre hasta grubunun daha yüksek atrofik gastrit oranı vardı. Hasta grubunda H. pylori pozitifliği yaşla birlikte progresif olarak azalmıştı. Takip eden yıllarda gastrik mukozadaki atrofi sonucu H. pylori yok olmuştu. Biz, atrofik mukozanın, H. pylorinin kolonizasyonu için uygun olmadığı sonucuna vardık.

Anahtar Kelimeler: Vitamin B12 eksikliği, H.pylori, gastrik atrofi

INTRODUCTION

Vitamin B12 deficiency affects 10-15% of the population over 60 years of age. The most common cause of this deficiency is pernicious anemia (PA) and cobalamin malabsorption from food. To a great extent, cobalamin is taken from animal products through diet (1, 2). Cobalamin in food creates a complex with R binding protein in stomach and it separates from R binding protein in

duodenum, and it binds again with intrinsic factor produced in stomach. In circulation, cobalamin is carried through another transport protein (3). In recent years, there have been discussions indicating that *Helicobacter pylori* (H. pylori) might cause cobalamin deficiency both immunologically and by affecting cobalamin absorption from food, and numerous researches are still being published (4).

H.pylori infection is among the most prevalent causes of gastric infection all around the world. It is believed that more than 50% of adults in developed societies and 90% of adults in developing countries are infected by this bacteria (5, 6). H.pylori infection and antral (Type B) gastritis are known to have a close connection (7). Some studies in the last few years underline that H.pylori infection is effective in setting out atrophic gastritis to be developed in coming years by infecting the stomach corpus (8). As is known, atrophic gastritis is one of the most significant causes of PA. It is assumed that PA appears via a complete loss of parietal cell mass due to atrophy as a result of gastritis commenced by H.pylori (9, 10). On the other hand, some of the researches claim that H.pylori infection does not have any role in developing atrophic gastritis in patients with PA (11, 12). We planned our study to prove the relation of vitamin B12 deficiency with H.pylori in patients that we were unable to establish the etiology of vitamin B12 deficiency.

MATERIAL AND METHOD

Fourty patients referred to Yildirim Beyazit Training Hospital 2nd Outpatient Clinic with the diagnosis of vitamin B12 deficiency were included the study and their results were evaluated retrospectively.

Patients who have history of gastrectomy, small intestine operation, ulcerative colitis, Crohn's disease, pancreatitis, and chronic alcoholism, and the ones diagnosed with cirrhosis were not included in the study. Patients who used PPI, antibiotics, and bismuth preparations in the last two months were excluded from the study. In the course of the study, two patients with vitamin B12 deficiency was endoscopically and pathologically diagnosed with adenocarcinoma were also excluded from the study. And patients with no anemia established in blood count and patients who underwent gastroscopy due to gastric complaints were included in the control group.

Vitamin B12 deficiency diagnosis was made by the existence of megaloblastic anemia, serum vitamin B12 value that was found below reference values, and response obtained by replacement treatment. Since Schilling test is not conducted at our center, patients were not tested with it.

Blood counts, biochemical examinations, vitamin B12, ferritin, and thyroid functions of patients in the study and control groups were all studied at the same laboratory. Patients included in the study were inquired in terms of their backgrounds, medical histories, and other diseases. Bone marrow biopsy was conducted on clinically suspected patients. By conducting upper gastrointestinal system endoscopy upon their consent, four biopsies – for H.pylori and pathologic evaluation, two from antrum and two from corpus – were carried out on both study and control groups. Stomach and duodenum were assessed in terms of visible pathologies during endoscopy. Through endoscopy, atrophic gastritis was reported due to a complete erasure of stomach plies and evident submucosal venous network in stomach. The obtained biopsies were then sent to pathology department in 10% formol solution for testing H.pylori and histology. The histopathological examinations of gastric biopsies were evaluated according to Sydney classification. Biopsy specimens were examined in terms of H.pylori, inflammation, atrophy, and metaplasia by staining with hematoxylin – eosin and giemsa. Metaplasia and atrophy were assessed as mild, medium, and severe.

Statistical Methods

Data on the patients and the control group included in the study were evaluated by SPSS (Statistical Package for Social Science) software. Comparisons between and within groups were conducted by student–t test, chi-square, Mann-Whitney U test, and Fisher's exact test. $P<0.05$ was found to be significant.

RESULTS

Included in the study were the patients group of 40 people that we established to have only vitamin B12 deficiency while searching for anemia etiology and other 25 people as the control group that went through endoscopy due to gastric complaints and that did not have anemia and vitamin B12 deficiency. In the patient group 24 (60%) of the patient group were female, 16 (40%) were male. In the control group, 14 (56%) were female, and 11 (44%) were male. Both groups had similar characteristics in terms of age and gender. A statistically significant difference was not observed between patient and control groups considering clinical properties ($p>0.05$) (Table 1).

Hemoglobin, leukocyte, and thrombocyte counts in the patient group was lower compared with the control group, but MCV values were significantly higher ($p<0.001$). A statistically significant difference was not found between patient and control group in glucose, ALT, AST, creatinine, and sedimentation values ($p>0.05$). LDH and bilirubin values were

Table 1: General characteristics and findings of patient and control groups

	Patient (n:40)	Control (n:25)	P value
Age (year)	54.32±14.86	56.68±10.92	>0.05
Gender F/M	24 /16	14/11	>0.05
Hemoglobin (g/dl)	8.76±2.02	13.00±1.11	<0.001
WBC (k/Ul)	4602±1854	6752±1556	<0.001
Platelet (k/uL)	129715±79115	285600±79258	<0.001
MCV (fL)	102.25±15.92	85.32±5.28	<0.001
Erythrocyte Sedimentation (mm/hour)	32.40±17.20	28.60±12.84	>0.05
ALT (u/L)	30.47±15.81	27.20±8.09	>0.05
AST (u/L)	26.35±14.68	25.28±8.29	>0.05
Creatinine (mg/dl)	0.82±0.24	0.78±0.20	>0.05
LDH (u/L)	489±151	328±61	<0.001
Total Bilirubin (mg/dl)	1.33±0.33	0.74±0.17	<0.001
Direct Bilirubin (mg/dl)	0.45±0.18	0.36±0.12	<0.05
Vitamin B12 (pg/dl)	143±35	380±117	<0.0001

significantly higher in the patient group (p<0.001). Mean vitamin B12 value of the patient group was 143±35 pg/dl, and that of the control group was 380±117 pg/dl in the control group (p<0.0001). A difference was not found between patient and control group in alcohol consumption and smoking (p<0.05).

In the endoscopic evaluations of patient and control groups included in the study, findings were normal endoscopy in 5% of the patient group, atrophic gastritis in 50%, antral gastritis in 17.5% and other endoscopic findings in 27.5%. Two patients that were found to have malignancy and diagnosed with adenocarcinoma were excluded from the study. Atrophic gastritis was not reported endoscopically in the control group. Findings observed were normal endoscopy in 36% of control patients, antral gastritis in 40%, and other pathologies in 24% of control patients (Table 2). When these values were compared, statistically significantly atrophic gastritis was higher in the study group (20/40) (p<0.001).

When evaluated patient and control groups in terms of H.pylori existence, 11/40 (27.5%) of the patient group and 16/25 (64%) of the control group had H.pylori. Comparison between the groups proved an evidently higher value of H.pylori in the control group than the patient group (p< 0.01) (Table 3).

Table 2. Endoscopic findings of patients in study and control groups

Endoscopic Findings	Patient Group	Study Group	P
Normal	2 (5%)	9 (36%)	<0.05
Atrophic Gastritis	20 (50%)	0	<0.0001
Antral Gastritis	7 (17.5%)	10 (40%)	<0.05
Other (gastroduodenitis, Gastric Ulcer, Esophagitis, Alkaline reflux gastritis)	11 (27.5%)	6 (24%)	>0.05

Pathologic evaluations of biopsy specimens were conducted and then compared with the control group. A statistically significant difference was not observed in degrees of inflammation of both groups in gastric biopsy (p<0.05).

In pathologic evaluation, gastric atrophy was observed in 19/40 (47.5%) of the patient group.

Table 3: H.pylori presence in pathologic examinations of patient and control groups

	Patient (n:40)	Control (n:25)	P value
H.pylori (+)	11 (27.5%)	16 (62.5%)	P<0.01
H.pylori (-)	29 (64%)	9 (36%)	P<0.01

Atrophic findings were graded in 11/40 (27.5%) of the patients as mild, in 5/40 (12.5%) as medium, and in 3/40 (7.5%) as severe. Only in 3/25 (12%) of the patients in control group had mild atrophy. When both groups were compared in terms of atrophy, it was significantly more common in the patient group (p<0.01) (Table 4).

Pathologic evaluations of biopsy in the patient group revealed intestinal metaplasia (IM); mild in 12/40 (30%) patients, medium in 5/40 (12.5%) patients, and severe in 2/40 (5%) patients. None of the patients were observed to have dysplasia.

When age and the existence of H.pylori in the patient group with vitamin B12 deficiency were compared, mean age of patients in the group that had H.pylori (+) was found lower. Mean age of patients with

Table 4: Atrophy findings in pathology preparations of patient and control groups

Atrophy	Patient (n: 40)	Control (n:25)	P value
Yes (+)	19 (47.5%)	3 (12%)	P<0.01
No (-)	21 (52.5%)	22 (88%)	P<0.01

H.pylori (+) in the group was 45±11, and in patients with H.pylori (-) in the group was observed as 57±14 (p<0.05). Endoscopically atrophic appearance was determined in 17/29 (58.6%) H.pylori (-) patients, and in 3/11 (27.3%) H.pylori (+) patients (p<0.05).

When the relation between H.pylori and the existence of atrophy was evaluated in the patient group, a statistically significant relation was not established between H.pylori and atrophy (p>0.05) (Table 5). Similarly, a significant relation was not observed between H.pylori and IM (p>0.05).

DISCUSSION

In this study, conducted on 40 patients with no known cause of vitamin B12 deficiency, H.pylori was

established in 11/40 (27.5%) patients, this rate was 16/25 (64%) in the control group. We endoscopically established atrophy in 50% (20/40) of patients with vitamin B12 deficiency. In the pathologic evaluation, the atrophy rate was 47.5% (19/40). In the light of this data, although atrophy is prevalent in patients with

Table 5: H.pylori and atrophy relation in patient group

	Atrophy (-)	Atrophy (+)	P value
H.pylori (-)	13 (44.8%)	16 (55.2%)	p>0.05
H.pylori (+)	8 (72.7%)	3 (27.3%)	P<0.05

vitamin B12 deficiency, H.pylori is rarer. It was established that the ages of patients with vitamin B12 deficiency and atrophy were more advanced, and H.pylori was found much less colonized. Patients with vitamin B12 deficiency become negative in terms of H.pylori as they grow older. As a result of the gastric mucosal atrophy caused in time by H.pylori infection, H.pylori colonization gets harder and the survival of the bacteria in such an environment becomes impossible.

So far, H.pylori is the most common cause of gastric infection throughout the world. H.pylori is thought to infect 50% of the population in the developed societies, and 90% in developing countries (13-15). In a study conducted in Turkısh society, H.pylori prevalence was found between 67.6%-81.3% (1, 2). The H.pylori infection prevalence in patients with vitamin B12 deficiency was reported in studies between 0% and 30%. H.pylori infection is generally found less compared with control groups (12, 17). In contrast, Kaptan et al. reported 56% H.pylori positivity in patients with vitamin B12 deficiency (1, 2). O'Connor et al. found 21.4% H.pylori in patients with PA [18]. In a study by Fong et al., 11% H.pylori was reported in PA patients (12). Also H.pylori infection decreased from >80% at age <20 years to 12% at >60 years (19). In our study, we found this rate as 27.5% at the mean age of 54 years.

Pernicious anemia is the most important cause of vitamin B12 deficiency. As is known, H.pylori is responsible for Type B antral gastritis in stomach. However, its relation with Type A (autoimmune) gastritis is not well-known. Atrophic changes in Type A autoimmune gastritis affect stomach mucosa (20, 21). Atrophic gastritis and vitamin B12 deficiency concomitance is frequently seen. Chronic atrophic gastritis is observed in patients with PA almost in an unchanged manner. There are contradictory reports on whether a connection exists between H.pylori and atrophic gastritis. Hebenbro et al. established a low H.pylori prevalence in patients with PA and atrophic gastritis (22). Contrarily, Cariani et al. observed a higher H.pylori prevalence in patients with PA and atrophic gastritis (23). Karnes et al. also found higher H.pylori infection prevalence in the same patient type. However, this study evaluated H.pylori presence by checking antibodies (8). In our study group, atrophic gastritis was observed in 50% endoscopically and 47.5% in the pathologic examination.

Why are H.pylori bacteria are observed less in patients with atrophic gastritis? There are a variety of opinions reported on the issue. As is known, H.pylori infects individuals in a society in quite higher rates. Infection that occurs for quite a long time causes dissolution and disappearance in gastric mucosa, and deterioration in glandular structure, thus making it difficult for H.pylori bacteria to colonize, and in time, H.pylori turns into negative (22). IM is more frequently observed in PA patients compared with other individuals. IM might be a factor preventing H.pylori from colonization in stomach mucosa with atrophic gastritis. Achlorhydria is also frequently observed in PA patients. And this (athrophic gastritis) is one of the most probable conditions preventing H.pylori colonization (18). In the light of these data, it could be said that PA patients are infected with H.pylori at early stages of their lives, and as a result of this long-lived infection, H.pylori bacteria transforms into negative due to a loss of proper environment by mucosal changes the bacteria cause. This comes to mean that H.pylori bacteria provide their own termination (21). In a research by Karneys et al., H.pylori antibodies were observed as high in patients with PA and atrophic gastritis. This demonstrates that these patients have previously been infected with the bacteria (8). H Pylori may disappear over time due to the hostile gastric microenvirement and past infection may be demonstrated by serological positivity to H.pylori in a large majority of patients with athrophic body gastritis or PA (23).

Why it is then that PA does not develop in all patients infected with H.pylori? This does not have a clear response, but the intensity of H.pylori infection, individual tendencies, and quite a variety of H.pylori strains are believed to have an effect. With which mechanism or mechanisms do H.pylori cause atrophic gastritis and vitamin B12 deficiency? There are a variety of opinions reported on the issue. The liposaccharide structure in 80% of H.pylori strains imitates the x and y blood types of Lewis that is among the human blood types. ß chain in proton pump of parietal cells has the Lewis y epitode found in most of the H.pylori strains (24). Antibodies the body produces against H.pylori probably creates a

cross-reaction against epitode in parietal cells and cause a decrease in IF release. In addition, H.pylori may contribute to PA pathogenesis through antigenic mimicry. Just like other bacteria, H.pylori forms a cellular and humoral immune response. At the end, it gives a cross-reaction with cellular antigens of the body. Most frequently, auto antibodies that appear against H+/ K+ adenosine triphosphatase proteins are observed in PA (25, 26). In fact gastric H+/ K+ ATPase has been recognised as the major autoantigen in experimental and human atrophic gastritis and autoreactive gastric CD4+T cells that recognize H+/ K+ ATPase and H.Pylori antigens have been recently described in atrophic gastritis (27).

Another assumption that H.pylori can be effective in causing vitamin B12 deficiency results from the idea that it causes cobalamin malabsorption from food. As is known, vitamin B12 is taken from animal products. In an acidic environment, cobalamin released as a result of digestion of peptides is bound to R protein. Cobalamin bound to R protein is degraded in duodenum and transferred by binding to intrinsic factor. IF-cobalamin complex is absorbed from ileum (14). Disorder of cobalamin absorption from food increase in parallel with age and H.pylori causes it to become even more severe (19, 28). H.pylori is closely related to Type B chronic gastritis. Numerous researchers also claim that there is a close connection between Type B chronic gastritis and food cobalamin malabsorption (26, 30).

Kaptan et al. found an increase in vitamin B12 levels solely through H.pylori eradication in 31 out of 77 patients with low serum vitamin B12 levels (4). Similarly, some researchers like Marino et al. established an increase in cobalamin levels through H.pylori eradication treatment in patients with cobalamin deficiency (31-33). In the light of this data, they claimed that H.pylori causes cobalamin malabsorption from food and an eradication treatment wipes out this mechanism. Kaptan et al. reported that H.pylori deteriorate digestion of peptides in stomach and prevents binding with IF by causing vitamin B12 disintegration (4). Some of the researchers objected to this claim. What they asked was that, first of all, did patients responding to eradication treatment have atrophic gastritis? If so, was it diffuse or focal? Secondly, did antibiotics given for eradication treatment purposes corrected vitamin B12 deficiency by preventing bacterial overproduction in small intestine? To these researchers, the effect of H.pylori bacteria on food-cobalamin malabsorption would gain clarity only if Kaptan et al. clarify these issues.

Consequently, the 27.5% H.pylori rate in patients with vitamin B12 deficiency was established as lower compared with the control group in our study. Besides, atrophic gastritis in patients with vitamin B12 deficiency was observed as higher compared with other individuals in the same age group. In our study, pathologic atrophy was found in stomach at a rate of 47.5% in the patient group. It is commonly known that atrophic gastritis is in unison with PA. In the light of these data, we believe that H.pylori infection triggers future atrophy development to occur in future through various mechanisms, and that it forms the basis for PA which is the most important cause of vitamin B12 deficiency. Since the atrophic stomach environment that appears in advanced age is not suitable for H.pylori infection, it is less or never observed compared with the same age group in the society. Our finding and other literatures support the idea that PA seems to be a long duration disease that is related to H.pylori, gastric achlorhydria and athrophy which begins many years before the establishment of clinical vitamin B12 deficiency.

However, in order to clarify this issue, it is necessary to follow patients infected with H.pylori for a long term, and to observe individuals who had eradication treatment as a control group. In the light of all these data, it can be claimed that H.pylori causes vitamin B12 deficiency in several ways, thus its treatment is effective both in preventing atrophy that occurs in advanced ages and prevention of food-cobalamin malabsorption.

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