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Orta Karadeniz Bölgesindeki Çocuklarda Helikobakter Pilori Enfeksiyonu Sıklığı ve Demir Eksikliği Anemisi ile İlişkisi

Pediatric Helicobacter Pylori Infection Prevalence and Iron Deficiency Anemia Coincidence among Children in North Central Turkey

Sibel Uçak Semirgin
Ondokuz Mayıs Üniversitesi Tıp Fakültesi Nükleer Tıp Anabilim Dalı

ÖZ

GİRİŞ ve AMAÇ: Çalışmanın amacı, Orta Karadeniz bölgesindeki çocuklarda Helikobakter Pilori (H.Pilori) pozitiflik oranının belirlenmesi; H.Pilori enfeksiyonunun, demir eksikliği anemisi (DEA) ve ilişkili hematolojik parametreler ile korelasyonunun değerlendirilmesidir.

YÖNTEM ve GEREÇLER: Çalışmaya gastrointestinal sistem semptomları nedeni ile C-14 üre nefes testi uygulanan çocuklar dahil edildi. Hemoglobin, hematokrit, ortalama eritrosit hacmi (n=852); serum demir düzeyi (n=175), demir bağlama kapasitesi (n=175), ferritin (n=197), transferrin satürasyonu (n=254) ve C-14 üre nefes testi sonuçları (n=1006) retrospektif olarak değerlendirildi. H.Pilori pozitiflik oranı belirlendi; H.Pilori pozitif ve negatif çocuklarda hematolojik parametreler karşılaştırıldı.

BULGULAR: Çalışmaya dahil edilen çocuk hastaların %46,8' inde H.Pilori pozitif idi. H.Pilori pozitif hastalarda hemoglobin ve hematokrit düzeylerinin negatif hastalara kıyasla anlamlı oranda düşük olduğu tespit edildi (hemoglobin için T: 4,014 P: 0,000; hematokrit için T: 3,486 P: 0,001). Ortalama eritrosit hacmi H.Pilori pozitif hastalarda düşük olmakla birlikte, istatistiksel olarak anlamlı değildi. Serum demir düzeyi (T: 2,297 P: 0,023), ferritin düzeyi (T: 2,19 P: 0,03) ve transferrin saturasyonu (T: 2,541 P: 0,012) H.Pilori pozitif hastalarda anlamlı düzeyde düşük saptandı. Demir bağlama kapasitesi açısından anlamlı fark izlenmedi. Anemik çocuklarda (x^2: 23,533 P: 0,000), transferrin düzeyi düşük olan çocuklarda (x^2: 4,948 P: 0,026), ferritin düzeyi düşük olan çocuklarda (x^2: 6,96 P: 0,008) ve ferritin düzeyi düşük olan anemik çocuklarda (x^2: 13,74 P: 0,00) H.Pilori pozitiflik oranının yüksek olduğu tespit edildi. Kızlarda ve erkeklerde H.Pilori pozitif çocuklarda anemi oranı anlamlı düzeyde yüksek bulundu (kızlarda x^2: 9,033 P: 0,003; erkeklerde x^2: 15,016 P: 0,000).

Sorumlu yazar yazışma adresi: Sibel UÇAK SEMİRGİN Ondokuz Mayıs Üniversitesi Tıp Fakültesi Nükleer Tıp A.D. Samsun
E-posta:

TARTIŞMA ve SONUÇ: Orta Karadeniz bölgesinde gastrointestinal sistem semptomu olan çocuklardaki H.Pilori pozitiflik oranının, ülkemizin diğer bölgelerindeki oranlar ile karşılaştırıldığında ortanca değer düzeylerinde olduğu düşünülmektedir. Çalışmaya dahil olan geniş pediatrik populasyondan elde edilen sonuçlar, H.Pilori enfeksiyonu ile DEA arasındaki ilişkiyi desteklemektedir.

Anahtar Kelimeler: Helikobakter Pilori, anemi, C-14 üre nefes testi

SUMMARY

INTRODUCTION: To estimate Helicobacter Pylori (H.Pylori) prevalence, coincidence of iron deficiency anemia (IDA) and related hematological parameters in children of North Central Turkey.

METHODS: Hemoglobin, hematocrit, mean corpuscular volume (n=852); serum iron level (n=175), iron binding capacity (n=175), ferritin (n=197), transferrin saturation (n=254) and 14C urea breath test results (n=1006) were reviewed in children with nonspecific gastrointestinal symptoms. H.Pylori prevalence was determined; hematological parameters were compared in H.Pylori positive and negative patients.

RESULTS: Overall H.Pylori prevalence was 46,8%. Hemoglobin and hematocrit values were significantly lower in H. Pylori positive patients (T: 4,014 P: 0,000 for hemoglobin; T: 3,486 P: 0,001 for hematocrit). Although MCV values were lower in H. Pylori positive patients, the difference was not statistically significant.Serum iron levels (T: 2,297 P: 0,023), ferritin levels (T: 2,19 P: 0,03) and transferrin saturations (T: 2,541 P: 0,012) were significantly lower in H.Pylori positive patients. Iron binding capacity was higher in H.Pylori positive patients but this was also not significant. H.Pylori positivity is significantly higher in anemic patients (x^2: 23,533 P: 0,000), in patients with low transferrin (x^2: 4,948 P: 0,026), low ferritin (x^2: 6,96 P: 0,008) and in patients with low ferritin and anemia together (x^2: 13,74 P: 0,00). In females and males, anemia was significantly higher in H.Pylori positive patients (x^2: 9,033 P: 0,003 and x^2: 15,016 P: 0,000 in females and males respectively).

DISCUSSION and CONCLUSION: H.Pylori positivity rate in the pediatric population of North Central Turkey seems to be a median value within the range of yet reported Turkish prevalence. There is an association between H.Pylori and IDA according to the results of a large pediatric population.

Keywords: Helicobacter Pylori, anemia, 14C urea breath test.

Introduction

Helicobacter Pylori (H.Pylori) is a worldwide common infectious agent with increasing childhood prevalence in developing countries up to 80%. Disease prevalence is higher in low socioeconomic levels (1). Several publications imply that H.Pylori infection causes gastrointestinal, hematological, vascular, autoimmune and respiratory complaints (2,3). An association between iron deficiency anemia (IDA) and H.Pylori infection was extensively researched. It's the most common cause of IDA in children and may be the only sign of H. pylori infection (4). The objective of this study was to investigate H.Pylori prevalence, coincidence of IDA and possible relations to other hematological parameters in children of North Central Turkey (Central Black Sea Region).

Methods

Current study is a retrospective analysis of 1006 pediatric patients (12,3±3,04 yrs) referred to nuclear medicine department during January 2007 and January 2014 for 14C urea breath test. This retrospective analysis was approved by the ethical committee of our institution.

All patients had nonspecific gastrointestinal symptoms such as nausea, vomiting and recurrent abdominal pain. Exclusion criteria were history of chronic or recent severe disease, usage of iron preparations or certain drugs (such as antibiotics, antacids, H2 receptor antagonists, proton pump inhibitors) within one month prior to admission. Children with equivocal results on 14C urea breath test were also excluded from the study. ^{14}Carbon urea breath test results (n= 1006) blood levels of hemoglobin (Hb) (g/dL) (n= 852), hematocrit (Htc) (%) (n= 852), mean corpuscular volume (MCV) (fL) (n= 852); serum iron level (µg/dL) (n= 175), iron binding capacity (IBC) (µg/dL) (n= 175), ferritin (ng/mL) (n= 197) and transferrin saturation (%) (n= 254) were evaluated. Lower normal limits of Hb, Htc, MCV and ferritin were determined according to WHO criteria; serum iron level, IBC and transferrin saturation were evaluated according to Dallman's criteria (5,6). All parameters were compared in 14C urea breath test positive and negative individuals. To investigate the relation between H.Pylori prevalence and age, patients were also evaluated in 4 subgroups for < 5 years, 5-9 years, 10-14 years and ≥ 15 years of age.

For 14C urea breath test, 37 kBq (1 µCi) of 14C-urea/citric acid composition (Helicap^{TM}, Isotopes, Budapest, Hungary) were orally administrated with 50 ml water. Patients exhaled into a breathcard system (Heliprobe BreathCard^{TM}, Kibion Stockholm, Sweden) after 10 minutes. Activity was counted in a Geiger Muller counter (Heliprobe^{TM} analyzer, Kibion, Stockholm, Sweden) for 250 seconds. Results were expressed in three categories in accordance with the instructions of the manufacturer:

^{14}Carbon measurements below 25 counts per minute (CPM) were classified as not infected. Values over 50 CPM were classified as infected and values between 25-50 CPM as equivocal.

The data obtained from the study was analyzed using SPSS 21.0 statistical package program. The descriptive findings were given as number and percentage distributions for categorical variables, mean- standard deviation and smallest-largest values for numerical variables. Chi-square test was used to determine the relationship between the presence of H.Pylori and categorical variables. In the evaluation of the relationship between H.Pylori and numerical independent variables, based on the central limit theorem, the T test was used regardless of normal distribution. P value <0.05 was accepted as significant.

Results

The total number of investigated patients was 1006. Gender distribution was as 461 males (45,8%) and 545 females (54,2%). Mean ages were 12,2±2,9 and 12,5±3,1 in males and females respectively. The difference between genders in age was not significant (T: -1,454; P: 0,144). Overall H.Pylori prevalence was 46,8%. Among 1006 patients, 471 were H.Pylori positive (216 males, 255 females). There was no difference in terms of H.Pylori positivity between genders (x^2: 0,000; P: 0,98). The mean age of H.Pylori positive group (471 of 1006) was significantly higher than that of negatives (T: -4,330, P: 0,00). In respect to age groups, increased H.Pylori prevalence with age was statistically significant and H.Pylori positivity was the highest in ≥15 aged group compared to other groups (x^2: 11,292; P: 0,010). Number and percentage of H.Pylori positive and negative patients in each age group was shown in table 1.

Table 1: Number and percentage of H. Pylori positive and negative patients in age groups.

Age (years)	H.Pylori negative n (%)	H.Pylori positive n (%)
<5	9 (69.2)	4 (30.8)
5-9	136 (60.4)	89 (39.6)
10-14	275 (53.1)	243 (46.9)
≥ 15	115 (46.0)	135 (54.0)

Hb, Htc and MCV values could be obtained in 852 patients, 405 were H.Pylori positive and 447 were H.Pylori negative. Hb and Htc values were significantly lower in H. Pylori positive patients (T: 4,014 p: 0,000 for Hb; T:3,486 P: 0,001 for Htc). Although MCV mean value was lower in H.Pylori positive

patients than negatives, the difference was not statistically significant (T: 1,411 P: 0,159). Mean values and standard deviations were given in table 2.

Table 2: Mean values and standard deviations of Hb, Htc and MCV values in H.Pylori positive and negative patients.

n=852	H.Pylori	Mean values	Standard deviation
Hb (g/dL)	Positive	12.76	1.38
	Negative	13.11	1.12
Htc (%)	Positive	37.26	3.72
	Negative	38.07	3.07
MCV (fL)	Positive	81.59	6.10
	Negative	82.14	5.19

Hb: Hemoglobin, Htc: Hematocrit, MCV: Mean corpuscular volume

In the analysis of patients whose serum iron level, IBC, ferritin levels and transferrin saturation rates can be obtained; serum iron levels (n= 175; T:2,297 P: 0,023), ferritin levels (n= 197; T:2,19 P: 0,03) and transferrin saturation rates (n= 254; T: 2,541 P: 0,012) were significantly lower in H.Pylori positive patients. Although IBC mean value was higher in H.Pylori positive patients, this was not statistically significant (n= 175; T: -1,313 P: 0,19). Number of patients, mean values and standard deviations of H.Pylori positive and negative patients were given in table 3.

Table 3: Mean values and standard deviations of serum iron level, IBC, ferritin and transferrin saturation in H.Pylori positive and negative patients.

	H.Pylori	n	Mean Values	Standard Deviation
Serum Iron Level (µg/dL)	Positive	86	61.0	34.84
(n=175)	Negative	89	72.85	33.40
IBC (µg/dL)	Positive	86	371.92	63.97
(n=175)	Negative	89	358.84	67.69
Ferritin (ng/mL)	Positive	105	19.65	16.02
(n=197)	Negative	92	25.34	20.42
Transferrin Saturation (%)	Positive	113	18.03	10.70
(n=254)	Negative	141	21.36	10.10

IBC: Iron binding capacity

Anemia was detected in 110 patients of which 76 (69,1%) were H.Pylori positive and 34 (30,9%) were H.Pylori negative. H.Pylori positivity rate was significantly higher in anemic patients (x^2:23,533 P: 0,000). H.Pylori positivity rate was also significantly higher in patients with low transferrin levels (x^2: 4,948 P: 0,026), low ferritin levels (x^2: 6,96 P: 0,008) and low ferritin and anemia together (x^2: 13,74 P: 0,00) (Table 4).

Table 4: Anemia rates and anemia related parameters in H.Pylori positive and negative patients.

		H.Pylori	
		Positive n(%)	Negative n(%)
Anemia (n=852)	Positive	76 (69.1)	34 (30.9)
	Negative	329 (44.3)	413 (55.7)
Ferritin (n=197)	Low	55 (64)	31 (36)
	Normal	50 (45)	61 (55)
Anemia and Ferritin together (n=188)	Low	25 (69.4)	11 (30.6)
	Normal	71 (46.7)	81 (53.3)
Transferrin saturation (n=254)	Low	48 (53.9)	41 (46.1)
	Normal	65 (39.4)	100 (60.6)

In females and males, anemia was significantly higher in H.Pylori positive patients than negatives (x^2: 9,033 P: 0,003 and x^2: 15,016 P: 0,000 in females and males respectively). The number and percentage of H.Pylori positive and negative anemic/nonanemic patients were given in table 5.

Table 5: Anemia rates and H.pylori positivity of male and female patients.

N=852	Anemia	H.pylori	
		Positive n (%)	Negative n (%)
Males (n=379)	Positive	24 (72.7)	9 (27.3)
	Negative	157 (45.4)	189 (54.6)
Females (n=473)	Positive	52 (67.5)	25 (32.5)
	Negative	172 (43.4)	224 (56.6)

Discussion

Helicobacter Pylori is a common pathogen and affects about half of the world population. One of the serious hematological problems caused by this bacterium is IDA. There are several publications about the relationship between H.Pylori and IDA in literature but it's a controversial issue yet. The objective of this study was to investigate the association between H.Pylori infection and anemia in children of North Central Turkey.

Several invasive and noninvasive diagnostic tests are used for the diagnosis of H.Pylori infections. Histopathological evaluation and culture of endoscopic biopsy specimens is the gold standard method but is not practical because of its invasive nature. A serologic test with H.Pylori specific IgG antibodies is commonly used in the determination of H.Pylori. Although it is noninvasive and practical, false negative results can be obtained due to low antibody levels in children especially under 10 years of age (7-9). Urea breath test with 13C or 14C is the other noninvasive diagnostic method (10). Although 13C urea breath test is now recommended due to its nonradioactive nature, 14C urea breath test has been applied for a long time as a simple, safe and accurate method for detection of H. Pylori in children. The test dose of 1 μCi is almost equals to the daily natural radiation levels (11-14). In our analysis, results obtained by 14C urea breath test were preferred due to the availability of higher amounts of digital archive data in our institution. Reported sensitivity of 14C urea breath test was 90-100% and specificity was 76-100% for H.Pylori detection in different studies (15-17).

The incidence of H.Pylori infection in developing countries is several times higher than in developed countries (18). Published positivity rate in pediatric population ranges between 7.1% and 86% in different countries (19-22). Data including symptomatic and asymptomatic children were available from different Turkish regions. As yet reported range of H.Pylori prevalence in Turkey is between 7,6% and 64.4% (23-29). Most investigations were carried out on patient populations including several hundred of children. Among these reports, reported H.Pylori prevalence was 7.6% in a study from Kırşehir (Central Turkey) including 1083 symptomatic children and was surprisingly lower compared to older studies in the same region (28). According to the authors, regional socioeconomic recovery and increasing educational level may have been the cause of this reduction. In another study including 1510 symptomatic children in Van (Eastern Turkey), H.Pylori prevalence was 39.9% (29). In our study group including 1006 symptomatic children from northern central Turkey (Black sea region), H.Pylori prevalence was 46,8% and was slightly higher than the latter regional investigation including also high number of patients. In our knowledge, there is no published data from North Central Turkey in both symptomatic and asymptomatic children and the current analysis is the first realized in this region. H.Pylori prevalence was found as 30,8% in children below the age of 5 years , increased gradually among age groups and reached 54,0% in children having ages of 15 years or above. This

finding was similar with already worldwide (including Turkey) published data reporting increased prevalence with age (21,23,30,31).

The possible relationship between IDA and H.Pylori was investigated by many authors yet no consensus been achieved. It was thought that H.Pylori affects iron absorption directly or indirectly. Decreased gastric ascorbic acid concentration was claimed to be the main cause of decreased iron absorption (32). In an interventional study, significantly decreased basal and stimulated (with pentagastrin) gastric acid output was found in H.Pylori positive individuals compared to negatives. They reported increased gastric acid output after H.Pylori eradication therapy (33). In H.Pylori positive children, lower serum ferritin levels and significantly higher prevalence of iron deficiency was reported. Iron absorption improved after eradication of bacteria even in therapy resistant anemia (34-36). On the other hand, there are some studies suggesting that there is no relationship between H.Pylori and anemia. In 6 cross-sectional studies from Latin America, Hb, ferritin and transferrin receptor levels were not associated with H.Pylori infection and no association was found between H.Pylori colonization and anemia (37). In some studies, controversial results were obtained from the same region about the relationship between H.Pylori and anemia. A study on 688 school aged child from rural Alaska implies a relationship between H.Pylori infection and iron deficiency anemia[8]. But in another report from the same region in the similar aged group, there was no significant improvement to be found in isolated iron deficiency or mild anemia up to 14 months after eradication treatment initiation (9). Few reports from Turkey emphasize a relationship between H.Pylori infection and anemia. In a study on 140 H.Pylori positive children between the ages of 6-16 years in Ankara, IDA was determined in 12,9% and they reported that a complete recovery of anemia was possible only after H.Pylori eradication (38). In a study from İstanbul, H.Pylori positivity rate was 53,8% and IDA was found in 46,2% of symptomatic children. There was no significant difference found in the frequency of H.Pylori infection between anemic and nonanemic patients(27). In another study on 70 symptomatic pediatric patients in Istanbul, H.Pylori positivity was 50% and IDA was detected in 57% of H.Pylori positive patients. They mentioned a relationship between H.Pylori and IDA but could not command on the underlying mechanism (26). The results we obtained in our study group indicate an association between H.Pylori and IDA. Especially significantly low Hb, Htc, serum iron and ferritin levels and transferrin saturations in the H.Pylori positive patients supported this association. Also mean MCV value was lower and mean IBC was higher in the H.Pylori positive patients but the differences were not significant. H.Pylori positivity rate was higher in anemic patients, in patients with low transferrin, low ferritin and also in anemic patients and with low ferritin.

In conclusion, our results indicate that H.Pylori positivity rate in the pediatric population of North Central Turkey seems to be a median value within the range of yet reported Turkish prevalence. Increasing H.Pylori positivity rate with age in our study was compatible with as yet reported data.

H.Pylori was associated with IDA, low ferritin and low transferrin in the study group. Although further well structured studies are needed, this study provided useful data on association between H.Pylori and IDA in a large pediatric population.

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