ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/pediatr.2023-96690

Frequency and Clinical Correlation of *Helicobacter pylori* Positivity in Children Admitted to a University Hospital in Türkiye: A Cross-Sectional Study

Türkiye'deki Bir Üniversite Hastanesine Başvuran Çocuklarda *Helicobacter pylori* Pozitifliğinin Sıklığı ve Klinik İlişkisi: Kesitsel Bir Çalışma

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ABSTRACT Objective: *Helicobacter pylori* has been shown to cause several gastrointestinal disorders and its frequency increases with age worldwide. Considering the changing nutritional habits and socioeconomic level in Türkiye, there is no current epidemiological study conducted on Turkish children. In this study, it was aimed to obtain the current frequency of *H. pylori* in childhood with fecal antigen test which demonstrates only active infection and to show its relationship with clinical findings. This is a cross-sectional study conducted between January 2019 and February 2021. Children who applied to the pediatric outpatient clinic were asked to give stool samples regardless of their presenting complaints. **Material and Methods:** Presence of *H. pylori* was determined with fecal *H. pylori* antigen test. The parents of the subjects were later asked to complete a questionnaire by telephone interview. The questionnaire solicited information on parents' demographic and socio-economic characteristics. **Results:** A total of 543 children were included in the study (M: 302, F: 241). Fecal *H. pylori* antigen test was positive in 11.8% of the children (n=64). The complaints of abdominal pain, halitosis and diarrhea were found to be significantly more common in *H. pylori*-positive children (p<0.001 for all). As for the socio-demographic characteristics, frequency of *H. pylori* positivity was shown to be higher in children living in more crowded houses and consuming unbottled water. No relation was found with parents' education level or breast milk intake. **Conclusion:** This study reflects the actual frequency of *H. pylori* positivity in İstanbul province. Also, remarkable associations of *H. pylori* positivity with clinical and socio-demographic characteristics have been demonstrated.

Keywords: Helicobacter pylori; prevalence; frequency; children; fecal antigen test

ÖZET Amaç: *Helicobacter pylori*'nin birçok gastrointestinal rahatsızlığa neden olduğu gösterilmiştir ve sıklığı dünya çapında yaşla birlikte artmaktadır. Türkiye'de değişen beslenme alışkanlıkları ve sosyoekonomik düzey dikkate alındığında Türk çocukları üzerinde yapılmış güncel bir epidemiyolojik çalışma bulunmamaktadır. Bu çalışmada sadece aktif enfeksiyonu gösteren fekal antijen testi ile çocukluk çağındaki *H. pylori*'nin güncel sıklığının elde edilmesi ve klinik bulgularla ilişkisinin gösterilmesi amaçlandı. Ocak 2019-Şubat 2021 tarihleri arasında yapılmış kesitsel bir çalışmadır. Çocuk polikliniğine başvuran çocuklardan şikâyetleri ne olursa olsun dışkı örneği vermeleri istenmiştir. **Gereç ve Yöntemler:** *H. pylori* varlığı fekal *H. pylori* antijen testi ile belirlendi. Daha sonra deneklerin ebeveynlerinden telefon görüşmesi yoluyla bir anket doldurmaları istendi. Ankette ebeveynlerin demografik ve sosyoekonomik özellikleri hakkında bilgi istendi. **Bulgular:** Çalışmaya toplam 543 çocuk dâhil edilmiştir (E: 302, K: 241). Çocukların %11,8'inde (n=64) dışkıda *H. pylori* antijen testi pozitifti. Karın ağrısı, ağız kokusu ve ishal yakınmalarının *H. pylori* pozitif çocuklarda anlamlı olarak daha sık olduğu saptandı (tümü için p<0,001). Sosyodemografik özelliklere bakıldığında, daha kalabalık evlerde yaşayan ve çeşme suyu tüketen çocuklarda *H. pylori* pozitiflik sıklığının daha yüksek olduğu gösterilmiştir. Ebeveynlerin eğitim düzeyi veya anne sütü alımı ile ilişki bulunmadı. **Sonuç:** Bu çalışma, İstanbul ilindeki *H. pylori* pozitifliğinin gerçek sıklığını yansıtmaktadır. Ayrıca, *H. pylori* pozitifliği ile klinik ve sosyodemografik özellikler arasında dikkate değer ilişkiler gösterilmiştir.

Anahtar Kelimeler: Helicobacter pylori; yaygınlık; sıklık; çocuklar; dışkı antijen testi

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Peer review under responsibility of Turkiye Klinikleri Journal of Pediatrics.

Received: 13 Mar 2023 ***Received in revised form:*** 02 Apr 2023 ***Accepted:*** 05 Apr 2023 ***Available online:*** 10 Apr 2023

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Helicobacter pylori is a gram-negative, microaerophilic, motile microorganism which has been shown to cause gastritis, recurrent peptic ulcer, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma. The incidence of this bacterium, which is thought to be taken into the body in the first 5 years of life, increases with age in both developed and developing countries.[1] The lifetime risk of occurrence of peptic ulcer in individuals carrying this bacterium has been reported as 10%, and the presence of *H. pylori* increases the incidence of peptic ulcer 5-7 times. Nevertheless, the relevant complications are less common in children and adolescents compared to adults.[2]

The presence of *H. pylori* is detected by both invasive and non-invasive methods. The latter include fecal antigen test, urea breath test and detection of antibodies to *H. pylori* in serum, urine or saliva. Although rapid urease test, tissue culture and polymerase chain reaction methods, which are among the interventional tests, are of high specificity, they are not preferred to be used in epidemiological studies involving healthy volunteers, as they require endoscopic procedures.[3] On the other hand, fecal antigen test and urea breath test have similar sensitivity and specificity to interventional methods.[4]

Although it is estimated that half of the world's population is infected with *H. pylori*, the frequency of *H. pylori*-associated infection is variable because *H. pylori* infection in earlier ages is seen more commonly in developing and poor countries than in developed countries.[5]

Numerous epidemiological studies on *H. pylori* and its relationship with socioeconomic status, dietary habits and age have been conducted. Considering the changing nutritional habits and socioeconomic level in Türkiye, there is no current epidemiological study conducted on Turkish children. In this study, it was aimed to obtain the current frequency of *H. pylori* in childhood with fecal antigen test and to show its relationship with clinical findings.

MATERIAL AND METHODS

STUDY DESIGN

This is a cross-sectional study conducted between January 2019 and February 2021. The first three children who applied to the pediatric outpatient clinic on working days were asked to give stool samples regardless of their presenting complaints. Volunteers who had used antibiotics in the four weeks prior to the study or proton pump inhibitors within two weeks were excluded. The parents of the subjects were later asked to complete a questionnaire by telephone interview. The questionnaire solicited information on parents' demographic and socio-economic characteristics. The patients were later stratified by age as follows: 0-6 months, 6-24 months, 2-5 years, 5-12 years and 12-18 years.

DETERMINING THE POSITIVITY OF H. PYLORI

Collected stool samples were stored at -80 °C degrees until analysis. Presence of *H. pylori* (urease antigen) was determined using fecal *H. pylori* antigen Enzyme-Linked ImmunoSorbent Assay (ELISA) kit (Epitope Diagnostics, Inc., CA, USA) including urease-specific monoclonal antibodies, as positive or negative.

STATISTICAL ANALYSES

Statistical analyses were made using SPSS 21.0 (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp, Armonk, New York) computer package program. Continuous data were expressed as mean±standard deviation, and categorical data as n (%). Chi-square and Fisher exact tests were used to compare categorical data in the analyses. Normally distributed variables were compared using the Student's t-test, and non-normally distributed variables were compared using the Mann-Whitney U test. A p value of 0.05 or lower was considered to be statistically significant.

After the study was completed, a post-hoc power analysis was conducted using G*Power3.1 (Erdfelder, Faul ve Buchner, Version 3.1 Germany) to test the proportion and showed that this study achieved a power of 90% at 5% alpha level.

ETHICAL APPROVAL

The study protocol was approved by the Clinical Research Ethical Committee of İstanbul University, Cerrahpaşa Medical Faculty (date: April 4, 2018, no: 83045809-604.01.02). Written informed consent for participation in the study was obtained from all participants' parents. This study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

A total of 543 children were included in the study (M: 302, F: 241). The median age was 47 months (lowest 0 largest 216). Fecal *H. pylori* antigen test was positive in 11.8% of the children (n=64). The characteristics and *H. pylori*-positivity rates of the participants stratified by age are shown in Table 1. The median age of the *H. pylori*-positive and negative children were 33 (2-132) months and 16 (0-142) months, respectively.

When the relationship between gastrointestinal complaints and *H. pylori* positivity was examined, only the complaints of abdominal pain and halitosis were found to be significantly more common in *H. pylori*-positive children (p<0.001 for all) (Table 2),

TABLE 1: The characteristics of the cases in groups stratified by age.

The groups stratified by age	n (%)	Male/Female	Number of *Helicobacter pylori* positive children	Rate of *Helicobacter pylori* positivity
0-6 months	80 (14.7)	50/30	2	2.5%
6-24 months	123 (22.7)	61/62	9	7.3%
2-5 years	108 (19.9)	59/49	12	11.1%
5-12 years	123 (22.7)	76/47	23	18.7%
12-18 years	109 (20.1)	56/53	18	16.5%
Total	543	302/241	64	11.8%

TABLE 2: Relation of *Helicobacter pylori* positivity with gastrointestinal complaints in the overall participants.

Gastrointestinal complaints	Answer	*Helicobacter pylori*-negative n (%)	*Helicobacter pylori*-positive n (%)	p value
Nausea	No	461 (88.5)	60 (11.5)	0.314
	Yes	18 (81.8)	4 (18.2)	
Vomiting	No	461 (88.8)	58 (11.2)	0.051
	Yes	18 (75.0)	6 (25.0)	
Diarrhea	No	476 (90.5)	50 (9.5)	**<0.001***
	Yes	3 (17.6)	14 (82.4)	
Stomach ache	No	458 (92.7)	36 (7.3)	**<0.001***
	Yes	21 (42.9)	28 (57.1)	
Halitosis	No	394 (91.4)	37 (8.6)	**<0.001***
	Yes	85 (75.9)	27 (24.1)	
Blood in stool	No	474 (88.1)	64 (11.9)	1.000
	Yes	5 (100.0)	0 (0.0)	
Melena	No	478 (88.2)	64 (11.8)	1.000
	Yes	1 (100.0)	0 (0.0)	
Gastro esophageal reflux	No	419 (88.4)	55 (11.6)	0.729
	Yes	60 (87.0)	9 (13.0)	
Gastrointestinal complaints in parents	No	286 (87.7)	40 (12.3)	0.668
	Yes	193 (88.9)	24 (11.1)	

*Significant at the level of p≤0.05.

TABLE 3: Relation of *Helicobacter pylori* positivity with socio-demographic data in all participants.

Socio-demographic data	Total (n=543)	*Helicobacter pylori* (-) (n=479)	*Helicobacter pylori* (+) (n=64)	p value
Mather's education level				
Primary school or below	296 (54.5)	263 (88.9)	33 (11.1)	0.614
High school or higher	247 (45.5)	216 (87.4)	31 (12.6)	
Father's education level				
Primary school or below	239 (44)	205 (85.8)	34 (14.2)	0.118
High school or higher	304 (56)	274 (90.1)	30 (9.9)	
Number of people in the house				
4 and below	340 (62.6)	312 (91.8)	28 (8.2)	0.001*
5 and upper	203 (37.4)	167 (82.3)	36 (17.7)	
Source of drinking water				
Unbottled water	224 (41.2)	188 (83.9)	36 (16.1)	0.009*
Bottled water	319 (58.8)	291 (91.2)	28 (8.8)	
Attending to school or kindergarten				
Yes	302 (55.6)	201 (83.4)	40 (16.6)	0.002*
No	241 (44.4)	278 (92.1)	24 (7.9)	
Gastric disease history in parents				
No	326 (60)	286 (87.7)	40 (12.3)	0.668
Yes	217 (40)	193 (88.9)	24 (11.1)	

*Significant at the level of p≤0.05

as well as diarrhea being significantly more common in *H. pylori*-positive children of all age groups except for 2-5 years (p=0.060).

As for the socio-demographic characteristics, a significant relationship with *H. pylori* positivity was determined with the number of people living at home, the source of drinking water and the history of going to a kindergarten. *H. pylori* positivity was significantly higher in the group ≥5 people living in the same house compared to ≤4 people (p<0.001). Also, *H. pylori* positivity was higher in those who went to school or kindergarten (p=0.002). However, since the rate of attending to school increases with age, this relationship was examined separately in each subgroup created according to age in order to exclude the effect of age, and the significance was lost. In the group drinking bottled water, *H. pylori* positivity was found to be less compared to the group drinking tap water (p=0.009). While the relationship between father's education level and *H. pylori* positivity could not be found in the overall group, a significant relationship was found when evaluated between the ages of 12-18 years. *H. pylori* positivity was found to be significantly higher in the group whose father's education level was at primary school or below, compared to those with a higher education level in this age group (p=0.010). The relationship of *H. pylori* positivity with breast milk was examined at 0-24 months and was not found (p=0.204). The relationship between socio-demographic characteristics and *H. pylori* positivity in all participants has been shown in Table 3.

DISCUSSION

Since its discovery 40 years ago, many studies have been conducted to determine the prevalence of *H. pylori* in the community. The results of these studies differ according to the age group and the socioeconomic characteristics of the region where the study was conducted.[6] In our study conducted in the province of İstanbul, this frequency was found to be 11.8% in the pediatric age group. While *H. pylori* positivity in studies conducted in developed countries such as Sweden or Canada was found to be 7.1% and 3.6%, respectively, in developing countries such as Bangladesh and India, this rate rises to 86% and 87%, respectively.[7-9] The difference in the results of the prevalence studies is thought to be due to the socioeconomic status of the countries, hygiene habits and crowded conditions.[9] As the socioeconomic levels of the countries increase, the positivity rate decreases.

In addition, positivity rates may vary depending on the socioeconomic structure that has changed over the years in the same country. In a study conducted in Estonian children in 1991, a positivity rate of 42.2% was found, while it decreased to 28.1% in 2002. This was attributed to the change in the socioeconomic structure of the country after the collapse of the Union of Soviet Socialist Republics.[10] Likewise, in a cross-sectional study conducted in Russia, it was shown that the positivity rate, which was 44% in 1995, decreased to 13% after 10 years.[11] In a cross-sectional study conducted in Turkish school children in 1990 and 2000, the positivity rate of 78.5% decreased to 66.3% after 10 years, which was attributed to changes in environmental conditions and socioeconomic development of the country.[12]

Many studies have been conducted to determine the frequency of *H. pylori* in the pediatric age group in Türkiye. In a study conducted in 1998 in asymptomatic children, the frequency of *H. pylori* was 17.4% under the age of 1, 15.5% between the ages of 1-4, 30.6% between the ages of 5-9, 47.3% between the ages of 10-14, and 58.4% between the ages of 15-19, and 33.1% in the overall children.[13] In 2002, Selimoglu et al. evaluated 466 healthy children aged 6-17 years by measuring *H. pylori* immunoglobulin G (IgG) antibodies in the blood and found a seropositivity of 64.4%.[14] Again, in the study conducted with the IgG test in 2002, 346 children were evaluated and a seropositivity of 43.9% was found.[15] The first prevalence study with *H. pylori* stool antigen in stool in Türkiye was conducted in 2005, and 148 symptomatic children aged 2-15 years, 25% were found.[16] In 2007, 275 children aged 1-15 years with gastrointestinal symptoms were evaluated together with blood serology and stool antigen test, and *H. pylori* positivity was reported as 23.6%.[17] In 2009, *H. pylori* stool antigen in stool was investigated in 165 asymptomatic children aged 2-12 years and it was found to be positive at a rate of 30.9%.[18]

In the present study, *H. pylori* positivity was found to be lower than previous studies conducted in Türkiye. The most probable reasons are that in other studies, the screening was performed among the children who have gastrointestinal symptoms.[16,17,19] Also, using serological tests, the children without active disease were also detected as positive.[14,15,20] In this study, the children were screened regardless of their complaints, and stool antigen test which is an indicator of active infection was performed. In the frequency studies conducted in the pediatric age group in our country, mostly serological methods and ELISA methods were used. Antibody IgG test against *H. pylori* by ELISA method may result in positive results for a long time.[21] It has been reported that serological tests, which were advantageous in terms of easy applicability and cheapness in the past, can continue to be positive for 3 years despite treatment.[22] For this reason, it is not reliable for diagnosis or treatment. The latest study in Türkiye with the same methodology as this study was conducted in 2009 with 165 children between the ages of 2-12 (mean 6.8±3 years), and the *H. pylori* frequency was found to be 30.9%.[18] Despite having the same methodology, the reason why this rate was found to be higher than the result in the present study may be that the average age of the children in our study was lower, and also, the prevalence of *H. pylori* may actually have decreased due to the improvement in standard of living and sanitation in Türkiye.[23,24]

Of all the gastrointestinal symptoms observed to be more prevalent in the *H. pylori*-positive group than in the *H. pylori*-negative group, diarrhea stood out as a particularly noteworthy finding. This finding supports a limited number of reports suggesting that *H. pylori* may cause diarrhea and raises the possibility that a temporary loss of the gastric acid barrier may be responsible for the observed association between *H. pylori* and diarrhea, although this hypothesis has not yet been confirmed.[25-27]

In this study, the relationship between *H. pylori* positivity and socioeconomic characteristics was also investigated, and it was shown that the number of people living at home increased the risk of *H. pylori* infection. It is well known that fecal-oral transmitted infections spread more rapidly in large families. Concordantly, *H. pylori* has been shown to be more common in houses where more people share the same bedroom.[28] It has been shown that *H. pylori* positivity is higher in children living in crowded homes, both in studies conducted in Türkiye and in other countries.[18,29-33] On the other hand, in one study con-

ducted in Türkiye, no relationship was found between the number of people living in the same house and *H. pylori*.[14] However, in that study, each individual in approximately one of every two families was reported to have his/her own room. It has been accepted that the crowded family structure poses a risk for *H. pylori*, but it can also be interpreted that this increase may be prevented by the increase in domestic hygiene and the number of rooms in the house.

As for the relationship between the education levels of the parents and *H. pylori* positivity, there are some conflicting results. The studies show a negative or no relation at all. In the present study, no significant relationship was found between parental education level and *H. pylori* positivity, in line with a prior study conducted in Türkiye.[14,15,18,34]

Drinking water and other environmental sources have also been shown to pose a risk for transmission of *H. pylori*. A positive relationship was found between tap water consumption and *H. pylori* positivity in studies conducted in different parts of the World.[29,35] Concordantly, *H. pylori* positivity was significantly higher in those who did not consume bottled water in our study.

The strength of this study is that unlike many studies conducted in symptomatic children, which have been mentioned above, children were sampled regardless of whether they had symptoms or not. In addition, the evaluation of positivity with stool antigen test enabled the determination of the frequency of active infection only. On the other side, this study only reflects the data in a certain region of Türkiye, which may be considered as a limitation.

CONCLUSION

In this study, the current *H. pylori* stool antigen positivity has been reported as 11.8% in children living in İstanbul province, regardless of whether they had symptoms. This rate was found to be lower than previous studies conducted in Türkiye. In addition, significant correlations were found between *H. pylori* positivity and symptoms and socioeconomic status. We suggest that positivity rates may vary depending on the socioeconomic structure that has changed over the years in the same country. Nevertheless, to determine the actual frequency in Türkiye, a national study with larger number of individuals should be conducted.

Source of Finance

This study was supported by Turkish Pediatric Association Research Fund (Project no: 11.10.2018-07)

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Tufan Kutlu, Hasan Karakaş, Gürkan Tarçın, Emel Gür;* ***Design:*** *Tufan Kutlu, Hasan Karakaş, Gürkan Tarçın;* ***Control/Supervision:*** *Tufan Kutlu, Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek;* ***Data Collection and/or Processing:*** *Tufan Kutlu, Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek, Doğukan Özbey;* ***Analysis and/or Interpretation:*** *Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek, Doğukan Özbey, Gülnaz Çiğ;* ***Literature Review:*** *Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek, Tufan Kutlu;* ***Writing the Article:*** *Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek, Tufan Kutlu;* ***Critical Review:*** *Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek, Tufan Kutlu, Emel Gür, Gülnaz Çiğ;* ***References and Fundings:*** *Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek, Tufan Kutlu, Emel Gür, Gülnaz Çiğ;* ***Materials:*** *Hasan Karakaş, Gürkan Tarçın, Bekir Kocazeybek, Tufan Kutlu, Emel Gür, Gülnaz Çiğ, Doğukan Özbey.*

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