Prevalence of *Helicobacter pylori* virulence genotypes among children in Eastern Turkey

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**Author contributions:** Ozbey G performed the majority of experiments including DNA extraction and PCR, designed the study and wrote the manuscript; Dogan Y and Demiroren K collected antrum samples from patients during endoscopy, analyzed the clinical and statistical data and edited the manuscript; all authors read and approved the manuscript.

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**Abstract**

**AIM:** To identify the virulence genotypes of *Helicobacter pylori* (*H. pylori*) if present in children in Eastern Turkey and if those genotypes are mostly associated with severe clinical presentations.

**METHODS:** A total of 49 *H. pylori* positive Turkish children (42 with antral nodularity and 7 with peptic ulcer) who underwent upper gastrointestinal endoscopy with abdominal symptoms during the period from March 2011 to September 2012 were enrolled in this study. Antral nodularity was diagnosed endoscopically by two of the authors. We determined for the presence of *cagA*, *vacA*, *cagE*, *iceA* and *babA2* genotypes of *H. pylori* isolates in DNA obtained directly from frozen gastric biopsy samples by polymerase chain reaction test using specific primers.

**RESULTS:** Of the 49 *H. pylori* isolates studied, 61.2%, 91.8%, 22.4%, 28.6%, 57.1% and 40.8% were positive for the *cagA*, *vacA* s1, *cagE*, *iceA1*, *iceA2* and *babA2* genes, respectively. We showed that the most common *vacA* subtype was s1a (79.6%). However, the s2 gene was found less frequently with an isolation rate of 8.2% of the *H. pylori* isolates. The genotypes *iceA2* and *vacA s1m2* were the most frequently found types in children with antral nodularity. In addition, the genotypes *iceA1*, *babA2* and *vacA s1m1* were found in similar ratios in all the *H. pylori* isolates obtained from children with peptic ulcer. The genotypes *vacA s2m1* and s1c were not observed in any of isolates studied.

**CONCLUSION:** This study showed that *vacA s1m2*, *cagA* and *iceA2* were the most common genotypes, and no association between antral nodularity and genotypes was observed.

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**Key words:** *Helicobacter pylori*; Children; Genotype; Polymerase chain reaction

**Core tip:** In this research we have attempted to determine the prevalence of some genotypes of *Helicobacter pylori* (*H. pylori*) among children in Eastern Turkey and to investigate the relationship between these genotypes with antral nodularity. Identifying the virulence genes among *H. pylori* isolates in children would allow for the development of new treatments and eradication policies in adults. The study results suggest that there was no significant association between antral nodularity and the presence of genotypes (*P* > 0.05).

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) infection is generally acquired...
during childhood, persists throughout life unless treated with antibiotics, and the infection is usually associated with the development of several gastroduodenal diseases such as gastritis, peptic ulcer, gastric carcinoma and mucosa-associated lymphoid tissue lymphoma[1-3].

The cytotoxin associated gene A (cagA) being a marker for the presence of the cag pathogenicity island (cag PAI) was the first recognized virulence gene in the H. pylori genome in both adults and children[5,6]. Cytotoxin associated gene E (cagE) is also a member of the cag PAI, and has been described as a potential virulence factor associated with duodenal ulcer in children[5]. The vacuolating cytotoxin (vacA) gene exists in different subtypes, varying in the signal (s1 or s2) and middle (m1 or m2) regions[6-8]. H. pylori vacA alleles differ in their ability to express an active toxin[5]. Inducement occurs via contact with the epithelium gene (iceA), has two allelic variants (iceA1 and iceA2), and has been determined through its upregulation after adherence of H. pylori to the gastric epithelium[9,10].

The blood adhesion binding antigen A (babA) adhesion of H. pylori, encoded by the babA2 gene is an outer membrane protein that binds to the fucosylated histoblood group antigens on the surface of gastric epithelial cells[10,11].

Despite a high prevalence of H. pylori infection among children and adults in Turkey, the published data on geographical distribution of the virulence genes in H. pylori strains among Turkish children are very limited, and relatively few studies have been reported on the prevalence of the cagA gene of H. pylori in Turkish children[11-13]. This study was performed to determine the prevalence of some virulence genes of H. pylori which were not previously reported among children in Eastern Turkey, and to investigate the association between these genotypes with clinical disease.

MATERIALS AND METHODS

A total of 49 H. pylori isolates were investigated for the presence of virulence genotypes. These isolates by polymerase chain reaction (PCR) were recovered from 101 Turkish children (53 girls and 48 boys, ranging between 4 and 18 years old, average 12 years) who underwent upper gastrointestinal endoscopy with abdominal symptoms at the clinic of the Pediatric Gastroenterology Department at the Firat University Hospital between March 2011 and September 2012. Antral nodularity was defined as being endoscopically characterized by the irregular appearance of the mucosa as like that of a “cobblestone pavement”[14]. Also, the presence of ulcers was determined by endoscopic examination.

Our study was approved by the Medical Ethics Committee of Firat University. All patients received informed consent that was signed by their parents before endoscopic procedures.

Isolation of H. pylori DNA and PCR detection of its genotypes

H. pylori DNA was prepared using the QIAamp DNA mini kit (Qiagen, Germany) following the manufacturer’s instructions. The extracted DNA was kept at -20 ℃ until tested.

PCR was carried out using oligonucleotide primers targeting the 298 bp fragment of the cagA gene; the fragment 259 bp or 286 bp in size for type s1 or s2; the 190, 187 and 213 bp fragments for s1a, s1b, and s1c; the 567 bp and 642 bp fragments for m1 and m2; the 508 bp fragment of the cagE gene; the 247-bp fragment of iceA1; the 229 or 334-bp fragments of iceA2; and the 271 bp fragment of the babA2 gene, in order to amplify the cagA, vacA, cagE, iceA and babA2 genes of the H. pylori isolates[15-20]. Ten μL of each PCR product was subjected to electrophoresis in a 1.5% (w/v) agarose gel.

All reactions were performed with positive controls containing the DNA of the HP 26695, HP J99, and some clinical isolates supplied by Dr. Yoshio Yamaoka, along with negative controls containing all PCR components with distilled water to substitute the DNA sample.

Statistical analysis

Statistical analysis was performed by statistical software program SPSS for Windows version 12.00 (SPSS, Chicago, IL, United States). The correlation between H. pylori genotypes and antral nodularity was assessed by Fischer’s exact and χ² tests. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the prevalence of cagA, vacA, cagE, iceA and babA2 genes with antral nodularity and peptic ulcers. The number of children with peptic ulcers in the present study was low; therefore further analysis was not carried out.

The cagA gene was found in 30 of the 49 isolates (61.2%). In our study, the vacA genes were observed in all isolates. The most predominant subtype was s1a (79.6%), followed by s1b (12.2%), then s2 (8.2%). The genotype s1m2, which was predominant in this study, was observed in 28 (57.1%) isolates. However, the genotypes s1m1 and s2m2 were detected in 17 (34.7%) and 4 (8.2%) isolates, respectively. Furthermore, the genotype vacA s2m1 and subtype s1c were not found in any of the isolates. The prevalence of cagE gene in children with antral nodularity and peptic ulcer was 8 out of 42 (19%) and 3 out of 7 (42.9%) isolates, respectively. The iceA gene was not observed in 4 of the 49 isolates. The iceA2 gene was positive in 28 (57.1%) isolates, while iceA1 was detected in 14 (28.6%) isolates. Three isolates (6.1%) were positive for both iceA1 and iceA2. The prevalence of iceA1 was higher in patients with peptic ulcers (57.1%), with no significance difference observed compared to patients with antral nodularity (23.8%). The babA2 gene was detected in 20 (40.8%) samples. The babA2 showed a higher proportion (57.1%) in patients with peptic ulcer compared to patients with antral nodularity (38.1%).

We emphasized no significant association between antral nodularity and the presence of the genotypes (P > 0.05).
Table 1 Prevalence of the virulence genotypes of Helicobacter pylori from children with antral nodularity and peptic ulcer n (%)

| Virulence factor genes | Antral nodularity | Peptic ulcer | Total |
|------------------------|-------------------|-------------|-------|
|                        | (n = 42)          | (n = 7)     | (n = 49) |
| cagA                   | 25 (59.5)         | 0 (0)       | 25 (59.5) |
| vacA s1                | 38 (90.5)         | 0 (0)       | 38 (90.5) |
| vacA s1a               | 32 (76.2)         | 7 (100)     | 39 (79.6) |
| vacA s1b               | 6 (14.3)          | 0 (0)       | 6 (14.3)  |
| vacA s2                | 4 (9.5)           | 0 (0)       | 4 (9.5)   |
| vacA m1                | 13 (31)           | 4 (57.1)    | 17 (57.1) |
| vacA m2                | 29 (69)           | 3 (42.9)    | 32 (65.3) |
| vacA s1/s1 m1          | 13 (31)           | 4 (57.1)    | 17 (57.1) |
| vacA s1/s2 m2          | 25 (59.5)         | 3 (42.9)    | 28 (57.1) |
| vacA s2/m2             | 4 (9.5)           | 0 (0)       | 4 (9.5)   |
| cagE                   | 8 (19)            | 3 (42.9)    | 11 (22.4) |
| iceA1                  | 10 (23.8)         | 4 (57.1)    | 14 (28.6) |
| iceA2                  | 25 (59.5)         | 3 (42.9)    | 28 (57.1) |
| Both iceA1 and iceA2   | 3 (7.1)           | 0 (0)       | 3 (7.1)   |
| Non iceA1 and iceA2    | 4 (9.5)           | 0 (0)       | 4 (9.5)   |
| babA2                  | 16 (38.1)         | 4 (57.1)    | 20 (40.8) |

DISCUSSION

Although only one study on virulence genes of H. pylori has been performed in adults in the Elazig Province in Eastern Turkey,[23] there is no data related to the prevalence of H. pylori genotypes among children in this region. However, there are a few studies on determining the prevalence of the cagA gene of H. pylori in Turkish children.[11-13]

The prevalence of the cagA gene in children among European countries varies from 22.4% to 76%.[2,25] Earlier studies performed in Turkish children showed the prevalence of the cagA gene was 55%-74.4%.[11-13]. In this study, we detected the prevalence of 61.2% of the cagA gene among Turkish children. The inconsistent findings may be due to adaptation of H. pylori to the environment in different geographic regions.[23]. Some studies had confirmed a significant correlation between the severity of histological changes and the presence of the cagA gene in the H. pylori genome,[2,25-26], whereas others have not emphasized this association.

It has been demonstrated that the geographic distribution for vacA alleles differs in many countries around the world[22]; s1 is the common strain in East Asia, while s1a is the prevalent strain in Northern Europe, and s1b in Portugal and Spain.[23]. The majority of H. pylori isolates identified as s1a; however, no subtypes s1c and s2 were found in this study. The vacA s1m1, s1m2, and s2m2 genotypes were found in 34.7%, 57.1%, and 8.2%, respectively. No s2m1 genotype was detected in the present study. Our data is consistent with the results reported in Poland[23] and Shanghai[23] where the s1m2 was the most prevalent genotype. In contrast, other predominant vacA genotypes were reported in Brazil, Slovenia, the Midwestern United States (s1m1), and Spain (s2m2)[2,23,25,26].

The prevalence of the iceA1 genotype was found to be 14% in Brazil[24], 37% in Israel[25], 44% in North America[27], and 62% in Slovenia[28]. The prevalence (28.6%) of the iceA1 gene in this study was similar to the Brazilian population (14%)[24], but lower than in Korea (76%)[29]. Although it has been shown that the iceA1 gene is associated with ulcer disease in adults,[19] no significant association between the iceA1 subtype and disease severity was found which is concordant with other studies.[23,27,28]. We found that the iceA2 gene (57.1%) was the predominant genotype, supporting the findings of pediatric studies in Brazil (68.9%), Israel (52%), and the Midwestern United States (84%)[2,23,29].

The prevalence of cagE was found in 24.5% of H. pylori isolates in Israel[28], 59% in Canada[19], and 41.7% in Bulgaria[30]. The cagE gene was detected in 11 (22.4%) out of 49 isolates, and no significant association was found between the cagE and peptic ulcers in children in this study, consistent with a study by Benenson et al.[21]. However, another study showed just such an association[9]. Furthermore, we observed that the cagE gene was predominantly detected in H. pylori isolates from children with peptic ulcers. Because of the relatively low number of children with peptic ulcers, statistical analysis was not carried out.

The prevalence of H. pylori babA2 was 17.2% in Portugal, 36% in the Midwestern United States, 84.4% in Brazil, and 66.7% in Bulgaria[2,23,26,29]. In the present study, the babA2 gene was detected in 40.8% of the H. pylori isolates. The low prevalence of babA2 in children can also be explained by the fact that H. pylori strains exhibit different patterns of adherence to gastric mucosa cells in adults and children, pointing out the importance of host characteristics in the selection of determinants of the infecting strain[26,27].

In conclusion, we feel that the clinical presentations observed are not correlated with the prevalence of the virulence genotypes because of small numbers of H. pylori isolates. However, the identification of virulence genotypes in this study will be important for future policies for the eradication of H. pylori in order to prevent severe diseases in adults.

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Background

There are a few studies on the virulence genotypes of Helicobacter pylori (H. pylori) in Turkish children and the correlation of these genotypes with clinical outcome. The present study aimed to describe the prevalence of cagA, vacA, cagE, iceA and babA2 genotypes of H. pylori in children in Eastern Turkey and to assess the association between these virulence genotypes and antral nodularity.

Research frontiers

In this study, the authors investigated the prevalence of cagA, vacA, cagE, iceA and babA2 genotypes of H. pylori among children in Eastern Turkey and evaluated the association between these genotypes with antral nodularity. There was no significant association between virulence factor genes with antral nodularity.

Innovations and breakthroughs

This is the first study on the prevalence of the vacA, cagA, cagE, iceA and babA2 genes among children in Eastern Turkey and the correlation of these virulence factor genes with antral nodularity. This research is useful not only in developing future strategies to control and eradicate H. pylori infection but also to contribute a better understanding of the epidemiology of H. pylori infection. In this study, they examined small numbers of H. pylori isolates. More large population and genotyping studies are needed for the development of the future policies to eradicate H. pylori infection.

Applications

The data obtained from this study will be useful in developing the future policies for the eradication of H. pylori in order to prevent severe diseases in adults.

Peer review

The authors studied the prevalence of H. pylori virulence genotypes among children in Eastern Turkey. This is a useful paper on a topic for which there is, as yet little information. It will certainly contribute to knowledge on the issue.

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