

Seroprevalence of *Helicobacter pylori* in children with constitutional height retardation

Konstitüsyonel büyüme geriliği olan çocuklarda *Helicobacter pylori* seroprevalansı

Ayşin TAŞAR¹, Erkan KIBRISLI², Yıldız DALLAR¹

Departments of ¹Pediatric, ²Family Physician Ankara State Hospital, Ankara

Background/aims: The objective of this study was to examine the relationship between *Helicobacter pylori* and constitutional height retardation in childhood. **Methods:** Forty-one children with a diagnosis of constitutional height retardation and 40 children with normal growth patterns attending to the Pediatric Endocrinology Clinic at Ankara Education and Research Hospital were invited to take part in this study. Each child was asked questions to identify whether they had abdominal pain or lack of appetite. In addition, the family members were also investigated for gastrointestinal complaints. *Helicobacter pylori* antibody levels were evaluated in both groups. **Results:** The patient group's anti-*Helicobacter pylori* Ig G and anti-*Helicobacter pylori* CagA Ig G positivities were 78% and 85.4%, respectively. Corresponding frequencies in the control group were 10% and 15%, respectively. **Conclusion:** The seroprevalence of *Helicobacter pylori* antibodies in the constitutional height-retarded group was significantly higher than in the control group ($p<0.001$). These results support the hypothesis suggesting that *Helicobacter pylori* infection is one of the environmental factors affecting growth.

Key words: *Helicobacter pylori*, height retardation, constitutional height retardation, childhood

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral, Gram-negative bacillus that has been associated with gastritis, peptic ulcer and gastric carcinoma. This bacterium also has a role in the etiology of mucosa associated lymphoid tissue (MALT) and lymphoma, and was classified in 1994 as the primary class of carcinogen by the World Health Organization (WHO) (1-6).

A total of 20-80% of the world's population is infected with *H. pylori*. The infection is acquired at early ages in developing countries (7-9), where the bacteria is also a responsible factor for chronic di-

Amaç: Bu çalışmanın amacı, çocukluk döneminde *Helicobacter pylori* ve büyüme geriliği arasındaki ilişkiyi incelemektir. **Yöntem:** Çalışmaya S.B. Ankara Eğitim ve Araştırma Hastanesi Çocuk Endokrinoloji Polikliniği'ne, boy kısalığı nedeniyle başvuran ve konstitüsyonel boy kısalığı tanısı alan 41 hasta ve normal büyüme eğrisi gösteren 40 çocuk alınmıştır. Çalışmaya alınan hastalarda karın ağrısı, iştahsızlık, aile fertlerinde gastrointestinal sistem şikayetleri sorgulanmış, hasta ve kontrol grubu çocukların serum *Helicobacter pylori* antikor düzeyleri değerlendirilmiştir. **Bulgular:** Hasta grubundaki *Helicobacter pylori* IgG ve *Helicobacter pylori* antiCagA IgG antikor pozitiflik oranları sırasıyla % 78 ve % 85.4, kontrol grubunda %10 ve %15 idi. Kontrol ve hasta gruplarının *Helicobacter pylori* IgG ve *Helicobacter pylori* antiCagA IgG düzeyleri arasında istatistiksel olarak anlamlı fark bulundu ($p<0,001$). **Sonuç:** Bu çalışmada, vaka sayısı az olmakla birlikte, konstitüsyonel boy kısalığı olan çocuklar kontrol grubu çocuklarla *Helicobacter pylori* seropozitiflik yönünden karşılaştırıldığında çalışma grubundaki seroprevalansın kontrol grubuna göre belirgin yüksek olduğu görülmektedir ($p<0,001$). Bu veriler *Helicobacter pylori* enfeksiyonun büyümeyi etkileyen çevresel faktörlerden biri olduğu hipotezini desteklemektedir.

Anahtar kelimeler: *Helicobacter pylori*, boy kısalığı, konstitüsyonel boy kısalığı, çocukluk dönemi

arrhea, malnutrition and growth retardation (10). Diagnosis and treatment of the infection are important in childhood due to the high incidence and morbidity in children (4).

It has been reported that children infected by *H. pylori* have shorter height compared to those who are noninfected (11-14). Thus, it is considered that *H. pylori* may have a role in growth retardation in childhood.

Helicobacter pylori infection is diagnosed by upper gastrointestinal endoscopy, an invasive procedure,

and biopsy. The examination of the material under light microscope, rapid urease test and cultures are also required (15, 16). However, some studies suggest that serological methods may be used at the time of the diagnostic procedure. It is reported that high serological titers show active *H. pylori* infection and may be suggested in childhood as noninvasive methods (17-20). Glassman and his colleagues compared the serological methods by measuring anti-*H. pylori* IgA and G levels with endoscopic biopsy results in children with chronic abdominal pain (17). They concluded that serological methods were useful in diagnosing the infection.

This study was conducted to compare *H. pylori* antibody levels between children with constitutional height retardation and children with normal growth parameters. The association of *H. pylori* infection with height retardation in childhood was investigated.

MATERIALS AND METHODS

The constitutional height-retarded children followed at the Pediatric Endocrinology Department of the Ministry of Health Ankara Education and Research Hospital were included in this study. All the children's height percentiles were under 3% and height standard deviation scores (HSDS) were under -2.2. The control group included children with normal growth parameters admitted to the outpatient department of pediatrics who were venipunctured for some other reason. The control group was age- and sex-matched.

This study was prospective, sectional and case controlled.

Patients were evaluated with regard to detailed history, and clinical and laboratory examination. They were sought if they had received treatment for *H. pylori* infection.

The physical examination of height-retarded children included measures of sitting height, HSDS, weight standard deviation score (WSDS), and parents' height. Laboratory examinations included hemogram, routine chemistry, urinalysis, stool examination, thyroid function and growth hormone tests and bone age. If HSDS was under -2, insulin and L-dopa provocation tests were performed. Children's growth velocity was followed for one year. The children diagnosed as constitutional growth retardation were included in the study.

A questionnaire was given to the parents in order to identify the number of individuals in the family, education levels of the family members, their monthly income, and also any gastrointestinal symptoms in the family members.

According to the Turkish Labor Investigation Center, in April 2002, monthly income of a family composed of four individuals must be at least 324, 683, 000 TL in order to have sufficient intake of food. If a family's monthly income was more than this amount it was considered as high income, if it was close to this amount it was considered as moderate income, and if it was lower than this amount it was considered low income (21).

Serum samples from 5 ml venous blood were obtained from all patients and were stored at -20°C. RADIM *H. pylori* IgG and *H. pylori* CagA IgG commercial kits were used to determine anti-*H. pylori* IgG and anti-*H. pylori* CagA in serum samples by ELISA method. Each sample's absorbance was considered as anti-*H. pylori* IgG and anti-*H. pylori* CagA concentration at RU/ml, which matches on standard curve for ELISA. If serum anti-*H. pylori* IgG values were lower than 15, it was considered negative, values between 15 and 30 were considered suspicious, and values higher than 30 were considered positive. If serum anti-*H. pylori* CagA IgG values were lower than 10, it was considered negative, values between 10 and 15 were considered suspicious, and values higher than 15 were considered positive.

Data were analyzed using SPSS version 10.0. All data were expressed as means \pm SD. The data of the patients and controls were analyzed using Student's t-test or Fisher's chi-square test. For all tests, p values \leq 0.05 were considered significant.

RESULTS

Forty-one children with constitutional height retardation, aged between 3.7 and 15.8 years (mean age 11.5 ± 3.1), were included in this study. Twenty-one of these children were girls, and 20 boys. Height percentiles of the cases were under 3% and mean HSDS values were recorded as -3.2 ± 0.7 . Mean WSDS according to age was -1.9 ± 0.7 .

The control group included 40 children between 3.2 and 12 years (mean age 9.3 ± 2.8) who had normal growth parameters. Seventeen of the children were girls and 23 boys. Their weight and height percentile values according to age were between

3% and 97%. The control group was matched to our study group for age and sex.

Anti-*H. pylori* IgG was positive in 78%, suspicious in 7.3% and negative in 14.6% of the patient group. On the other hand, anti-*H. pylori* IgG was positive in 10%, suspicious in 12.5% and negative in 77.5% of the control group ($p < 0.001$) (Figure 1). Mean anti-*H. pylori* IgG values in patient and control groups were 90.1 ± 50.4 RU/ml and 15.6 ± 29.5 RU/ml, respectively, and the difference was significant ($p < 0.001$).

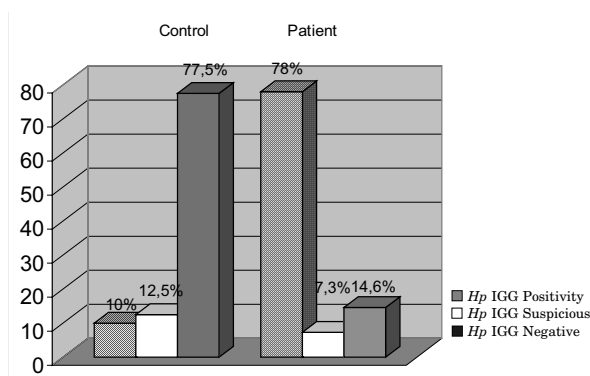


Figure 1. Anti-*H. pylori* IgG values in control and patient groups ($p < 0.001$)

Anti-*H. pylori* CagA IgG was found positive in 85.4%, suspicious in 2.4% and negative in 12.2% of the patient group, whereas in the control group it was positive in 15%, suspicious in 5%, and negative in 80% ($p < 0.001$) (Figure 2). Anti-*H. pylori* CagA mean values in patient and control groups were 174.4 ± 108.7 RU/ml and 21.7 ± 57 RU/ml, respectively, and the difference between them was significant ($p < 0.001$).

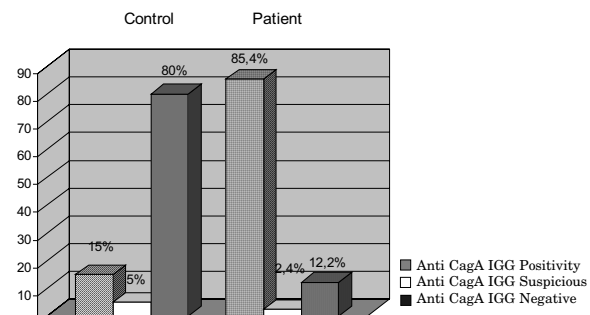


Figure 2. *H. pylori* anti CagA IgG values of control and patient groups ($p < 0.001$)

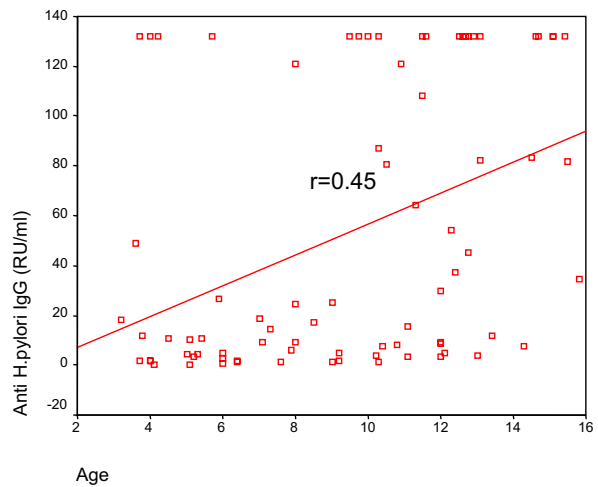


Figure 3. Age and anti-*H. pylori* IgG results ($p < 0.001$, $r = 0.45$)

The study groups (constitutional height retardation and control) were divided into two groups according to age. 18.7% of the children aged between 3.2 and 8 years had anti-*H. pylori* antibodies; however, 61% of the children aged between 8.5 and 15.8 years had seropositivity. The frequency of *H. pylori* seropositivity increased in association with age ($p < 0.001$, $r = 0.45$) (Figure 3).

Among the patient group, *H. pylori* seropositivity was 15.6% in the families with less than five members, and 84.4% in the families with five or more. The difference was significant ($p < 0.05$). Two children's parents had no education at all and one of these had *H. pylori* seropositivity. Among the 34 children whose parents had primary or secondary school education, 26 (84%) were positive for *H. pylori* antibodies, and among the five children whose parents had high school education, all (100%) were positive for *H. pylori* antibodies. *H. pylori* seropositivity was 50% in the low-income group, 43.8% in the moderate income group and 6.3% in the high income group. The difference was not statistically significant ($p > 0.05$). 80.5% had abdominal pain. *H. pylori* seropositivity rate was established in 93.8% of children with and in 6.3% of children without abdominal pain. The significance was statistically significant ($p < 0.001$). *Helicobacter pylori* antibody positivity was 97.7% among children with constitutional height retardation whose family members had gastrointestinal system complaints versus only 55.6% among children whose family members were without gastrointestinal system complaints; the difference was statistically significant ($p < 0.001$).

DISCUSSION

Helicobacter pylori has been primarily associated with gastritis, peptic ulcer and gastric carcinoma (1-4). Many studies have evidence to support an association between *H. pylori* infection and height retardation (11-14). Conflicting results also exist, however, reporting that *H. pylori* does not cause height retardation (22, 23).

Perri and colleagues proposed some mechanisms for *H. pylori* infection to cause growth retardation (14), as follows: infection causes peptic symptoms, and dyspeptic symptoms causes malnutrition; when the infection exists for a long time some cytokines affecting growth are released and a chronic, low-degree gastric inflammation persists; *H. pylori* is frequent among families with low socioeconomic level; and those children who have associated malnutrition and chronic infections may also grow slowly.

In developing countries, high incidence of growth retardation is associated with a high incidence of chronic diseases and malnutrition. *H. pylori* infection is acquired at young ages, and there is also poor hygiene and low socioeconomic levels in developing countries. *H. pylori* contributes to growth retardation like other chronic illnesses (13, 24-26). In addition, *H. pylori* infection prevalence has been detected as being higher in developing countries (10, 13, 24). Protein losing enteropathy, gastroenteritis, malnutrition and iron deficiency anemia have also been reported in children with *H. pylori* infection, all of which might cause growth retardation (27-29).

Helicobacter pylori infection incidence has been found higher in children who were followed up for height-growth retardation in comparison to control group in many studies. Richter and colleagues investigated the effect of *H. pylori* infection on growth parameters in 3, 315 asymptomatic children (30). Infection prevalence was found in 6.1% of girls and in 7.2% of boys with C^{13} urea breath test (UBT); mean height of children who were infected with *H. pylori* was found as 117.6 ± 5.5 cm, while it was 118.9 ± 5.7 cm for children who were not infected, and the difference was statistically significant. As a result, they reported that *H. pylori* infection is associated with growth retardation and short stature. Ertem *et al.*, using the method of UBT, reported that *H. pylori* infection had a higher incidence in both sexes in children with height retardation (31). In another study conducted in

our country among children with height retardation and delayed puberty, the seropositivity rate was 66.6%, whereas in the control group it was 37.5%; the difference was statistically significant (11). Raymond and his colleagues established that *H. pylori* antibody positivity rates were 55.2% in children with growth retardation (12). In our study, anti-*H. pylori* IgG seropositivity was 78% in the height retardation group whereas it was 10% in the control group. Anti-*H. pylori* CagA was positive in 85.4% of the height retardation group versus in 15% of the control group. The difference in seropositivity rate between the two studies may be due to our being a developing country.

Determining anti-*H. pylori* CagA in serum samples by ELISA is a method to establish infections due to noncytotoxic species. In our study, anti-*H. pylori* IgG seropositivity was 78% and anti-*H. pylori* CagA positivity was 85.4% in the constitutional height retardation group. This finding suggests that children's height is more affected if they are infected by cytotoxic species.

In a study conducted in Scotland, *H. pylori* infection was detected by measuring IgG antibodies with ELISA method in saliva (13). These children, aged between 6.5-7.5 years, were followed up for four years. Pubertal delay was seen in children with *H. pylori* infection, especially in girls. In another report, *H. pylori* negative children between ages 12-60 months were followed up for two and a half years and during this period if the child became infected with *H. pylori*, height velocity had declined 0.5 cm/year (32). However, because this report was sectional, final height parameters were not evaluated.

In a study from Italy, UBT was performed in children between 3 and 14 years of age (14). Eight of 49 children (16.3%) with *H. pylori* infection and 7.8% of children without *H. pylori* infection were under 25th percentile for height. The difference was statistically significant when the same children were at 8.5-14 years old. Thirty-one (25.8%) infected children's height measurements in this group were under 25th percentile, whereas in noninfected children the rate of falling under the 25th percentile was 8.3%. The study groups (constitutional height retardation and control) were divided into two groups according to age, and age and anti-*H. pylori* IgG were found to correlate.

Factors such as crowded family, low socioeconomic levels, and poor hygiene, which are associated

with *H. pylori* infection, also cause growth retardation in children (13, 24, 33). Perri and his colleagues proposed that *H. pylori* infection is an environmental factor affecting growth (14). They investigated *H. pylori* infection in 216 children aged between 2 and 14 years by performing UBT, and established that this infection, which causes growth retardation, is associated with low socioeconomic levels and crowded families. This finding is compatible with the hypothesis that infection is one of the environmental factors affecting growth. Ertem and colleagues reported that *H. pylori* and short stature are independent of poor hygiene, but people with low socioeconomic status are more frequently infected (31). Patel and colleagues could not determine an association between *H. pylori* infection and socioeconomic level of the family (13). The report from Brazil establishes that the most important factor to prevent *H. pylori* infection is a high education level (34). In this study, *H. pylori* antibody positivity was significantly high if there were five or more family members. But there was no statistical significance between family income and parents' education levels and *H. pylori* antibody positivity rate.

Kuipers and colleagues reported an association between serologically high antibody titers of *H. pylori* IgG and dyspeptic complaints (35). They suggested that high *H. pylori* IgG titers support active *H. pylori* infection. The rate of *H. pylori* seropositivity was higher among the patient group with abdominal pain in this study.

In this study, *H. pylori* antibody positivity was significantly high among children with height retar-

dation whose family members had dyspeptic complaints. A study in our country determined that 54% of *H. pylori* infected children's family members had dyspeptic symptoms (36). A report from Russia pointed out a high prevalence of peptic ulcer presence among family members of children infected with *H. pylori* (37). Consequently, we think that children living in crowded conditions and having family members with dyspeptic complaints acquire *H. pylori* infection in early childhood through close contact, and with the contribution of other factors, their height/growth are affected.

In our study, the height-retarded children had high *H. pylori* seroprevalence compared with the control group. Our study supports the hypothesis that *H. pylori* infection is one of the environmental factors affecting height and development.

In conclusion, in developing countries, *H. pylori* is an infection acquired early in childhood and it adversely affects children's growth. *H. pylori* infection prevalence is high among children living in crowded families and having family members with dyspeptic complaints because of close contact with family members. *H. pylori* infection is diagnosed with endoscopic biopsy, an invasive procedure, with rapid urease test and culture evolution (15, 16). Although positive serology cannot determine whether it is an active, chronic or past infection, it shows that a patient has been confronted with *H. pylori* (38). We thus conclude that antibody seropositivity is a useful method for *H. pylori* seroprevalence evaluation.

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