

Helicobacter Pylori Infection in Pediatric Candidates for Kidney Transplantation

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Introduction. Chronic kidney failure was suggested to have a protective effect against *Helicobacter pylori* infection in adults. However, data about this effect in children is lacking. This study was designed to ascertain the prevalence, endoscopic findings, and histopathological features accompanying the *Helicobacter pylori* infection in children with end-stage renal disease.

Materials and Methods. Data were collected from 117 children with end-stage renal disease aged 5 to 18 years that underwent routine upper gastrointestinal endoscopy before kidney transplantation between 1998 and 2009. The specimens that were taken from the antrum were stained with hematoxylin-eosin and Giemsa to detect *Helicobacter pylori*.

Results. Gastrointestinal symptoms were reported in 12% of the patients. *Helicobacter pylori* was detected in 24% of the children. The prevalence of *Helicobacter pylori* infection was high in children with abnormal endoscopic findings ($P = .02$). There was no correlation between *Helicobacter pylori* infection and gender, dialysis status, duration of dialysis, underlying diseases, and gastrointestinal symptoms. *Helicobacter pylori* infection had a significant correlation with histopathological features ($P = .005$), age older than 10 years ($P = .003$), and upper gastrointestinal endoscopic findings ($P = .001$).

Conclusions. In this study, *Helicobacter pylori* infection had a high prevalence in children with end-stage renal disease, especially in older ones. The majority of children with *Helicobacter pylori* infection were asymptomatic, while they had abnormal findings on upper gastrointestinal endoscopy and chronic active gastritis features in histopathological assessment.

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INTRODUCTION

Helicobacter pylori is a gram-negative bacterium that neutralizes gastric acid by urease, penetrates the mucus layer by the flagella and the mucolytic enzyme, and attaches to the gastric epithelium by specific receptor.¹ Although *H pylori* is seen in 20% to 40% of the general population, it is accepted as an etiologic factor in peptic ulcers, chronic gastritis, dyspepsia, gastric cancer, and mucosal-associated

lymphoid tissue lymphoma.²

The prevalence of *H pylori* infection is related to the socioeconomic status and living conditions during early life. End-stage renal disease (ESRD) was suggested as a protective factor against *H pylori* infection in adult population. Its prevalence decreases with long duration of dialysis.³ The reported prevalence of *H pylori* infection in uremic adult patients varied from 25% to 70% depending

on diagnostic measures, studied populations and correlates possibly with HLA-DR12.⁴⁻⁶ While the majority of investigators used biopsy, serologic testing or rapid urease test to identify the bacterium, other studies were based on specific histopathological staining.

Prevalence database of *H pylori* infection in children with ESRD is very scant. In some studies using rapid urease test, it was reported to be as high as 60% to 80%.⁷⁻¹⁰ In this regard, we aimed to assess the prevalence, clinical and endoscopic findings, and histopathological features of *H pylori* infection among children who were candidates for kidney transplantation by using specific tissue staining methods.

MATERIALS AND METHODS

One hundred and seventeen patients aged 5 to 18 years with ESRD (glomerular filtration rate < 15 mL/min/1.73 m²) were enrolled in a cross-sectional study. This study was conducted from March 1998 to March 2009 in Ali-Asghar Children's Hospital, in Tehran, Iran. Protocol of the study was approved by the ethic committee of human study in Tehran University of Medical Sciences. Consent form was obtained from parents prior to the gastrointestinal (GI) endoscopy and biopsy.

Glomerular filtration rate was estimated using the Schwartz formula. Esophagogastroduodenoscopy (EGD) was postponed for 3 months in patients who were taking a proton pump inhibitor, H₂-blocker, or antacid because of their interference with histological findings.¹¹ Demographic data of all children with ESRD who were a candidate for kidney transplantation were recorded, including age, gender, underlying disease, dialysis status, and duration of dialysis.

At least 1 biopsy specimen was taken from the stomach antrum. Because of the strong association between *H pylori* infection, increased acid production, and peptic ulcers, which may induce esophageal irritation and ulcers, in the case of gastrointestinal symptoms, 2 more specimens were taken from the esophagus and duodenum other than the stomach antrum.¹² Also, in the presence of any abnormality in EGD, biopsies were undertaken.

All specimens were immediately fixed in formalin. Five serial sections were prepared and stained with the hematoxylin-eosin method.

All samples were specifically stained with the Giemsa method to detect *H pylori* and in the case of identifying this microorganism, the patient was termed *H pylori* positive. All sections were examined by a pathologist. Chronic active gastritis (CAG) was defined by the presence of neutrophils within the glandular and superficial epithelial layer. Lymphoid cell aggregation containing germinal centers within the mucosa was defined as chronic follicular gastritis. Chronic inactive gastritis (CIG) was defined as the infiltration of lymphocyte and plasma cells within the mucosal layer in the absence of erosion.¹³

All the *H pylori* positive patients were treated with metronidazole, omeprazole, and amoxicillin or clarithromycin for at least 2 weeks. In the case of postponing kidney transplantation for more than 1 year, the second EGD was performed according to the protocol of the local kidney transplantation center. The transplantation was not permitted, unless the recent EGD and histopathological evaluation were normal, and they had not *H pylori* infection.

Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). The independent Student *t* test was used for comparison of continuous variables. The chi-square test was performed to show frequency and odds ratio (95% confidence interval). Binary logistic regression was used to evaluate correlations. A *P* value less than .05 was considered significant.

RESULTS

Of 117 children with ESRD who were candidates for kidney transplantation (65 boys and 52 girls), 14 (12%) were complaining from GI symptoms, including nausea, vomiting, and abdominal pain. All patients underwent routine EGD before transplantation. The mean duration time of dialysis was 2.3 ± 1.9 years in 71 patients (60.7%). Forty-six of 117 patients were candidates for preemptive kidney transplantation. *H pylori* was histologically detected in 28 patients (24.0%). The mean age of *H pylori*-positive and *H pylori*-negative patients were 12.75 ± 2.6 years and 10.7 ± 2.9 years, respectively (*P* = .001). Two of 14 symptomatic patients (14.3%) were *H pylori* positive. However, 26 of 103 patients (25.0%) without any related GI symptoms were *H pylori* positive (*P* = .51).

In our study, abnormal endoscopy findings in the esophagus and stomach were seen in 6 (5%) and 55 (47%) patients, respectively. Among patients with abnormal endoscopy findings, 16 patients were *H pylori* positive. Abnormal endoscopy of the duodenum was found in 30 (25.6%) patients and 9 of them were *H pylori* positive. Twenty of 62 patients (32.3%) with abnormal upper GI endoscopy findings were *H pylori* positive, while 8 of 55 patients with normal EDG had *H pylori* infection (odd ratio, 2.2; 95% confidence interval, 1.06 to 4.62; $P = .03$).

The prevalence of *H pylori* infection in children with ESRD who were candidates for kidney transplantation was 24% (28 of 117). *H pylori* infection was detected in 9 of 46 patients (20.0%) who were candidates for preemptive transplant, 19 of 68 patients (28.0%) on hemodialysis, and none of the patients on peritoneal dialysis ($P = .25$).

Chronic active gastritis was reported in 44 patients (37.5%). More than half of the children with CAG were *H pylori* positive (56.8%). The Table shows the frequency of pathological findings in our studied group.

There were 32 children who showed CAG and 19 (59.3%) were *H pylori* positive. One of 4 patients with CIG had *H pylori* infection. None of the patients with chronic follicular gastritis

were *H pylori* positive, and only 1 patients (2.7%) with normal histopathology evaluation had *H pylori* infection ($P < .001$; likelihood ratio, 31.26). Among candidates for preemptive transplant, 6 of 12 patients with CAG were *H pylori* positive. One patient with CIG and none of the patients with normal histopathology evaluation had *H pylori* infection ($P < .001$; likelihood ratio, 17).

Ten patients underwent a second EGD because of postponing kidney transplantation. Half of them were *H pylori* positive compared with 22% of the children who were transplanted on the scheduled time ($P = .06$).

Using Binary logistic regression, there was no correlation between *H pylori* infection and gender, dialysis status, duration of dialysis, underlying disease, or presence of GI symptoms. However, there was a significant correlation between histopathology features ($P = .005$), EGD findings ($P = .001$), and an age greater than 10 years ($P = .003$).

DISCUSSION

More than 20% of the studied population had *H pylori* infection regardless of gender, dialysis status, or duration of dialysis. Patients with ESRD and GI symptoms with abnormal UGI endoscopy findings had a more than twice higher risk for *H pylori* infection. Esfahani and colleagues studied 69

Demographic and Clinicopathological Data of Pediatric Candidates of Kidney Transplantation

Variables	Preemptive Patients	Dialysis Patients	P
Age, y	10.9 ± 2.7	11.3 ± 3.2	.58
Sex			
Male	29 (6)	36 (10)	
Female	17 (3)	35 (9)	.56
Endoscopy			
Esophagus			
Erythema	3 (1)	3 (1)	
Ulcer	0	0	.50
Stomach			
Erythema	15 (2)	21 (5)	
Nodularity	7 (2)	10 (6)	
Ulcer	0	2 (1)	.60
Duodenum			
Erythema	9 (1)	19 (7)	
Ulcer	0	2 (1)	.60
Pathologic examination			
Normal	28 (1)	36 (0)	
Chronic active gastritis	16 (7)	28 (18)	
Chronic follicular gastritis	1 (0)	0	
Chronic inactive gastritis	1 (1)	7 (1)	.001

*Values in parentheses are *Helicobacter pylori*-positive patients.

children on maintenance hemodialysis and found that 80% were complaining from GI symptoms and 21% had *H pylori* infection.¹⁴ The majority of children in our study was asymptomatic. However, they almost had a higher percentage rate of *H pylori* infection.

Emir and coworkers found that 10 out of 26 (38%) children, who were on dialysis in average of 13 years, had a positive rapid urease test for *H pylori*.⁷ They found a high prevalence rate of *H pylori* infection in symptomatic patients despite normal endoscopic examination. In this regard, they suggested performing EGD only in symptomatic patients and in endemic areas.⁷

Our findings showed that *H pylori* infection was as frequent in children with ESRD as in those with normal renal function. The infection rate was not different between asymptomatic and symptomatic patients. The reported prevalence of *H pylori* infection varied widely from 20% to 70% among adults with ESRD using rapid urease test on biopsy. In a four year cohort study on 400 hemodialysis patients, Sugimoto and colleagues reported lower rate of *H pylori* infection in patients who were on dialysis for a long duration time.³ By contrast, Ozgur found a high rate of *H pylori* infection in hemodialysis patients with GI symptoms while they did not find any relation between the prevalence of *H pylori* infection and duration of dialysis.¹⁴ In a study by Mortazavi and associates, patients on a long duration time of dialysis had a lower rate of *H pylori* infection.⁸ Hruby and coworkers reported a higher rate of *H pylori* colonization (62%) in transplant patients who had GI symptoms compared with dyspeptic patients with (35%) and without ESRD (44%). However, they found a lower occurrence rate of active gastritis in transplant patients compared with the other studied groups.¹⁴ On the other hand, results of UGI endoscopy on asymptomatic hemodialysis patients suggest that, EGD alone is not a confirmatory method and histological examination is recommended.¹⁵ Results of a cohort study on 500 uremic patients during a six-year post transplant follow up period revealed that, seropositive and seronegative *H pylori* patients did not have a significant difference regarding the disorders of GI system. In this study, 1.3% of seropositive patients developed gastroduodenal malignancies.¹⁶

There are a few studies about the rate of *H*

pylori infection in children candidate for renal transplantation.⁷⁻¹⁰ Giordano and colleagues evaluated for the presence of anti-*H pylori* antibody in 23 transplant children and 36 healthy subjects using enzyme-linked immunosorbent assay. They suggested kidney transplant is not a risk factor for *H pylori* infection.⁹ Other studies, reported a higher frequency rate of *H pylori* infection in symptomatic dialysis children by using rapid urease test on biopsy.^{7,8,10}

We applied Giemsa staining as a specific histological staining method to detect *H pylori* infection. The infection rate was lower in ESRD children compared to children with normal renal function. It should be noted that the majority of children with ESRD were asymptomatic. To the best of our knowledge, this is a first study for detecting *H pylori* infection in children candidate for renal transplant by performing specific histological staining method. Shousha and coworkers used specific histological staining and found a 2-fold higher risk of *H pylori* infection in normal adult population compared with ESRD patients.⁶ Nieves and associates, compared 312 histological findings of 26 adults with ESRD with 26 healthy volunteers. This study revealed that, 54.5% of ESRD patients and 47.2% of healthy subjects had *H pylori* infection. This organism was more located in the antrum area. In addition, chronic active gastritis and superficial gastritis were more common in *H pylori* positive patients with ESRD.¹⁹ In a study on four groups, including patients with the chronic renal failure, hemodialysis patients, renal transplant patients, and normal population; higher rate of *H pylori* infection accompanying gastric and duodenal mucosal lesions was found in uremic patients.²⁰ Atrophic gastritis, high ammonia in gastric juice, and high serum gastrin level was shown in symptomatic *H pylori* positive hemodialysis adults. Although *H pylori* infection had a low prevalence in hemodialysis patients, peptic ulcers were more reported in this group.³

Many studies were conducted on uremic patients with dyspepsia. In our study, less than one third of ESRD children were symptomatic. The rate of *H pylori* infection was similar between two studied groups. Correlation was seen only between symptomatic *H pylori* infection and histological features in the patients' group. Limitations of our study were as follows: biopsy was only taken from

the gastric antrum; however, the density of *H pylori* is higher in this part of the stomach. In addition, Giemsa staining method has a low sensitivity and high specificity, especially in patients with gastrointestinal bleeding;¹ however, none of our patients had GI bleeding. We also did not find atrophic changes or intestinal metaplasia following chronic gastritis in both groups. Mucosal-associated lymphoid tissue lymphoma is occasionally reported in *H pylori* positive adult transplant patients, and it could be eradicated by standard therapy. This malignancy has not been reported in transplant children.^{2,18,22,23} The second limitation of the present study was including GI symptomatic children as a control group which indicates to a selection bias. Despite this bias, we did not find any difference between the prevalence of *H pylori* infection in two studied groups. Thus, routine EGD to detect *H pylori* infection in candidates for renal transplantation seems a reasonable approach. To evaluate the advantages and/or disadvantages of *H pylori* eradication therapy before transplant, conducting a prospective cohort clinical trial is recommended.

CONCLUSIONS

In this study, despite the majority of children with ESRD did not have GI symptoms, the prevalence of *H pylori* infection in children with ESRD was similar to the children with normal renal function. Moreover, considerable percentage of the patients had CAG.

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CONFLICT OF INTEREST

None declared.

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