Gastrointestinal Evaluation in Pediatric Kidney Transplantation Candidates

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Introduction. Our aim was to determine the frequency of peptic ulcer and *Helicobacter pylori* infection by gastrointestinal evaluations in pretransplantation phase in children with end-stage renal disease (ESRD).

Materials and Methods. Twenty-four children with ESRD (13 girls and 11 boys) with a mean age of 14.7 ± 3.4 years on maintenance hemodialysis were included in this study. Upper gastrointestinal endoscopies were performed and 4 gastric, antral, and duodenal biopsy specimens were obtained for urease test and histological study. Serum gastrin levels were measured in all patients, too. A control group was chosen to compare the rate of *H pylori* infection between children with ESRD and healthy children.

Results. Gastrointestinal symptoms were present in 16 (66.7%) of 24 patients. Seventeen (70.8%) patients had abnormal upper gastrointestinal endoscopic findings. Infection with *Helicobacter pylori* was detected in 16 patients and 5 healthy children (66.7% versus 20.0%, $P < .001$). The frequency of dyspeptic symptoms was not different significantly between uremic patients with and without *H pylori* infection ($P = .67$). The same results were found regarding the upper gastrointestinal abnormalities found by endoscopy ($P = .65$). Oral alkalizing supplement was received by 63% of symptomatic and 80% of asymptomatic patients. Serum gastrin levels were significantly higher in infected patients than in noninfected patients with *H pylori* ($P < .001$).

Conclusions. We found a significant number of patients with peptic ulcer diseases, *H pylori* infection, and secondary hypergastrinemia. This study showed that clinical symptoms are not a reliable predictor of gastrointestinal problems and this is more confusing in patients who received alkalizing solutions. Our results emphasize the importance of periodic and pretransplant gastrointestinal evaluation in these patients to detect and manage their problem appropriately.

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INTRODUCTION

Patients with end-stage renal disease (ESRD) experience a high incidence of upper gastrointestinal (GI) diseases.[1] Various GI symptoms are among the major clinical manifestations of uremia. Anorexia, vomiting, and other dyspeptic symptoms are common in children with ESRD.[2,3] Growth rate in children with chronic kidney disease is lower due to insufficient food and calorie intake caused by GI problems. There are many studies about GI

complications in adults suffering from ESRD, but few in children.[4-11]

There is no doubt that upper GI endoscopy before transplantation should be considered in patients with GI symptoms or those with a history of peptic ulcer disease.[4] Although direct evidence is lacking, it is recommended that kidney transplantation be postponed in patients with active peptic ulcer until they are fully treated and are asymptomatic.[5] Many centers and authors believe there is no role for routine screening for peptic ulcer disease in asymptomatic patients.[4,5] They also recommend no routine serologic testing for *Helicobacter pylori*.[4-6] On the other hand, there are many reports showing upper GI abnormalities are common among adult uremic patients even in the absence of symptoms.[7-10] Hence, making decision for upper GI endoscopy based on the clinical symptoms may be confusing. The aim of this study was to evaluate the rate of histological gastritis and peptic ulcer using upper GI endoscopy and biopsy, their clinical features, and also their correlation with H pylori infection to assess the importance of GI evaluation in pretransplantation phase in children with ESRD.

MATERIALS AND METHODS

In this descriptive-analytic study carried out from September 1999 to August 2001, we evaluated 24 children (13 girls and 11 boys) with ESRD who were candidates for transplantation. Patients on maintenance hemodialysis in Shiraz Pediatric Hemodialysis Unit who were candidates for kidney transplantation were included. They were excluded if they had a history of upper GI surgery, and/or they were smokers or alcohol abusers. Patients who had received antibiotic or antacid or H2 receptor inhibitor therapy during the past 2 months before study were also excluded. All parents and older patients enrolled the study provided written informed consent for upper GI endoscopy procedures and multiple biopsy sampling before participation. The study was approved by the human research committee of the Shiraz University of Medical Sciences.

General information of each patient (age, sex, duration and frequency of hemodialysis, the underlying kidney disease, and administered drugs) were recorded. Fasting blood samples were taken before starting dialysis for measurement of blood urea nitrogen (BUN) and serum creatinine levels. The fasting blood samples were also centrifuged and stored at -20°C for serum gastrin measurement using a commercially available kit (Biohit, Helsinki, Finland) by enzyme-linked immunosorbent assay (upper reference limit, less than 108 ng/L).

Upper GI endoscopy was performed by a pediatric gastrointestinologist for all of the patients and 2 gastric antral biopsy specimens were obtained for urease test and histological study. Two other specimens were taken from the duodenum for histological examination. Another specimen was obtained from the lower part of the esophagus in 4 patients based on endoscopic findings. Fresh 3.9% urea solution was used for urease test. Pink discoloration in less than 24 hours was assumed a positive urease test. All biopsy specimens were examined by one pathologist for histological findings and for presence of *H pylori*. Presence of *H pylori* in pathologic examination and/or positive urease test was defined as *H pylori* involvement. We divided uremic patients into 2 groups twice; first, according to *H pylori* infection, and second, according to endoscopic findings.

A control group was chosen among patients recruited at the gastroenterology outpatient clinic of the Namazi Hospital during the years of the study for comparison of the rate of *H pylori* infection. All patients with normal kidney function who were referred for removing the swallowed foreign bodies by upper GI endoscopy were included. Inclusion criteria were mental retardation, treatment with antibiotics during the past 2 months, and taking drugs interfering with gastric acid production and function during the past 2 months, such as nonsteroidal anti-inflammatory drugs, antacid, proton pump inhibitors, and anti-H2 receptor antagonists. Other exclusion criteria which were using for the study group were also considered for the control group.

The SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA) was used for statistical analyses. The frequency of *H pylori* infection was evaluated by means of cross-tables regarding age group, sex, predialysis BUN level, dialysis duration, symptoms, medication; Shohl's solution, abnormal endoscopic findings, and serum gastrin levels. These variables were examined by the chi-square test and the Fisher exact test. The same evaluation was made for the frequency of endoscopic upper GI abnormalities.

P values less than .05 were considered significant.

RESULTS

A total of 24 patients were enrolled in this study, including 13 girls and 11 boys aged 8 to 20 years old (mean, 14.7 ± 5.8 years). The underlying kidney diseases are shown in Table 1. In the control group, of the initial 35 children, 2 were excluded because of severe mental retardation. Furthermore, 8 children were excluded because of taking antibiotics, antacid, and ibuprofen. A total 25 children met the inclusion criteria for the control group. They were 15 boys and 10 girls aged 1 to 18 years old (mean, 8.7 ± 4.3 years). Swallowing of coins in 14 children, disc batteries in 4, safety pins in 3, needle in 2, and pins and nails in 2 were the reasons for referral in the control group.

Sixteen uremic patients (66.7%) and 5 children in the control group (20.0%) had *H pylori* diagnosed by urease test and histological examination ($P < .001$). The uremic patients were categorized based on *H pylori* infection and endoscopic findings and their mean ages, hemodialysis duration, predialysis serum BUN level, GI symptoms, and drugs were compared between the patients with positive and negative findings (Tables 2 and 3). There were no significant differences between the study groups regarding the abovementioned parameters. Dyspepsia was present in 10 out of 16 infected uremic children (62.5%) and in 12 of 17 patients with abnormal endoscopic findings (70.6%).

Seventeen patients had 25 abnormal upper GI endoscopic findings, ie, 10 patients with 1 lesion, 6 with 2 lesions, and 1 with 3 lesions (Table 4). Antral gastritis, followed by duodenal lesions, was the most frequent disorder found by endoscopy in the uremic patients. None of the patients had a history of gastric surgery or any evidence of atrophic gastritis on upper GI endoscopy or histopathology. Of the symptomatic patients, 12 (75.0%) had abnormal endoscopic findings and 10 (62.5%) had a urease test positive for *H pylori* infection. While, these rates were 3 (37.5%) and 6 (75.0%) in the asymptomatic group, respectively. Sixty-three percent of the symptomatic patients and 80.0% of the asymptomatic patients were receiving oral alkalizing supplementation.

High serum gastrin levels were detected in of 12 *H pylori*-infected patients and 1 noninfected patient (75.0% versus 12.5%, $P < .001$). Infected patients had a mean serum gastrin level of 208 ng/L. In noninfected uremic patients, this value was 95.2 ng/L.

Table 1. Etiologies of Kidney Failure in Children on Hemodialysis Who Underwent Endoscopic Examination*

Primary Kidney Disease	Patients (%)
Reflux nephropathy	7 (29.2)
Recurrent UTI	3 (12.5)
FSGS	3 (12.5)
Nephrolithiasis	2 (8.3)
MPGN	2 (8.3)
Lupus nephritis	2 (8.3)
Tubulointrestitial nephritis	1 (4.2)
Oxalosis	1 (4.2)
Lawrence-Moon-Biedl syndrome	1 (4.2)
Unknown	2 (8.3)

*UTI indicates urinary tract infection; FSGS, focal segmental glomerulosclerosis; and MPGN, mesangioproliferative glomerulonephritis.

Table 2. Demographic and Clinical Characteristics in *Helicobacter pylori*-Infected and Noninfected Children on Maintenance Hemodialysis*

Variable	Positive H Pylori	Negative H Pylori	*P*
Number of Patients	16	8	…
Sex			
Male	5 (31.3)	6 (75.0)	
Female	11 (68.7)	2 (25.0)	.08
Mean age (range), y	15.4 ± 2.8 (9 to 20)	12.6 ± 3.1 (8 to 16)	.51
Mean dialysis duration (range), mo	22.5 ± 18.5 (1 to 48)	26.9 ± 32.5 (1 to 84)	.47
mean predialysis serum BUN (range), m/dL	84.8 ± 30.6 (32 to 157)	90.1 ± 26.4 (67 to 145)	.96
Symptomatic dyspepsia	10 (62.5)	6 (75.0)	.67
Shohl's solution	10 (62.5)	6 (75.0)	.67
Abnormal endoscopic findings finding	12 (75.0)	5 (62.5)	.65
Median serum gastrin, ng/L	208.0	95.2	< .001

*Values in parentheses are percents unless otherwise indicated. BUN indicates blood urea nitrogen and ellipsis, not applicable.

Table 3. Demographic and Clinical Characteristics in Children on Maintenance Hemodialysis With and Without Abnormal endoscopic Findings*

Variable	Abnormal Endoscopic Findings	Normal Endoscopic Findings	*P*
Number of Patients	17	7	…
Sex			
Male	7 (41.2)	4 (57.1)	
Female	10 (58.8)	3 (42.9)	.66
Mean age (range), y	14.5 ± 3.5 (10 to 19)	14.4 ± 3.1 (8 to 20)	.51
Mean dialysis duration (range), mo	17.2 ± 17.05 (1 to 48)	40.4 ± 29.7 (1 to 84)	.36
mean predialysis serum BUN (range), m/dL	76.8 ± 18.3 (32 to 115)	110.2 ± 36.9 (61 to 157)	.41
Symptomatic dyspepsia	12 (70.6)	4 (57.1)	.65
Shohl's solution	12 (70.6)	4 (57.1)	.65
H pylori infection	12 (70.6)	4 (57.1)	.65

*Values in parentheses are percents unless otherwise indicated. BUN indicates blood urea nitrogen and ellipsis, not applicable.

Table 4. Endoscopic Findings in Children on Maintenance Hemodialysis

Endoscopic Findings	Lesions*
Nonulcer lesion	22
Gastritis	13
Duodenitis	3
Duodenal erosion	3
Esophagitis	1
Gastric erosion	1
Gastric atrophy	1
Ulcer lesion	3
Esophageal ulcer	1
Gastric ulcer	1
Bulb ulcer	1

*Seven patients did not have any lesions and 17 had 1 to 3 lesions: 10 patients with 1 lesion, 6 with 2, and 1 with 3. Percentages are calculated as in 24 patients.

DISCUSSION

Although the true incidence of peptic ulcer disease in childhood is unknown, it is accepted to be much less than that in adults.[3] Gastrointestinal disorders are common in uremic patients and seem to be more frequent than those in nonuremic population. Reviewing the literature, we found great variation in the reported prevalence (7.4% to 74%) of GI inflammation in uremic patients.[3,7-10] Upper GI disorders were found in 70.8% of our patients. In our study, mucosal lesions were detected more commonly (68.8%) than ulcers (9.4%). These findings are similar to what reported by Emir and associates.[3] Antral gastritis was the most common lesion followed by duodenitis and duodenal erosion. It is difficult to compare our uremic children on hemodialysis with the general pediatric population, as peptic diseases are very rare in childhood. However, our data suggests that upper GI disorders are common in children with ESRD.

Although GI symptoms and dyspepsia can predict the possibility of GI disorders in nonuremic patient, they are not a good predictor in children with ESRD. Dyspepsia was reported in 66.7% of our patients. Upper GI disorders in endoscopic examination are more frequent in dyspeptic patients, but we found about one-third of abnormal GI endoscopic findings in asymptomatic children. Therefore, alimentary symptoms are not a reliable predictor of upper GI disorders. Lack of symptoms in uremic patients may be due to factors such as severity, the stress level of the patients, duration of these lesions, and alkalizing supplementation.[3] On the other hand, GI symptoms without detectable lesion on endoscopy or histological examination may be present due to uremia, drugs, and hyperthyroidism.[1,5]

Helicobacter pylori has been identified as a major factor in the pathogenesis of peptic ulcer disease and gastritis in the general population.[12-14] With the exception of patients with gastrinoma and those taking nonsteroidal anti-inflammatory drugs, more than 95% of patients with duodenal ulcers and more than 80% of patients with gastric ulcers are infected with *H pylori*.[15,16] This microorganism is a gram-negative spiral urease-producing bacterium which survives in acidic milieu.[17] This is thought to be due to increased converting urea to ammonia, by possessing a powerful urease, which provides protection against the low pH of the gastric environment. Since patients with kidney failure have an increased concentration of gastric urea, they may be more susceptible to colonization with *H pylori*, as these bacteria can convert the increased gastric urea content to ammonia. Thus, longer survival period

is predicted for them. Many reports suggested a higher frequency of *H pylori* infection in uremic patients,[18,19] but some authors unexceptionally found an association of *H pylori* infection with lower levels of blood urea.[20-22] Alteration of bacterial colonization in the small intestine followed by inhibition of *H pylori* colonization has been suggested.[21] Others believe higher toxic waste product accumulation in severe uremia may have protective effect against *H pylori* infection.[22]

Helicobacter pylori infection was detected in 66.7% of our patients and 20.0% in the control group. In other reports, this rate varies from 17% to 80% in uremic patients.[3,15,18-23] Higher incidence of *H pylori*-positivity among our uremic children may be related to their poor socioeconomic condition and poor quality of life. The patients with *H pylori* infection had lower serum urea value compared to those without infection, although there was no statistical difference. As blood urea nitrogen level is determined by the rate of its production and also excretion, low serum level of urea may be due to malnutrition, which is expected in uremic patients with a low socioeconomic status.

We found *H pylori* among 75% of asymptomatic and 62.5% of symptomatic (dyspeptic) uremic children. Despite lack of any significant difference, higher frequency of infection in asymptomatic uremic children shows unreliability of symptoms as the predictor of *H pylori* infection in children with ESRD. Our results showed Shohl's solution (as alkalizing supplementation) can hide alimentary symptoms in uremic patients and asymptomatic presentation of GI lesions and *H pylori* infection is frequent. Hence, clinical symptoms in patients who receive alkalizing supplementation are more confusing. The high incidence of *H pylori* infection among our patients with GI lesions suggests that *H pylori* may play an important role in the pathogenesis of these lesions in children with ESRD. But, about 30% of the patients with abnormal endoscopic findings had no infection, which suggests the role of other factors other than *H pylori* for upper GI problems. Infection with *H pylori* may facilitate the development of endoscopic abnormalities when associated with other risk factors in this group of patients.[3]

In our study, serum gastrin measurement showed close correlation with *H pylori* infection. We found that serum gastrin concentration was significantly higher in *H pylori*-positive uremic children than noninfected children with ESRD. High serum gastrin level has been reported in kidney failure.[11,19] Hypergastrinemia associated with chronic kidney failure may be due to multiple factors. Reduced excretion of gastrin by the kidney undoubtedly plays a role.[24,25] The mechanisms that lead to exaggerated gastrin secretion in *H pylori* infection are unclear. One theory is that ammonia generation by *H pylori* urease creates an alkaline environment in the vicinity of G cells, which subsequently stimulates gastrin release.[23] Another possible mechanism rests on the finding that both the antral mucosal somatostatin concentration and the number of antral somatostatin-producing D cells are lower in *H pylori*-infected individuals than in uninfected controls.[26-28] Since endogenous somatostatin is known to be an important inhibitor of gastrin secretion, an *H pylori*-induced decrease in somatostatin concentration at the antral mucosa could result in hypergastrinemia. There is also evidence to suggest that gastrin release may be affected by the presence of gastric inflammation. Gastric epithelial cells and mucosal inflammatory cells that are attracted and activated by *H pylori* release cytokines such as tumor necrosis factor, interleukin-8 and interferon-γ, all of which are capable of stimulating gastrin release by the G cells.[29]

CONCLUSIONS

This study showed the frequency of endoscopically and histologically diagnosed upper GI lesions were high in children with ESRD. We also observed a significant number of patients with *H pylori* infection and secondary hypergastrinemia. This study showed that clinical symptoms are not a reliable predictor of GI problems and this matter is more confusing in patients who receive alkalizing solutions. Our results emphasize the importance of periodic and also pretransplant GI evaluation in these patients to discover their problem and manage it appropriately.

CONFLICT OF INTEREST

None declared.

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