Jpn. J. Infect. Dis., 66, 433-435, 2013

Short Communication

Helicobacter pylori Infection among Children with Phenylketonuria

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(Received August 1, 2012. Accepted May 20, 2013)

SUMMARY: This study aimed to determine the frequency of *Helicobacter pylori* infections in children with phenylketonuria (PKU). Sixty-six children with PKU (35 boys, 31 girls; mean age, 8.2 ± 6.7 years) and 32 outpatient controls (15 boys, 17 girls; mean age, 9.6 ± 4.7 years) were studied. Socioeconomic factors did not differ between the two groups. The frequency of *H. pylori* infections was higher in patients with PKU (28.1%) than in healthy controls (9.4%). In particular, a higher frequency of infection was detected in patients with PKU with poor metabolic control (51.8%). The frequency of *H. pylori* infection in patients with PKU with good metabolic control was only 10.2%. There was no difference in the mean total WISC-R score between the poor and good metabolic control groups. A high frequency of *H. pylori* infection in children with PKU with poor metabolic control could be related to many factors. Advanced and standardized clinical studies on *H. pylori* infections in children with PKU are required.

Phenylketonuria (PKU; OMIM 261600) is an autosomal recessive disorder involving mutations in the phenylalanine (Phe) hydroxylase gene, which inhibits the normal metabolism of Phe, an amino acid found in all proteins (1). As a result, Phe cannot be converted to tyrosine and accumulates in the blood and other tissues (2). Untreated PKU is associated with severe mental retardation (IQ < 30), seizures, severe behavioral difficulties, and other symptoms (3–5). The main goal of PKU treatment is to maintain blood Phe concentrations within a safe range through a Phe-restricted diet. A carefully maintained dietary regimen prevents mental retardation and other complications and allows optimum growth and development (6,7). During Phe-restricted diet treatment, some factors influence blood Phe concentrations. Poor adherence to the dietary regimen, intercurrent infections, trauma, and surgical interventions may cause increased blood Phe concentrations. Development of mental retardation and other neurological complications are inevitable in patients with PKU with poor metabolic control (blood Phe levels > 600 μmol/L).

Helicobacter pylori typically colonizes the human gastric mucosa, leading to chronic gastritis and, in some cases, to peptic ulceration, gastric adenocarcinoma, or gastric lymphoma (8,9). *H. pylori* infection is mostly acquired in childhood and continues throughout life if left untreated (8,10,11). Poor socioeconomic conditions and overcrowding during childhood are major risk factors for acquisition (12,13). Humans are considered to be the sole natural hosts of *H. pylori*, suggesting that person-to-person contact plays a key role in its transmission. Physically and mentally disabled children are particularly vulnerable to microorganisms because of their different feeding abilities, toilet needs, and sanitary arrangements. A high frequency of *H. pylori* infection has been shown among children with mental retardation (14–19); however, there are no data regarding *H. pylori* infection in other metabolic diseases with mental retardation in the literature. Therefore, we evaluated the frequency of *H. pylori* infections among children with PKU.

Sixty-six patients with PKU and 32 healthy controls were evaluated. Eighty-five percent of the patients were diagnosed through the newborn screening program. The remaining patients were diagnosed during investigations for mental retardation etiology between 2–8 years of age. All the children with PKU were treated with Phe-restricted diets. The Wechsler Intellignece Scale for Children-Revised (WISC-R) test records of patients with PKU were evaluated.

Using 2-year cumulative data retrieved from individual medical records, mean values of blood Phe concentrations were calculated for each patient. Blood Phe concentrations were simultaneously measured using with the stool antigen test for the detection of *H. pylori* infection in patients with PKU.

A questionnaire inquiring medical history and family demographics was filled for each child, and all of participants underwent physical examinations and stool *H. pylori* antigen tests. Parents (single or both) were asked to fill the questionnaire, which was designed to obtain information about the socioeconomic status of the family.

Social status assessment was evaluated according to the Hollingshead Index of Social Position (20). Blood Phe concentrations were measured using a fluorometric method (21). Stool samples were analyzed using the *H. pylori* stool antigen enzyme-linked immunosorbent assay (HpSA ELISA) (Meridian, Cincinnati, Ohio, USA), according to the manufacturer's instructions. Samples were read by spectrophotometry (450/630 nm) with the following cut-off values: negative, <0.100; undeter-

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Table 1. Comparison of children with phenylketonuria and control subjects

	Children with PKU (n = 66)		P[3]	Control subjects (n = 32)	P[4]
	Poor metabolic control (n = 27)	Good metabolic control (n = 39)			
Age (yr), mean (SD)	8.4 (7.5)	7.8 (6.2)	>0.05	9.6 (4.8)	>0.05
Sex (male/female)	18/15	17/16	>0.05	15/17	>0.05
H. pylori infection, no. (%)	14 (51.8)	4 (10.2)	<0.01	3 (9.4)	<0.05
Blood Phe concentration (μmol/L), Mean (SD)[1]	912.3 (352.2)	475.6 (320.2)	<0.05		
WISC-R	89.64 (15.3)	92.1 (14.4)	>0.05		
Socioeconomic status[2]	Lower-middle (56.5 ± 15.7)	Lower-middle (59.7 ± 17.0)	>0.05	Lower-middle (59.7 ± 16.5)	>0.05

[1]: Blood Phe concentration values measured at the time of the *H. pylori* stool antigen test application.
[2]: Evaluated according to the Hollingshead Index of Social Position.
[3]: Comparison of patients with PKU: patients with poor metabolic control versus patients with good metabolic control.
[4]: Comparison of all patients with PKU versus control subjects.
PKU, pheylketonuria; Phe, phenylalanine; WISC-R, Wechsler Intelligence Scale for Children-Revised.

mined, 0.100–0.119; and positive, ≥0.120.

The mean ages were 8.2 ± 6.7 and 9.6 ± 4.7 years, and the male/female ratios were 35/31 and 15/17 in the PKU and control groups, respectively. There was no significant difference in the age or sex between the two groups ($P > 0.05$). According to the educational and occupational level of their parents, children with PKU and those in the control group were included in the lower-middle socioeconomic status category. There was no difference in the Hollingshead Index of Social Position between the two groups ($P > 0.05$) (Table 1).

Among all patients with PKU, 27 (40.9%) had mean blood Phe concentrations >600 μmol/L (poor metabolic control). In these patients, the mean WISC-R total score was 89.64 ± 15.3. The mean WISC-R total score was 92.1 ± 14.4 in patients with PKU with good metabolic control (blood Phe concentrations <600 μmol/L).

Among the 66 children with PKU, 18 (27.3%) were diagnosed with *H. pylori* infection; however, among the 27 children with poor metabolic control, 14 were diagnosed with *H. pylori* infection (51.8%). In the control group, 3 cases had *H. pylori* infections. The frequency of *H. pylori* infection was higher in patients with PKU than in controls ($P < 0.05$, Table 1). When compared between the poor and good metabolic control groups of patients wih PKU, the frequency of *H. pylori* infection was significantly higher in the poor metabolic control group of patients with PKU ($P < 0.01$, Table 1).

Standard *H. pylori* eradication treatment consisting of lansoprazole, amoxicillin, and clarithromycin for 14 days was provided to all *H. pylori*-positive patients. Treatment efficacy was evaluated using the stool antigen test 2 months after completion of the *H. pylori* eradication treatment in all the cases.

This study demonstrated that children with PKU with poor metabolic control have a high prevalence (51.8%) of *H. pylori* infection. However, the prevalence of *H. pylori* infection was similar in children with PKU with good metabolic control and in control subjects. The difference in prevalence of *H. pylori* infection between patients with PKU with poor metabolic control and in other groups of the same socioeconomic class could be related to poor hygenic conditions of these patients due to possible neurological damage caused by high blood Phe levels.

Despite the worldwide spread of *H. pylori* infection, the exact route of transmission remains uncertain. Even though person-to-person spread is considered the most common route, confirmatory epidemiological evidence for fecal-oral and oral-oral routes of transmission is absent. Assuming that *H. pylori* colonizes only the human gastric mucosa, it has been postulated that gastro-oral transmission may occur, and this may be a possible route of spread during epidemic vomiting or regurgitation in children (22,23). This hypothesis has been supported by experimental (24–26) and clinical data (27–29). Poor personal hygiene may account for an increased risk of *H. pylori* infection in mentally disabled children, possibly following chronic gastric regurgitation or frequent vomiting by infected cohabiting children, either within or outside the family (e.g., at day care centers or kindergarten).

The first limitation of the study concerns the lack of examination of family history for *H. pylori* infection, which is mostly observed in families where feeding premasticated food to infants, spoon sharing and bed sharing are common. The urea breath test and histopathological evaluation of endoscopic biopsy specimens are more reliable tests for the diagnosis of *H. pylori* infection. The second limitation of the study is the method used for the detection of *H. pylori* infection. There have been patient compliance issues while performing the urea breath test, and there were no symptoms that required upper gastrointestinal endoscopy.

H. pylori eradication treatment in asymptomatic persons remains unclear. All the patients infected with *H. pylori* were treated. It is known that acquisition of primary *H. pylori* infection predominantly occurs in childhood and continues for life if left untreated. It has been previously proposed that treating infected children could reduce the transmission of the infection and prevent or reduce the incidence of gastric cancer in adults (30).

In conclusion, the frequency of *H. pylori* infection is higher in children with PKU with poor metabolic control than in those with good metabolic control or in healthy subjects in Turkey. This could be related to many factors such as insufficient personal hygiene, care provided by family members or institutions, and administration of special diets. Further studies are

required on this subject.

Conflict of interest None to declare.

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