pISSN: 2234-8646 eISSN: 2234-8840
http://dx.doi.org/10.5223/pghn.2016.19.2.96
Pediatr Gastroenterol Hepatol Nutr 2016 June 19(2):96-103

Review Article

PGHN

Updates on the Diagnosis of *Helicobacter pylori* Infection in Children: What Are the Differences between Adults and Children?

Hye Ran Yang

Department of Pediatrics, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Helicobacter pylori infection is acquired mainly during childhood and causes various diseases such as gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and iron deficiency anemia. Although *H. pylori* infection in children differs from adults in many ways, this is often overlooked in clinical practice. Unlike adults, nodular gastritis may be a pathognomonic endoscopic finding of childhood *H. pylori* infection. Histopathological findings of gastric tissues are also different in children due to predominance of lymphocytes and plasma cells and the formation of gastric MALT. Although endoscopy is recommended for the initial diagnosis of *H. pylori* infection, several non-invasive diagnostic tests such as the urea breath test (UBT) and the *H. pylori* stool antigen test (HpSA) are available and well validated even in children. According to recent data, both the ^{13}C-UBT and HpSA using enzyme-linked immunosorbent assay are reliable non-invasive tests to determine *H. pylori* status after eradication therapy, although children younger than 6 years are known to have high false positives. When invasive or noninvasive tests are applied to children to detect *H. pylori* infection, it should be noted that there are differences between children and adults in diagnosing *H. pylori* infection.

Key Words: *Helicobacter pylori*, Diagnosis, Endoscopy, Urea breath test, Stool antigen test, Child

INTRODUCTION

Helicobacter pylori infection is one of the most common infectious diseases in children and adults [1]. The majority of *H. pylori* infection in adults is the result of infection during childhood [2]. Because natural eradication is rare, infection is sustained a lifetime unless appropriate treatment for infection is applied [3,4]. Although *H. pylori* is mainly acquired in childhood and most of the infected individuals are initially asymptomatic, *H. pylori* infection is clinically important because it may cause a variety of gastro-

Received : June 9, 2016, Accepted : June 15, 2016

Corresponding author: Hye Ran Yang, Division of Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea. Tel: +82-31-787-7285, Fax: +82-31-787-4054, E-mail: hryang@snubh.org

intestinal diseases, including gastritis, gastric or duodenal ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer throughout the patient's lifetime [3,5]. Additionally, *H. pylori* infection is also associated with extraintestinal problems such as subnormal growth, malnutrition, and iron deficiency anemia, especially in children [5]. For these reasons, the diagnosis and the treatment of *H. pylori* infection in children are of great importance.

There is a large body of evidence indicating that *H. pylori* infection in children differs from that in adults. The differences include epidemiology, pathogenesis and host response, clinical features, related diseases, diagnosis, as well as treatment strategies. Therefore, there are limits to directly applying the findings of adult studies to childhood *H. pylori* infection, a topic with insufficient scientific literature. In the past, noninvasive diagnostic methods have been used in children despite their relatively low diagnostic accuracy since invasive investigations like endoscopy are difficult to apply to infants or young children. However, with the development of medical technology, endoscopy can be more easily implemented than before, even in infancy, and various noninvasive methods have been developed and validated for the diagnosis of *H. pylori* infection in children.

In this article, updates on the differences between children and adults in the diagnosis of *H. pylori* infection will be systematically reviewed and summarized.

INVASIVE ENDOSCOPIC DIAGNOSIS OF *H. PYLORI* INFECTION

Endoscope-based diagnosis of *H. pylori* infection

Like adults, diagnostic testing for *H. pylori* infection in children is recommended when the patients have the first-degree relatives with gastric cancer, rather than to solely determine the presence or absence of *H. pylori* infection itself [5]. However, children with refractory iron deficiency anemia without any other known cause may also be considered for *H. pylori* testing, as per the evidence-based guidelines from European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) for *H. pylori* infection in children [5].

For the initial diagnosis of the presence of *H. pylori*, rapid urease test, culture for *H. pylori*, and tissue staining using gastric tissues obtained by endoscopy of the upper gastrointestinal tract are required to confirm *H. pylori* infection in both adults and children [5,6]. With regard to histological examination, it is necessary to collect at least two tissue samples from the gastric antrum and the body, according to evidence-based guidelines for *H. pylori* infection in children [5]. The collected tissues are stained with hematoxylin-eosin to determine the presence and severity of inflammation, atrophy, and intestinal metaplasia of the gastric mucosa, on the basis of the updated Sydney classification on the histopathology of gastritis [7]. Most *H. pylori* are found in high density in the antrum. Special staining, such as Warthin-Starry silver stain, Giemsa stain, and Genta stain and immunohistochemistry, lend much help to the diagnosis of *H. pylori* infection [5,7].

When performing a rapid urease test and histopathological examination of the biopsy samples, it is recommended, if possible, that the culture for *H. pylori* be obtained at the same time. When histology and rapid urease tests are both positive or when the culture for *H. pylori* is positive, it is reasonable to diagnose *H. pylori* infection in children according to the guidelines from ESPGHAN and NASPGHAN [5]. If the result of histopathological examination and rapid urease testing do not match, diagnosis is determined by carrying additional non-invasive tests such as the urea breath test (UBT) or the *H. pylori* stool antigen (HpSA) test [5].

Differences in endoscopic findings of *H. pylori*-infected between children and adults

Endoscopic findings of gastric mucosa infected with *H. pylori* in children are distinct from those seen in adults. If *H. pylori* infection occurs during childhood, it coexists with epithelial cells during the pa-

tient's lifetime and leads to chronic gastritis. If colonization continues even in asymptomatic children, the severity of lesions that appear in the gastric mucosa can get worse [8].

If there are nodular changes in the antrum or erosions and ulcers in the duodenum on endoscope, *H. pylori* infection should be suspected in children [5]. Nodular gastritis, referred to as antral nodularity, nodular antritis, gastric lymphoid hyperplasia, follicular gastritis, or lymphofollicular gastritis, is a common endoscopic manifestation of *H. pylori* infection in children, with a gross appearance of gooseflesh-like markings on the gastric mucosa [9,10]. In chronic *H. pylori* infection of childhood, numerous small nodules are observed on the endoscope in 44-67% of *H. pylori*-infected children [9], in contrast to 0.19% of adults according to a previous study [11]. The adult study revealed that nodular gastritis was accompanied by peptic ulcers or gastric cancers in about 13% of the patients [11].

On the other hand, nodular gastritis on endoscopy of the upper gastrointestinal tract indicates that *H. pylori* will be identified in about 90% of the gastric mucosa in children. Therefore, it may be a pathognomonic endoscopic finding of childhood *H. pylori* infection with relatively high specificity and low sensitivity, for a high grade *H. pylori* colonization and chronic active gastritis [9,12]. Although the mechanisms underlying nodular gastritis in children is not clear yet, it is thought that lymphoid follicles with germinal center form nodules on gastric mucosa or that inflammatory reaction associated with *H. pylori* infection results in an exaggerated appearance of a normal gastric mucosa [13].

Differences in histopathologic findings of *H. pylori*-infected between children and adults

As in adults, diagnosis of *H. pylori* infection in children is made on the basis of histopathological examination, rapid urease test, and culture for *H. pylori* using gastric tissues [6]. Standard histopathological investigation of the gastric tissue includes observation for the presence and severity of inflammation, atrophy, and intestinal metaplasia on the basis of the updated Sydney classification [7]. In a previous study that compared histopathological parameters of *H. pylori*-associated gastritis in children with those findings in adults, the degree of chronicity, the activity of gastritis and the summed gastritis score, were not significantly different [14]. However, children with antral nodularity had significantly higher histological scores, suggesting that antral nodularity may be the important sign of higher grade gastritis in young children [14]. In another study by Gallo et al. [15], histological findings of gastric mucosa were also compared between children and adults, and higher severity of gastritis was significantly associated with higher density of *H. pylori* and *cag*A-positive strains.

Main histological features of acute gastritis associated with *H. pylori* infection are surface epithelial degeneration and polymorphonuclear cell infiltration [16]. Differences in immune response to *H. pylori* infection between children and adults are responsible for the differences in the histological findings of chronic gastritis associated with childhood *H. pylori* infection between children and adults. Acute active inflammation (infiltration of neutrophils) is less prominent in children compared to adults, while chronic inflammation (infiltration of lymphocytes and plasma cells) is more prominent [17-19]. Furthermore, unlike adults, there is a significant correlation between endoscopic findings of nodular gastritis and histological findings demonstrating enlargement of lymph follicles in pediatric patients with *H. pylori* infection [10].

In contrast to adults, atrophy and intestinal metaplasia are rare, while gastric cancer and MALT lymphoma are known to be extremely rare in children [20]. However, a study reported a significantly higher prevalence of gastric atrophy and low-grade intestinal metaplasia in *H. pylori*-infected children compared to *H. pylori*-uninfected children [21]. Since both gastric atrophy and intestinal metaplasia are considered as premalignant lesions [22], it would be useful to apply an updated Sydney classification to all children suspected of *H. pylori* infection and to eradicate *H. pylori* in the early stages of infection [21].

Although MALT lymphoma is a rare disease in childhood, a previous study reported that histopathological findings of nodular gastritis caused by *H. pylori* infection were similar to those of early stage gastric MALT lymphoma, suggesting that these changes may indicate a high risk for gastric MALT lymphoma [23]. Our recent study also revealed that nodular gastritis on endoscopy indicates gastric MALT on histology of gastric tissues in children with *H. pylori* infection and that the degree of antral nodularity, density of *H. pylori*, neutrophil activity, and gastritis score correlated with MALT grades, producing a recommendation for gastric MALT evaluation in cases of *H. pylori*–infected children that manifest severe nodular gastritis on endoscopy [10].

NON-INVASIVE DIAGNOSIS OF *H. PYLORI* INFECTION

As gastric malignancy is rare in childhood, the implementation of upper gastrointestinal endoscopy is often not necessary. In addition, endoscopy is a relatively invasive method that may cause complications or inflict psychological burden on children and their parents. Thus, there are limitations to using endoscopy on children, especially after the eradication of *H. pylori*. For this reason, the need for non-invasive diagnostic method with high diagnostic accuracy has been raised. Some non-invasive methods to diagnose *H. pylori* infection without endoscopy have been developed and these include the UBT, HpSA test, and *H. pylori* antibody tests in serum, urine, or saliva [5,24].

In the past, *H. pylori* immunoglobulin G (IgG) antibody test was commonly used in clinical practice and for epidemiologic studies. However, high rate of false negative results and low diagnostic accuracy has greatly reduced the value of serology. Meanwhile, non-invasive ^{13}C- UBT and HpSA test have been well validated and used primarily in children [5,24].

Differences in the urea breath test between children and adults

UBT is a good example of a non-invasive diagnostic test that can be performed safely and easily, for it does not require an experienced examiner and costs less when compared to endoscopy. It is known as a convenient and accurate test for confirming the presence of *H. pylori* infection a non-invasive manner in both adults and children. Diagnostic accuracy of the UBT is high, with a sensitivity and specificity of about 95%, even in children, according to a recent meta-analysis [25].

In particular, the sensitivity and the specificity of the UBT reach almost 100% after the eradication therapy of *H. pylori* in children. Hence the guidelines from ESPGHAN and NASPGHAN for *H. pylori* infection in children indicated ^{13}C-UBT as the most reliable noninvasive method in lieu of endoscopy to confirm the eradication of *H. pylori* in children [5,24].

However, in children less than 6 years of age, clinical application of UBT is somewhat limited because of relatively low specificity and high rate of false positive results compared to adults and older children [25-27]. False positive was 8.3% in children younger than 6 years of age compared to 0.85% in children older than 6 years according to our previous study [27]. There are several possible explanations for high false positive results in children younger than 6 years [26-28]. UBT measures the isotopic ratio of $^{13}CO_2/^{12}CO_2$, and endogenous CO_2 production differs according to age, gender, body weight and height. Therefore, the ingestion of an identical amount of ^{13}C-urea in both adults and children may increase the isotopic ratio of $^{13}CO_2/^{12}CO_2$ in young children compared to adults. In previous studies, including ours, urea hydrolysis rate corrected for the effects of age, weight and height, was suggested as providing a better result than a conventional cutoffs using a delta over baseline [28,29]. Another explanation for high false positive results is the presence of urease-producing microorganisms such as *Streptococcus salivarius*, *Proteus mirabilis*, and *Klebsiella pneumoniae* that live in the oral cavity, as young children tend to retain ^{13}C-urea in the mouth [30]. This was supported by a study that compared direct administration of ^{13}C-urea through nasogastric or gastrostomy tubes and administration by oral ingestion [31]. There are additional ways to

reduce the false positive results in young children. Young children are encouraged to rinse their oral cavity with fluids after ingesting ^{13}C-urea to reduce degradation by oral flora [5]. It might be useful to apply the optimal cutoff of 7.0‰ to children less than 6 years of age, whereas conventional cutoff 2.4-4.0‰ is applied to adults and children aged 6 years or older [27].

Differences in *H. pylori* stool antigen test testing between children and adults

HpSA using enzyme-linked immunosorbent assay (ELISA) methods is also a non-invasive method to detect *H. pylori* infection with high diagnostic accuracy for adults and children of any ages [32]. It appears to be a useful method for follow-up after eradication therapy [33]. Accordingly, guidelines from ESPGHAN and NASPGHAN for *H. pylori* infection in children recently recommended the HpSA test using validated ELISA as a reliable test to determine whether *H. pylori* has been eradicated [5]. According to these guidelines, HpSA test is regarded as more convenient in children than the UBT [5]. In actual fact, it can be easily performed on infants or toddlers merely by collecting stool samples, and there is an added advantage of not requiring expensive equipment such as mass spectrophotometer, as for the UBT.

The conventional HpSA test using ELISA detects *H. pylori* antigen from the feces using polyclonal antibody or monoclonal antibody [34-38], and there is a rapid stool antigen test using immunochromatography also available in both adults and children [39-42].

Diagnostic accuracy of HpSA test using ELISA for the initial diagnosis of *H. pylori* infection in children was high with a sensitivity of 87-100% and specificity of 82-100% as in adults [35,36]. Recent two meta-analyses on HpSA tests using monoclonal antibody revealed a pooled sensitivity of 96.2-97% and specificity of 94.7-97% in children, whereas polyclonal HpSA tests revealed a lower diagnostic accuracy with a sensitivity of 88-92% and specificity of 93% [37,38].

After the eradication therapy of *H. pylori* infection, the sensitivity of HpSA decreased from a mean sensitivity of 92.6% before treatment to 80.9% after treatment in children, whereas the sensitivity of HpSA was still high with a mean specificity of 97.2% after treatment according to recent meta-analysis [38].

Rapid stool antigen test using monoclonal antibody is a useful office-based test that can be easily available anytime and anywhere. However, diagnostic accuracy of this one-step HpSA test was relatively lower with a sensitivity of 86-95% and specificity of 88-100% in children, when compared to those by conventional HpSA using ELISA method [37-42]. Recent two meta-analyses reported a sensitivity of 88.0-88.1% and specificity of 93-94.2% for rapid monoclonal HpSA in children [37,38].

Therefore, HpSA using ELISA with monoclonal antibody is the most accurate non-invasive diagnostic method that can replace UBT in children [5].

H. pylori antibody tests in serum, urine, or saliva

IgM may rise during the early stages of *H. pylori* infection, but in the cases of chronic infection, IgA and IgG antibodies are detected in blood, urine, and saliva. Tests to detect antibodies using ELISA have been used mostly for epidemiological studies and research purposes [24], and many tests are available commercially.

The serum *H. pylori* IgG antibody test may be a useful tool for screening *H. pylori* infection in adults, but a low sensitivity of 79.2% with a high specificity of 92.4% were reported in young children due to low antibody titers as a result of relatively short infection period and immature immune response to *H. pylori* in childhood [43-46]. For this reason, the serodiagnosis of *H. pylori* infection may be inappropriate in young children. Additionally, serum *H. pylori* IgG antibody test is also inappropriate to monitor *H. pylori* status after treatment because elevated serum titers of *H. pylori* IgG antibody persist for a long time [47].

Therefore, as suggested in the guidelines from ESPGHAN and NASPGHAN for *H. pylori* infection in children, antibody tests for *H. pylori* in serum, urine,

or saliva are not reliable for use in children [5].

CONCLUSION

Diagnosis of *H. pylori* infection in children differs from that of adults in many aspects. Unlike adults, nodular gastritis is relatively common and may be indicative of *H. pylori* infection on endoscopy in children. Moreover, histologic findings tend to show predominance of lymphocytes and the formation of gastric MALT in children. Non-invasive tests such as the UBT and HpSA are preferred in the pediatric population due to excellent diagnostic accuracy before and after *H. pylori* eradication therapy. As children younger than 6 years tend to have high false positive rates in applying the UBT, HpSA testing is more suitable in this age group.

In conclusion, when invasive or noninvasive tests are applied to children to detect *H. pylori* infection, clinicians should remember that there are clear differences between children and adults that require appropriate changes to the diagnostic approach.

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