EXTRAGASTRIC AND ORODENTAL MANIFESTATIONS IN PEDIATRIC INFECTION WITH *HELIcobacter pylori*. A REVIEW

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Abstract

*Helicobacter pylori* is a worldwide spread infection mostly manifested in childhood. Many - both invasive and non-invasive diagnostic tests - are now available. The colonisation effect of gastric mucosa and its consequences are well known and studied. *H. pylori* can also induce extra-gastric manifestations, like iron-deficiency anemia. The role of oral cavity colonisation is not clearly defined, several studies stating that the oral cavity represents a reservoir for *H. pylori*. The presence of this rod in the dental plaque may lead to periodontitis, dental caries, dental calculus and tooth loos. Dental treatment associated with eradication therapy decreases the prevalence of oral *H. pylori* and improves the eradication rate of gastric *H. pylori*. Dental treatment in *H. pylori* infection management should be taken into consideration, especially in children and teens.

**Keywords**: children, *Helicobacter pylori*, orodental diseases

1. INTRODUCTION

*Helicobacter pylori* is a gram-negative microaerophilic rod which colonizes the gastric mucosa in 50% of the population worldwide. The incidence of the infection is associated mostly with childhood, as well as with the socio-economic and sanitary conditions. *H. pylori* infection plays a major role in antral and corporeal gastritis, peptic ulcer disease; a causal relation between *H. pylori* infection and the risk of gastric malignancies, including cancer and gastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, has been supported by epidemiological and interventional studies [1]. Although *H. pylori*-associated gastric cancer has not been reported in children, MALT lymphomas have been described in a few *H. pylori*-infected pediatric patients. In children, it may also be associated with iron-deficiency anemia [2]. In the developed countries, less than 10% of children younger than 12 years are infected; however, seropositivity increases with age at a rate of 0.3-1% per year. Studies of seropositivity in adults in the developed countries revealed prevalences of 30-50%. The annual incidence is of 3-10% in the population of the developed countries, compared with 0.5% in the developed countries. Worldwide, more than one billion people is estimated to be infected with *H. pylori* [3].

2. DIAGNOSTIC METHODS

In *H. pylori*, the “gold standard” diagnostic test is considered as a histological examination. Many diagnosis methods are available, each one with its advantages and disadvantages. A reference diagnostic method should fulfill criteria such as sensitivity, specificity, availability, cost, rapidity of the results and reproducibility. Diagnostic tests can be classified as invasive (histology, culture, rapid urease test and molecular methods) and non-invasive methods (urea breath test, stool antigen test, antibody-based tests).

An invasive test requires a gastric biopsy during endoscopy. In histology, several stains, like hematoxylin-eosin, Giemsa, Warthine-Starry, acridine orange, Genta, Dieterle, toluidine blue or McMullen, are used. A novel method used on histological samples is Fluorescent in situ hybridization (FISH), which detects a specific bacterial feature (such as antibiotic resistance) and a virulence factor in a short period of time (3 hr), however it is expensive and laborious. The sensitivity and specificity of histology is influenced by the biopsy samples (site, size, and
number), prior to antibiotherapy and proton-pump inhibitors (PPI) [4]. A H. pylori culture was realized from gastric biopsy specimens having sensitivity over 90% and a specificity of 100%. Culture tests are challenging, because bacteria require a special growth medium and atmosphere (microaerophilic environment). This method can be used to isolate H. pylori from extra-digestive sites and to study its presence in saliva and dental plaque [5]. It is a well-known fact that H. pylori produces urease. The rapid urease test (RUT) is performed from a gastric biopsy specimen placed in a special medium with a pH index. RUT sensitivity is between 85-95% and specificity between 95-100%, and the result can be provided within 1-24 hr. A disadvantage of this method is that sensitivity is influenced by bacterial density (minimum 10⁴ organisms per biopsy specimen) and form (spiral or coccoid), recent intake of antibiotics, PPIs, bismuth compounds, and also in patients with achlorhydria [6]. RUT is an inexpensive method, widely available, providing a rapid diagnostic. Molecular methods are more and more often used in H. pylori diagnosis, because they assure an accurate and sensitive detection, as well as information on antibiotic resistance, bacterial quantification and virulence. The polymerase chain reaction (PCR) can be performed from different biological samples, such as gastric biopsy specimens, stool, saliva, dental plaque and oral ulcerations. The PCR technology is a rapid developing field, with many modifications, from increased specificity and sensitivity to amplification methods, DNA-enzyme immunoassay and usage of reverse transcription to real-time PCR in quantification of genomic DNA. This method is considered to be more rapid and sensitive than culture techniques. In future, the PCR technique may be proposed as a gold standard, due to its complex role in diagnosis, bacterial genotype identification and eradication control [7].

The urea breath test (UBT) is non-invasive, easy and rapid to perform, with specificity and sensitivity over 90%. In pediatric population, UBT has a heterogeneous accuracy, with specificity and sensitivity ranging between 75-100%; factors like urease activity from the oral bacterial flora, tracer dose, pretest meal, cut-off value, were incriminated [8]. Stool antigen (SAT) is a non-invasive, safe and inexpensive test, especially useful in children. Sensitivity and specificity vary when the test in performed as a diagnostic method or eradication control. Newer methods, like the monoclonal enzyme-linked immunosorbent assay, are considered the most efficient non-invasive diagnostic tests, independent on children’s age [9]. To identify antibodies against H. pylori, several tests are available, the enzyme immunoassay (EIA) method being the most frequently used. Some important factors - like prevalence, geographic variations, host immune response, antigenic variable strains - should be taken into account when evaluating the quality of the serology test. This test is recommended to patients with gastric atrophy, bleeding ulcer or recent intake of antibiotics and PPIs [10].

3. EXTRA-GASTRIC MANIFESTATION

Helicobacter pylori is considered to be the main etiological factor for peptic ulcer disease and gastritis. The potential role of H. pylori infection in other extra-gastric pathologies has been extensively studied. Most of these studies start from the assumption that local inflammation has systemic effects, being a prolonged process which leads to chronic inflammatory and immune response with the potential to induce local lesions positioned at some distance from the primary infection site [11]. The proven and widely accepted role of H. pylori in extra-intestinal diseases is in unexplained iron deficiency anemia (IDA) and idiopathic thrombocytopenic purpura (ITP). In iron deficiency anemia, it is recommended to consider H. pylori infection as the etiology, after excluding a gastrointestinal bleeding, celiac disease, inflammatory bowel disease and cases of refractory to iron supplementation anemia or frequent relapses. Several mechanisms are proposed to explain the relationship between IDA and H. pylori. In some studies performed on children infected with H. pylori and hypochlorhydria, laboratory data showed decreased serum iron and transferrin saturation [2]. It is widely accepted that, in idiopathic thrombocytopenic purpura, eradication of H.
 pylori infection may lead to incomplete or complete remission. Recent studies suggest that H. pylori may play a role in pathogenesis of ITP, as the antibodies to H. pylori components cross-react with the antigens found on platelets surface. Further studies are required to confirm these hypotheses [12]. The effect of H. pylori infection on growth is controversial. The infection may interfere with the linear growth through altering micronutrients absorption, appetite and metabolism. Some studies suggest that a predisposing factor to malnutrition and growth deficiency might be H. pylori colonization in early infancy [13]. Some studies reported a negative association between asthma and atopic diseases. H. pylori might act as a protective factor against developing asthma in children, yet further studies are required [14]. In chronic urticaria, it was concluded that eradication of H. pylori was associated with a remission of symptoms, however other investigations led to opposite results [15].

Some studies try to establish the risk of infection in families with an infected member. In couples, the risk tends to be higher in stable and long-term relationships. In most families, a H. pylori-positive parent represents an increased risk for children to be infected. A factor for intrafamilial spread may be the presence of H. pylori in the subgingival dental plaque of children and of their families, possibly acting as a reservoir. An efficient oral hygiene and a healthy periodontal status could reduce this transmission. In terms of occupational exposure to H. pylori, some authors tried to assess the risk in medical professions. Gastroenterologists have a higher prevalence of infection, superior to that found in dentists and iatrogenic transmission during endoscopy or dental maneuvers, but both these categories are at high risk [16].

4. ORODENTAL MANIFESTATION

H. pylori gastric infection is treated with systemic antibiotics, however, in some cases, a persistent infection was observed. This phenomenon led to the conclusion that, besides the gastric reservoir, there is another way for bacteria survival and their capacity to reinfect a host. One of the transmission paths is considered to be the oral-oral way. Recent studies concluded that the oral cavity may represent a reservoir for H. pylori as, inside it, the bacteria are covered by a biofilm, which acts like a shell and provides protection against systemic eradication therapy. The bacterium was detected in the dental plaque, periodontal pockets, saliva, dorsum mucosa of the tongue and surface of oral ulcerations or oral neoplasia. The methods used to diagnose H. pylori in the oral cavity are culture and PCR. Due to the large number of oral germs, the bacterial culture leads to a high false negative rate. PCR has a high sensitivity and specificity, but it cannot be used to monitor treatment efficiency, because this method detects H. pylori DNA even if the bacterium is dead. A new method, namely the saliva H. pylori antigen test (HPS), may be useful in this respect. HPS is a rapid (from 5 to 30 min) immuno-chromatographic assay based on a double antibody sandwich (flagellin and urease) used to detect H. pylori in human saliva. There was no interference or cross-reactivity with the other bacteria in the oral cavity. In children, HPS was not validated [17,18].

In the gastroesophageal reflux disease (GERD), the role of H. pylori infection is not clearly defined; some studies indicate a possible protective role, on the other hand some publications consider the presence of the bacteria as a risk factor. The effects of exposing the oral cavity to the acid content of the stomach are various, with unspecific symptoms, such as a burning sensation or tooth sensitivity. However, dental erosions, with the progressive damaging of the dental enamel and of tooth composition are common manifestations of GERD, so that the association with H. pylori should be considered [19].

In the dental plaque, H. pylori was first isolated in 1989, in Canada, by Krajden; since then many studies tried to establish the relationship between the presence of bacteria and the transmission routes, treatment failure and the long-term consequences. Most studies consider that the dental plaque is the first extra-gastric reservoir for H. pylori and a source of reinfection, and that a triple therapy has limited efficacy to eradicate the bacteria from the oral cavity. A specific distribution pattern for H. pylori
in the oral cavity was observed, with a higher prevalence in plaque samples taken from molars, than in those from premolars or incisors. Some authors suggested that periodontitis, associated with deep periodontal pockets (over 5 mm) induced by poor periodontal health, may represent an increased risk factor for *H. pylori* infection [20]. Oral sub-mucous fibrosis (OSF) is consistently associated with mucosal inflammation of the upper aero-digestive tract, mainly manifested as stomatitis and glossitis. The presence of bacteria in the dental plaque is associated with a higher risk of mucosal inflammation and periodontal disease. The detection rate of *H. pylori* in saliva is lower than in the dental plaque. Recent studies suggest that saliva may be a possible source of infection and it is more likely to contain the entire DNA from every bacterial strain. Positive *H. pylori* saliva is strongly associated with the appearance and development of oral diseases. [21]

Studies on children with gastric infection caused by *H. pylori* have shown that the prevalence of caries is highly associated with the presence of bacteria. Some authors suggested that positive *H. pylori* in the dental plaque, associated or not with gastric infection, is a risk factor for dental caries, a possible explication being that pathogenic microflora conducts to depolymerization and demineralization of tooth enamel. In children, *H. pylori* has been detected by PCR in the dental plaque, and root canal samples and colonies have grown from root canals, thus showing that infected teeth are a source of *H. pylori*. PCR was also used to determine *H. pylori* distribution in oral specimens, sore pulp tissues and saliva samples collected from children and adolescents; the test was positive in inflammed pulp but not in saliva specimens, suggesting that an infected root canal may represent a reservoir for *H. pylori*. The DNA-DNA hybridization method was applied to determine the root canal microbiota profile in endodontic infections, like apical periodontitis, a higher count of gram-negative including *Helicobacter pylori* being detected. Some studies indicate that as much as 100% of the children with *H. pylori* digestive tract infection also presented oral infestation, on long term this situation evolving towards a chronic inflammatory process [22]. Some authors concluded that, during the orthodontic treatment, the prevalence of bacteria in the dental plaque decreased. In patients with amalgam dental fillings, a lower frequency of *H. pylori* colonization has been observed, although the eradication rates decreased. The presence of bacteria was strongly related with dental calculus and tooth los. The oral presence of the bacterium may be an obstacle in curative treatments [23]. Studies on groups of adolescents have shown that the presence of the bacterium in the dental plaque is not necessarily dependent upon the level of hygiene. Samples from adolescents with poor oral hygiene gave almost the same results as the studies on groups of patients with good oral hygiene [24].

Aphthous stomatitis, or canker sores, is an inflammatory disease of the oral cavity characterized by the presence of erosions and ulcerations, having a recurrent character. Canker sores have a high prevalence, but their pathogenesis is still unclear. There are studies suggesting that therapy eradication of *H. pylori* infection may reduce the risk of occurrence and recurrence of this condition [25].

In a recent study, a strong association has been established between the triple therapy efficiency and periodontal treatment. In patients with gastric and positive oral *H. pylori*, besides the triple therapy periodontal treatment, mouth-rinses were studied. Periodontal treatment consists in removal of the dental plaque and calculi and eradication of the periodontal pockets; as mouth-rinse, a product containing a glucose chlorhexidine solution (0.15%) was used. The study proved that the association between the medical and dental treatment reduced the prevalence of oral *H. pylori* and improved the eradication rate of gastric *H. pylori* [26]. Some authors proposed some simple recommendations in the dental treatment of patients infected with *H. pylori*, such as professional dental plaque removal (in the beginning of the eradication treatment, a week after and at the end of the treatment), changing of the tooth brush, a good daily oral hygiene, such as brushing with toothpaste, cleaning of all surfaces and mouth wash twice a day with a disinfection solution, cleaning of the tongue and hard palate with a
special tooth brush, and cleaning of the interdental spaces [27].

5. CONCLUSIONS

*Helicobacter pylori* is a widely-spread infection with multiple gastric and extra-gastric effects. The oral cavity may be considered a reservoir for bacteria, consequently, special attention should be given to the combined medical and dental treatment, as a manner of increasing eradication and long-term prognosis. Further research about the dental treatment and its role in multidisciplinary clinical management of *H. pylori* infection is required, along with validation of non-invasive tests for bacterial detection in children’s oral cavity.

References


