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Review Article

Intrafamilial Helicobacter Pylori Transmission in Children

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Abstract

H. Pylori are a major cause of peptic ulcer disease. H. Pylori have also been related to other diseases such as non ulcer dyspepsia, vitamin B12 deficiency, iron deficiency anemia or idiopathic thrombocytopenic purpura disease; it has been observed to be involved in most of the gastric cancer cases as well. Incidence and prevalence of the infection depends on many factors related to both the host and to the environment, i.e.: age, gender, ethnicity, geographical situation and socioeconomic status. Children with gastrointestinal symptoms must undergo control of the infection. The presence of infection justifies an upper endoscopy in order to detect H. Pylori in culture and in histological examination. Non-invasive diagnostic tests, such as the urease test, have high detection accuracy. Treatment was applied to children who have first-degree relatives with a history of gastric cancer and also to children with refractory iron-deficiency anemia after other causes have been excluded. Treatment consisted of a combination of a Proton-pump inhibitor (PPI) along with two antibiotics: amoxicillin combined either with clarithromycin or metronidazole. However, during the last years resistance of certain strains has increased. Intra-familial transmission is the predominant route of transmission for H. Pylori, especially during childhood. The mother is considered an important route of transmission due to their intimate relation with children during birth, breastfeeding and education concerning hygienic habits. Finally, the number of siblings also plays an important role, with older siblings being the source of H. Pylori transmission to the younger ones.

Keywords: *Helicobacter pylori; Intrafamilial transmission and Childhood*

Introduction

H. pylori is discovered [1] by Dr. Barry Marshall and Dr. Robin Warren in Australia, who examined the antral mucosa biopsies of patients with chronic gastritis, duodenal ulcers, or gastric ulcers and detected spiral or curved bacilli. Marshall and Robin found [2] that treatment with the ulcer healing agent bismuth alone was not sufficient to eliminate the infection and gastritis in long-term. Only when bismuth was combined with the antibiotics amoxicillin or tinidazole was long-term elimination of both the bacteria and the gastritis possible. Antimicrobial treatment can be also useful in some other diseases in which H. pylori is involved such as gastric lymphomas and possibly early gastric cancer resulting in their regression.

H. pylori is a major cause of peptic ulcer disease [3,4]. It has been linked to other diseases, such as non-ulcer dyspepsia, vitamin B12 deficiency, iron-deficiency anemia and immune thrombocytopenic purpura.

H. pylori is also involved in the majority of gastric cancer cases [5] and it has been classified from 1994 by the World Health Organization (WHO) as a class I carcinogen [6]. The infection by H. pylori is responsible for about 75% of all non-cardia gastric cancers (cancers that can be found in various other areas of the stomach except the top portion of the stomach close to the junction of the esophagus) and 63.4% of all stomach cancers worldwide [7].

Several virulence factors help the bacterium H. pylori to establish life-long infections. Such factors also modulate the host immune response and cellular processes in such a way to benefit the bacterium. Among the virulence factors are adhesion molecules that allow the bacterium to attach to the epithelial cells, factors that allow the bacterium to evade host defense (flagella and motility, urease system, induction of hypochlorhydria), factors that injure the tissue (heat shock proteins A and B, vacuolating cytotoxin A, neutrophil activating protein of Hp, and cytotoxinassociated gene A) and various other factors that activate the innate immune response, offer resistance to phagocytosis, modulate the activity of dendritic and regulatory T cells, and produce proinflammatory cytokines [8,9,10]. The pathogenicity of the infection [11] is complicated because it depends on the interaction between genetic factors of the H. pylori and factors that are specific to host and environment.

H. pylori is a bacterium with remarkable diversity which makes it capable to optimize the use of the resources in a variety of environmental microniches. It can avoid various constraints of the host, such as the host immunity or due to developmental changes the variable acidity and nutrients availability of gastric epithelium. The infection therefore persists, if untreated, for life despite the changes in the host microenvironment that take place during the host development and growth [12]. The genetic diversity of H. pylori is further enhanced with the uptake of DNA that is released by other H. pylori strains residing in the same microenvironment.

According to the data of epidemiological studies, H. pylori infection is very common. The incidence and prevalence of H. pylori infection depends on many factors, either pertaining to the host or environment, such as age, ethnicity, gender, geography and socioeconomic status [13].

According to WHO, the global prevalence of H. pylori infection is more than 50%. In developed countries the prevalence is generally under 40%. It varies significantly between countries but it also varies in different areas within the same country. In general, the H. pylori seropositivity rates increase with age (cohort phenomenon). However in developing countries, which have higher prevalence, the H. pylori infection is much more prevalent at younger ages than in developed countries. More than 80% of the population of young ages is infected some developing countries, such as Bangladesh, India and Libya, [13,14].

Eusebi ., *et al*. who performed a recent search on Medline and PubMed databases on the epidemiology of H. pylori for the period of April 2013-March 2014, have found that the prevalence of H. pylori remains high in many countries [15]. It is usually higher than 50% in south and east Europe, South America, and Asia. In north European and North American countries about one-third of adults are infected.

H. Pylori Infection in Children

Epidemiology

In both developing and developed countries H. pylori is mostly acquired in childhood and almost always before the age of 10 years, [16]. Prevalences in children vary among countries. It is for example 6% in Texas, USA, 13% in Sardinia, Italy, 30.9% in Nigeria, 38% in Mexico City, 30.8% in Cuban symptomatic children, and 78.1% in Sherpa residents in Nepal, as has been reported in 2013 [17].

The low socioeconomic level in childhood seems to be the most important risk factor for H. pylori infection. In populations with higher socioeconomic status the prevalence is low because of better environmental conditions, and it is higher in developing countries where there are poor hygiene and water supply conditions with a high number of persons living in the household [18]. The higher prevalence in developing countries is also reflected in the differences between natives and immigrants living in developed countries. For example, in a study of Belgian asymptomatic children and young adults [19], it was found that the country of origin is a significant risk factor. Those born in high prevalence countries from foreign parents had a high prevalence (60%) compared to those born in Begium (3.2 %). The importance of living conditions has been shown in a large cohort study in the Czech Republic [20]. This study found that independent of gender, H. pylori infection is only 7.1%. The authors conducted a cross-sectional, population-based study in 1545 asymptomatic Czech children (ethnically but not socioeconomically homogenous), aged 0-15 years, using monoclonal stool antigen. The low prevalence was attributed by the authors to the improvements in living standards and housing conditions as well as to the decreasing family size. Lower

prevalence was also reported for Japanese children. H. pylori prevalence in these children is approximately 1.8%, much lower than in Japanese adults aged 20-29 in which is 23%, [21,22] and new infection in children is rare [23].

Contrary to the situation in Japan, a very high prevalence was found in Portuguese children [24]. It was 66.2% among 13-year-old children from Porto, a prevalence which is higher than in most European countries and even higher than in many South American, African and Asian settings, where it ranges from less than 10% to 64%. Because of the birth cohort phenomenon, being that aged people had a higher incidence of infection in the past because of poor hygienic conditions, the prevalence increases with the age in both developed and developing countries and it is therefore higher in adults than in children [25,26].

There are however some cases that do not exhibit the generally observed relation of H. pylori infection and socioeconomic status. For example, a study in 390 symptomatic adults and children in the Republic of Georgia who underwent diagnostic endoscopy [27] showed that the commonly mentioned in literature risk factors, such as household crowding, low socioeconomic status and poor sanitation, were not associated with the infection, with the factors however in this case being underdermined.

Diseases Caused by H. Pylori in Children

Ulcers

Some infected children develop gastrointestinal diseases, such as gastritis, peptic ulcers, gastric malignancies and functional dyspepsia while many other have no consequences for many decades [28]. According to the results of 45 studies [29] contacted in the period 1983-1994 in children of age 0-18 years, the prevalence of H pylori infection in children with duodenal ulcers was high (range, 33%-100%; median, 92%) compared with children with gastric ulcers (range, 11%-75%; median, 25%). In another study H. pylori infection was found to be high in children with duodenal ulcer (62%) but only 20% in children with gastric ulcers [30].

However, a multicenter European prospective study with children undergoing upper gastrointestinal endoscopy which had been performed during 1-month simultaneously in 19 centers among 14 European countries, showed low implication of H. pylori in both gastric and duodenal ulcers [31]. From the other side the incidence of peptic ulcer in children [32] varies among countries from 1.8% to 19.5% as reviewed in several studies. Contrary to the study by Kalach., *et al*. [31] mentioned above, in a recent study [33], a strong association between H. pylori and duodenal ulcers in children in Chile was found.

Extragasric Disorders

H.pylori infection was found to be correlated with several extraintestinal disorders [28].

Some epidemiologic studies in children and adolescents showed an association between H. pylori infection and increased prevalence of Iron Deficiency, ID [34,35,36]. However other studies have not found such an association [37-42]. In a prospective study of 123 children [43], it was found that serum iron and transferrin saturation levels were significantly lower in H. pylori-infected children with hypochlorhydria than in infected children without hypochlorhydria. The conclution from the above study was that a combination of H pylori infection and/or inflammation, and hypochlorhydria, is probably related with the aetiology of ID.

Data also shows that H. pylori may be involved in the pathogenesis of Idiopathic Thrombocytopenic Purpura (ITP) in children. According to the Maastricht III consensus conference, ITP is one of the two extraintestinal diseases for which H. pylori infection detection and eradication is indicated [44]. This consideration however is opinion-based rather than evidence-based.

An association has been reported in literature between Henoch-Schonlein Purpura (HSP) a leukocytoclastic vasculitis of small vessels which affects many organs, and H. pylori infection [45].

Recent meta-analyses have showed an inverse relationship between H. pylori infection and childhood asthma [46,47]. However, large-scale multicenter studies have been recommended to clarify the relation between H. pylori and allergic disorders.

Insufficient evidence exists at the moment for the children's growth benefit from the treatment of H. pylori infection. Though it is assumed that the damages in the gastric acid barrier caused by H. pylori, may lead to chronic diarrhea and consequently malnutrition [48] because of insufficient nutrient absorption, direct nutrient losses, or increased metabolic requirements, contradictory results have been published for the association of H. pylori infection and children´s growth. For example some studies suggest [49,50] a negative effect of H. pylori infection on the growth of children, while Sood., *et al*. [51] found no association.

H. pylori-infected children may have decreased appetite because of the low plasma ghrelin levels, a hormone that regulates food intake and has strong growth hormone-releasing activity [52].

Little evidence also exists for the association of H. pylori infection with Mucosa-Associated Lymphoid Tissue, MALT, in childhood.

Diagnosis

According to ESPGHAN/NASPGHAN recommendations, the testing of the H. pylori infection in children with gastrointestinal symptoms is required if thre is a suspected disease which is serious enough to justify upper endoscopy [53]. The testing could be also recommended in children who have first-degree relatives with gastric cancer as well as in children with refractory iron deficiency anemia in the case that other causes for the anemia have been excluded.

The current standard for H. pylori diagnosis in symptomatic children is upper intestinal endoscopy and biopsies for histology and culture or rapid urease test (RUT). After treatment non-invasive tests are performed to confirm the eradication. Non-invasive tests cannot distinguish whether or not the disease is caused by H. pylori infection and therefore are not recommended in symptomatic children [54]. Further data concerning the health risks for H. pylori-infected children or the availability of vaccination or future different treatment options are required for the use of non-invasive tests [54].

The detection of H. pylori infection in children has been done using several types of invasive and non-invasive diagnostic tests, such as identification of H. pylori in culture, histological examination, and the rapid urease test (RUT), urea breath test (UBT), antibody-based detection test in different fluids and antigen detection in stool [55]. Among the used tests, the antibody-based tests can be distinguished as having the advantages of simplicity, low cost, speed, and minimal patient discomfort.

A systematic review and meta-analysis of studies published in PubMed, EMBASE, and LILACS databases by Lee., *et al*. found that the use of ELISA monoclonal antibodies for the detection of H. pylori antigen in stools is an efficient test for diagnosis in children [56]. According to the authors, the ELISA monoclonal antibodies test had the best performance (sensitivity and specificity of 97%) in comparison with other tests for antigen-detection. The ELISA polyclonal antibodies test had lower sensitivity (92%) and specificity (93%). The one-step monoclonal antibody tests had even lower sensitivity (88%) with the same specificity as the ELISA polyclonal antibodies test. The preferred detection method for developing countries that have limited laboratory resources for more elaborated tests are the ELISA because it is simple, fast and of low cost.

The accuracy of three invasive diagnostic tests (rapid urease test, histology, and culture) and one non-invasive test (IgG serology) have been recently compared in a prospective study [57]. It was found that the association of urease test and histology with serology offers higher accuracy.

The efficiency of the H. pylori stool antigen test (SAT) for the diagnosis of the infection in children using ELISA monoclonal antibodies was also shown in a recent meta-analysis of forty-five published studies [58] that included 5931 patients. This study has also shown that the available one-step and polyclonal SAT tests are unreliable.

A comparison of the urea breath tests and the stool antigen tests concluded that the latter are the most effective tests for children in populations with both high and low prevalence of H. pylori infection [59].

There are however several serologic tests with low sensitivity, despite high specificity. The low sensitivity of these tests in children was attributed by Ueda ., *et al*. to the diferent production of antibodies to H. pylori in children than this in adults because of immature immunologic response in children [60]. Another explanation for the low sensitivity is the influences on the production of antibodies in response to H. pylori infection caused by the transfer of maternal IgG antibodies to children. It is known that seropositive mothers transfer maternal H. pylori IgG transplacentally to their infants that disappear by 6 months of age in almost all cases [61].

Treatment

Guidelines for the management of H. pylori infection in children in Europe and North America were published in 2011 by the European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN) [53]. The guidelines have concluded with the review of 738 articles that appeared in literature from January 2000 to December 2009. According to these the"test and treat" approach is not recommended for pediatric patients. It is exceptionally applied under specific circumstances such as for children who have first-degree relatives with a history of gastric cancer or for children with refractory iron-deficiency anemia for which other causes have been excluded. Additionally, testing for H. pylori is not recommended for children with abdominal pain.

Therapies applied to adults seem to not be suitable for children [62]. The recommended first-line therapy for children is a combination of a proton pump inhibitor (PPI) and two antibiotics (clarithromycin plus amoxicillin or metronidazole). Bismuth-based triple therapy or sequential therapy was recommended as alternate first-line regimens and quadruple therapy with PPI, metronidazole, amoxicillin, and bismuth, as second line therapy or salvage therapy [53].

The sequential therapy is even more efficacious in children than the standard triple-therapy regimen according to data from pediatric studies that have been published from April 2011 up to March 2012 [63].

However the success of the eradication therapies has been reduced in recent years because of the development of H. pylori resistant strains [64]. The appearance of such resistant strains varies geographically such that the geographic location became an important parameter in the efficacy of various eradication methods. In Europe [65], the primary resistance refers to clarithromycin and metronidazole which was found in 20% and 23% of the strains respectively. Secondary resistance appears in 42% and 35% of the strains that were recovered after at least one failed treatment.

In developing countries the resistance is higher for metronidazole because of its frequent use in parasitic infections [65].

Similarly the resistance to antibiotics [66] such as amoxicillin or clarithromycin is due to their extensive administration for other infections.

It has been shown that the eradication faillure of H.pylori [67] is related to the development of resistant strains. For example it was found in a study of 382 children with positive biopsy for H. pylori that the failure of eradication was due to metronidazole resistance.

Resistance varies with the genetic type of the strain. Significant clarithromycin resistance [68] was observed in cagE-, iceA1-, babA2-, and vacAs1c-positive groups and metronidazole resistance in vacAs1 and vacAs1c positive groups.

Intra-familial Transmission of H. Pylori Infection in Children

The modes of transmission of H. pylori are fecal-oral and oral-oral [69], as well as through environmental sources such as drinking water.

The predominant route of transmission is the intra-familial one. The fact that infection occurs mostly in childhood shows that transmission takes place from parent to child, and not vice versa.

Evidence from person-to-person transmission came a few decades ago from the study of Drumm., *et al*. [70] who detected intra-familial clustering of H. pylori infection. The authors tested the H. pylori infection in gastric-antrum biopsy specimens of 93 children that had upper gastrointestinal symptoms and underwent gastroscopy. The intra-familial route of infection has been supported by studies of the genomic profiles of H. pylori strains inside families.

Transmission takes place mostly from mothers to children and between siblings through gastro-oral, oral-oral and faecal-oral routes [71] which suggest that an intimate person-to-person contact is important for the transmission.

Different Routes of Transmission to Children in Developing and Developed Countries

Though in developed countries the major route of transmission is intra-familial, the situation seems to be different in some very poor developing countries. For example, the genetic analysis of H. pylori stains inside families in Peru has showed that the genetic comparison of the isolated strains supports a community based on environmental reservoir model instead of the all-in-the-family model of industrialized countries [72].

Similarly, genetic analysis of H. pylori strains supports a horizontal transmission inside the community instead a vertical one inside the families [73]. Given that the studied community had a reticulated supply of treated tap water and flushing toilets, which excludes water and sanitation as a source of infection, the authors attributed the horizontal transmission probably to a transmission among children at school.

In developed countries there are cases in which there is a difference in prevalence between rural and urban areas as well as cases with no difference. Sýkora., *et al*. did not detect any differences of H. pylori prevalence rates between rural and urban areas in Czech Republic [20], but Dore., *et al*. have found that the seroprevalence of H. pylori infection in northern Sardinia, Italy, was significantly higher among children in rural areas (37%) than in urban areas (13%) [74].

Household Crowding

There have been long-standing associations between overcrowding at home and the risk of H. pylori infection. Mendall., *et al*. in 1992, found that among the living conditions of that time in UK, only the number of children living in the household was independently associated with H. pylori infection [75]. The authors concluded that most British adults were infected with H. pylori by household contact in childhood.

A recent study by Melius., *et al*. has confirmed the importance of crowding as a risk factor for the infection. The authors studied the H. pylori infection in the Northern Plains American Indian reservation. They found that the risk of infection was increasing as the number of rooms in the homes decreased and consequently crowding was increasing [76].

Mothers

The intrafamilial transmission of H. pylori takes place mostly through infected mothers as a large study of 1221 preschool-aged children in Germany [77], showed. The authors determined the H. pylori infection by 13C-urea breath test. They found that the crude odds ratio (OR) for H. pylori infection of children whose mothers were infected was 16.5 (95% CI, 8.9-30.8). After adjustment for potential confounders, the OR was found to be 7.9. On the other hand, the OR was small for fathers. The confounding factors, according to the authors, were the nationality, place of residence in the first year of life, sex, age, and years of education of both the father and the mother, history of antibiotic use, housing density, and history of breast-feeding.

A recent study [78], has provided evidence that family could be the main source of H. pylori infection in children, showing that in all families of infected children checked at least one more member was infected. In this study upper gastrointestinal endoscopy and carbon 13-urea breath test (13C-UBT) was performed in 100 consecutive children, 94 of Greek and 6 of Albanian origin, with upper gastrointestinal symptoms, that is, epigastric or abdominal pain, vomiting and upper gastrointestinal bleeding. A 13C-UBT was also

performed in all family members of each index patient with a written consent signed by the parents. According to the findings of the study, infected mother or siblings as well as infected father, with a lower odds ratio however, are risk factors for infection of the children.

A suggested route of transmission from mothers to their infants, due to their close contact, is the mouth secretions of the mother [79].

H. pylori has been also detected in the dental plaque which could be a source of H. pylori from which it can be transmiited to the children. Evidence that oral and hand carriage of H. pylori is involved in the transmission of infection has been provided by the study of Dowsett., *et al*. in an isolated, rural population in Guatemala [80]. According to the authors such a route of transmission could explain the clustering of infection within families.

Newborns during delivery can be also infected from mothers [81], through vaginal yeasts that carry the H. pylori [81]. It was found in the above mentioned study that oral and vaginal Candida yeasts carry H.pylori, detecting the presence of H.pylori-specific genes in the total DNA of yeasts by PCR. The study found a significant correlation between the frequency of H.pylori genes in vaginal yeasts and that in oral yeasts of normally delivered neonates. This suggests that yeasts from mother's vagina and those in neonate's oral cavity may have a common source.

Breastfeeding is another factor involved in H. pylori infection in children. Rothenbacher., et al. in their study in Germany, found that breastfeeding does not protect against H. pylori infection [82]. On the contrary, the authors found that the duration of breastfeeding is positively associated with the H. pylori prevalence in pre-school age children, especially for children breastfed for 6 months or more because of the close contact between the child and their mother during breastfeeding which facilitates the transmission.

Other studies however reached different conclusions concerning breastfeeding. It was found in a study of children in northeastern Brazil [83], that the H. pylori prevalence is similar between breastfed and never breastfed children (55% vs. 52%) even when children were breastfed for more than 6 months. It was also found that the prevalence of infection was much higher in children with H pylori infected mothers concluding that an infected mother iss an important risk factor for the transmission of H. pylori to the children.

It seems that the relation of brestfeeding and H. pylori infection depends on the economic conditions in each country. A protective effect of breast feeding to children in less developed countries was found by Carreira., *et al*. who examined recently 38 published studies [84]. According to the authors, breastfeeding for 4-6 months is associated with a lower risk of H. pylori infection only in middle-income countries. This is because the breast-fed children in these countries have a better nutritional status and have more resistance to infections in general.

Siblings

The number of the infected siblings is also a risk factor for the H. pylori infection. Fialho., *et al*. examined the prevalence of H. pylori in families from a low-income urban community in the Northeast of Brazil which had a high H. pylori prevalence [85] and found that the number of infected siblings was an independent risk factor, after adjusting for the infection of the mother and the number of children in the house.

The role of infected siblings was further specified by Cervantes., *et al*. [86] who found that the older sibling is a source of H pylori transmission for younger siblings, especially when the difference in the age was less than or equal to 3 years. The authors observed that H. pylori infection occurred always first in the older sibling and later in the younger sibling. A persistently infected older sibling increased the rate of a persistent infection in a younger sibling by eight-fold. When the age difference of the siblings was three years or less the increase was 17-fold. The seropositivity of the mother was also associated with the persistent H. pylori infection of the younger sibling; however the effect was stronger for the persistently infected older sibling.

The study by Muhsen., *et al*. [87], in Israeli Arab children aged 3–5 that were followed up for 3–4 years, has also shown the role of the infected siblings in the transmission of H. pylori. The authors performed a multivariate analysis including three variables; crowding, maternal education, and H. pylori positivity in a sibling with the variable ''crowding'' correlated with the ''number of siblings'', and ''number of people living in the household'' and the 'variable 'maternal education'' correlated with ''family income''. The study showed that the presence of infected siblings in the household was the only significant factor associated with early and persistent H. pylori infection. The general conclusion of the authors was that the only predicting factor of early and persistent H. pylori infection was an H. pylori-infected sibling.

The number of adults in the household had no influence in the transmission. Another study concluded that the number of older siblings had the strongest effect in comparison to other crowding factors [88]. The author studied the H. pylori infection in a population-based sample of 685 Inuit persons in Greenland by enzyme-linked immunosorbent assay (ELISA) for H. pylori IgG antibodies and multivariate logistic regression models.

Grandmothers

In a recent study, Urita., *et al*. examined the seroprevalence of children and family members in Japanese families [89]. They found that seropositive children had mothers and siblings who were seropositive in significantly higher rates than those of seronegative children. Interestingly, the study concluded that infected grandmothers was an important risk factor for infection in the index children while infected fathers or grandfathers was not an independent predictor for infection in these children.

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