

EVIDENCE OF MOTHER-CHILD TRANSMISSION OF *Helicobacter pylori* INFECTION

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ABSTRACT – Background - Low socioeconomical status is a major risk factor for natural acquisition of *Helicobacter pylori* (*H. pylori*) infection in developing countries. Its transmission route is unknown but studies suggest person-to-person transmission. **Aim** - To evaluate seropositivity of anti-*H. pylori* antibodies in family members of infected symptomatic index patients as compared to family members of symptomatic uninfected index patients. **Patients and Methods** - One hundred and twelve family members of 38 patients who underwent endoscopy to exclude peptic disease were studied. Patients were deemed *H. pylori* infected or not infected when rapid urease test and histology were both positive or both negative. The family members underwent ELISA serology using the Cobas Core II Kit (Roche) and were classified into three groups: I - 29 family members of 10 *H. pylori* (+) duodenal ulcer index patients; II - 57 family members of 17 *H. pylori* (+) index patients without duodenal ulcer; III - 26 family members of 11 *H. pylori* (-) index patients. **Results** - Seropositivity of group I and II (infected patients) was higher than the control group, 83% vs 38%, specially in mothers, 81% vs 18%, and in siblings 76% vs 20%. Differences between fathers' seropositivity was not statistically significant in the three groups: 100% vs 86% vs 70%. Seropositivity of all family members (mother, father and siblings) between infected group (I vs II) was similar. **Conclusions** - Prevalence of *H. pylori* infection was higher in family members of infected patients, but was similar among family members of infected patients with and without duodenal ulcer. *H. pylori* infection is more frequent in mothers and siblings of infected index children. A common source of infection cannot be excluded, but facts suggest that person-to-person transmission occurs, specially from mother to child.

HEADINGS – *Helicobacter pylori*. Serologic tests. Mothers. Child. Family.

INTRODUCTION

Helicobacter pylori (*H. pylori*) commonly infects children of developing countries. Birth-cohort patterns from more developed countries suggest that most infections in adults are mainly acquired in childhood⁽⁵¹⁾.

The infection persists throughout life; spontaneous eradication is rare. The pathway of *H. pylori* transmission is not fully clarified. *H. pylori* is thought to live normally only in the stomach. *H. pylori* is presumed to enter humans via feces, saliva or vomitus.

Intrafamilial clustering of *H. pylori* infection suggests person-to-person transmission or common source exposure. The person-to-person transmission is suggested by the high prevalence in institutionalized mentally deficient subjects living⁽⁷⁾, among digestive endoscopists^(33, 34) and intrafamilial clustering^(18, 54, 63). High risk of *H. pylori* infection in cohabiting persons has been confirmed by evidence of the same strain among family members^(6, 23, 58, 61, 66, 67). Studies have reported a higher frequency of *H. pylori* infection among families of infected symptomatic children than among controls. Studies in family clustering are required considering that *H. pylori* infection is mainly acquired during infancy.

In this study, we investigated whether there was clustering of *H. pylori* infection within family members on the basis of the results of *H. pylori* status of an index patient.

PATIENTS AND METHODS

Collection of blood for detection of sero antibodies to *H. pylori* was performed in 112/132 family members of 27 *H. pylori* infected and 11 noninfected patients during 3 subsequent months. These dyspeptic patients were submitted to upper digestive endoscopy with gastric biopsies and were classified into *H. pylori* (+) infected index subject and *H. pylori* (-) noninfected index subject according to the rapid urease test and histology, both positive and both negative respectively. The age of 38 patients ranged from 2 to 20 years (median 11 y), 50% were male and 50% were female. The patients and their familiars were classified into three groups:

Group I - 33 family members of 10 *H. pylori*+ duodenal ulcer patients (6 males and 4 females), being 9/10 regularly attending our outpatient department with a previous diagnosis of *H. pylori* duodenal ulcer and 1 diagnosed during this study. The age of 10 duodenal ulcer patients on the occasion of the first endoscopy (ranged from 6 to 13 years, mean 11.2 y \pm 2 y), but the mean age at blood collection was 14.8 \pm 3.9 y (range 6 to 20 y). The family size ranged from 3 to 6 (mean 4.3 \pm 0.9).

Group II - 61 family members of 17 *H. pylori*+ dyspeptic patients without duodenal ulcer. The age of 17 patients ranged from 8 to 14 y (mean 10.8 y \pm 1.67 y), 10 females and 7 males. Endoscopy showed antral

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nodularities in six, enanthema in eight, duodenal enanthema in one and no abnormalities in two. Family size ranged from 2 to 9 (mean 4.6 ± 1.6).

Group III - 29 family members of 11 noninfected patients. The age of 11 patients ranged from 2 to 11 y (mean $5.6 \text{ y} \pm 3.3 \text{ y}$), 6 males and 5 females. Endoscopy showed esophageal enanthema in three, duodenal enanthema in one and was normal in seven. Family size ranged from 3 to 5 (mean 3.6 ± 0.88).

All family members were invited to collect blood for serology. Each subject filled out a standard questionnaire. The questionnaire asked information on: a) demographical factors such as age, race, gender, dyspeptic symptoms, socioeconomic and educational level. The questionnaire was answered by 112/123 (83%) of the family members.

Exclusion criteria – Patients with chronic digestive and extradigestive diseases, immunosuppressive disease and patients using immunosuppressor or chemotherapy drugs, antiinflammatory or with nitroimidazole for 2 months prior to endoscopy were excluded. Also patients with previous endoscopy, except for those with a previous duodenal ulcer, those who did not agree to participate in this study and those with discordant results of rapid urease test and histology were excluded. The minimum number of familiars accepted to be included in this study was 2/3.

This study was approved by the Medical Ethics Committee of Federal University of São Paulo, SP, Brazil. The parents or guardian give their written informed consent for each patient.

METHODS

Endoscopy was performed under general anesthesia or conscious sedation in children up to 10 y, with meperidine (1 mg/kg) associated to midazolam (2 mg/kg) by the intravenous route using videoendoscope Pentax EG 2430, after overnight fasting. Antral biopsies were taken from the antrum within about 2 cm of the pyloric channel for histology (two fragments) and rapid urease test (two fragments).

Rapid urease test - A homemade solution containing 1 mL distilled water, two drops of 1% phenol red and 0.1 g urea was used. The test was considered positive when the color changed from yellow to red and was observed up to 24 hours.

Histology - The specimens were placed on filter paper, fixed in 10% formaldehyde solution and stained with hematoxylin & eosin, and modified Giemsa. An expert pathologist characterized the presence of spiral bacteria in the mucosal layer or on the surface of epithelial cells as a positive test.

Serology – A venous blood sample was obtained from each family. IgG detection was done using the ELISA method (enzyme-linked immunosorbent assay-“Cobas Core II”- Roche, Hoffman La Roche Ltd., Switzerland). The results were considered positive when titers were greater than 7 U/mL, according to the manufacturer.

Statistical Analysis – The association between groups and positivity was tested through an extension of Fisher's exact test (Montecarlo SPSS method)⁽¹⁾ to evaluate the multiple variables the ANOVA test and multiple comparison with Bonferroni and/or Tanhame was employed⁽⁴¹⁾. Level of significance was $P < 0.05$.

RESULTS

Serology was performed in 112/123 (91%) of the subjects: in 38/38 of mothers, in 32/37 of fathers (1 father dead), in 38/44 of siblings, in 2/2 of nieces, in 1/1 uncle and in 1/1 cousin.

The age of the 112 households ranged from 2 to 54 years (median 28 y). There was no statistical significance in the three groups in relation to age ($P = 0.429$). The age of 38 mothers, ranged from 21 to 52 years (mean age $35 \text{ y} \pm 7.6 \text{ y}$), and the difference was statistically significant only in Group I vs Group III ($P = 0.004$), Group I vs II ($P = 0.397$), Group II vs III ($P = 0.080$). The age of 32 fathers ranged from 22 to 54 years (mean $38 \text{ y} \pm 8.26$). There was no significant difference between fathers' age of Group I vs II ($P = 0.999$), and in Groups II vs III ($P = 0.071$), but was significant in Group I vs Group III ($P = 0.027$). The age of 38 siblings ranged from 3 to 27 y (median 11). Age difference was not significant between the three Groups ($P = 0.763$).

Environmental conditions – All families reported to live in houses provided with electricity, refrigerator, running water in the interior of the house, public garbage collection, covered floor. Eighty-five (89%) of the family members older than 8 years were literate, 25 (25%) finished elementary school, and 7 (7%) had a complete university education. There was no difference between the three groups regarding educational level ($P > 0.05$).

Peptic disease in family members - 31% (32/102) reported dyspeptic symptoms, 29/32 of them underwent endoscopy and 9/29 reported an ulcer diagnosis.

Serology – *H. pylori* antibody positivity was observed in 72% (81/112), in 75% of the adults and in 67% of the children, becoming more frequent with age. In the first decade of life, serology was positive in 61.5% (8/13); in the second, in 70% (14/20); in the third, in 54% (13/24); in the fourth, in 77.4% (24/31); in the fifth or older, in 92% (22/24). Serology was positive in 82% of the males and in 63% of the females ($P = 0.035$).

Serology was positive in 79% (23/29) of Group I patients, in 84% (48/57) of Group II patients and in 38% (10/26) of Group III patients ($P = 0.001$). Difference between serum positivity of the infected Groups (I + II) and the noninfected (Group III) was statistically significant ($P = 0.001$) (Tables 1, 2), but there was no statistically significant difference comparing Group I vs. Group II ($P = 0.5$).

Serology of mothers – was positive in 63% (24/48), with 80% (8/10), 82% (14/17) and 18% (2/11) in Groups I, II and III, respectively. Serum positivity in the infected Groups (I + II) compared to the noninfected (Group III) was statistically significant ($P = 0.001$) in contrast to that of Groups I vs II ($P = 0.8$) (Tables 1, 2).

Serology of fathers – was positive in 84% (27/32), with 100% (8/8), 86% (12/14) and 70% (7/10) in Groups I, II and III, respectively ($P = 0.3$) (Tables 1, 2).

Serology of siblings – was positive in 68% (26/38), with 56% (5/9), 83% (20/24), 20% (1/5) in Groups I, II and III, respectively. Serum

TABLE 1 - Serology in family members (groups I and II)

Groups Family member	Positive group I (%)	Positive Group II (%)	P
Mother	8/10 (80)	14/17 (82)	0.8
Father	8/8 (100)	12/14 (86)	0.3
Siblings	5/9 (56)	20/24 (83)	0.17
Other	2/2 (100)	2/2 (100)	---
Total	23/29 (79)	48/57 (84)	0.5

TABLE 2 - Serology in family members (groups I + II and III)

Groups Family member	Positive groups (I + II) (%)	Negative group III (%)	P
Mother	22/27 (81)	2/11 (18)	0.001
Father	20/22 (91)	7/10 (70)	0.3
Siblings	25/33 (76)	1/5 (20)	0.027
Other	2/4 (50)	0/0 (0)	----
Total	71/86 (83)	10/26 (38)	0.001

positivity of the infected Groups (I + II) in regard to the noninfected (Group III) was statistically significant ($P = 0.003$). On comparing Groups I and II there was no statistically significant difference ($P = 0.17$).

Serology of the pair mother-father – here the agreement of serology results was 78% (27/32), with 62% positive in both members (20/32) and 16% negative in both (5/32). There was a statistically significant difference between the infected Groups (I + II) vs the noninfected (Group III) ($P = 0.004$) but not between Group I and Group II ($P = 0.768$).

DISCUSSION

The results suggest that the infected mothers, in contrast to the fathers, may play a role in the intrafamilial transmission of *H. pylori* infection to infected children. Several studies show a high correlation between the infection of the mother and her child^(19, 26, 36, 39). Other persons to acquire great importance in this period are the older brothers^(25, 36). Intrafamilial transmission seems to be more important than the extrafamilial⁽⁶³⁾.

The high *H. pylori* prevalence in the families of infected patients^(36, 39, 54, 63, 69) is widely described, while others do not emphasize this relationship^(2, 42, 56). The strong association between the infection of the mothers and that of their children may be explained by a greater opportunity of personal contact, which is stronger and more frequent when the child is young, a period in which a greater acquisition of the infection is described. Studies show that children acquire *H. pylori* during the first 5 years⁽⁵¹⁾ and infection usually lasts for life. Indirect evidence which could support this hypothesis is the observation that the annual seroconversion rate ranges from 0.3 to 0.5 in adults^(30, 31, 47). Transmission could be through saliva, gastric secretions, feces. Transmission by saliva could occur during close contact with the child, through kisses, testing food, sharing bed, spoon, etc. Transmission through feces could occur due to inadequate hygienic habits of the mothers, specially those of low cultural and socioeconomic level. Transmission of *H. pylori* via the fecal-oral route is very probable. Viable *H. pylori* has been isolated from feces, making us sure of this form of transmission^(28, 29, 62, 65). Person-to-person transmission, either oral or gastric-oral would be facilitated by close contact due to agglomeration because of lack of space and/or many people to share this space.

In some studies it was suggested that *H. pylori* transmission could be due to contaminated water^(27, 29) which would explain the high prevalence in developing countries and decrease in *H. pylori* incidence when economic conditions of the countries improve⁽⁴⁾. This hypothesis is strengthened by studies which on evaluating prevalence of hepatitis A and *H. pylori* found a similarity^(21, 35, 55).

Serum positivity of fathers was very high in the two groups and showed no relationship with that of the child. The result of our

study was similar to those of other studies⁽⁴⁰⁾. A possible explanation could be that the father has less contact with the child (as compared to the mother). It is known that transmission of other bacteria (e.g. *Streptococcus mutans*) frequently occurs orally from the mother to the child⁽³²⁾. On the other hand, we should consider that the father may acquire the infection from an extra-domiciliary source, increasing his risk for contamination.

Other studies showed the importance of joint infection of both partners, similarly to our study^(11, 46, 59). The significant relationship between positivity of the partners makes us think of oral-oral and gastric-oral transmission, but they also could become contaminated through a common source. Another explanation would be exposure of the partners to the same environmental conditions during childhood⁽³⁷⁾.

We included infected patients with and without duodenal ulcer in order to analyze if there would be interference by other factors, but we did not observe a difference in infection between the two Groups. Since duodenal ulcer is infrequent in childhood (four to six cases a year in great centers)⁽¹⁴⁾, we included only 10 patients. The control Group consisted of 11 patients because the *H. pylori*- family members of some of the patients who could be included in the study did not show up for blood collection.

Size of the sample was influenced by some factors. We included only family members with blood collected from more than 2/3 of the family members, but have to consider that those who show up for blood collection tend to be those who are symptomatic or with peptic disease and thus are more probable to be *H. pylori*^(8, 50, 57). Patients who already underwent endoscopic examination were excluded with the purpose of avoiding a possible contamination by the endoscopy apparatus. There are reports suggesting that endoscopic examination may act as *H. pylori* transmitter^(5, 15, 24); others report that manually and specially mechanically performed sterilization is effective in decontaminating the endoscope^(17, 68). Patients who presented disagreeing results of the rapid urease test and histology were also excluded.

Serum positivity of intradomiciliary contacts could contribute to a possible *H. pylori* transmission. Thus, all people who live together with the patient in the same house were included. But, in spite of the fact that several family members usually live in the same house in developing countries, we observed only four different family members (cousin, uncle, two nieces).

Diagnosis of infection was performed through serology in family members, as in most studies of the literature^(2, 18, 63). It is a practical test of low cost for epidemiologic studies when compared with the respiratory test using ¹³C-urea as used in some studies⁽⁵⁴⁾. However, serology presents less sensitivity in children below the age of 10-12 years^(16, 43). This may have influenced the result of the Group of brothers where 53% were less than 12 years old.

According to many studies from different parts of the world it is known that *H. pylori* prevalence increases with age and is directly related to the socioeconomic conditions of the country^(3, 9, 10, 12, 13, 20, 22, 38, 45, 48, 49, 60, 64). Age is a very important variable in studies on *H. pylori*. No statistical difference was found between the ages in the three Groups of family members ($P = 0.43$) as well as regarding age of brothers ($P = 0.76$), but on analyzing the Groups of mothers and fathers, their age was higher in those with ulcer (Group I) as compared to the control Groups (III). This fact could be explained by the fact

that randomly the noninfected patients had a lower age, and patients with ulcer had an older age and consequently their parents too. In nine patients with ulcer, the diagnosis was established before blood collection of family members. This was due to the lower number of *H. pylori*⁺ patients with ulcer. But, considering the high *H. pylori* prevalence in Brazil and the fact that the infection is more frequently acquired in childhood, it is assumed that family members of *H. pylori*⁺ patients were already contaminated at the time of *H. pylori*⁺ ulcer diagnosis in their children. The statistical difference between the ages of fathers and mothers in Groups I and III did not interfere in the results of the study.

In our study, serum positivity increased per decade, being high (72%), 75% in adults and 67% in children. It should be recalled that some of the family members of our patients are symptomatic or with peptic disease, which contributes to increase in positivity. Other Brazilian studies showed a prevalence in adults and children of 62.1⁽⁵²⁾ and 34.1⁽⁴⁴⁾, 90% and 72%, 84.7 and 77.5%⁽⁵³⁾, respectively. These great differences in prevalence reflect the socioeconomic conditions of these regions.

Although a high prevalence of *H. pylori* antibodies is well documented among family members, the types of strains which infect the children and their family members are not well studied. Similarity between the strains to be found in the families would give more arguments in support of person-to-person transmission, but this finding is not constant in the studies. It is also known that a person may have several *H. pylori* strains, which could confound the results. Up to now it was not possible to securely

define the source and mechanism of *H. pylori* transmission. It is important to obtain information of epidemiological value as well as knowledge on risk factors for people who live with the patient. We cannot affirm if our patients, and their family members were contaminated by a common source, e.g. water, but since the socioeconomic conditions are similar, with all having running water, the same cultural level, living in the same environment, the observed difference in prevalence between family members of infected patients and controls is not justified.

CONCLUSIONS

Family members of infected patients presented more infection with *H. pylori*. Infection with *H. pylori* was more frequent in mothers and brothers of infected patients, but was not statistically different between fathers. Serum positivity was similar between family members of infected patients with and without duodenal ulcer. There is congruity in the serology results insofar as the pair of mother-father was concerned.

We may not exclude a common source of infection, but the data suggest that transmission is person-to-person and especially from mother to child.

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RESUMO: O estrato socioeconômico baixo é o maior fator de risco para a aquisição natural da infecção por *Helicobacter pylori* em países em desenvolvimento. As vias de transmissão são desconhecidas embora estudos sugerem transmissão pessoa-pessoa. **Objetivo** - Avaliar a soropositividade de anticorpos anti *H. pylori* em familiares de pacientes sintomáticos infectados comparados a de pacientes não infectados. **Casística e Métodos** - Foram estudados 112 familiares de 38 pacientes encaminhados para afastar doença péptica. Os pacientes foram submetidos a exame endoscópico, sendo realizadas quatro biopsias gástricas para pesquisa de *H. pylori*: duas para teste rápido da urease e duas para histologia (HE/Giemsa). Foi considerado infectado por *H. pylori* quando ambos os exames resultaram positivos. Nos familiares foi realizada sorologia com método ELISA, utilizando-se o Kit Cobas Core II (Roche), sendo considerado resultado positivo a titulação $\geq 7U/mL$. Os familiares foram divididos em três grupos: grupo I: 29 familiares de 10 pacientes com úlcera duodenal *H. pylori*⁺; grupo II: 57 familiares de 17 pacientes sem úlcera duodenal *H. pylori*⁺; grupo III: 26 familiares de 11 pacientes *H. pylori*⁻. Foi testada a associação entre grupos e positividade através de uma extensão do teste exato de Fisher (método de Montecarlo SPSS), sendo analisada a soropositividade em cada um dos membros da família: pai, mãe, irmãos e o binômio mãe/pai e para a avaliação de múltiplas variáveis utilizou-se ANOVA. **Resultados** - Os familiares de pacientes *H. pylori*⁺ apresentaram maior soropositividade comparado com o grupo controle, 83% vs 38%, sendo maior nas mães 81% vs 18% e irmãos 76% vs 20%. A soropositividade do pai não foi estatisticamente significante, quando comparados os três grupos de pacientes: 100% vs 86% vs 70%. A soropositividade de todos os membros da família, mãe, pai e irmãos nos grupos de úlcera duodenal *H. pylori*⁺ e sem úlcera duodenal *H. pylori*⁺ foram semelhantes. **Conclusão** - Familiares de pacientes infectados apresentam mais infecção por *H. pylori*. A soropositividade foi semelhante entre os familiares dos pacientes infectados com e sem úlcera duodenal. Infecção por *H. pylori* é mais freqüente em mães e irmãos de pacientes infectados; ao contrário, nos pais não houve diferença estatisticamente significante nos três grupos. As crianças apresentam mais infecção quando ambos os pais são *H. pylori*⁺ e existe uma concordância do resultado da sorologia entre os cônjuges. Não podemos afastar uma fonte comum de infecção, mas os fatos nos sugerem que a transmissão acontece de pessoa a pessoa e especialmente da mãe para filho e entre os irmãos.

DESCRITORES – *Helicobacter pylori*. Testes sorológicos. Mães. Criança. Família.

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