Risk factors for *helicobacter pylori* infection in children: is education a main determinant?

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SUMMARY

To investigate potential risk factors associated with *Helicobacter pylori* (Hp) infection, we performed a case-control study in 167 consecutively selected hospitalized children in Salvador, Brazil. Hp infection was identified by the presence of IgG against Hp in serum samples. Data were gathered using a structured questionnaire, 38·3 % children were found to be seropositive and classified as cases, and 61·7 % were seronegative controls. After multivariate analysis, independent variables associated with Hp infection included: the educational attainment of the child's provider ≥ 11 years (OR 0·1, 95 % CI 0·01–0·9), poor garbage disposal service (OR 2·2, 95 % CI 1·0–4·9), thumb sucking (OR 4·6, 95 % CI 1·1–19·8), brushing teeth more than once a day (OR 5·6, 95 % CI 1·8–17·7), having a pet dog (OR 2·5, 95 % CI 1·0–6·1), and a history of chronic urticaria (OR 4·0, 95 % CI 1·5–10·8). The risk factors identified are consistent with some, but not all, previous studies supporting either oral–oral or faecal–oral transmission of Hp. Our data suggested that a higher educational attainment might play an important role in preventing Hp infection.

INTRODUCTION

Helicobacter pylori (Hp) is a spiral-shaped microaerophilic Gram-negative bacterium that colonizes the gastric mucosa and induces a strong inflammatory response with release of various bacterial and host-dependent cytotoxic substances [1]. It is now recognized as the main causative agent of several gastroduodenal diseases, such as chronic gastritis, recurrence of peptic ulcers, and is also a risk factor for the development of gastric carcinoma [2–5]. Infection with Hp has a worldwide distribution and it is

estimated that up to 50% of the world's population are infected [6]. In recent years an explosion of research has focused on Hp as it has become apparent that it may be the most common human bacterial infection. Thus the public health impact of Hp infection seems obvious, and in order to design prevention strategies, elucidation of the mode of the spread of these bacteria will be crucial.

Acquisition of Hp infection seems to occur in early childhood and to persist throughout life. It is also known to cluster in families, however, whether transmission occurs through a common exposure source or through contact between individuals remains unknown and is a topic of debate [7–10]. No certain environmental source has been identified. Recently

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reported findings of *Helicobacter* species in water are of great interest [11]. Many investigators suggest a person-to-person spread, since a higher seroprevalence has been found among children who live in close contact with each other or in institutions [9]. Hp has been cultured from faeces [12], and the faecal—oral route of transmission is further supported by the fact that serological markers for Hp infection have been found to correlate strongly to contaminated water [13]. Alternatively, the microorganism may be transmitted orally as it has been detected in dental plaque and saliva, but the hypothesis that oral microflora may be a permanent reservoir of Hp remains controversial [14].

In previous studies, both in developing and developed countries, most risk factors for Hp infection are closely related to poor living conditions in childhood such as: low socioeconomic status, poor hygiene conditions, sharing a bed, and overcrowding [8–10]. A better understanding of the epidemiology of Hp infection in children is required to understand the natural history of this infection and to identify the most common mode(s) of transmission, as well as how, when and where to break the chain of transmission. Therefore, we conducted a case-control study of children in the city of Salvador in northeastern Brazil. The aim of this study is to investigate potential risk factors for Hp infection in a hospitalized-based sample of children.

MATERIAL AND METHODS

This study was conducted in a non-profit-making, public, 90-bed paediatric hospital (Hospital da Criança) in Salvador, Bahia State, in northeastern Brazil. Salvador is the third largest city in Brazil, with an ethnically diverse population of 2·3 million.

Subject selection

We enrolled, in the present study, 167 out of 177 consecutively selected children, aged between 1 and 12 years old, admitted to the Hospital da Criança over a 6-month period (August 2001 to February 2002). Thus, the response rate was 94%. Case and control status were determined on the basis of the presence or absence of immunoglobulin G (IgG) antibodies to Hp respectively. The refusal rate was similar among parents of cases and control subjects. The groups also did not differ in regard to chief complaints at hospital admission.

Data collection

A structured questionnaire, containing approximately 88 items, was administered by trained and certified interviewers in person to either parent of each child. The interviewers were not aware of the control/case status of the study subject at the time the interview took place; the same was true for the parents of the children. The interview took 30–45 min to complete. The protocol was approved by the Hospital Ethical Committee, and the staff conducting the study received no specific funding and had no competing interests. Written informed consent was obtained from all children's parents before enrolment in the study.

The data collection instrument included questions on demographic and household characteristics. A crowding index was calculated by dividing the number of household members by the number of rooms in the home. Water was considered to be inadequately stored if kept in either an open 55-gallon drum or a smaller uncovered container, and adequately stored if kept in a closed container with a tap or a narrownecked bottle/vase. Drinking-water quality was defined as good, fair or poor. Good drinking-water quality included water from a municipal source (chlorinated water), adequately stored. Poor water quality included non-chlorinated water, inadequately stored. Fair water quality included a combination of either chlorinated water and inadequate storage or non-chlorinated water and adequate storage. The garbage disposal system was classified as good or poor. Good systems included scheduled garbage collection and absence of garbage in children's playgrounds (household vicinity). Poor systems included non-scheduled garbage collection or presence of garbage in children's playgrounds. The household sanitation system was also classified as good or poor. Good systems included either the municipal sewer or a septic tank with leach field, and poor systems included cesspools and portables. The sewage exposure index was defined as low or high. Low exposure index included households with a good sanitation system (as defined above) and absence of sewage in children's playgrounds, whereas high exposure index included households with a poor sanitation system and presence of sewage in children's playgrounds. History of chronic urticaria was defined as self-report of repeated occurrence of short-lived cutaneous weals accompanied by redness and itching. We also examined hygiene practices, sharing of utensils and presence of pets in the home.

Serology

Serum was separated, frozen, and stored at -20 °C until being assayed. Hp status was determined by the presence of anti-Hp IgG antibodies in the enzymelinked immunosorbent assay (ELISA), using a commercially available kit (Enzignost® Anti-Hp II/IgG; Dade Behring, Marburg, Germany). All testing was performed according to the manufacturer's instructions. This ELISA uses inactivated Hp antigen (detergent extract from a CagA- and VacA-positive strain isolate) absorbed to reaction wells. A sample was considered positive for IgG antibodies to Hp if the corrected absorbance reading of the serum sample was 0.250 or more (cut-off). The specificity and sensitivity were estimated to be 98.8 and 93.4% respectively (Dade Behring, data on file). It has been shown that this and other serological tests distinguish between those who are currently infected with Hp and those who are not [15]. All sera were tested blindly.

Statistical analysis

We performed univariate analysis to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) and logistic regression to adjust these estimates for age. In addition, because we wished to study the unconfounded effects of the variables examined, we entered these terms into a multivariate model in order to estimate ORs and CIs adjusted for selected covariates. *P* values less than 0.05 were considered statistically significant. All analyses were conducted with the use of the SPSS statistical program (SPSS, Inc., Chicago, IL, USA).

RESULTS

Data were obtained from 167 patients, 64 children were found to be seropositive for Hp and classified as cases, and 103 were seronegative controls. The most common chief complaints at hospital admission included respiratory tract diseases (29·9%), urinary tract diseases (15·6%), skin/muscle infection (10·8%) and gastrointestinal tract diseases (6·0%). The variables associated with Hp-seropositive children, in the crude and age-adjusted analyses, are depicted in Table 1.

We found black ethnicity to be twice as likely among children with positive serostatus for Hp infection compared to those seronegative. Our data also showed that Hp infection was inversely associated with the educational attainment of the child's provider. A similar inverse relation was also observed in regard to family income, but it was not statistically significant (Table 1). Among cases, the odds of having a crowding index greater than 3·0 was twice that of controls, whereas the odds of lower values of crowding index were virtually the same among cases and controls (Table 1).

Poor drinking-water quality seemed to be associated with positive serostatus for Hp, but failed to reach the significance level in both crude and ageadjusted analyses (Table 1). A poor garbage disposal system significantly increased the odds of Hp infection by 2·4. Although our results suggested that a poor domestic sanitation system also increased the odds of Hp seropositivity, the difference was not statistically significant. Nonetheless, an index of high sewage exposure was significantly associated with Hp infection (Table 1).

In our data, brushing the teeth more than once a day, having a dog in the home, or reporting chronic urticaria were all associated with higher odds for Hp seropositivity (Table 1). There was no association between sharing of drinking glass/cup (OR 1·3, 95 % CI 0·7–2·4), bed sharing (OR 1·2, 95 % CI 0·6–2·3), fingernail biting (OR 1·3, 95 % CI 0·6–2·5), or having a cat in the home (OR 0·8, 95 % CI 0·3–2·5), and Hp infection. We also failed to demonstrate a significant association between gender, thumb sucking, or blood group and Hp infection in both crude and age-adjusted analyses (Table 1).

Multivariate analysis

After adjusting for selected covariates using logistic regression, the variables remaining independently associated with seropositivity to Hp were: the educational attainment of the child's provider \geqslant 11 years (OR 0·1), poor garbage disposal system (OR 2·2), brushing teeth more than once a day (OR 5·6), thumb sucking (OR 4·6), having a dog in the home (OR 2·5), and a history of chronic urticaria (OR 4·0), as shown in Table 2.

DISCUSSION

The sources and routes of transmission of Hp infection are still a topic of debate. This case-control study was designed to investigate putative risk factors for Hp infection, focusing on those operative in childhood.

Table 1. Crude and age-adjusted odds ratios for the associations between selected characteristics and Helicobacter pylori infection in 167 children, 1–12 years of age, Salvador, Brazil, 2001–2002

	Controls n (%)	OR (95 % CI)†	
Cases n (%)		Crude	Age adjusted
19 (29.7)	44 (42.7)	1 (reference)	
28 (43.8)		1.7 (0.76–3.66)	
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	. ()	(
36 (56.2)	58 (56.3)	1 (reference)	1 (reference)
			1.0 (0.53–1.90)
20 (10 0)	(/)	10 (00. 100)	10 (0 22 1 30)
29 (45.3)	65 (63.1)	1 (reference)	1 (reference)
			2.3 (1.18–4.34)*
33 (34 1)	30 (30 7)	21 (110 30))	2 3 (1 10 + 5+)
40 (76.6)	64 (62.1)	1 (reference)	1 (reference)
			1.0 (0.43–2.11)
	, ,		0.1 (0.01–0.50)**
1 (1.3)	19 (16.4)	0.1 (0.01–0.33)	0.1 (0.01–0.20)
24 (27.5)	25 (24.2)	1 (C)	1 (6)
			1 (reference)
			0.6 (0.28–1.17)
7 (10.9)	19 (18·4)	0.4 (0.14–1.08)	0.4 (0.14–1.10)
			1 (reference)
			1.0 (0.48–2.06)
9 (14·1)	16 (15·5)		1.0 (0.39 - 2.71)
7 (10.9)	6 (5.8)	2.0 (0.60–6.63)	2.2 (0.65–7.46)
16 (25)	18 (17.5)	1.6 (0.74–3.37)	1.6 (0.74–3.48)
			2.4 (0.83–6.88)
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45 (70.3)	82 (79.6)	1 (reference)	1 (reference)
			1.4 (0.60–3.08)
			3·1 (0·81–11·76)
			1.9 (1.00–3.62)*
			1.7 (0.73–3.82)
14 (21'9)	14 (157)	1.9 (0.79–3.39)	11/(01/3-3182)
24 (27.5)	(1 (50.2)	1 (22622222)	1 (==f=======)
			1 (reference)
40 (62.3)	42 (40.8)	2.4 (1.27–4.39)***	2·4 (1·26–4·61)**
22 (50 0)	(0./(1.0)	4 (0)	4 (0)
	, ,		1 (reference)
	, ,		1.5 (0.78–2.81)
14 (21.9)	13 (12·6)	1.9 (0.85–4.45)	1.9 (0.81–4.37)
53 (82.8)	96 (93·2)	1 (reference)	1 (reference)
11 (17·2)	7 (6.8)	2.8 (1.04-7.78)*	2.9 (1.02-8.55)*
5 (7.8)	28 (27.2)	1 (reference)	1 (reference)
			4·4 (1·56–12·23)*
39 (32.7)	13 (12.8)	44 (10-12-11)	44 (1.30–12.23)
56 (07 5)	00 (05 1)	1 (rafaranas)	1 (rafaman aa)
	, ,		1 (reference)
8 (12.3)	3 (4.9)	2.8 (0.8/-8.9/)	3.0 (0.92–9.69)
	19 (29·7) 28 (43·8) 10 (15·6) 7 (10·9) 36 (56·2) 28 (43·8) 29 (45·3) 35 (54·7) 49 (76·6) 14 (21·9) 1 (1·5) 24 (37·5) 33 (51·6) 7 (10·9) 24 (37·5) 9 (14·1) 7 (10·9) 16 (25) 9 (14·1) 45 (70·3) 13 (20·3) 6 (9·4) 34 (53·1) 14 (21·9) 24 (37·5) 40 (62·5) 32 (50·0) 14 (21·9) 53 (82·8)	19 (29·7)	Cases n (%)

	G	Controls n (%)	OR (95% CI)†	
	Cases n (%)		Crude	Age adjusted
Having a pet dog $(n=133)$				
No	26 (50.0)	57 (70.4)	1 (reference)	1 (reference)
Yes	26 (50.0)	24 (29.6)	2.4 (1.15-4.90)*	2.3 (1.10-4.92)*
History of chronic urticaria				
No	45 (70·3)	91 (88.3)	1 (reference)	1 (reference)
Yes	19 (29.7)	12 (11.7)	3.2 (1.43-7.17)**	3.0 (1.33-6.78)**
Blood group $(n=157)$				
A	24 (38·7)	29 (30·5)	1 (reference)	1 (reference)
В	11 (17·7)	15 (15.8)	0.9 (0.31 - 2.53)	0.8 (0.83–3.47)
AB	3 (4.8)	4 (4.2)	0.9 (0.14-5.50)	0.9 (0.30 - 2.09)
O	24 (38·7)	47 (49·5)	0.6 (0.28–1.37)	0.6 (0.28–1.24)

^{*} P < 0.05; ** P < 0.01.

We found black ethnicity to be associated with increased risk for Hp infection in both univariate and age-adjusted analyses; however this association did not remain statistically significant after adjusting for socioeconomic status and sanitary conditions, suggesting that it was due to confounding. Malaty et al. [16] reported an almost identical prevalence of Hp infection among white Hispanic and black children. In another study the seroprevalence of Hp was substantially higher among non-Hispanic blacks (52·7%) and Mexican–Americans (61·6%) than among non-Hispanic whites (26·2%), but this difference also decreased after controlling for other factors associated with Hp infection [17].

Most previous studies examining childhood conditions show an inverse correlation between seropositivity and socioeconomic factors, and it has been stipulated that factors related to social class are important determinants of the risk of Hp infection in populations [8–10]. Klein et al. [18] however, observed that socioeconomic status in Peru was a less important risk factor than water source in acquiring Hp infection. In our data, family income seemed to be related to Hp infection, but after adjusting for other covariates measuring sanitary conditions, the association was no longer apparent. In contrast with family income, education - another component of socioeconomic status - remained significantly associated with Hp infection after multivariate adjustment. Thus, parents' higher education attainment seemed to have protected children from acquiring Hp infection regardless of sanitary conditions. Furthermore, our findings suggest that higher education might result in lower risk of Hp infection despite a high prevalence of environmental risk factors. Characteristics such as personal hygiene, habits of individual family members, house cleaning practices, attitudes and behaviour towards sanitary matters, all depend heavily upon education, and may mediate the relationship described herein.

Crowding in childhood has been reported as a risk factor for infection with Hp, suggesting personto-person spread or a common source transmission [9, 10]. Our results showed an association of Hp infection with the highest category of crowding index (>3) in both univariate and age-adjusted analyses. In the multivariate model, however, the categories of crowding index had virtually the same odds for Hp infection, indicating that this association might also be due to confounding. Similarly, Redlinger et al. [19] have also found an association of crowding with Hp infection, which did not remain significant after adjusting the results by multivariate analysis. Bed sharing, also a marker for person-to-person transmission, has been a strong and independent risk factor for Hp infection in some studies [9, 10], but not in ours. Therefore, these results are not consistently supportive of person-to-person transmission as the most plausible route of Hp infection.

We did not find a significant association between poor drinking-water quality and Hp infection, although the strength of the association (OR 3·2) suggested there was one. Several studies have implicated water as a transmission route for Hp infection

[†] Odds ratio (95% confidence interval).

[‡] Non-black children are comprised of white (n=6) and mixed (n=88) ethnicity.

[§] In American dollars (US\$).

Table 2. Results of multivariate analysis of selected study variables and their association with Helicobacter pylori infection in 167 children, Salvador, Brazil, 2001–2002

OR (95 % CI)† Multivariate	P value
1.8 (0.81–3.91)	0.15
1 (reference)	
0.1 (0.01 - 0.90)	0.04*
1 (reference)	
1.0 (0.26-4.26)	0.96
1 (reference)	
1.0 (0.44 - 2.16)	0.95
1.2 (0.35–3.16)	0.81
3.2 (0.68–14.63)	0.14
2.2 (1.00-4.94)	0.05*
2.4 (0.71–8.04)	0.16
5.6 (1.76–17.72)	0.004**
4.6 (1.09–19.79)	0.04*
2.5 (1.00–6.06)	0.05*
4.0 (1.50–10.77)	0.006**
	Multivariate 1·8 (0·81–3·91) 1 (reference) 0·1 (0·01–0·90) 1 (reference) 1·0 (0·26–4·26) 1 (reference) 1·0 (0·44–2·16) 1·2 (0·35–3·16) 3·2 (0·68–14·63) 2·2 (1·00–4·94) 2·4 (0·71–8·04) 5·6 (1·76–17·72) 4·6 (1·09–19·79) 2·5 (1·00–6·06)

^{*} P < 0.05; ** P < 0.01.

[11, 13, 18], whereas others have found no differences in seropositivity between users of piped water or users of wells or streams [20]. Hp has not been cultured from environmental sources; it is not known to be present and is unlikely to be viable in municipal or private water sources that meet minimal standards of sanitation. Post-delivery contamination of the water during storage in household containers may be an important factor, irrespective of whether the family uses chlorinated water or not, as shown by Klein et al. [18]. In fact, we found the strength of the association between inadequate water storage and Hp seropositivity to be greater than the one between non-chlorinated water and Hp infection (OR 2·4 and 1·6 respectively).

In our data a high index of sewage exposure significantly increased the risk of Hp acquisition by almost threefold, but our study sample might have lacked enough statistical power for this association to remain significant in the multivariate analysis. One can argue that difficulties in measuring such an exposure may result in non-differential misclassification, leading to attenuation of or failure to acknowledge an association with Hp infection. It has been suggested that in populations of low socioeconomic level, transmission of Hp may be facilitated by precarious sanitary conditions [6, 8, 12]. Kelly et al. [12] were able to isolate colonies of Hp from faeces suggesting environmental transmission. In Chile, the consumption of uncooked vegetables irrigated with untreated sewage water seemed to be a risk factor in the transmission of Hp [13]. However, there is also evidence against environmental transmission; Friis et al. [21] have reported that sewage workers have a similar prevalence of infection as other labourers.

It has been shown that the housefly has the potential for mechanical transmission of Hp. Grubel et al. [22] fed freshly hatched flies on actively growing Hp plates for 6 h, the flies were then sampled for the presence of culturable Hp. The bacteria were recoverable from the external surface of the fly for up to 12 h and from the gut and excreta for up to 30 h. In the present study, poor garbage disposal service more than doubled the risk of Hp seropositivity. Accumulation of garbage with organic matter allows for a high density of flies around the living area. These abundant vectors might be able to pick up Hp in human waste, mechanically carry it, and then deposit contaminated fly excreta on food.

Nabwera et al. [23] identified plate sharing, *a priori*, as a possible risk factor for Hp infection. In another study, Hp was detected by polymerase chain reaction (PCR) in the saliva from 15 out of 45 (33%) infected subjects and in the chopsticks from one (2%), however, the risk of contracting the infection via the use of this utensil was low, since Hp was rarely detected in chopsticks after eating [24]. In our study, sharing a glass or toothbrush did not increase the likelihood of Hp infection, thus not supporting the view that Hp is transmitted from person-to-person by the oral—oral route through salivary contamination of utensils.

Hp has been detected from dental plaque, periodontal pockets and the dorsum of the tongue [25, 26], however the number of organisms in individual samples was very low, suggesting that dental plaque or other sites within the mouth are not an important reservoir for Hp and are probably not a significant factor in its transmission [26, 27]. In our study, brushing the teeth more than once daily was strongly

[†] Odds ratio (95% confidence interval).

[‡] In American dollars (US\$).

[§] Reference is one time per day or less.

associated with Hp infection. Repeated microtrauma to the gums might cause small disruptions of the mucous membrane, which would serve as a port of entrance for Hp present in contaminated water or food. Further studies are needed to test this hypothesis. Hp has also been detected from beneath the nail of the index finger of a subject's dominant hand [26]. We found thumb sucking to be strongly associated with Hp infection, but not with fingernail biting. Thus, it remains unclear whether the hand may be instrumental in the transmission of Hp.

There was an increased risk for Hp infection among children keeping a dog in the home, whereas having a cat in the household did not pose any increased risk. Some domestic animals have been suggested as a reservoir of Hp disease, but the data are inconsistent [28, 29]. Recent observations have demonstrated the ubiquitous character of these helicobacteria by showing their presence in the stomach of man, dogs and cats. This has led some authors to consider the potential zoonotic risk of the human infection by *Helicobacter heilmannii*, *felis* or *pylori* [30].

Our results indicated a strong association between Hp seropositivity and history of chronic urticaria (CU). Several papers have also suggested a possible relationship between Hp infection of the gastric mucosa and dermatological diseases such as rosacea, CU, and alopecia areata [31, 32]. Valsecchi et al. [33] reported a high prevalence of Hp infection in CU patients, but earlier studies showed conflicting results on Hp eradication in CU. There is currently no definitive evidence of the involvement of Hp as a cause of CU, although it could have an indirect role.

Persons of blood group O are at a higher risk for peptic ulcers [34]; increased density of colonization of epithelial cells and higher inflammatory responses to Hp among persons of this blood group might contribute to increased susceptibility to peptic ulceration [35]. In our data, there was no greater risk for Hp infection among blood group O subjects, suggesting that although this characteristic might increase Hp-related morbidity; it does not affect susceptibility to Hp infection.

Methodological merits and limitations

Case-control studies are known to be more vulnerable to bias. In our study, a consecutive sample of subjects with a high participation rate has made it unlikely that selection bias might have occurred. Parents and interviewers were both blinded to the case-control status of the children, thus preventing information and observational bias respectively. Finally, we selected hospital-based controls to maximize the representativeness of the controls to the study base where the cases came from. One limitation of this study is related to the difficulties in measuring variables reflecting sanitary and environmental conditions. As we had to rely on self-report when assessing these characteristics, this might have posed an additional source of inaccuracy to our data, which is likely to result in non-differential classification error and attenuation of the associations measured. Our study might also have lacked statistical power to investigate some of the potential associations we hypothesized.

CONCLUSIONS

The educational attainment of the child's provider had the strongest association with Hp infection. No other variable, whether correlated with education or not, diminished the predictive power of education or could account for the effect of this single variable when tested jointly by multivariate analysis. Other risk factors for acquisition of Hp infection identified in our population are consistent with some, but not all, of the previous studies supporting either oral—oral or faecal-oral transmission of Hp. In spite of systematic collection and analysis of many putative variables, we could not define any specific source or clear transmission route. This difficulty in demonstrating a specific route of transmission could indicate a ubiquitous presence of Hp in the environment. Regardless of the mode of transmission, our data strongly suggested that higher educational attainment and possibly better hygiene practices might both play an important and decisive role in the prevention of Hp infection. Future research should assess the impact of improving education and personal hygiene in preventing Hp infection. Further studies are also warranted on the zoonotic transmission of Hp.

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