

Helicobacter pylori-associated hypochlorhydria in children, and development of iron deficiency

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ABSTRACT

Aims Acute *Helicobacter pylori* infection is associated with transient hypochlorhydria. In *H pylori*-associated atrophy, hypochlorhydria has a role in iron deficiency (ID) through changes in the physiology of iron-complex absorption. The aims were to evaluate the association between *H pylori*-associated hypochlorhydria and ID in children.

Methods Symptomatic children (n=123) were prospectively enrolled. Blood, gastric juice and gastric biopsies were taken, respectively, for haematological analyses, pH assessment and *H pylori* determination, and duodenal biopsies for exclusion of coeliac disease. Stool samples were collected for parasitology/microbiology. Thirteen children were excluded following parasitology and duodenal histopathology, and five due to impaired blood analysis.

Results Ten children were hypochlorhydric (pH>4) and 33 were *H pylori* positive. In *H pylori*-positive children with pH>4 (n=6) serum iron and transferrin saturation levels % were significantly lower (p<0.01) than *H pylori*-positive children with pH≤4. No differences in ferritin, or total iron binding capacity, were observed. In *H pylori*-negative children with pH>4, iron and transferrin saturation were not significantly different from children with pH≤4.

Conclusions Low serum iron and transferrin in childhood *H pylori* infection is associated with hypochlorhydria. In uninfected children, hypochlorhydria was not associated with altered serum iron parameters, indicating a combination of *H pylori* infection and/or inflammation, and hypochlorhydria has a role in the aetiology of ID. Although *H pylori*-associated hypochlorhydria is transient during acute gastritis, this alters iron homeostasis with clinical impact in developing countries with a high *H pylori* prevalence.

INTRODUCTION

Helicobacter pylori infection has been associated with many extraintestinal conditions.¹ Among these, iron deficiency (ID) and iron deficiency anaemia (IDA) have been extensively evaluated, but studies on the relationship between *H pylori* infection and iron disturbance are variable.²⁻³ The majority of paediatric studies have been non-invasive,⁴⁻⁷ and with limited exceptions,⁸⁻⁹ almost all have failed to include endoscopic analyses to exclude patients with comorbidity resulting in abnormal iron absorption, such as coeliac disease, peptic ulcers, oesophagitis and duodenal mucosal abnormalities. In addition, of relevance to studies in developing countries, other enteric infections affecting iron absorption, or producing abnormal iron losses, have not been evaluated.

Recent meta-analyses indicates *H pylori* eradication results in improved iron status of children and adults with ID/IDA compared with iron therapy alone. Importantly, iron supplementation in *H pylori*-infected children has no effect on impaired iron status in absence of eradication therapy.¹⁰⁻¹² This suggests underlying changes in gastric inflammation, or infection-related perturbations in gastric physiology may contribute to ID in *H pylori* infection.¹³ *H pylori* infection is also associated with marked reduction in gastric juice ascorbic acid,¹⁴ which binds to reduced ferrous iron facilitating iron transport and uptake.

In adults, hypochlorhydria in *H pylori*-associated corpus atrophy has a role in ID through changes in physiology of iron-complex absorption.¹⁵ Although *H pylori* is acquired early in life,¹⁶ atrophy is not a feature of childhood infection. Clinically acute *H pylori* infection is associated with transient hypochlorhydria of variable duration¹⁷⁻¹⁸ which is also observed in animal models.¹⁹ The role of hypochlorhydria in *H pylori*-associated ID in childhood has not been previously investigated. The aim of this study was to evaluate the association between *H pylori*-associated hypochlorhydria and ID in symptomatic children undergoing upper gastrointestinal endoscopy.

METHODS

Patients

The study was approved by the local IRB (Pontificia Universidad Católica de Chile).

Signed informed consent forms by patients, or parents, were obtained for study inclusion. One hundred and twenty-three consecutive children with abdominal symptoms were enrolled. Exclusion criteria included antibiotic use, H₂ antagonist or proton pump inhibitors (PPIs) in the previous 28 days, antacids on day of endoscopy, peptic ulcers, coeliac disease, enteropathies with villous atrophy, confounding enteric infections, oesophageal varices, coagulation disorders, acquired or congenital immunosuppression, renal failure, haematologic disorders and neoplasias. Following endoscopy, additional exclusion criteria were: undiagnosed coeliac disease, and any non-specific duodenal inflammation.

A detailed clinical history was obtained from each patient, or their parents, including presence, severity and duration of abdominal pain, acute diarrhoea, chronic diarrhoea, vomiting, antecedent of weight loss and fever. Nutrition status was assessed by weight, height and body mass index (BMI). Clinical indication of endoscopy was classified according to the referral physician's indication, as recurrent abdominal pain, acute vomiting, recurrent

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abdominal pain with family history of peptic ulcers, gastro-oesophageal reflux disease, or past history of upper gastrointestinal bleeding.

Endoscopy and *H pylori* infection

Endoscopic procedures were performed in the Hospital Clínico of the Pontificia Universidad Católica de Chile, between 2008 and 2010. Blood collection for iron profile was undertaken at moment of venous puncture for sedation. Gastric juice was obtained at the beginning of endoscopy, and pH determined on pH indicator strips (pH 0–14 Universal indicator, Merck, Germany). Biopsies were taken from antrum, corpus and second part of duodenum for histology, and antral biopsies for urease test and microbial culture. A subject was considered *H pylori*-positive if one of the rapid urease tests (Pronto Dry, Ecifarma, Chile), culture or gastric histology was positive. A week after endoscopy, stool samples were collected for microbial culture, immunoassay for rotavirus, ova and parasite analysis.

H pylori were grown on 5% (v/v) horse blood agar plates for 3–7 days in a microaerophilic atmosphere, and identified based on their characteristic morphology and urease, oxidase and catalase activities. Multiple colony sweeps of bacteria were harvested for DNA extraction and *cagA* determination by PCR as previously described.²⁰

Histopathology

Sections of antral and corpus mucosa were stained with H&E or Gimenez stain, and examined for *H pylori* and associated pathology by one pathologist (MMW) in a blinded fashion. Histopathology was scored for active and chronic gastritis, lymphoid follicles, atrophy and intestinal metaplasia, according to the Sydney grading system. Sections of duodenal mucosa were assessed for confounding-associated pathology. Six children, with unsuspected coeliac disease, or non-specific duodenal inflammation in the absence of duodenal gastric metaplasia, were excluded.

Blood analysis

Serum iron, total iron-binding capacity (TIBC) and transferrin saturation were determined by colorimetric spectrophotometer (Modular P, Roche Diagnostics GmbH, Mannheim, Germany) and ferritin by immunoassay by direct chemiluminescence (ADVIA Centauro, Siemens Healthcare Diagnostics Inc, USA).

Statistical analysis

Comparisons between groups were performed using a Student t test for parametric data, and a Mann–Whitney test for non-parametric data. Categorical data were analysed using a χ^2 test and Fisher's exact test. Pearson's correlation coefficient was used to examine the correlation between gastric juice pH and serum iron parameters. A p value less than 0.05 was considered significant.

RESULTS

Patients and *H pylori* status

A total of 123 consecutive children (51 males, 72 females, age range 4–16 years, mean age 10.7±3.1) who fulfilled the entry criteria were recruited. After endoscopy, 18 patients were excluded for at least one criterion: coeliac disease (2); non-specific duodenal inflammation (4); parasitic infections (9, two of whom had duodenal inflammation); and incomplete blood analysis (5). In the 105 patients analysed, there was no significant difference in gender distribution, mean age, nutritional status, symptoms as reported by questionnaires, or symptoms,

Table 1 Demographic and clinical characteristics of children according to *Helicobacter pylori* status

	<i>H pylori</i> (–), n (%)	<i>H pylori</i> (+), n (%)	Total, n (%)	p Value
	72 (69)	33 (31)	105 (100)	
General characteristics				
Male, n (%)	31 (43)	15 (45)	46 (44)	ns
Female, n (%)	41 (57)	18 (55)	59 (56)	ns
Average age, mean±SD	10.5±3.0	10.8±3.5	10.6±3.1	ns
Weight kg, mean±SD	39.3±12.2	41.4±12.9	39.9±12.4	ns
Height cm, mean±SD	143.9±16.4	144.9±18.2	144.2±16.9	ns
BMI, mean±SD	18.7±2.9	19.3±2.6	18.8±2.8	ns
Symptoms*				
Abdominal pain	55 (76)	29 (90)	84 (80)	ns
Acute diarrhoea	18 (25)	7 (21)	25 (24)	ns
Chronic diarrhoea	6 (8)	3 (9)	9 (9)	ns
Vomiting	25 (35)	18 (55)	43 (41)	0.05
Weight loss	28 (39)	12 (36)	40 (38)	ns
Indication for endoscopy†				
Recurrent abdominal pain (RAP)	48 (67)	23 (70)	71 (68)	ns
Vomiting	7 (10)	2 (6)	9 (9)	ns
RAP+family history	8 (11)	4 (12)	12 (11)	ns
Gastro-oesophageal reflux disease	7 (10)	4 (12)	11 (10)	ns
Upper gastrointestinal bleeding	1 (1)	0 (0)	1 (1)	ns

*Symptoms as reported by clinical questionnaire.

†Clinical indication for endoscopy according to referring physician.

BMI, body mass index; ns, not significant.

according to the referring physician, between the 33 *H pylori*-positive and 72 *H pylori*-negative children (table 1).

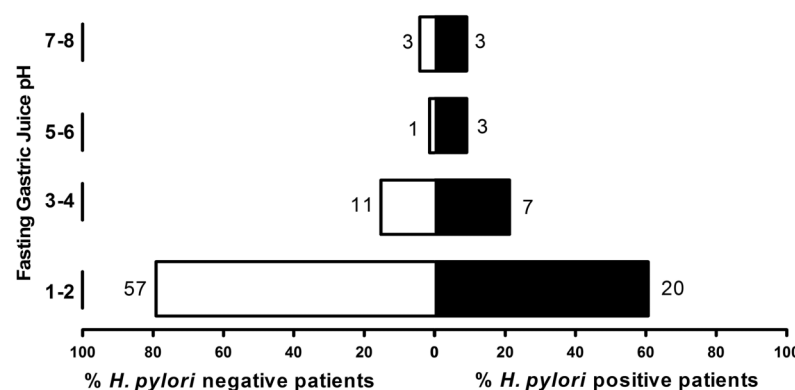
There were no significant differences between *H pylori*-infected and non-infected children, with respect to serum iron and transferrin saturation. By contrast, TIBC was higher in infected, compared with non-infected children (348±39.6 vs 317.8±39.4 µg/dl, $p<0.001$), and ferritin concentrations reduced (33.5±24.9 vs 39.9±21.2 ng/ml, $p<0.05$). Fifteen of the *H pylori* isolates cultured were *cagA* positive and 12 *cagA* negative. (Two children with *cagA*-negative isolates were excluded, based on associated coinfections). There was no difference in serum iron, TIBC, serum ferritin or transferrin saturation between children with *cagA*-positive and *cagA*-negative *H pylori*.

Gastric pH and pathology

The numbers of *H pylori*-negative and positive children with fasting gastric juice of pH 1–2, 3–4, 5–6 and 7–8 are shown in figure 1. A significantly higher ($p<0.05$) percentage of *H pylori*-infected children had gastric juice pH above 4.0 (6/33, 18%) compared with *H pylori*-negative children (4/72, 6%). Among children with hypochlorhydria (pH>4.0), 60% (6/10) were infected with *H pylori* compared with 28% (27/95) in children with normal gastric pH (pH≤4.0) ($p<0.05$). *H pylori*-infected children had higher fasting gastric juice pH (mean±SD, 3.0±1.9) than uninfected children (2.4±1.3). No difference in *H pylori cagA* status was observed in culture-positive children with gastric juice pH>4.0 and pH≤4.0.

In *H pylori*-positive children, gastric histopathology in those with gastric juice pH>4.0 and pH≤4.0 was compared (table 2). There was no evidence of atrophy or intestinal metaplasia in children with, or without, hypochlorhydria. Antral lymphoid

Figure 1 Fasting gastric juice pH in *Helicobacter pylori*-negative (n=72) and *H pylori*-positive children (n=33). Bars represented percentage of total of each group. Numbers of patients are given beside the blocks. Comparison of *H pylori*-positive and negative children in pH categories 1–4 and 5–8 ($p<0.05$, Fisher's exact test).



follicles, but not corpus follicles, were less frequent ($p<0.05$), and antral chronic gastritis was lower ($p=0.05$) in children with hypochlorhydria compared with those with gastric juice $pH\leq 4.0$. No differences in active gastritis were observed in relation to gastric juice pH. Three of the *H pylori*-negative children with gastric juice $pH>4$ had histologically normal gastric mucosa, and one child had mild chronic corpus inflammation. Three of the four hypochlorhydric *H pylori*-negative children had sera available for *H pylori* IgG serology, and all were seronegative.

Impact of gastric pH on iron parameters

Children with gastric juice $pH>4$ (mean \pm SD=7.0 \pm 1.2) were similar in gender distribution, age, weight, height and BMI, as compared with children with normal gastric juice pH ($pH\leq 4.0$, 2.1 \pm 0.6) (table 3). Hypochlorhydric children had a significant increase in vomiting, as reported by clinical questionnaires

($p<0.05$), and vomiting as the main indication for endoscopy, according to their referring physician ($p=0.01$).

H pylori-infected children with gastric juice $pH>4$ had significantly lower serum iron concentrations ($p<0.01$) and transferrin saturation ($p<0.01$), but similar levels of TIBC and ferritin than children with gastric juice $pH\leq 4.0$ (figure 2). However, in uninfected children, no differences in serum iron and transferrin saturation were evident between those with gastric juice $pH>4$ and $pH\leq 4.0$ (data not shown). In *H pylori*-positive children, fasting gastric juice pH was negatively correlated with serum iron (Pearson's $r=-0.33$, $p=0.05$) and transferrin saturation ($r=-0.35$, $p<0.05$). No significant correlation was observed between gastric juice pH and TIBC or serum ferritin concentrations.

Table 2 Histology of *Helicobacter pylori*-infected children according to gastric pH

Histology	Antrum n (%)		p Value	Corpus n (%)		p Value
	pH \leq 4	pH>4		pH \leq 4	pH>4	
Chronic gastritis*:						
Absent	1 (4)	0 (0)	ns	2 (7)	0 (0)	ns
Present	25 (96)	5 (100)		25 (93)	6 (100)	
Lymphoid follicles†:						
Absent	5 (19)	4 (67)	0.02	15 (56)	3 (50)	ns
Present	21 (81)	2 (33)		12 (44)	3 (50)	
Chronic gastritis*, grade:						
Absent	1 (4)	0 (0)		2 (7)	0 (0)	
Mild	15 (58)	4 (80)	0.05	21 (78)	4 (66)	ns
Moderate	10 (38)	0 (0)		3 (11)	2 (33)	
Severe	0 (0)	1 (20)		1 (4)	0 (0)	
Polymorphonuclear infiltrate*, grade:						
Absent	10 (38)	3 (60)		17 (63)	2 (33)	
Mild	15 (58)	2 (40)	ns	10 (22)	4 (67)	ns
Moderate	1 (4)	0 (0)		0 (0)	0 (0)	
Severe	0 (0)	0 (0)		0 (0)	0 (0)	
Gastric atrophy*:						
Absent	26 (100)	5 (100)		27 (100)	6 (100)	
Intestinal metaplasia*:						
Absent	26 (100)	5 (100)		27 (100)	6 (100)	

*Two patients are missing for evaluation in antrum: one insufficient sample, another with many lymphoid follicles unable to evaluate gastritis accurately.
†One patient is missing for evaluation in antrum; ns, not significant.

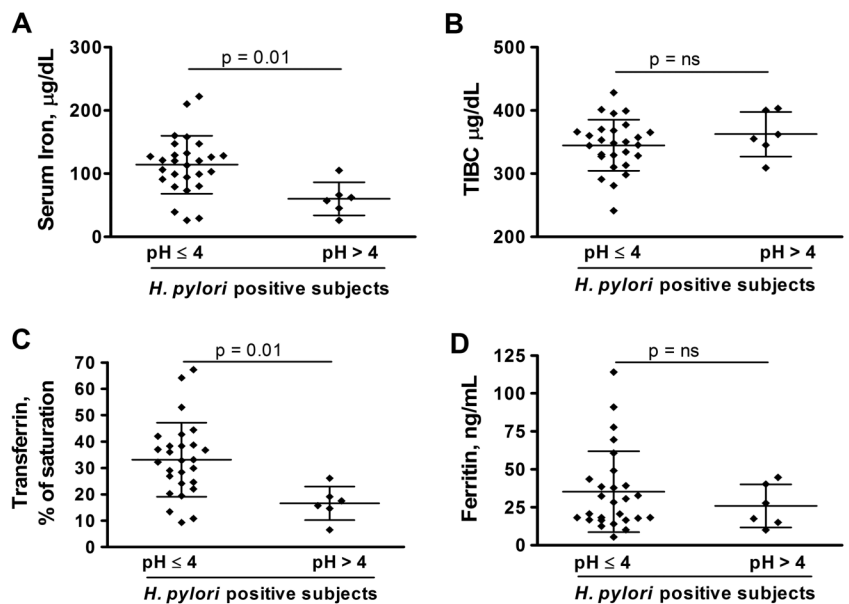
Table 3 Demographic and clinical characteristics of children according to gastric pH

	pH \leq 4	pH>4	Total	p Value
General characteristics				
pH, mean \pm SD (range)	2.1 \pm 0.6 (1–4)	7 \pm 1.2 (5–8)	2.6 \pm 1.5 (1–8)	
—n (%)	95 (90)	10 (10)	105 (100)	
Male, n (%)	40 (42)	6 (60)	46 (44)	
Female, n (%)	55 (58)	4 (40)	59 (56)	
Average age, mean \pm SD	10.7 \pm 3	9.5 \pm 4.3	10.6 \pm 3.1	ns
Weight kg, mean \pm SD	40.2 \pm 12.4	37.8 \pm 12.9	39.9 \pm 12.4	ns
Height cm, mean \pm SD	145.1 \pm 16.1	135.9 \pm 22.4	144.2 \pm 16.9	ns
BMI, mean \pm SD	18.7 \pm 2.8	19.8 \pm 2.8	18.8 \pm 2.8	ns
Symptoms*, n (%)				
Abdominal pain	76 (80)	8 (80)	84 (80)	ns
Acute diarrhoea	23 (24)	2 (20)	25 (24)	ns
Chronic diarrhoea	9 (9)	0 (0)	9 (9)	ns
Vomiting	36 (38)	7 (70)	43 (41)	0.05
Weight loss	36 (38)	4 (40)	40 (38)	ns
Indication for endoscopy, n (%)†				
Recurrent abdominal pain (RAP)	65 (68)	6 (60)	71 (68)	ns
Vomiting	6 (6)	3 (30)	9 (9)	0.01
RAP+family history	12 (13)	0 (0)	12 (12)	ns
Gastro-oesophageal reflux disease	10 (11)	1 (10)	11 (10)	ns
Upper gastrointestinal bleeding	1 (1)	0 (0)	1 (1)	ns

*Symptoms as reported by clinical questionnaire.

†Clinical indication for endoscopy according to referring physician.
BMI, body mass index; ns, not significant.

Figure 2 Iron markers in *Helicobacter pylori*-infected individual children according to gastric pH ($\text{pH} \leq 4$) or hypochlorhydria ($\text{pH} > 4$): serum iron mg/dl (A), total iron-binding mg/dl (B), transferrin % saturation (C) and ferritin ng/ml (D).



DISCUSSION

ID and IDA are the most common nutritional disorders worldwide, particularly in developing countries.²¹ They can result in developmental delay in height and weight,^{22–23} and increases in mortality and morbidity.²⁴ In this study, the relation between gastric juice pH and ID in *H. pylori*-infected children undergoing upper gastrointestinal endoscopy has been investigated. *H. pylori* infection was significantly more frequent in children with hypochlorhydria ($\text{pH} > 4$) compared with those with gastric juice $\text{pH} \leq 4$. Additionally, fasting gastric juice pH was higher in *H. pylori*-infected children concurring with recent non-endoscopic studies on basal and pentagastrin-stimulated gastric acid output in preschool children in Bangladesh.²⁵ Importantly, in the latter study, successful eradication of *H. pylori* increased gastric acid output,²⁵ strongly indicating that *H. pylori* is causing impairment of acid secretory responses, rather than infection resulting as a consequence of hypochlorhydria.

Hypochlorhydria in *H. pylori*-associated corpus atrophy in adults¹⁵ has a role in ID through changes in the physiology of iron-complex absorption. The present study now identifies that *H. pylori*-infected children with hypochlorhydria in the absence of corpus atrophy have significantly reduced serum iron and transferrin saturation. Importantly, hypochlorhydria in absence of *H. pylori* infection was not associated with these changes, suggesting a combination of both *H. pylori* and hypochlorhydria is aetiologically important in ID. In this study, strict criteria excluded children taking, or recently using acid inhibitory drugs. In addition, duodenal pathology and stool parasitology/microbiology excluded children with other infectious or pathological/inflammatory conditions impacting on iron status. The hypochlorhydric children with *H. pylori* infection had significantly reduced antral lymphoid follicles, potentially indicative of earlier stages of infection.

Bioavailability of non-soluble ferric iron for absorption requires reduction to ferrous iron by gastric acid, and binding to ascorbic acid for transportation and duodenal absorption mediated by many proteins and transporters under the regulation of hepcidin.²⁶ Hepcidin has recently been identified in parietal cells, and *H. pylori* infection has been reported to upregulate gastric hepcidin.²⁷ Previous studies have shown that urinary hepcidin concentrations are not modified by *H. pylori* infection in

children,²⁸ and similar observations were made on serum hepcidin concentrations in the present study (data not shown).

The mechanisms of *H. pylori*-induced hypochlorhydria in children in absence of gastric atrophy are not well understood. In adults, acute *H. pylori* infection results in gastric hypochlorhydria which resolves over variable time periods.¹⁷ *H. pylori* may induce hypochlorhydria through increased gastric interleukin (IL)-1 β and tumour necrosis factor (TNF)- α ,^{13–29–30} which inhibit acid secretion, induce parietal cell apoptosis, and decrease enterochromaffin-like cell histamine release.^{31–32} Gene polymorphisms encoding IL-1 β and IL-1 receptor antagonist, associated with increased IL-1 β expression, are related to corpus atrophy and hypochlorhydria in *H. pylori*-infected adults.³² Although these polymorphisms are also related to gastric cancer risk, scarce information is available regarding IL-1 gene cluster polymorphisms as a risk factor for ID in *H. pylori*-infected children.

In this study, no differences in serum iron, TIBC, serum ferritin or transferrin saturation between children with *cagA*-positive and *cagA*-negative *H. pylori* infections were observed. Elegant in vitro studies have shown *H. pylori* CagA protein induces perturbations in cellular trafficking of the transferrin receptor in polarised epithelial monolayers.³³ *In vivo*, however, local immune responses against such virulence factors may modify their cellular function.

Dufour *et al*³⁴ first demonstrated ID/IDA refractory to iron supplementation improved following *H. pylori* eradication. Further consistent observations have been decreased serum ferritin in *H. pylori*-seropositive patients, and increased *H. pylori* prevalence in IDA.^{4–35} Most are descriptive epidemiological studies with non-invasive (serologic) determination of *H. pylori* status.³⁵ There are diverse results on effects of *H. pylori* eradication on ID in different geographic areas and age groups.^{7–36–38} These apparent discrepancies may relate to confounding variables, such as absence of evaluation of intestinal comorbidity (coeliac disease, parasitic infections), and absence of evaluation of drug use (eg, PPIs).

While the association between acute *H. pylori* infection and transient hypochlorhydria in adults is well documented,¹⁷ less data are available in children.^{25–39} Recent functional studies indicate that *H. pylori* impairs gastric acid secretion in children, which resolves following bacterial eradication.²⁵ Even though *H. pylori*-associated hypochlorhydria is a transient period, the

present study identifies iron homeostasis is altered in children with hypochlorhydria and *H pylori* infection, which may have a marked clinical impact in developing countries with a high prevalence of *H pylori*.

What this study adds

Helicobacter pylori infection is associated with ID, but the pathogenic mechanisms are unclear. Acute *Helicobacter* infection in adults and animal models results in transient hypochlorhydria. The role of hypochlorhydria in *H pylori*-associated ID in childhood is unknown.

- ▶ Reductions in serum iron and transferrin saturation occur in *H pylori*-infected children with hypochlorhydria, implicating perturbations in acid homeostasis in *H pylori* infection in the aetiology of ID in children.
- ▶ Transient *H pylori*-associated hypochlorhydria alters iron homeostasis, and will have clinical impact in developing countries with a high *H pylori* prevalence.

Take-home message

- ▶ Reductions in serum iron and transferrin saturation occur in *H pylori*-infected children with hypochlorhydria, implicating perturbations in acid homeostasis in *H pylori* infection in the aetiology of ID in children.

Contributors JEC and HJW hypothesis, obtained funding and coordinated EU CONTENT project; PRH and JEC concept, study design; PRH gastroenterology and clinical evaluation; MMW and ID histopathological evaluation; AV, CAS, MT study organisation, experimental work; PRH, HJW, MMW and JEC data analysis and interpretation; PRH and JEC wrote manuscript.

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Competing interests None.

Patient consent Obtained.

Ethics approval Institute Review Board Pontificia Universidad Catolica de Chile and also there was a review of ETHICS by the European Commission.

Provenance and peer review Not commissioned; externally peer reviewed.

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***Helicobacter pylori*-associated hypochlorhydria in children, and development of iron deficiency**

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