Age dependent hypergastrinaemia in children with Helicobacter pylori gastritis – evidence of early acquisition of infection

W A McCallion, J E S Ardill, K B Bamford, S R Potts, V E Boston

Abstract

Acute Helicobacter pylori associated gastritis causes achlorhydria, a powerful stimulus to gastrin secretion. If H pylori infection is acquired primarily in early childhood, then the degree of hypergastrinaemia in seropositive children should be age dependent. Anti-Helicobacter antibodies and fasting gastrin concentrations were measured in 439 children aged 4 to 13 years attending hospital for routine day case surgery not connected with any gastrointestinal disorder. Thirty per cent were seropositive for H pylori. There was an inverse relationship between the fasting gastrin concentration and age; the mean fasting gastrin in children aged 4–5 years, 155 ng/l, was significantly higher than that seen in children aged 12–13 years, 90 ng/l. The more noticeable hypergastrinaemia seen in young children with H pylori associated gastritis may reflect achlorhydria associated with acute H pylori infection and suggests that this is primarily acquired in early childhood.

Keywords: Helicobacter pylori infection, childhood, hypergastrinaemia.

Helicobacter pylori is believed to be uncommon in children in developed countries. In England the prevalence of H pylori gastritis among school children is reported to range from less than 1%1 to 5%.2 In a study of 466 children from Belgium, the prevalence of H pylori infection among children aged 2–8 years was 5% compared with 13% in those aged 8–14 years.3 We have recently reported an unusually high prevalence of H pylori in children in Northern Ireland. Thirty per cent of 242 children aged 4 to 13 years were seropositive, with a significantly higher prevalence among children from lower socioeconomic backgrounds.4 Furthermore, Webb et al in Stoke on Trent, an area possibly comparable to the Belfast area from which our children were recruited, have suggested that close person to person contact in childhood is an important determinant of seroprevalence of H pylori in adulthood. They proposed that the infection is transmitted directly from one person to another and may be commonly acquired in early life.5

Beyond childhood, H pylori infection rates continue to rise. In one study, 10% of 20 year olds were seropositive compared with 70% of 80 year olds,6 while in another, 10% of 20 year olds and 60% of 60 year olds had H pylori associated gastritis.7 Intrafamilial infection has been demonstrated,89 and it has been suggested that a cohort effect may contribute to the pattern of increasing prevalence with increasing age. This is supported by the finding that only six of 86 subjects known to be seronegative for H pylori in 1969 seroconverted over the next 21 years.10

The association between H pylori gastritis and hypergastrinaemia is well established. Levi et al demonstrated that basal and meal stimulated gastrin concentrations were higher in duodenal ulcer patients with H pylori than in a control group who were H pylori negative,11 and it is known that eradication of H pylori reduces the gastrin response by 50%.12 While it is recognised that approximately 95% of duodenal ulcers occur in patients with H pylori associated gastritis,13–15 Chittajallu et al have shown that the degree of hypergastrinaemia is the same in H pylori positive subjects irrespective of the presence of duodenal ulceration.16

From human ingestion studies, it has been shown that acute H pylori gastritis results in transient achlorhydria.17,18 After ingestion of the organism, the gastric pH seems to remain acidic for the first week followed by a period of achlorhydria which may last several months. Thereafter, gastric acid production returns to normal. Achlorhydria is a powerful stimulant to gastrin secretion.19 It is therefore postulated that acute H pylori gastritis is associated with a considerably raised circulating gastrin and that thereafter, following the return of gastric acidity, the plasma gastrin concentration gradually falls to that seen in adults with chronic H pylori gastritis.

The aim of this study is to determine if the degree of hypergastrinaemia in children with H pylori gastritis is age dependent.

Patients and methods

Four hundred and thirty nine children aged 4–13 years (mean 7-3 years) attending the Royal Belfast Hospital For Sick Children for routine day case surgery were recruited over a six month period. Venepuncture was performed on the children under general anaesthetic.

Serum (1 ml) and plasma (2 ml) were stored at −20°C and assayed in batches for anti-Helicobacter IgG antibodies and fasting gastrin respectively. Anti-Helicobacter antibodies were detected in serum using a commercial ELISA method (HelicoG, Porton
Cambridge Ltd. The assay had previously been validated in 100 children undergoing upper gastrointestinal endoscopy in whom three antral biopsy specimens had been taken for histology, culture, and rapid urease test (CLOtest, Delta West Pty Ltd, Australia) respectively. A diagnosis of *H pylori* gastritis was made if at least two of the three specimens were positive for *H pylori*. The sensitivity of the ELISA was 100% and specificity was 92%. The fasting plasma gastrin concentration was measured by a radioimmunoassay using antisera R98 which is directed towards the C-terminus of gastrin and detects Component I, G34, G17, G14 in equimolar quantities. It binds both sulphated gastrins and requires C-terminal amidation. Cross reaction with cholecystokinin is 0·005%. The assay has a sensitivity of 5 ng/l and the intra-assay and interassay variations were 6·6% and 9·4% respectively at 25 ng/l.20 21

To ensure that socioeconomic factors did not confound the age related seroprevalence, the socioeconomic background of each child was determined, according to parental occupation, as non-manual (Registrar General's class I, II, or III non-manual), or manual (Registrar General's class III manual, IV, or V),22 and the ratio of children of non-manual and manual backgrounds was calculated for each age group.

STATISTICAL ANALYSIS
A Mann-Whitney U test was used to compare the prevalences and fasting gastrin concentrations at different ages in children seropositive and seronegative for *H pylori*. The Spearman rank correlation test was used to calculate correlation coefficients. The χ² test was used to compare seropositivity in different socioeconomic groups.

ETHICS
The study was approved by the Research Ethical Committee of The Queen's University of Belfast. Informed parental consent was obtained in each case.

**Table I** Age related prevalence of *Helicobacter pylori* infection in children in Northern Ireland

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>No</th>
<th><em>H pylori</em> seropositive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5</td>
<td>130</td>
<td>33 (25)</td>
</tr>
<tr>
<td>6-7</td>
<td>120</td>
<td>38 (32)</td>
</tr>
<tr>
<td>8-9</td>
<td>80</td>
<td>19 (24)</td>
</tr>
<tr>
<td>10-11</td>
<td>54</td>
<td>22 (41)</td>
</tr>
<tr>
<td>12-13</td>
<td>55</td>
<td>22 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>439</td>
<td>134</td>
</tr>
</tbody>
</table>

Results
Of 439 children studied, 134 (30%) were seropositive for *H pylori*. Table I shows the age related prevalence of *H pylori* infection. There was a positive correlation between seroprevalence and age (Rs=0·70) with a significant increase in the rate of infection from the age of 4 to 13 years (p=0·025).

Details of parental occupation, and hence socioeconomic class, were available for 431 children. Of 175 children from non-manual backgrounds, 32 (18%) were seropositive for *H pylori* compared with 94 of 256 children (37%) from manual backgrounds (p<0·001). In Table II, socioeconomic background is shown according to age. In the age groups 4-5 and 6-7 years, a higher proportion of the children came from non-manual backgrounds. The ratios of non-manual to manual were 0·74 and 0·84 respectively compared with values of 0·51, 0·63, and 0·58 for the age groups 8-9, 10-11, and 12-13 years respectively. Since *H pylori* infection is more common among children from lower socioeconomic classes, seroprevalence may indeed have been underestimated in the youngest children studied.

The Figure shows the plasma gastrin concentrations according to age in children seropositive and seronegative for *H pylori*, showing the more noticeable hypergastrinaemia at an earlier age. The mean (SEM) fasting gastrin in the seropositive children (127 (12) ng/l) was significantly higher than that found in children seronegative for *H pylori* (53 (2) ng/l) (p<0·001). Furthermore, there was correlation between age and fasting gastrin concentration in both groups of children. In those seropositive for *H pylori*, Rs=−0·27 (p<0·001) and in those seronegative, Rs=−0·21 (p<0·001).

Discussion
Most epidemiological studies to date have reported a low prevalence of *H pylori* seropositivity in children in the developed world and an increasing prevalence with age. In the present study, the prevalence data challenge this view and the importance of low socioeconomic class as a risk factor for the acquisition of *H pylori* infection during childhood has been shown. This is in broad agreement with other studies in which socioeconomic class was determined in terms of parental occupation, family income, and the standard of education.23 All

**Table II** Age related socioeconomic background of the children studied

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Non-manual background</th>
<th>Manual background</th>
<th>Non-manual/manual ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5</td>
<td>56</td>
<td>76</td>
<td>0·74</td>
</tr>
<tr>
<td>6-7</td>
<td>54</td>
<td>64</td>
<td>0·84</td>
</tr>
<tr>
<td>8-9</td>
<td>26</td>
<td>51</td>
<td>0·51</td>
</tr>
<tr>
<td>10-11</td>
<td>20</td>
<td>32</td>
<td>0·63</td>
</tr>
<tr>
<td>12-13</td>
<td>19</td>
<td>33</td>
<td>0·58</td>
</tr>
</tbody>
</table>

Fasting gastrin concentrations in children with and without anti-*Helicobacter* antibodies (mean (SEM)).

![Graph showing fasting gastrin concentrations in children with and without anti-*Helicobacter* antibodies.](http://gut.bmj.com/Downloaded from http://gut.bmj.com/ on June 23, 2017 - Published by group.bmj.com)
of these probably reflect more direct risk factors of childhood living conditions such as overcrowding and bed sharing thereby facilitating faecal oral or oro-oral spread of the organism. Mitchell et al., in a large cross sectional study in southern China, have suggested that age dependent seroprevalence and the acquisition of H pylori infection. The first occurs in early childhood and the second is a 'steady-state condition' whereby seroprevalence increases by approximately 1% per year. Differences in the prevalence of infection between different regions and countries may therefore be explained by differing rates of acquisition of H pylori infection in early childhood. In the present study, seroprevalence among the youngest children (4 to 7 years) may have been underestimated since the proportion of these children who came from higher social classes was greater than that in the older age groups studied.

A link between childhood H pylori associated gastritis and hypergastrinaemia has been questioned. Oderda et al. failed to show a correlation between serum gastrin concentrations and H pylori status26 and Tsai demonstrated that children with peptic ulcer disease did not have high fasting serum gastrin levels when compared with age matched controls.27 The present study, however, clearly shows that H pylori seropositive children have a significantly higher circulating fasting gastrin value than seronegative children. The Figure illustrates the age dependent nature of this association. In adults with normal H pylori gastritis, the circulating fasting gastrin is increased by approximately 70%. By comparison, the fasting plasma gastrin in children aged 4 to 5 years was increased by 167%, reducing with age to a 75% increase in the 10 to 11 years age group. While chronic H pylori gastritis is associated with normal or raised gastric acid secretion, acute H pylori infection results in transient achlorhydria, which in turn is a stimulus to gastrin production. It is possible, therefore, that the considerably raised fasting gastrin value seen in young children with H pylori gastritis is a reflection of achlorhydria associated with acute infection. This provides more evidence that H pylori associated gastritis is frequently acquired in early childhood.

The upper limit of normal for fasting gastrin in children seronegative for H pylori in this study (mean (±2 SD)), 125 ng/l, is higher than that found in adults who are negative for H pylori, 95 ng/l.21 An inverse relationship between age and the basal gastrin value has been reported previously – the highest values for fasting gastrin being observed in children less than 18 months of age29 and it was suggested by the authors that this physiological hypergastrinaemia seen in young children may play an important role in the trophic development of the stomach. Alternatively, since we have shown here that children are commonly infected by H pylori at an early age, the relative hypergastrinaemia seen in young children who have no detectable anti-Helicobacter IgG may be due to those who have recently become acutely infected with this organism and have not had sufficient time to generate a systemic IgG response.

In conclusion, the degree of hypergastrinaemia seen in children with H pylori associated gastritis is greater than that seen in adults with this infection. Hypergastrinaemia was most noticeable in young children and may reflect the period of achlorhydria associated with acute H pylori infection. In view of these findings, it is suggested that H pylori infection is commonly acquired in early childhood.


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