Role of Helicobacter pylori Infection in the Development of Pernicious Anemia

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It is now accepted that most patients with atrophic gastritis of the stomach have been infected with Helicobacter pylori. Several investigators have also suggested the possibility that H. pylori is involved in the early stages of pernicious anemia, which leads to severe atrophic gastritis of the fundus. In this article, studies investigating the association of this specific form of atrophic gastritis and H. pylori infection are reviewed. Most of the published studies indicate that patients with pernicious anemia are infected with H. pylori less often than are age-matched controls. However, because H. pylori infection may be present before the development of pernicious anemia, prospective studies during the pre-pernicious anemia stage of gastritis are needed.

Cobalamin deficiency is the most common cause of pernicious anemia, a type of megaloblastic anemia. Cobalamin is present in food and is released as a stable complex with gastric R binder, one of a group of related glycoproteins. In the duodenum, the cobalamin–R binder complex is digested; the cobalamin is released and then binds to intrinsic factor that is produced by the parietal cells of the stomach. Cobalamin is transferred to another transport protein, transcobalamin II, which is then secreted into the circulation [1, 2]. Inadequate production of intrinsic factor is the most common cause of cobalamin malabsorption (table 1). Pernicious anemia is most frequently seen in descendants of northern Europeans and in African-Americans, and it may be less common in southern Europeans and Asians [3]. It is considered a disease of elderly individuals; the mean age at which pernicious anemia is diagnosed is about 60, and it rarely occurs in persons younger than age 30 [4].

Chronic atrophic gastritis is invariably present in patients with pernicious anemia. Type A chronic atrophic gastritis, which leads to atrophy of gastric glands, is most severe in the body of the stomach; acid secretion is decreased, and there is an autoimmune component as well as a high prevalence of antibodies to parietal cells and intrinsic factor [5, 6].

Atrophy of gastric glands in type B chronic atrophic gastritis first affects the antral mucosa; acid secretion is normal, and apparently an autoimmune component is involved. There are numerous studies suggesting that Helicobacter pylori infection is highly associated with this type of gastritis [7–9].

It has been proposed that pernicious anemia may represent the final phase of a process that begins with H. pylori–associated gastritis and evolves through progressive levels of atrophy until parietal cell mass is entirely lost [10]. Several studies have investigated the role of H. pylori in pernicious anemia; in this article, these studies are reviewed, and their findings are summarized.

Literature Review

One of the first studies that investigated the possible association of H. pylori infection and pernicious anemia showed, by means of histological methods, a significantly lower prevalence of H. pylori infection in patients with pernicious anemia (21.4%) than in age- and sex-matched controls (93%; P = .006) [11]. However, no difference in the presence of chronic atrophic gastritis and/or intestinal metaplasia was observed between patients with pernicious anemia and controls.

My colleagues and I, like other researchers, also investigated the association of H. pylori infection with pernicious anemia (which accompanies type A gastritis); we found a highly significant negative association between the two entities [12]. These data further support the observation that gastric tissue associated with pernicious anemia may be refractory to H. pylori colonization. In this study, we found that patients with pernicious anemia more frequently had IgA antibodies to H. pylori than IgG antibodies to H. pylori. Seropositivity with IgA antibodies, but not with IgG antibodies, is uncommon in H. pylori–infected individuals. There is not a clear explanation of the higher rates of seropositivity with IgA antibodies among patients with pernicious anemia than among controls.

We previously demonstrated that symptomatic H. pylori–infected patients presented with a vigorous immune response of both IgA and IgG antibodies to whole-cell antigen preparations [13]. However, in asymptomatic volunteers, the immune response of IgA antibodies was highly specific but poorly sensitive, and it has not been used for diagnostic purposes. Possible explanations for the higher rates of seropositivity with IgA antibodies, but not with IgG antibodies, among patients with pernicious anemia are that pernicious anemia may represent the final phase of a process that begins with H. pylori–associated
H. pylori rates of gastritis and that the immune response of IgG antibodies fades faster than that of IgA antibodies.

Other studies [14–16] confirmed the observation that the rates of H. pylori infection among patients with pernicious anemia are lower than those among age- and sex-matched controls (table 2). Some of the studies established the status of H. pylori infection on the basis of only serology [16]. In the studies in which biopsy specimens were obtained [14, 15], the specimens were usually from different sites (the fundus in patients with pernicious anemia and the antrum in controls). In a recently reported study by Haruma et al. [17], histological findings for fundus and antrum specimens from patients with pernicious anemia and controls were compared in parallel, and the results were similar to those of the above-mentioned reports. The main finding was that no H. pylori infection was observed in patients with pernicious anemia. In contrast, >60% of the controls were infected with H. pylori.

Possible explanations for the differences observed between patients with pernicious anemia and controls are that the number of H. pylori organisms in the gastric mucosa varies widely between patients with and without pernicious anemia and that the lack of documentation of H. pylori infection in patients with pernicious anemia is the result of the low sensitivity of the histological assay (sensitivity of this assay may vary between 60% and 95%). However, the fact that serological assays have sensitivities in the range of 90%–95% and the fact that in theory these assays sample the whole stomach have produced similar results suggest that the differences between patients with pernicious anemia and controls are real and are not the results of differences in the sensitivity of the methodologies used.

Discussion

In summary, patients with pernicious anemia (type A gastritis) develop atrophic gastritis mainly in the fundus with an autoimmune component. In contrast, patients with H. pylori infection (type B gastritis) develop atrophic gastritis in the antrum that over 15 to 20 years may progress to involve the entire stomach, but this type of gastritis usually occurs without an autoimmune component. Atrophic gastritis of the fundus with an autoimmune component, which may eventually lead to pernicious anemia, is more frequently seen in women than in men [18]. This phenomenon is not unique since it is well known that females produce more vigorous cellular and humoral immune reactions and have autoimmune diseases more frequently than males [19, 20]. In contrast, atrophic gastritis is most commonly seen in men with H. pylori infection [6].

Other evidence against the role of H. pylori infection in pernicious anemia is that in countries with a high prevalence of H. pylori infection and a high prevalence of atrophic gastritis, pernicious anemia appears to be uncommon [4, 15]. However, this observation might reflect surveillance artifacts. Finally, some patients with pernicious anemia are infected with H. pylori, and histological follow-up shows that the infection may persist for >5 years despite the development of atrophic gastritis [14]. These findings indicate no causal relationship between H. pylori infection and pernicious anemia.

There is little information available on the possible association of H. pylori infection with other types of megaloblastic anemias. One study that investigated the association between H. pylori infection and megaloblastic anemia examined patients with food-cobalamin malabsorption [21]. The investigators found that patients with low levels of serum cobalamin had a higher seroprevalence of H. pylori infection. Although in this case low serum cobalamin levels were not related to pernicious anemia, there is evidence that some patients with food-cobalamin malabsorption subsequently develop pernicious anemia [22], and the association between H. pylori infection and food-cobalamin malabsorption suggests that gastritis induced by H. pylori infection predisposes to a more severe form of food-cobalamin malabsorption.

Further studies are needed to explain the possible associations between cobalamin deficiency anemias and H. pylori infection. Currently, there is not sufficient evidence to propose.

Table 1. Classification of the megaloblastic anemias.

<table>
<thead>
<tr>
<th>Cobalamin deficiency</th>
<th>Protein deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Inadequate intake (rare) (i.e., strictly vegetarian diet)</td>
<td>a. Inadequate production of intrinsic factor</td>
</tr>
<tr>
<td>II. Malabsorption</td>
<td>b. Gastric dysfunction</td>
</tr>
<tr>
<td></td>
<td>c. Disorders of terminal ileum (i.e., tropical sprue, nontropical sprue, regional enteritis)</td>
</tr>
<tr>
<td></td>
<td>d. Competition for cobalamin (i.e., fish tapeworm, bacteria)</td>
</tr>
<tr>
<td></td>
<td>e. Drugs (i.e., p-aminosalicylic acid)</td>
</tr>
<tr>
<td></td>
<td>III. Other (nitrous oxide, transcobalamin II deficiency)</td>
</tr>
</tbody>
</table>

NOTE. Data are from [1].

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Discussion

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Table 2. Prevalence of Helicobacter pylori infection in patients with pernicious anemia and age-matched controls.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Patients with pernicious anemia</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[12]</td>
<td>Los Angeles</td>
<td>0.0</td>
<td>40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>[14]</td>
<td>London</td>
<td>3.5</td>
<td>*</td>
<td>NA</td>
</tr>
<tr>
<td>[15]</td>
<td>Los Angeles</td>
<td>11.0</td>
<td>71</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>[16]</td>
<td>Helsinki</td>
<td>10.0</td>
<td>81</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>[17]</td>
<td>Hiroshima</td>
<td>0.0</td>
<td>67</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

NOTE. NA = not applicable.
* No control group was included.
a causal relationship between \textit{H. pylori} infection and cobalamin deficiency anemia. However, a recent study was done to determine whether evidence of \textit{H. pylori} infection may disappear during the course of the illness [23]. My colleagues and I found a seroreversion rate of \textgreater6\% per year among 47 patients with pernicious anemia who were studied prospectively. This result is consistent with the hypothesis that \textit{H. pylori} infection precedes at least some cases of pernicious anemia.

In conclusion, prospective studies during the pre–pernicious anemia stage of gastritis are needed to clarify the putative role of \textit{H. pylori} infection in pernicious anemia.

\section*{References}