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EDITORIAL

Helicobacter pylori virulence factors in duodenal ulceration: A primary cause or a secondary infection causing chronicity

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Abstract

Reports from countries with a high prevalence of *Helicobacter pylori (H pylori)* infection do not show a proportionately high prevalence of duodenal ulceration, suggesting the possibility that *H pylori* cannot be a primary cause of duodenal ulceration. It has been mooted that this discrepancy might be explained by variations in the prevalence of virulence factors in different populations. The aim of this paper is to determine whether the published literature gives support to this possibility. The relevant literature was reviewed and analyzed separately for countries with a high and low prevalence of *H pylori* infection and virulence factors. Although virulent strains of *H pylori* were significantly more often present in patients with duodenal ulcer than without the disease in countries with a low prevalence of *H pylori* infection in the population, there was no difference in the prevalence of virulence factors between duodenal ulcer, non-ulcer dyspepsia or normal subjects in many countries, where the prevalence of both *H pylori* infection and of virulence factors was high. In these countries, the presence of virulence factors was not predictive the clinical outcome. To explain the association between virulence factors and duodenal ulcer in countries where *H pylori* prevalence is low, only two papers were found that give little support to the usual model proposed, namely that organisms with the virulence factors are more likely than those without them to initiate a duodenal ulcer. We offer an alternative hypothesis that suggests virulence factors are more likely to interfere with the healing of a previously produced ulcer. The presence of virulence factors only correlates with the prevalence of duodenal ulcer in countries where the prevalence of *H pylori* is low. There is very little evidence that virulence factors initiate duodenal ulceration, but they may be related to failure of the ulcer to heal.

HELICOBACTER PYLORI VIRULENCE FACTORS AND DUODENAL ULCERATION

Following Warren and Marshall's historic paper in 1984[1], evidence for an association between duodenal ulceration and *Helicobacter pylori (H pylori)* infection has been strengthened. Earlier publications, however, were from developed countries, where the overall prevalence of *H pylori* infection was between 40% and 60%. The difficult problem that remained was why everyone with *H pylori* infection did not develop duodenal ulceration. This problem was increased by the reporting of the "African enigma" from the savannah regions of the West Coast of Africa[2,3], where the prevalence of *H pylori* infection was much higher (> 90%), but the prevalence of duodenal ulceration was relatively low. This was followed by an increasing number of reports from other countries, where a high prevalence of *H pylori* infection did not correlate with a high prevalence of duodenal ulceration (Africa[4-8], India[9-11], China[12,13], Japan[14,15], Korea[16], Peru[17], Iran[18], Vietnam[4]).

When it was later reported that some strains of *H pylori* were more virulent than others, this seemed a possible explanation of the paradox. In the more developed countries, the virulent factors, cagA (cytotoxin associated antigen) and vacA (vacuolating factor), were present in between 40% and 60% of *H pylori* strains, and it was suggested that these strains might prove to be the causal factors in duodenal ulceration and account for the discrepancies[19-24].

There is no doubt about the association of these factors with duodenal ulceration in countries, where the overall prevalence of *H pylori* infection and virulence factors is relatively low, compared with countries where it is high. However, an increasing number of reports from countries, where *H pylori* infection is almost ubiquitous (70-90+%) and 77%-88% of the strains carry the viru-

lence factors cagA and vacA, have shown no relationship between these factors and clinical outcome (South Africa[6], India[25,26], China[27-31], Japan[32-43], Korea[44-47], China Taiwan[48], Thailand[49], Sudan[50], Turkey[51-53], Nigeria[54,55], Sri Lanka[56], Bangladesh[57], Serbia Montenegro[58], Estonia[59], Brazil[60], Singapore[61,62], Mexico[63]). A few similar reports have also come from countries with a low prevalence (Germany[45,64], France[65,66], Finland[67], UK[68,69], USA[70]).

Most cagA positive strains also carry the vacA gene. When present, the cagA gene secretes the toxic CagA protein, but not all vacA strains secrete a toxigenic protein. There are different allelic types of vacA, the types vacAs1 and vacAs1m1 are toxic and strongly associated with duodenal ulceration, mostly in countries with a relatively low prevalence of *H pylori* infection. Once again, however, reports from countries with a high prevalence of these factors show no link between the presence of vacAs1 [6,26,29,38,44,47-49,56,57,60,71] or vacAs1m1[25,26,29,41,44,52,55,59,65,71] and clinical outcome.

Other virulence markers have been reported: ice-A1gene [induced by contact with gastric epithelium] and babA2 gene (blood group antigen binding adhesin), which binds to Lewis B present on gastric epithelial cells, show an association with duodenal ulceration in countries, where the prevalence of *H pylori* and these strains is low. However, reports from many countries with a high prevalence of *H pylori* and these virulence markers again show that in these areas they are not predictive of the clinical outcome (iceA1[6,26,31,41,45,48,52,55,57,61,62,72-74], babA2[6,32,39,41,42,47,61]).

Thus, there remains the anomaly that, although duodenal ulceration is strongly associated with *H pylori* infection and certain virulence factors in countries with a relatively low prevalence of both *H pylori* infection and virulence factors, this association disappears in many countries[75] where these prevalences are high, and where *H pylori* infection and virulence factors do not predict clinical outcome. This casts doubt upon whether *H pylori* initiates duodenal ulcer. This doubt is strongly supported by the finding that most patients with a short history[76] or all with less than 6 month`s history[77] of duodenal ulcer symptoms were uninfected with *H pylori*.

Nonetheless the importance of *H pylori* infection and virulence factors cannot be dismissed. There is no doubt that the eradication of *H pylori* infection leads to healing of duodenal ulceration and the risk of recurrence is greatly reduced. There is also no doubt about the strong association of *H pylori* and virulence factors with duodenal ulceration in countries where the overall prevalence of *H pylori* infection is relatively low.

The tendency for *H pylori* to be absent in the early case suggests that the organism is not the primary cause producing duodenal ulcer. The evidence that the chronic course of healing→recurrence→etc. of the typical chronic duodenal ulcer is converted in most cases into stable healing by eradicating *H pylori* suggests that the organism, when present, interferes with the healing process.

There remains the question why the virulence factors are related to the presence of duodenal ulceration in the countries with a low prevalence of *H pylori* infection. It is possible that colonization of nearby areas of antral epithelium or of gastric metaplasia in the duodenum by *H pylori* leads to the local release of toxins that produces the duodenal ulcer. However, this straightforward model has not been substantiated. The toxins concerned have been demonstrated and their toxic effects are determined mostly by their interaction with gastric epithelium[19] and there are only two papers reporting about the damage caused by toxins to duodenal mucosa. One paper[78] reports about the prevention of healing of mechanically abraded human duodenal epithelium *in vitro* by strains of wild *H pylori,* particularly those carrying the vacA gene, and also by supernatant fluid containing the vacA cytotoxin. The other paper[79] reports about increased duodenal mucosal permeability, when exposed to *H pylori* culture fluid in rats. It must be emphasized that neither paper reports about the *initiation* of ulceration.

As an alternative explanation, we advance the following more complicated model which we have partly suggested before[11,77]. *H pylori* is killed by excess acid[80,81]. In countries, where the overall prevalence of *H pylori* infection is low, duodenal ulcer patients initially may be free from *H pylori* infection because of their high acid output. In the early stages of ulceration, many subjects, prior to seeking definitive treatment, control their symptoms with antacids, some including H2 antagonists, which are available without prescription. This reduces the defense against infection with the organism in patients who have hitherto been resistant (since they start *H pylori* negative). This partial reduction in resistance can be overcome by virulent, but not by non-virulent strains, so there is an association between the virulent strains and the chronic ulcer patients, most of whom have become *H pylori*-positive for the organism by 6 months time[76,77]. The high baseline of infection with virulent strains, in the countries with a high prevalence, obscures this effect.

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