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Decision making

Non-ulcer dyspepsia: does *Helicobacter pylori* matter?

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Summary

Non-ulcer dyspepsia is a heterogenous disorder characterised by chronic or recurrent abdominal or retrosternal discomfort lasting for more than four weeks for which no cause can be determined. *Helicobacter pylori* has been implicated as a potential cause in a subset of patients but the association has not been proven and *H pylori* eradication in patients with non-ulcer dyspepsia has had variable results. Large well-controlled studies are needed to clarify the relationship.

Keywords: non-ulcer dyspepsia, *Helicobacter pylori*

Helicobacter pylori

Features:
- a spiral, Gram-negative rod with 4–6 unipolar flagellae.
- easy to culture under microaerobic conditions on special media
- has an extremely high urease activity
- colonises the sub-mucus layer of the human gastric epithelium predominantly in the antrum being always related to cells derived from gastric type mucosa
- diagnosis can be made by histology, culture, CLO test, serology and urea breath test
- modes of transmission could be faecal–oral or oral–oral; this explains the higher prevalence in closed communities, disadvantaged socio-economic groups and developing countries

Box 1

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Introduction

Dyspepsia is an extremely common gastroenterologic complaint consuming large amounts of medical and economic resources. It encompasses a spectrum of diseases from non-ulcer dyspepsia at one end of the scale to carcinoma of the stomach at the other. The label of non-ulcer dyspepsia is currently given to patients who present with dyspepsia but have either no demonstrable lesion in the upper gastrointestinal tract or have abnormalities of uncertain significance. It is important, therefore, that a positive approach to non-ulcer dyspepsia is pursued, though therapy at present remains largely empirical.

Non-ulcer dyspepsia is defined as chronic or recurrent upper abdominal or retrosternal discomfort lasting for more than four weeks with symptoms unrelated to exertion and for which no cause can be found on investigation.[1] It is a heterogenous disorder which has been classified into various subgroups according to symptom clusters. These categories include 'ulcer-like', 'reflux-like', 'dysmotility-like', and 'non-specific' dyspepsia.[2] Unfortunately, many patients fall into two or more groups and a sizeable proportion do not fit into any category.[3]

Causes

Non-ulcer dyspepsia was previously considered to be purely psychosomatic in origin but this is probably untrue in many cases.[4] Abnormal upper gastrointestinal motility[5] including delayed gastric emptying and post-prandial antral hypomotility together with visceral perception of bloating, earlier satiety, nausea and post-prandial distress are disturbances noted to be associated with increased sensitivity to gastric acid.[6] These abnormalities have not, however, been identified in all patients.

Since its discovery, *Helicobacter pylori* has been implicated as a potential cause of non-ulcer dyspepsia in a subset of patients.[7] Tytgat *et al* found *H pylori* positivity in 50% of patients with functional dyspepsia.[8] However, as *H pylori* also occurs in asymptomatic persons it is unclear whether or not it plays a pathogenic role in non-ulcer dyspepsia. Those who invoke *H pylori* as a cause of non-ulcer dyspepsia stress that the gastrin release from antral G cells initiated by a meal or bombesin is elevated in infected subjects and returns to normal after *H pylori* eradication.[9,10] Toukan *et al*[11] found significantly increased number of neutrophils in the gastric mucosa of patients with non-ulcer dyspepsia.

Czinn *et al*[12] noted a positive correlation between the severity of histologic gastritis and the severity of epigastric pain, nausea and flatulence. Moore and co-workers[13] showed an inverse correlation between the degree of gastritis and post-prandial antral motor activity, suggesting that gastric mucosal inflammation may be associated with an alteration in gastric motility. Symptoms in *H pylori* positive subjects are also more severe than in the uninfected non-ulcer dyspepsia[14] and in population studies an increase in dyspeptic symptoms was observed in *H pylori* infected subjects.[15,16] Following eradication there was a significant and marked reduction noted in the symptoms over a period of one year when compared with the *H pylori* positive patients.[17]

The temptation to attribute non-ulcer dyspepsia to *H pylori* gastritis if no other cause is found on investigation has to be resisted.[18] To establish that *H pylori* causes non-ulcer dyspepsia it has to be proved that the association is real and not due to chance occurrence of two common events.[19,20] The increased prevalance of *H pylori* in non-ulcer dyspepsia is due to the use of flawed control groups giving rise to misconceptions regarding the importance of *H pylori* in non-ulcer dyspepsia. This misconception usually occurs due to a type 1 error,[18] where a chance association is inevitable when multiple symptoms are analysed and no correction for the multiple comparisons is undertaken. Eight studies have reported no association between specific symptoms or syndromes of non-ulcer

Helicobacter pylori

Associations:
- over 50% of the world's population is infected
- *H pylori* infection always causes gastric inflammation
- over 95% of duodenal ulcer patients are *H pylori* positive
- 85% of gastric ulcer patients are *H pylori* positive
- over 80% of chronic active gastritis patients are *H pylori* positive
- epidemiological data indicate that *H pylori* plays a role in the development of gastric cancer in the setting of multifocal chronic atrophic gastritis
- gastric B-cell lymphomas are associated with previous *H pylori* infection and may regress following *H pylori* eradication
- there is little evidence to suggest that *H pylori* is a major factor in non-ulcer dyspepsia. It may have a role in a subgroup of patients

Box 3

Helicobacter pylori

Management:
- the outcome of *H pylori* infection is dependent upon a combination of host factors, environmental factors and the virulence of the organism
- *H pylori* can be eradicated in around 90% of patients by a 7 day course of triple therapy (omeprazole, clarithromycin, and tinidazole)
- once infected *H pylori* usually remains for life until treated or it loses its niche due to gastric atrophy
- once eradicated in developed countries the reinfection rate with *H pylori* in adults is below 1% per year

Box 4

Learning points

- non-ulcer dyspepsia is a heterogenous disorder including 'ulcer-like', 'reflux-like', 'dysmotility-like' and 'non-specific' dyspepsia
- differential diagnosis includes irritable bowel syndrome and reflux eosophagitis
- *H pylori* may play a role in a small sub-group of patients
- *H pylori* eradication in non-ulcer dyspepsia is controversial
- management of non-ulcer dyspepsia is difficult. Patients need reassurance and may respond to changes in life style
- empirical treatment with acid suppression, *H pylori* eradication or prokinetic drugs may be tried if symptoms are persisent and troublesome

Box 5

dyspepsia and *H pylori* positivity in patients with functional dyspepsia. One proposal is that *H pylori* causes symptoms when there is increased neutrophil activity in association with intraluminal acid.[21] Pain, it is suggested, originates from paracrine neurotransmitters which have been stimulated by inflammation and patient variability explains the symptom variability in non-ulcer dyspepsia.[8] However the intermittent occurrence of symptoms of non-ulcer dyspepsia cannot be explained by the presence of active gastritis which is unlikely to fluctuate.[22] Nearly one-third of non-ulcer dyspepsia cases are related to irritable bowel syndrome[23,24] and some patients have pathological gastro-oesophageal reflux.[25]

Increased concentration of immunoreactive-somatostatin and immunoreactive-Substance P in the gastric mucosa of 'ulcer like' non-ulcer dyspepsia when compared to 'motility like' non-ulcer dyspepsia and peptic ulcer syndrome suggests that there may be two distinct subgroups, with non-ulcer dyspepsia not being only a stage within the spectrum of peptic ulcer disease.[26]

Management

The management of non-ulcer dyspepsia is difficult. Patients need reassurance, especially about the absence of any serious disease. Life-style modification may be helpful such as avoiding alcohol and coffee, losing weight and counselling to relieve anxiety, stress, and depression. Drugs have not proven to be effective in controlled trials but may work in day-to-day practice, albeit through a placebo effect. Nearly 60% of the patients benefit from placebo treatment.[27] Drugs should only be used if the risk: benefit ratio is extremely low. They should also be avoided if symptoms have persisted for many years without compromising the quality of life. When prescribed, medication should be given for as short a time as possible.[6]

H pylori eradication in non-ulcer dyspepsia remains controversial. O'Morain has shown that *H pylori* eradication kept his non-ulcer dyspepsia patients asymptomatic at one year while his *H pylori* positive patients continued to be symptomatic. However, his study was open, not blinded. Numerous other trials have been done using bismuth or antibiotics, singly or together. The reason why a clear picture has not emerged from these trials is manifold. Bismuth darkens the stool and hence it is difficult to perform a double-blind trial. Apart from having an anti-*H pylori* effect bismuth also binds to mucus glycoproteins which reduces acid attack on the gastric mucosa,[29] inhibits pepsin,[30] stimulates prostaglandin synthesis by the gastric mucosa,[31] increases mucosal bicarbonate secretion[32] and inhibits peptic degradation of epidermal growth factor.[33] Using antibiotics alone to eradicate *H pylori* also confounds the issue as they have their own gastrointestinal side effects.

Conclusions

In summary there is little evidence that *H pylori* is a major player in the pathogenesis of non-ulcer dyspepsia. There is some suggestion that it may have a role in a subgroup of patients, perhaps causing hyperacidity as a result of hypergastrinaemia and leading to an increase in the parietal cell mass. This may have some effect upon gastric motility. Large, well-controlled, clinical trials are needed to answer these questions, until then treatment will remain empirical.

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