REVIEW

HELICOBACTER PYLORI INFECTION IN CHILDREN

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Introduction

In young children, peptic ulceration is more commonly due to noxious agents such as corticosteroids and non-steroidal anti-inflammatory drugs, or following major stresses. Under such circumstances, upper gastro-intestinal tract (GIT) haemorrhage, vomiting or perforation are the main presenting features. The ulcers due to these conditions tend to be self-limiting and tend not to recur following healing if the offending agents are removed or underlying disorders successfully treated.

Helicobacter pylori (HP) induced gastritis causing mucosal ulceration either in the antrum or the proximal duodenum is a relatively uncommon event in children compared to adults. In older children and adolescents, the clinical presentations and natural history of peptic ulcers are more comparable to those observed in adult populations.

Primary gastritis

HP induced gastritis is well documented in children.[1-10] Hill et al reported four children with HP infection presenting with abdominal pain, nausea and failure to thrive. All four children had histologically proven gastritis.[1] Among a series of 25 children who underwent endoscopy for various reasons, eight had HP infection and more severe endoscopic and histologic lesions were noted among HP positive patients.[2] Nodular antral gastritis was noted among five children with HP gastritis.[3] In a study of 270 consecutive patients younger than 20 years of age, Prieto et al[6] noted that HP was associated with 100% of chronic gastritis, 75% of gastric ulcer, 91% of duodenal ulcer. Similar association of HP with chronic gastritis and HP infection had also been documented in Asia.[9-11]

Recurrences of HP-associated ulceration are markedly reduced by treatment directed at eradicating the infection. Duodenal ulcer recurrence rate in HP infected children have been reported to be reduced from 65% at one year of follow up if ulcers healed with acid suppressive agents alone compared to below 10% if HP is eradicated at the same time.

Diagnosis

There are two categories of tests for detecting HP infection. Invasive diagnosis is by biopsy specimens obtained at gastroduodenoscopy for rapid urease test and for histology. Micro-biological culture can also be done. Non-invasive tests include detection of antibodies to HP in serum and ^{13}C-urea breath test.

There are a number of urease tests which show a change in colour to indicate infection. The test result can be obtained within a few minutes or up to one hour. These rapid urease tests are inexpensive and a positive test within 30 minutes is quite specific for HP infection. One added advantage of rapid urease test is that the biopsy specimen can be retrieved from the test gel and cultured for the organism. Windson et al,[12] using CLO tests, were able to culture successfully in 93% in the first hour post-endoscopy. Isolation would improve if the CLO tests were stored in 4°C and plated within four hours.

Microbiological culture is expensive but it is useful to know the antibiotic resistance pattern of local strains of HP to guide treatment. It is particularly helpful after proven treatment failure. In Singapore, metronidazole resistance is common. In ten consecutive positive cultures from paediatric patients, six were resistant to metronidazole.[13] HP is a very fastidious organism and does not survive in 21% oxygen. Hence, biopsy specimen for cultures should be placed in suitable transport medium and sent to the laboratory immediately or kept at 4°C awaiting transport.

Urea breath test is highly specific and sensitive in adult studies. The patient should be fasted and he swallows a small amount of labelled urea. The urease from HP in the stomach rapidly converts the urea to bicarbonate, which is expired as labelled CO_2. In Japan, Yamashiro et al[14] had shown that it is useful even in paediatric population.

Kalach et al[15] had shown that ^{13}C-urea breath test exhibited sensitivity, specificity and positive predictive values of 100% in children. Single-sample analysis obtained at 40 minutes gave a comparable sensitivity and a slightly reduced specificity. Cadranel et al showed that the test could be simplified and its accuracy improved using only the 0 and 20 minutes breath samples and a cutoff of 3.5% instead of the classical 5% used in adults.[16] In experienced hands, urea breath test is more sensitive than serology but comparable in specificity.[17] However, the experience in young children is limited. It is fairly costly to perform and is not widely available among paediatric centres.

With regards to serology, serum IgG antibody assay is more reliable than the commercial kits. Abnormal levels of IgG or IgA against HP identified infected children with 95% sensitivity and 84% specificity.[18] Eradication of the infection would be accompanied by a significant decrease in IgG and IgA titre. However, this would take many months. Hence, elevated antibody against HP is an indication of infection but it does not indicate the status of the infection and should not be used as an indication to start treatment.

Malignancy

Recent studies have implicated that HP infection acquired in childhood is a causative factor in gastric cancer in later life[19-26] and gastric lymphoma in association with HP infection has also been reported in children. Sharon et al[27] reported a 14 year old girl with HP associated gastric lymphoma. She presented with abdominal pain and dyspepsia lasting for a year. Endoscopy showed a gastric ulcer in the lesser curvature and histology showed large B-cell lymphoma. She was treated with chemotherapy and HP was eradicated with Omeprazole and amoxicillin. Seventeen months post-treatment, there was no evidence of disease.

Resolution of HP-associated gastric lympho-proliferative disease in another 14-year-old girl with only treatment of HP without adjuvant chemotherapy or surgery was reported by Blecken et al.[28] These reports clearly demonstrated the role of HP in the pathogenesis of gastric malignancy.

Indications for investigation in children

In paediatric age group, there is no evidence demonstrating a link between HP associated gastritis and abdominal pain except in those cases in which gastric or duodenal ulcer disease is present. Screening for HP infection should not be performed routinely in children with upper GIT symptoms, including abdominal pain. Radhakrishnan et al[29] has shown that the prevalence of HP infection was similar both in symptomatic and asymptomatic children. Hardikar et al[30] also demonstrated the negative association between HP infection and recurrent abdominal pain. Furthermore, spontaneous clearing of HP infection can occur.[31-33]

The Asia Pacific consensus statement on the management of HP infection in adults had been published in 1998[34] and the position paper of

European HP study groups and European Society of Paediatric Gastroenterology, Hepatology and Nutrition had just been published.[35] It is generally agreed that children should be investigated for HP only when their symptoms are severe enough to justify the risk of therapy and endoscopy is the preferred method of investigation when the upper GIT symptoms are suggestive of organic disease.[35] It is because endoscopy provides a more complete information in the disease process. It allows the identification of causes of pain such as oesophagitis and peptic ulceration. At the same time, biopsies can be performed to diagnose gastritis. Culture and antibiotic sensitivity of the organism can be performed.

In children with recurrent abdominal pain, the prevalence rate of HP infection is inconsistent. In an analysis of 45 studies, Macarthur et al[36] found a median infection rate of only 22%. It is even lower in children meeting the Apley's criteria (6%).

When to treat

It is obvious that HP infection in children should be treated if peptic ulceration is present. On the other hand, the rate ratio of antral gastritis in children with HP infection (compared with uninfected children) ranged from 1.9 to 71.0 (medium 4.6). The prevalence of HP infection in children with duodenal ulcer was high (range 33 to 100%, median 92%) compared with children with gastric ulcer (range 11–75%, median 25%).[36] Successful eradication of HP is accompanied by ulcer healing and improvement of antral gastritis. However, there is no evidence to show that HP eradication is important in the prevention of peptic ulcer disease recurrence. Huang et al[37] followed up 26 children with duodenal ulcer and HP antral gastritis treated with triple therapy. HP infection was eradicated in 25 (96%) of 26 patients who underwent upper GIT endoscopic follow up. During a mean follow up of nearly two years, the annual ulcer relapse rate was estimated to be 9%. Among those with ulcer relapse, two out of three were HP positive.

Currently, there is no data to support treatment for HP infection in children who have a strong family history of duodenal ulcer or gastric malignancy. It is prudent to determine whether the duodenal ulcers and gastric malignancy among the family members are HP associated. The HP infection in the affected children should be confirmed either by endoscopy with biopsy for histology and urease test or ^{13}C-urea breath test.

As shown by Macarthur et al,[36] the prevalence of HP infection among children with recurrent abdominal pain is inconsistent. Children with RAP should not be treated for HP infection unless ulcer disease is present.

There are a number of unusual presentations of HP infection in children. Protein losing enteropathy has been reported.[38] This feature may be a consequent of the gastritis. Recovery from protein losing enteropathy was accompanied by a return to normal of the gastric histology.[38] Iron deficiency anaemia associated with HP infection is due to microscopic blood loss. Sideropaenic anaemia[39] refractory to iron administration has also been reported. H pylori eradication is necessary before the refractory anaemia can be corrected.

HP infection may be a cause of failure to thrive in infancy.[40] This is based on epidemiological study. More studies are needed to validate this observation and currently HP infection is not accepted as a cause of failure to thrive in young children.

In conclusion, antral gastritis and duodenal ulcer are indications for treatment in children with HP infection. Children with recurrent abdominal pain which meets Apley's criteria is not an indication for investigation and treatment for HP. As in adults, triple therapy is effective.[41,42]

References

1. Hill R, Pearman J, Worthy P, Caruso V. *Campylobacter pyloridis* and gastritis in children. Lancet 1986; I: 387.
2. Cadranel S, Bucchi F, Gambino MC, Cerletti C. *Campylobacter pyloridis* in children. Lancet 1986; I: 735–6.
3. Czinn SJ, Dahms BB, Jacobs GH, Kaplan B, Rothstein FC. *Campylobacter*-like organisms in association with symptomatic gastritis in children. J Pediatr 1986; 109: 80–3.
4. Drumm B, Sherman P, Cutz E, Karmali M. Association of *Campylobacter pylori* on the gastric mucosa with antral gastritis in children. N Engl J Med 1987; 316: 1557–61.
5. Drumm B, O'Brien A, Cutz E, Sherman P. *Campylobacter pyloridis*-associated primary gastritis in children. Pediatrics 1987; 80: 192-5.
6. Mahony MJ, Wyatt JI, Littlewood JM. *Campylobacter pylori* gastritis. Arch Dis Child 1988; 63: 654-5.
7. Prieto G, Polanco I, Larrauri J, Rota L, Lama R, Carrasco S. *Helicobacter pylori* infection in children: clinical, endoscopic, and histologic correlations. J Pediatr Gastroenterol Nutr 1992; 14: 420-5.
8. Ashorn M, Ruuska T, Karikoski R, Valipakka J, Maki M. Gastric mucosal sell densities in *Helicobacter pylori*-positive and -negative dyspeptic children and healthy controls. J Pediatr Gastroenterol Nutr 1994; 18: 146-51.
9. Yamashiro Y, Oguchi S, Otsuka Y, Nagata S, Shioya T, Shimizu T. *Helicobacter pylori* colonization in children with gastritis and peptic ulcer. I. The colonization rate and effects of colonization on mucin content and mucosal inflammation in the antrum. Acta Paediatr Jap 1994; 36: 167-70.
10. Tsai CJ, Chang MH, Tsai TC, Huang FC, Yang JC, Shun CT. *Helicobacter pylori* infection and duodenal ulcer in children and adolescents. Acta Pediatr Sin 1996; 37: 415-9.
11. SH Quak, CK Wong. Recurrent abdominal pain: an aetiological study among Singapore children. Int Med J 1997; 4: 209-14.
12. Windson HM, Ho GY, Marshall BJ. Successful recovery of *H pylori* from rapid urease test (CLO Tests). Am J Gastroenterol 1999; 94: 3181-3.
13. B Ho. Department of Microbiology, National University of Singapore. (personal communication).
14. Yamashiro Y, Oguchi S, Otsuka Y, Nagata S, Shioya T, Shimizu T. *Helicobacter pylori* colonization in children with peptic ulcer disease III: diagnostic value of the urea breath test to detect gastric *H pyloric* colonization Acta Paediatr Jap 1995; 37: 12-6.
15. Kalach N, Briet F, Raymond J, et al. The ^{13}Calon urea breath test for the non-invasive detection of *Helicobacter pylori* in children: comparison with culture and determination of minimum analysis requirement. J Pediatr Gastroenterol Nutr 1998; 26: 291-6.
16. Cadranel S, Corvaglia L, Bontems P, et al. Detection of *Helicobacter pylori* infection in children with a standardized and simplified ^{13}C-urea breath test. J Pediatr Gastroenterol Nutr 1998; 27: 275-80.
17. Corvaglia L, Bontems P, Devaster JM, et al. Accuracy of serology and ^{13}C-urea breath test for detection of *Helicobacter pylori* in children. Pediatr Infect Dis J 1999; 18: 976-9.
18. DeGiacomo C, Lisato L, Negrini R, Licardi G, Maggiore G. Serum immune response to *Helicobacter pylori* in children: Epidemiologic and clinical applications. J Pediatr 1991; 119: 205-10.
19. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. Lancet 1991; 338: 1175-6.
20. Solte M, Eidt S. Healing gastric MALT lymphomas by eradicating *H pylori*? Lancet 1993; 342: 568.
21. Forman D, Webb P, Newell D, et al. An international association between *Helicobacter pylori* infection and gastric cancer. Lancet 1993; 341: 1359-62.
22. Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet 1993; 342: 575-77.
23. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. New Engl J Med 1994; 330: 1267-71.
24. Calvert R, Randerson J, Evans P, et al. Genetic abnormalities during transition from *Helicobacter-pylori*-associated gastritis to low-grade MAL Toma. Lancet 1995; 345: 26-7.
25. Williams MP, Pounder RE. *Helicobacter pylori:* from the benign to the malignant. Am J Gastroenterol 1999; 94 (supl): S11-S16.
26. D'Elios MM, Amedei A, Manghetti M, et al. Impaired T-cell regulation of B-cell growth in *Helicobacter pylori*-related gastric low-grade MALT lymphoma. Gastroenterology 1999; 117: 1105-12.
27. Sharon N, Kenet G, Toren A, et al. *Helicobacter pylori*-associated gastric lymphoma in a girl. Pediatr Hematol Oncol 1997; 14: 177-80.
28. Blecker U, McKeithan TW, Hart J, Kirschner BS. Resolution of *Helicobacter pylori*-associated gastric lymphoproliferative disease in a child. Gastroenterology 1995; 109: 973-7.

29. Radhakrishnan S, Al Nakib B, Kalaoui M, Patric J. *Helicobacter pylori*-associated gastritis in Kuwait: endoscopy-based study in symptomatic and asymptomatic children. J Pediatr Gastroenterol Nutr 1993; 16: 126-9.
30. Handikar W, Feekery C, Smith A, Oberklaid F, Grimwood K. *Helicobacter pylori* and recurrent abdominal pain in children. J Pediatr Gastroenterol Nutr 1996; 22: 148-52.
31 Kehrt R, Becker M, Brosicke H, Kruger N, Helge H. Prevalence of *Helicobacter pylori* infection in Nicaraguan children with persistent diarrhoea, diagnosed by the ^{13}C-urea breath test. J Pediatr Gastroenterol Nutr 1997; 25: 84-8.
32. Perri F, Pastore M, Clemente R, Festa V, Quitadamo M, Niro, et al. *Helicobacter pylori* infection may undergo spontaneous eradication in children: A 2-year follow up study. J Pediatr Gastroenterol Nutr 1998; 27: 181-3.
33. Ganga-Zandzon PS, Michaud L, Vincent P, Husson QO, Wizla-Derambure N, Delassale EM. Natural outcome of *Helicobacter pylori* infection in asymptomatic children: a two-year follow-up study. Pediatrics 1999; 104: 216-21.
34. Lam SK, Talley NJ. Helicobacter pylori consensus: Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection. J Gastroenterol Hepatol 1998; 13: 1-12.
35. Drumm B, Koletzko S, Oderda G. *Helicobacter pylori* infection in children: a consensus statement. J Pediatr Gastroenterol Nutr 2000; 30: 207-13.
36. Macarthur C, Saunders N, Feldman W. *Helicobacter pylori,* gastroduodenal disease, and recurrent abdominal pain in children. JAMA 1995; 273: 729-34.
37. Huang FC, Chang MH, Hsu HY, Lee PI, Shun CT. Long-term follow up of duodenal ulcer in children before and after eradication of *Helicobacter pylori*. J Pediatr Gastroenterol Nutr 1999; 28: 76-80.
38. Hill ID, Sinclair-Smith C, Lastovica AJ, Bowie MD, Emms M. Transient protein losing enteropathy associated with acute gastritis and *Campylobacter pylori*. Arch Dis Child 1987; 62: 1215-9.
39. Dufour C, Brisigotti M, Fabretti G, Luxardo P, Mori PG, Barabino A. *Helicobacter pylori* infection and sideropenic refractory anemia. J Pediatr Gastroenterol Nutr 1993; 17: 225-7.
40. Fall CHD, Goddin PM, Hawtin P, Fine D, Duggleby S. Growth in infancy, infant feeding, childhood living conditions and *Helicobacter pylori* infection at age 70. Arch Dis Child 1997; 77: 310-4.
41. Shashidhar H, Peters J, Lin CH, Rabah R, Thomas R, Tolia V. A prospective trial of Lansoprazole triple therapy for pediatric *Helicobacter pylori* infection. J Pediatr Gastroenterol Nutr 2000; 30: 276-82.
42. Moshkowitz M, Reif S, Brill S, et al. One week triple therapy with omeprazole, clarithromycin and nitroimidazole for *Helicobacter pylori* infection in children and adolescents. Pediatrics 1998; 102(1)e: 14.