Helicobacter pylori Gastritis in Children – Assessment of Resistance to Treatment on the Casuistry of the Ist Pediatric Clinic Tîrgu Mureș

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Background: It is generally recognized the role of Helicobacter pylori in the pathogenesis of peptic ulcer disease in adults and children. Some cases raise serious concern regarding the therapeutic approach because they do not heal with normal treatment schemes or have frequent relapses due to the fact that the microorganism has virulence factors that determine resistance to therapy.
The **purpose** of this work was to analyze the cases of gastritis due to H. pylori in children from our casuistry, which have not healed despite a properly conducted treatment to eradicate the bacteria.
Material and methods: This was a prospective study carried out on 1,041 children aged between 2 and 18 years, diagnosed with different types of gastritis in Ist Pediatric Clinic from Tîrgu Mureș, admitted between January 2001 and March 2010. We have had 539 cases of gastritis due to H. pylori; for these patients a specific treatment was prescribed in order to eradicate the infection and to cure gastritis (accor-ding to the current internationally accepted recommendations).
Results: The average age of patients in the study group was 12.9 years, with a higher incidence in the 7–12 (33.02%) and 13-18 years (62.89%) age group, predominantly among female patients (63.45%) and those from rural areas (55.84%). From the patients diagnosed with Helicobacter pylori gastritis, 478 cases presented for review; after proper treatment with anti-infectives in combination with proton pump inhibitors, clinical-histological healing of the disease after a month was found in 426 cases (89.12%); a number of 52 patients remained positive (10.87%). Two months after treatment the endoscopical and histopatological modifications persisted in 26 cases (5.43%); a total of six cases (1.25%) remained positive for Helicobacter pylori infection after therapy.
Conclusions: The resistance of Helicobacter pylori infection to therapy is caused by the continued action of favoring factors, the virulence of the microorganisms in association with a genetic predisposition present in some individuals.

Keywords: gastritis, children, Helicobacter pylori

Introduction

Gastritis is the inflammatory process of the gastric mucosa, clinically manifested as a dispeptic syndrome with alimentary regularity and seasonal periodicity [1]. It is well known that gastritis and ulcer have a multifactorial etiology, being the result of an inflammatory process generated by the imbalance between the cytoprotection factors (property of the gastric mucus, cell barrier, bicarbonate secretion, growth factors, etc) and the cytotoxic factors of the gastric and duodenal mucosa (high serum levels of gastrine, parietal cell mass, high acid secretion, pepsinogen secretion, oxigen free radicals, nitrogen monoxide), associated with genetic factors, environmental factors and other exogen risk factors [2].

There are no accurate figures related to the incidence of gastritis in children [1], but Helicobacter pylori (H. pylori) is recognized currently as the main pathogenic factor of chronic gastritis, peptic ulcer disease, and gastric cancer. H. pylori infection is one of the most common enteric infections world-wide with up to 50% of the world population infected [3]. The current state of knowledge in digestive pathology approves that H. pylori causes gastritis and peptic ulcer, and that the long-term infection is associated with a high risk for gastric adenocarcinoma or malignant lymphoma in adults [2].

There is a direct correlation between low socio-economic level and H. pylori infection. The greatest incidence of infection is in the developing or undeveloped countries (Africa and South America), and the lowest incidence is recorded in the countries of Western Europe and North America [4]. While up to 80% of children in developing countries are infected, there is a rapid decline in the prevalence of the infection in developed countries. In chronic active gastritis the prevalence of the infection exceeds 80% [5–7].

H. pylori is clustered in families and having an infected mother or an infected older sibling has been shown to be a risk factor for infection [8–10].

Several theories affirm that the virulence factors help the microorganism to fix itself in the gastric mucosa and to generate the disease in the host organism. These virulence factors are classified in colonisation factors and factors responsible for tissue injury.

The potent urease activity of H. pylori is an important virulence factor of this bacteria [11,12]. Flagella are also important for the virulence of H. pylori; they confer motility, allowing it to move through the gastric mucus [13].

The cytotoxin-associated cagA gene has been identified as a marker for more virulent H. pylori strains [14,15]. The incriminated genes (cagA, vacA, with their subtypes and alele) encode the synthesis of some enzymes with a higher agressivity (CagA, VacA) [15,16–20].

The relation between H. pylori infections and the response to treatment

The correct treatment of gastritis and ulcer in children brings a regression of premalignant histological modifica-

tions. The treatment of H. pylori infections implies a double antibiotic therapy (Amoxicillin + Clarithromycine or Amoxicillin + Metronidazole or Clarithromycine + Metronidazole for 2 weeks and proton pump inhibitors for 4 weeks) [21].

Some cases of gastritis or ulcer in patients with H. pylori infection do not respond to treatment or they relapse, in spite of a correct treatment. It has been shown that the polimorphism of specific genes (CZP2C19 and MDR1) is incriminated for relapse after treatment or for resistance to treatment with proton pump inhibitors. Similarly, the polimorphism of pro-inflammatory citokines like IL1 β and TNF α, are associated with individual differences regarding the inflammation of the gastric mucosa and the response to the infection with H. pylori infection [22].

H. pylori infection may present itself as acute or chronic gastritis, duodenal or gastric ulcer, gastric carcinoma, B lymphoma (Maltoma), having also extra-digestive manifestations like iron deficiency anaemia, urticaria, low stature [4,16].

Children with gastritis due to H. pylori may show symptoms of: irritable stomach, gastric hipomotility (postprandial epigastric wholeness, decrease of appetite, prolonged wholeness, disinclination for food, nausea), gastro-esophageal reflux, flatulence and dispepsia (distended abdomen, eructation); acide dispepsy (undue postprandial epigastric pyrosis, hunger or nocturnal pains, which are relieved after the administration of antiacid drugs), nonspecific symptoms [1,4].

The diagnosis of gastritis due to H. pylori involves superior digestive endoscopy, histologic identification of the bacteria (by Warthon-Starry silver coloration, modified Giemsa, acridine orange or cresyl violet colorations), H. pylori culture (by inoculating the bioptic fragments in agar-blood plate in microaerophilia at 37°C), Urease rapid test (a color reaction for detection of bacteria from gastric mucosa specimens disposed into urea media), respiratory test (urea breath test) marked with 13C (a non-invasive diagnostic method with 100% sensitivity and 92% specificity, used as a method to evaluate the efficacy of the treatment), serological tests (ELISA for detecting IgG or IgA antibodies in the serum), detection of saliva specific IgG, immunoenzymatic technique for the detection of H. pylori antigenes in the stool, HpSA (also a non-invasive method), PCR and DNA-enzyme immunological tests [23].

Superior digestive endoscopy is the elected procedure for the diagnosis of gastritis and peptic ulcer. Dohil et al. use the endoscopic classification of gastritis to define an erosive and non-erosive form, and a topographical classification to define antral gastritis, gastritis of the gastric body or pangastritis [4]; the endoscopic aspect in gastritis due to H. pylori is characterized by a micronodular antral mucosa (in over 50% of cases) or a paving-stone appea-rance (98–100% of cases); the classification of gastritis uses the Sydney (endoscopic, histologic, etiologic) criteria.

The aim

Recent theories and assumptions regarding the genetical predisposition of the infection with Helicobacter pylori, as well as the genic polimorphism that influences the pharmacokinetics and the treatment's efficiency, have led us to perform some clinical, and paraclinical analyses (in terms of endoscopical, histological, imunological, and other aspects) on cases of gastritis in children with H. pylori infection.

The purpose of this paper was to analyze cases of gastritis due to Helicobacter pylori in children, which, despite of a properly conducted treatment to eradicate the microorganism, have not healed.

Material and methods

We carried out a prospective study on 1,041 children aged between 2 and 18 years, admitted with different types of gastritis to the Department of Pediatric Gastroenterology from Tîrgu Mureș between January 2001 and March 2010.

We had 539 cases of gastritis due to Helicobacter pylori; diagnosis was established by corroborating clinical findings with mucosal appearance at upper gastrointestinal endoscopy, rapid urease test, serology and results of histological examinations of fragments of mucosa biopsies; for some patients we were able to perform HpSA (H. pylori antigenes detection in the stool, which were positive).

The study was conducted based on case report forms, clinical examination, endoscopic appearance and histology of the gastric mucosa, reassessing the effectiveness of therapy by clinical and endoscopic reevaluation after one month and two months of treatment.

Patients diagnosed with gastritis due to H. pylori received an internationally accepted treatment in order to eradicate the infection and to cure gastritis, consisting of the antibiotics Amoxicillin and Metronidazole, and in case of relapse/recurrence, Amoxicillin and Clarithromycin or Clarithromycin and Metronidazole for 14 days, associated with proton pump inhibitors for four weeks [23,24].

A number of 478 cases were reevaluated after therapy; the remaining cases followed the prescribed treatment incorrectly, they have interrupted medication on their own initiative, without a reason, without a medical indication, or did not show up for reevaluation after one and/or two months.

Inclusion criteria

- clinical criteria of gastritis (recurrent abdominal pains, epigastric pains, sometimes rhythmic with eating, periombilical pains, nausea, vomiting and heartburn, loss of appetite with weight loss);
- acute or chronic gastritis diagnosed by clinical, endoscopical and histological criteria, in children with endoscopic changes suggestive for H. pylori infection and documented by diagnostic tests;
- cases of gastritis due to H. pylori which after the diagnosis have followed the recommended specific treatment;

- patients with gastritis due to H. pylori who followed the treatment and were reevaluated after one month and two months respectively.

Exclusion criteria

- gastrointestinal symptoms not specific for gastritis; documented parasitosis or urinary tract infections; functional abdominal pain, abdominal epilepsy;
- acute or chronic gastritis of another cause (the absence of H. pylori infection);
- patients who refused digestive endoscopy;
- endoscopic appearance highly suggestive for H. pylori, but infection not confirmed by diagnostic tests (or testing not performed for technical reasons);
- gastritis without confirmed H. pylori infection or endoscopic changes suggestive for H. pylori infection;
- patients who followed the prescribed treatment incorrectly, or have interrupted medication on their own initiative;
- patients with gastritis due to H. pylori who after the diagnosis have started the recommended treatment but were not submitted to subsequent reevaluations.

Results

The average age of patients in the study group was 12.9 years, with a higher incidence in the 7–12 (33.05%) and 13–18 years (62.97%) age groups. There were 302 girls and 176 boys in the study group, and most of the patients – 318 cases (66.52%) came from a rural environment.

At the first presentation, patients in our group had the following subjective complaints (the symptoms were intricate, overlapping, with more than one subjective complaint for a patient):

- abdominal pain in 249 cases (52.09%), of which epigastric pain in 192 cases (77.10%), periumbilical pain in 31 cases (12.44%), and diffuse pain in 26 cases (10.44%);
- nausea, vomiting in 98 cases (20.50%);
- loss of appetite in 29 cases (6.06%);
- weight loss in 4 cases (0.83 %);
- other events (bitter taste, heartburn, constipation, rash) in 99 cases (20.71%).

If we relate to the total number of children enrolled, a percentage of 40.16% had abdominal pain with epigastric localization, 6.48% have accused pain in the periumbilical region and 5.43% had abdominal pain without a precise location, including diffuse sensitive situations.

The upper gastrointestinal diagnostic endoscopy performed with an Olympus fibroscope revealed at the initial presentation the following:

- antral changes in 100% of the 478 cases, as follows: granular, follicular mucosa – 140 cases; paving stone appearance or mosaic aspect – 230 cases; congestion – 99 cases; gastric ulcer – 5 cases; denudation, erosion – 4 cases;
- changes in the esophagus – 82 cases;
- changes in the gastric corpus or the entire stomach – 314 cases;
- changes in the duodenum – 72 cases, 6 ulcerations and 4 cases with suffusions, erosions and bleeding spots.

Out of these, in 158 cases we found lesions on two levels, in 51 cases on three levels, and in 12 cases we found injuries in the esophagus, as well as at gastric, antral and duodenal levels.

Histopatologicaly, we found the following changes:

- H. pylori acute gastritis in 56 cases;
- chronic gastritis with marked activity and H. pylori in 231 cases;
- H. pylori chronic gastritis in 26 cases, from which foveolar regenerative hyperplasia in 9 cases, atrophic gastritis in 2 cases and intestinal metaplasia in 1 case;
- in 121 samples there were no detectable histological changes, normal mucosa appearance, or there was not enough material; in these cases the diagnosis of H. pylori gastritis was based on the clinical aspect, rapid urease test and/or positive serological tests, faecal antigen detection, knowing that the gastrointestinal mucosa may be affected in plots and biopsy material can be taken from healthy tissue, without possibility of thus excluding the H. pylori infection.

Evolution

The recommended treatment in cases of gastritis includes a hygienic-dietary regime (no smoking, alcohol or excitants, prohibiting the use of aspirin and NSAIDs); the patient will have a normal diet, excluding (customized) foods that are not tolerated and those that cause pain (spices, pickles, fried, smoked, etc.) and medication, including antacids, antisecretory anticholinergics, H2-receptor antagonists or proton pump inhibitors, gastroprotectives and sucralfate.

For H. pylori infection an antibiotic treatment was prescribed, with Amoxicillin 20–30 mg/kg/day and Metronidazole 15–20 mg/kg/day, associated with proton pump inhibitors for four weeks [23,24].

From all the patients diagnosed with gastritis due to H. pylori, 478 cases presented for reevaluation; after proper treatment with antibiotics in combination with proton pump inhibitors, clinical-histological healing of the disease after a month has been found in 426 cases (89.12%); a number of 52 patients remained positive (10.87%).

After one month of treatment, 52 cases were detected with H. pylori infection. Control gastrointestinal endoscopy revealed:

- antral changes in 100% of the 52 cases (congestion – 5 cases, granular, follicular mucosa – 5 cases, mosaic or paving stone appearance – 41 cases, gastric ulceration – 1 case);
- changes in the esophagus – 11 cases;
- changes in the corpus or full stomach – 12 cases;
- changes in the duodenum – 13 cases.

Of these, we detected lesions on two or more levels in 21 cases.

The first control histopathologic examination revealed:

- chronic gastritis due to H. pylori with activity – 26 cases;
- changes of chronic gastritis – 18 cases;
- 8 cases without microscopically detectable changes, but with endoscopic changes suggestive for H. pylori infection or positive diagnostic tests (Urease test, HpSA).

In these cases of relapse/recurrence, a treatment consisting of Amoxicillin 20–30 mg/kg/day and Clarithromycin 7.5–15 mg/kg/day or Clarithromycin and Metronidazole (in doses mentioned aove) for 14 days was prescribed, associated with proton pump inhibitors for 4 weeks. At two months after the second treatment schedule, a number of 26 cases remained positive, with the following endoscopic changes:

- antral changes in all cases (simple congestion – 1 case, granular, follicular mucosa – 11 cases, mosaic or paving stone aspect – 14 cases);
- changes in the esophagus – 4 cases;
- changes in the corpus or full stomach – 11 cases;
- changes in the duodenum – 8 cases.

Out of these, in 16 cases we detected lesions on two levels (10 cases) or three levels (6 cases).

From the casuistry included in our study group, a number of 6 patients remained positive for H. pylori infection; there were five girls (aged 4, 11, 15, 16 and 17 years) and one boy (13 years old), the first three girls and the boy coming from rural areas. Endoscopic antral changes were found in all six cases – four cases of mosaic aspect, a case of follicular mucosa and one with simple congestion, while the histopathological examination described in all cases chronic gastritis due to H. pylori and activity.

We mention that in these cases, at least one family member was found positive for H. pylori, which is consistent with data from the literature [5,9,10].

Conclusions

We had cases of relapse because of the continued action of favoring-factors, the presence of Helicobacter pylori infection in other family members and because of the microorganism's virulence factors that determine resistance to therapy and genetic predisposition present in some individuals.

Hopefully this study emphasizes the need to be able to perform detection of CagA and VacA using ELISA or immunodifusion methods, as well as immunological DNA studies, which could bring special information with a great clinical significance.

Optimizing the treatment of infections with these types of organisms would decrease the amount of relapses and recurrences. There is a need to significantly reduce the risk of recurring infections with Helycobacter pylori, as well as the risk of gastric cancer by choosing the right therapy and by individualizing the treatment according to each person's genotype, which could represent an important step forward in the practice of pediatric gastroenterology.

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