

## ATROPHIC GASTRITIS: *HELICOBACTER PYLORI* VERSUS DUODENOGASTRIC REFLUX

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### Abstract

**Objectives.** The objective of this study was to assess the prevalence of atrophic gastritis in children. We also wanted to compare the clinical manifestation, endoscopic appearance and the degree of the gastric atrophy in children and to identify the possible causes which determine gastric atrophy.

**Methods.** We evaluated 247 children with chronic gastritis (153 female/94 male, mean age 12.32 years). Atrophy was defined as the loss of normal glandular components, including replacement with fibrosis and/or intestinal metaplasia.

**Results.** The prevalence of the atrophic gastritis was 16.6% (41 cases), mean age 11.59+/-1.75 years, male-to-female ratio 16:25. The clinical manifestations were correlated with the patient age (infants and toddlers were evaluated mostly for weight loss – 4 cases, and older children for abdominal pain – 22 cases). The endoscopic appearance was described as either nodular (15 cases), or erythematous gastritis (10 cases), or normal (10 cases). According to the Sydney System, the degree of atrophy was found to be mild in 3 patients, moderate in 25, and severe in 13 patients; 14 cases were associated with duodenogastric reflux, 5 with *Helicobacter pylori* and 2 with *Helicobacter heilmannii* infection, but in 17 cases the etiology was unknown.

**Conclusions.** Atrophic gastritis is present in childhood, even at very young ages (infants, toddlers). The endoscopic appearance is not characteristic for the presence of atrophy. The degree of the atrophy is not correlated with the age of the children. Because of the relatively high number of duodenogastric reflux associated with gastric atrophy, further studies need to evaluate the potential causes and clinical course.

**Keywords:** atrophic gastritis, *Helicobacter pylori*, duodenogastric biliary reflux.

### Introduction

Clinical studies have confirmed that gastric mucosal atrophy is not limited to adult patients [1]. Mucosal atrophy is considered a precancerous stage in adults, but because it is not a routine histological test in all the endoscopic evaluation in children, its prevalence in pediatric population varies from 0-72% according to different studies [2,3]. Most studies are related to children with *H. pylori* infection, and as a result, the prevalence of gastric atrophy due to other etiologies remains unknown. Studies in children reported varying degrees of atrophy of the gastric mucosa, whereas adult studies only consider

moderate and severe grades, so the prevalence reported in children may be overestimated [1].

In the precancerous cascade the first recognized histological change is active chronic inflammation, which may persist (non-atrophic chronic gastritis) or progress to multifocal atrophic gastritis, considered the first true precancerous stage. The next steps are intestinal metaplasia (first complete, then incomplete), then dysplasia, initially low grade, then high grade, the latter being equivalent to the "on site carcinoma" [4]. It is known that *H. pylori* infection causes chronic gastritis, mostly asymptomatic, while according to Correa's theory the precancerous cascade requires the time factor [4]. As such, the early infection with *H. pylori* increases the risk of developing gastric cancer, so it is good to know when gastric atrophy occurs during childhood for monitoring the gastric mucosal changes.

Manuscript received: 15.11.2012

Received in revised form: 04.03.2013

Accepted: 01.04.2013

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## Objectives

The aims of our study were to evaluate the prevalence of atrophic gastritis in children and their clinical outcome during the study, associated with the identification of other causes, beside *H. pylori*, that lead to gastric atrophy. We also wanted to identify the age of onset of gastric atrophy, and compare the clinical manifestation, endoscopic appearance and the degree of mucosal atrophy.

## Material and method

This was a retrospective study carried out over a period of 30 months (January 2009-June 2011), in the Second Pediatric Clinic, in 1706 children who had gastrointestinal symptoms (diffuse abdominal pain or recurrent epigastric pain, vomiting, heartburn, early satiety, anorexia, haematemesis), or were suspected of malabsorption (failure to thrive, weight loss, anemia, chronic diarrhea). All the patients underwent gastroduodenal endoscopy. The study included patients found with macroscopic changes in the gastric mucosa, gastric or duodenal ulcer, and the diagnosis of gastritis was confirmed histologically. One or two biopsies were taken from the antrum for rapid urease test and histological examination. For the diagnosis of *H. pylori* infection the rapid urease test, serological tests (IgG anti *H. pylori* antibodies) and histological examination were performed. A child was considered infected with *H. pylori* if 2 tests (out of 3) were positive. For the study the consent of the Commission for the Assurance of the Quality of Clinical Researches of the Emergency University Hospital for Children in Cluj-Napoca was obtained.

To describe the endoscopic lesions the Sydney endoscopic classification was used, based on which we divided the gastritis into erythematous, erosive, polypoid, atrophic, hemorrhagic and with giant folds. The histological samples were assessed by the histopathologist working in the Department of Pathology of the Children's Emergency University Hospital in Cluj-Napoca. Samples were stained with hematoxylin-eosin (HE) and Giemsa stain to identify *H. pylori*. Using the Updated Sydney Classification System, the intensity of the inflammation, the activity of gastritis, *H. pylori* density, and the presence of atrophy and the intestinal metaplasia were classified into 3 grades: 1, mild; 2, moderate; or 3, severe.

Statistical analysis was performed using SPSS 16.0 for Windows. The  $\chi^2$  test was used for analyzing the differences between qualitative variables. The differences between the means of the continuous quantitative variables was evaluated with the Student test. The Mann-Whitney U and the Kruskal-Wallis test were used to compare differences between two or more independent groups when the dependent variable was not normally distributed. A p value <0.05 was considered statistically significant for all analyses.

## Results

During a period of 30 months (January 2009-June 2011) in the Second Pediatric Clinic 1929 consecutive upper gastrointestinal endoscopies were performed, in 1706 children presenting with gastrointestinal symptoms or suspected of malabsorption; 827 biopsies were taken and 247 cases had histological confirmed diagnosis of chronic gastritis, with a mean age of  $12.32 \pm 4.87$  years, age range 23.83 (2 months-24 years), 94 boys (38.1%). Forty-one children with atrophic gastritis (16.6%) were detected, with a mean age of  $11.59 \pm 1.75$  years, age range 21.92 (2 months-22 years 1 month), 16 of whom were male (Table I).

**Table I.** Patients with gastric atrophy.

Age groups	Number of patients		Atrophy grades Median; range
	Male	Female	
Infant	0	2	2.5; 2-3
Toddler	0	2	2; 2-2
Preschool age	2	3	3; 2-3
School age	7	7	2; 0-3
Adolescent	7	11	2; 0-3
Total	16	25	2; 0-3

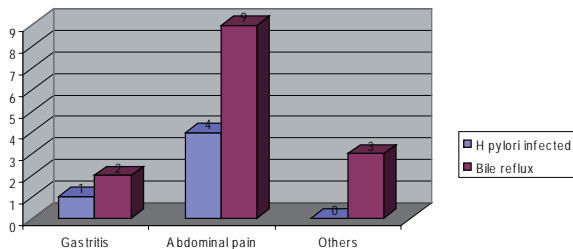
The mean age of girls was  $11.08 \pm 6.25$  years (Confidence Interval CI 95% 8.50-13.66), lower than the mean age of boys  $12.40 \pm 4.37$  years (CI 95% 10.07-14.73), but the difference between them was not statistically significant.

Seven (17%) patients with atrophic gastritis were infected with *Helicobacter* (5 with *H. pylori*, 2 with *H. heilmannii* respectively) and other 14 (34%) presented duodenogastric biliary reflux. One had celiac disease, one had inflammatory bowel disease and a third one severe malnutrition. In 24 (58%) patients with atrophic gastritis the etiology was unknown. The mean age of the patients with atrophic gastritis due to biliary reflux was  $12.83 \pm 4.87$  years (CI 95% 10.02-15.63), lower than those with *H. pylori* infection, which was  $14.08 \pm 3.38$  years (CI 95% 9.88-18.28), but the difference was not statistically significant.

In infancy the only etiological factor of atrophic gastritis found was severe malnutrition. In the toddler and preschool period there was only one patient (a girl 4 years and 10 months of age) with known etiology, respectively duodenogastric biliary reflux. In school aged and adolescents there were more patients with gastric atrophy due to biliary reflux (7 and 6 respectively) and *H. pylori* infection (2 and 3 respectively), compared to other age groups (p<0.05). Atrophic gastritis caused by *H. heilmannii* was reported only in adolescents.

Twenty patients (all of them were school age children and adolescents, 15 girls) were evaluated because of epigastric pain, other 2 because of diffuse abdominal pain, and 7 children (5 girls) with failure to thrive and weight loss (4 patients younger than 3 years). Two children were investigated because of anorexia, two because of vomiting, and 4 patients with autoimmune diseases (one

Crohn disease, two other forms of IBD, one celiac disease). Four children were previously known with gastritis (2 girls of 4 and 17 years with chronic reactive gastritis, an 11-year-old boy with *H. pylori* gastritis, and a 15-year-old girl with antral gastritis). Most of the patients with atrophic gastritis of known etiology were investigated because of abdominal pain: 64% of patients with atrophic gastritis due to biliary reflux, and 80% of those infected with *H. pylori* (Figure 1).

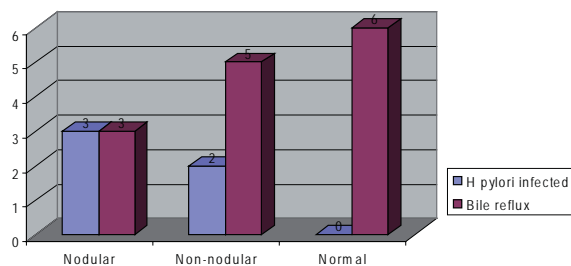


**Figure 1.** Comparison of the clinical symptoms of children with *H. pylori* infection and bile reflux.

Upper gastrointestinal endoscopy showed an erythematous aspect in 16 (39%) cases, normal endoscopic appearance in 17 (41%) cases and erosive lesions in another 4 (10%) cases. Only 4 patients (10%) had macroscopic appearance of atrophic gastritis. No endoscopic aspect mentioned in the Sydney endoscopic classification was significantly associated with the histologically diagnosed atrophic gastritis (p=NS).

On the other hand, by dividing the patients, on the ground of the nodular aspect of their gastric mucosa, into two groups, with nodular and non-nodular gastritis respectively, it appeared that atrophic gastritis was significantly associated with the non-nodular aspect (p<0.05).

Most patients with atrophic gastritis due to biliary reflux had normal (43%) or non-nodular (36%) endoscopic appearance compared to those infected with *H. pylori*, which had predominantly nodular gastritis (60%). There wasn't any case with *H. pylori* infection and normal endoscopic mucosa (Figure 2).



**Figure 2.** Comparison of endoscopic appearance of children with *H. pylori* infection and bile reflux.

Sixteen patients with atrophic gastritis also had

esophagitis (14 of grade 1, 2 of grade 2) and other 6 duodenitis. One case was associated with gastric ulcer and another one with duodenal ulcer.

Most of the patients presented atrophy of grade 2 (25, 13 girls), followed by thirteen cases (10 girls) of grade 3 atrophy, respectively other three cases of grade 1 atrophy (2 girls). All three cases with grade 1 atrophy, but only one case with severe atrophy was associated with biliary reflux (Table II).

**Table II.** Comparison of atrophy grades between patients with *H. pylori* infection and biliary reflux.

Atrophy grades	<i>H. pylori</i> infection (n=5)	Biliary reflux (n=14)
Mild (grad 1)	0	3
Moderate (grad 2)	2	9
Severe (grad 3)	3	2

The median degree of atrophy in boys and girls was 2 (range 0-3), the difference between the sexes wasn't statistically significant (p=NS). The median degree of atrophy in age groups varied from 2 (range 2-2) in toddlers to 3 (range 2-3) in preschool age children, the difference was not statistically significant (p=NS) (see table I).

The degree of inflammation was significantly higher in the *H. pylori* infected group compared to those with biliary reflux, but there was no statistically significant difference between the two groups regarding the activity, atrophy or intestinal metaplasia (Table III).

**Table III.** Comparison of histological parameters between patients with *H. pylori* infection and bile reflux.

Histological parameter	<i>H. pylori</i> infection (n=5)	Biliary reflux (n=14)
	Median; range	
Inflammation	2; 0-3*	0; 0-2*
Activity	0; 0-3	0; 0-0
<i>H. pylori</i> density	1; 1-1	0; 0-0
Atrophy	2; 0-3	2; 0-3
Intestinal metaplasia	0; 0-3	0; 0-3

\*p<0.05

### Discussion

Our study shows that the presence of precancerous lesions in childhood is a reality. Our results report a prevalence of 16.6% of atrophic gastritis. Studies by Kolho in Finland, Cohen in Argentina and Campbell in Africa did not describe any cases of gastric atrophy in the pediatric population, despite the fact that in some areas, such as Gambia, the prevalence of *H. pylori* infection may reach 96% by the age of 3 years (a phenomenon described as "African enigma") [2,5,6,7]. On the other hand, the study by Guarner in the U.S. reports a prevalence of 63% of atrophic gastritis in *H. pylori*-positive patients and 22% in *H. pylori* negative, and intestinal metaplasia in 21% of patients, all *H. pylori* positive [8]. Boukthir et al. in a study conducted in Tunisia, another region with high prevalence of *H. pylori*

infection (>60%), reported a prevalence of 9.3% atrophic gastritis in patients with gastrointestinal pathology [9].

Kato et al., in a study made in Japan on a group of 196 children (131 *H. pylori* positive), reported antral atrophy in 52% of *H. pylori*-positive children and 11% in *H. pylori*-negative patients, and corpus atrophy in 35%, respectively 8% of children [10]. Other authors, who had conducted several studies regarding children with *H. pylori* infection reported a much lower rate, up to 4%, of gastric atrophy [1].

Our results show that atrophic gastritis occurs in childhood, even in very young ages. The mean age of children with atrophic gastritis was 11.59±1.75 years, lower than the mean age of the entire group (12.32±4.87 years), but the difference was not statistically significant. Most cases (78.05%) were of school age, and adolescents respectively (14 and 18). Other studies also place the mean age of atrophic gastritis during school age or adolescence. Boukthir, in a study of 345 children with a mean age of 8.6 (SD=3.7) years, reported atrophic gastritis in 32 patients with a mean age of 9.4 (SD=3.4) years [9]. Kato et al. performed a study in 131 children, and reported 15 patients with grades 2 and 3 atrophy, with a mean age of 12.3 years (80% of children with ≥11 years and the youngest having only 4 years) [11]. Ricuarte et al. have described, in children in Columbia, 16/115 cases of atrophic gastritis, the median age being 15 years (7-17 years interval), the smallest child being 9 years old [12].

There is no clinical symptom suggestive for gastric atrophy. Most cases are discovered during investigations for various gastrointestinal symptoms, but the prevalence of asymptomatic cases is unknown [3,13,14] (Table IV).

In our study 22 patients were evaluated for abdominal pain, followed by 7 children with weight loss and failure to thrive (4 patients were younger than 3 years).

Four other children were previously known with gastritis (2 girls of 4 and 17 years with chronic reactive gastritis, a 11 year old boy with *H. pylori* gastritis, and a 15 years old girl with antral gastritis). This supports Correa's theory, which underlines that the development of gastric atrophy needs a certain period of time starting from chronic gastritis [4].

Endoscopic atrophic gastritis is diagnosed when the vascular ramifications are visible if the stomach is not over distended. Additional pearly-whitish mucosal discoloration is common, as is the flattening or absence of the fold

pattern in the gastric body. Occasionally, nodularity may be present, accentuated with dye scattering. Collections of lipid-filled macrophages, known as xanthelasma, may become visible in severe atrophic gastritis [15].

The diagnosis of gastric atrophy is usually performed by a histopathologist. However, endoscopists usually encounter various endoscopic appearances of the gastric mucosa in their common practice and attempts to classify the gastritis are made during a gastroscopy [16]. Such changes are known to be related to the histomorphology and presence of *H. pylori* in the general population [17]. Studies regarding the concordance between the endoscopic aspects and histology in cases with gastritis have been made, but the outcomes showed a disappointing correlation. However, in general, the concordance was good in the severe forms of gastritis, and normal endoscopy has excluded active gastritis [18].

Our study had slightly different results from those mentioned here. According to the Sydney endoscopic classification we described 16 cases (39%) with erythematous aspect, 17 with normal endoscopic appearance (41%) and 4 (10%) cases with erosive lesions. Only 4 patients (10%) had macroscopic appearance of atrophic gastritis. Our different results can be explained by the fact the aforementioned studies were carried out in adults, especially in populations with high incidence of gastric cancer.

By extension with adult gastric diseases, in clinical practice, the Updated Sydney System has been used as standard to assess and report gastritis [19]. Its role is to establish the severity of changes using visual analogue scales for a uniform evaluation by different histopathologists. Atrophic gastritis is defined as the reduction/loss of gastric glands which are replaced by fibrous tissue or by intestinal metaplastic cells. However, the interposition of inflammatory cells between the stomach's glandular cells may inappropriately orientate the pathologist to the diagnosis of atrophy when one is not actually present. Sampling interpretation is observer-dependent and this was emphasized by several studies [20,21,22]. Without strictly validated criteria, the severity assessment of gastric atrophy remains subjective and difficult to reproduce [23]. Some studies include only atrophy of grade 2 and 3 [11], while others do include atrophy of grade 1 as well [3,9]. This could be a source of error explaining the large differences between the prevalence of atrophic gastritis reported by

**Table IV.** Studies reporting gastric atrophy in children.

Authors	Number of patients	Mean age (years)	Atrophic gastritis	Symptoms
Guarner (2003)	64	9	10	Upper chronic digestive symptoms
Ozturk (2003)	27	12	14	Chronic abdominal pain
Levine (2004)	95	14	1	Gastro-esophageal reflux, epigastric pain, collagenous gastritis
Usta (2004)	175	12	5	Persistent upper gastrointestinal symptoms
Kato (2006)	196	11.3	14	Upper abdominal symptoms
Boukthir (2009)	345	8.6	32	Recurrent abdominal pain (67.2%), vomiting

different studies. Our study included atrophy of grade 1, although the number of cases was limited (3 cases).

To create a pathology report suggested by the updated Sydney System, it is recommended that at least five biopsy specimens are evaluated in adults (2 antral, 2 from the body and one from the angulus), but no consensus on the optimal number of biopsies needed in children is available [1]. The studies performed on the pediatric population also differ in this respect, some taking 3-4 biopsies [8,9], while others 1-2 [11]. Our study used retrospective data where in most cases biopsies were taken only from the antrum (1 for histology, 1 for the rapid urease test) and only a few of them had biopsies also taken from the body (although that data were not processed in this study since no biopsy from the body revealed atrophy of the gastric mucosa).

The main histological differences between atrophic gastritis of children and adults seem to be related to the characteristics of inflammatory response accompanying mucosal atrophy. In most studies comparing children and adults, the degree of gastric mucosa colonisation by *H. pylori* seems to be significantly more important in children, but the severity of gastric inflammation is more important in adults [1].

It was considered for a long time that *H. pylori* is the only etiological factor of atrophic gastritis in children. The role of *H. pylori* infection is indisputable, but several studies report gastric atrophy without infection [3,8,24]. Atrophic gastritis in adults has been associated with autoimmune pathology and anti-gastric-parietal cell (APC) antibodies in up to 50% of cases, but there are few data in children [25]. Studies suggested that adult anti-gastric-parietal cell antibodies could be used as a marker of severity of gastric atrophy, but there are no studies in children [1].

There is also a report on the synergistic effect of *H. pylori* and the refluxed biliary acids in the development of gastric atrophy [19,26]. Studies show that, in adults, the incidence of the cancer in the remnant stomach after Billroth II reconstruction is higher than after Billroth I reconstruction [27]. The toxic effect, possibly carcinogenic, of biliary reflux on the stomach has been confirmed in animal experiments. However, there have been few studies on the effect of bile acids that reflux into the stomach in association with duodenogastric reflux on atrophy in cases with no history of gastric resection [26]. In the last decade there have been more studies related to histological changes in reactive gastropathy on unoperated stomach, even in the pediatric population [28,29].

Our results show that only 17% of atrophic gastritis were associated with *H. pylori* and *H. heilmannii* infection, and 34% had the duodenogastric biliary reflux as the only etiological factor. Also, although 17 cases (41%) had unknown etiology (we did not have enough evidence to associate them with *H. pylori* infection or biliary reflux), the histological changes were described as chronic reactive gastritis, due to a biliary reflux.

The number of cases of gastric atrophy associated with primary biliary reflux in children requires further study in order to identify the role of duodenogastric biliary reflux in addition to *H. pylori* infection in the development of precancerous lesions.

### Conclusions

Atrophic gastritis is present in childhood, even in infants and toddlers. The prevalence of atrophic gastritis is relatively high in case of child chronic gastritis. The endoscopic appearance is not characteristic for gastric atrophy. The degree of atrophy is not correlated with the age of the children. *H. pylori* is not the only etiological factor associated with atrophic gastritis; reactive gastritis caused by biliary reflux can also lead to gastric atrophy.

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