Intestinal Metaplasia and Gastric Atrophy in Children is not as Frequent as Adults

İntestinal Metaplazi ve Gastrik Atrofi Çocuklarda Erişkinlerdeki Kadar Sık Değildir

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ABSTRACT Objective: Atrophic gastritis and intestinal metaplasia are frequently seen among adult patients and are thought to be premalignant. The prevalence of these lesions among children is not well known. The aim of the study is to investigate the prevalence of gastric atrophy and intestinal metaplasia in children. **Material and and Methods**: Children with gastrointestinal symptoms admitted to our clinic were evaluated. The data about urea breath test, upper gastrointestinal endoscopy macroscopical findings and histopathological evaluation with modified Sydney classification were evaluated retrospectively from patient records. **Results:** A total of 357 children underwent upper gastrointestinal system endoscopy. Histopathological evaluation revealed no gastric atrophy but intestinal metaplasia in 2 children. Both of the children had positive urea breath test, gastritis and were positive for *Helicobacter pylori* histologically. One of these children also had a peptic ulcer. The children underwent endoscopy again after *H.pylori* eradication therapy, and intestinal metaplasia was not seen on the biopsy materials. **Conclusion:** Precancerous lesions are very rarely reported among children. These are particularly seen together with *H. pylori* infection and around 10-years of age. Our results show that intestinal metaplasia is seen in *H.pylori* positive children and the incidence is very low. The reason of low prevalence is suggested to be depending on the host, microorganism and the pathologists.

Key Words: *Helicobacter pylori*; child; metaplasia

ÖZET Amaç: Atrofik gastrit ve intestinal metaplazi erişkinlerde sık görülen ve premalign potansiyeli olan lezyonlardır. Bu lezyonların çocuklardaki prevalansı iyi bilinmemektedir. Çalışmamızın amacı, çocuklarda gastrik atrofi ve intestinal metaplazi prevalansını araştırmaktır. **Gereç ve Yöntemler:** Kliniğimize gastrointestinal sistem bulguları ile başvuran hastalar çalışmaya alındı. Bu hastaların üre nefes testi, üst gastrointestinal sistem endoskopisindeki makroskopik bulguları ve yeniden düzenlenmiş Sydney sınıflaması ile histolojik sonuçları geriye dönük olarak değerlendirildi. **Bulgular:** Toplam olarak 357 çocuğa endoskopi yapılmıştı. Histopatolojik değerlendirmede hiç gastrik atrofi saptanmadı, 2 hastada intestinal metaplazi olduğu görüldü. Her ikisinin de hem üre nefes testleri hem de histopatolojik sonuçları ile, *Helicobacter pylori* pozitifti. Bir hastada peptik ülser görülmüştü. *H.pylori* eradikasyonu sonrası yapılan tekrar endoskopisinde de intestinal metaplazi saptanmadı. **Sonuç:** Çocuklarda prekanseröz lezyon çok nadir bildirilmiştir. Bu lezyonlar genelde *H.pylori* enfeksiyonu ile birlikte ve 10'lu yaşlarını süren gençlerde bildirilmiştir. Bizim sonuçlarımıza göre, intestinal metaplazi *H.pylori* pozitif çocuklarda çok nadiren görülmektedir. Bu düşük prevalansın nedenleri konağa, mikroorganizmaya ve materyali değerlendiren patoloğa bağlı olarak birden fazla etkene bağlanabilir.

Anahtar Kelimeler: *Helicobacter pylori*; çocuk; metaplazi

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Since the discovery of *Helicobacter pylori (H.pylori*) in adult patients by Marshall and Warren, much has been learned.[1] Today *H.pylori* infection is known as the cause of gastritis, peptic ulcer disease, gastric cancer and gastric mucosa-associated lymphoma.[2,3] Moreover, the infection is suggested

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to lead to an increased risk of developing precancerous gastric conditions especially when the infection occurs in childhood.[4] The International Agency for Research on Cancer (IARC) monograph committee classified *H.pylori* as a class 1 carcinogen to humans in 1994.[5] The hypothesized path is chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, epithelial dysplasia and finally gastric cancer evolution.[5] Intestinal metaplasia and gastric atrophy are systematically sought for in adult stomach biopsies because of cancer pathology, thus both are frequently reported in adult patients.[6-8] However the frequency and presence in children is questionable. There are quite high numbers of *H. pylori* prevalence reports in Turkey, and the prevalence ranges from 43.9% to 64.4%.[9,10] There is still no clear consensus about *H.pylori* presence and gastric cancer, even precancerous lesions in childhood. Here we aimed to investigate the prevalence of gastric atrophy and intestinal metaplasia among children.

MATERIAL AND METHODS

Children with gastrointestinal symptoms admitted to Department of Pediatrics were enrolled in this study. The records of children admitted to the Pediatric Gastroenterology, Hepatology and Nutrition Clinic between November 2007 and January 2010 were evaluated retrospectively. Children underwent upper gastrointestinal endoscopy (UGE) because of abdominal pain, failure to thrive and upper gastrointestinal bleeding. Upper gastrointestinal endoscopy was performed after an informed consent was taken. A total of minimum 4 biopsies, 2 from the antrum, 2 from the corpus of stomach were taken according to ESPGHAN guidelines.[11] *H. pylori* infection was diagnosed when ^{14}C-urea breath test (^{14}C-UBT) and gastric histology were positive. In patients undergoing UGE, macroscopical findings were noted, antral and/or body biopsies were taken from all cases. Histological diagnosis was made in accordance with updated Sydney system.[12] Children having intestinal metaplasia had a second UGE, and new gastric biopsies were taken. These biopsies were evaluated according to updated Sydney classification and compared to the first.

PATHOLOGY

Two biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E). The pathologist at the hospital provided a diagnosis for treatment purposes. A second, blinded review was performed in all cases by the study pathologist (SA). Mucosal type (corpus or antrum) of the biopsy samples was determined histologically. The visual analog scale of the updated Sydney classification for gastritis was used to grade density of *H. pylori*, amount of active and chronic inflammatory infiltrate, and the of atrophy and intestinal metaplasia.[12] Lymphoid aggregates were counted in each biopsy specimen.

STATISTICS

All statistical analyses were performed by using SPSS 10.0 for Windows. Data were expressed as the mean [± Standard deviation (SD)]. Descriptive statistics were calculated for patient characteristics.

RESULTS

A total of 357 children were included in the study. There were 149 male and 208 female children. The age range was 4-17 years (11.46±2.60). The major complaint of the children were abdominal pain (n=312; 87.3%), pyrosis and/or belching (n=17; 4.7%), failure to thrive (n= 31; 8.6%), and upper gastrointestinal bleeding (n=4, 1.1%). Family members of 186 children had gastric complaints and/or proven gastritis.

Endoscopically, the most commonly observed finding was nodular gastritis (59.57%), in which multiple nodularities were observed, predominantly in the gastric antrum. Forty-seven patients had peptic ulcers (13.16%). Of these patients, 38 (80.85%) were *H.pylori* positive and 9 (19.15%) were *H.pylori* negative. Atrophy was not seen in any biopsy specimen (0%), but intestinal metaplasia was noticed in 2 children in the antrum (0.56%). A detailed overview of the study is shown in Figure 1.

CASE 1

A 9-year-old boy was admitted to our clinic for abdominal pain. He had positive ^{14}C-UBT, and endo-

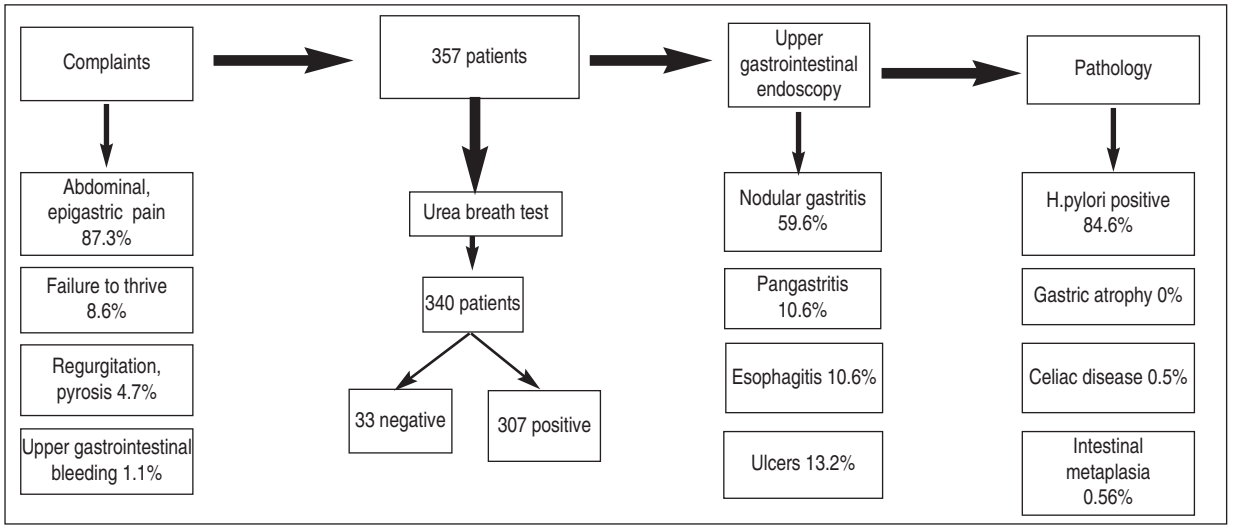

FIGURE 1: The data of the children who underwent upper gastrointestinal system endoscopy.

scopical examination revealed antral nodularity, hiperemia of the body of stomach, normal bulbus and duodenum. Histological examination revealed *H.pylori* gastritis. Intestinal metaplasia was seen in one biopsy taken from the antrum. *H.pylori* eradication was given and control UBT was done 8 weeks after treatment. Final UBT was negative, control endoscopy was performed 9 weeks after the first endoscopy and revealed normal mucosa. Multiple biopsies were taken from antrum and body of stomach. No *H.pylori* and intestinal metaplasia was seen on histology.

CASE 2

The patient was an 12 years old girl. She was admitted for abdominal pain as well. She had positive ^{14}C-UBT. Upper gastrointestinal endoscopy revealed a hyperemic stomach, antral nodularity, and an ulcer of approximately 1 cm diameter in the antrum. Bulbus and duodenum mucosae were macroscopically normal. Histological evaluation revealed *H.pylori* gastritis and intestinal metaplasia, but no gastric atrophy. *H.pylori* eradication was given and control UBT was done 8 weeks after treatment. The patient's final UBT was negative, control endoscopy revealed normal macroscopical findings. No *H.pylori* and intestinal metaplasia was seen on histology, as case 1 (Table 1).

DISCUSSION

H.pylori infection is suggested to lead to a 4 to 9 folds increased risk of developing precancerous gastric conditions, especially when the infection occurs in childhood.[4] This knowledge leads us to search for precancerous lesions, namely intestinal metaplasia and gastric atrophy, among children. Kim et al. have reported the prevalence of atrophy and intestinal metaplasia in a cohort which consisted of 389 adult patients from Korea, without significant gastroduodenal diseases.[13] The authors found atrophy in 42.5% in the antrum and 20.1%

TABLE 1: The data of the patients with intestinal metaplasia showing age, sex, urea breath test, endoscopic findings and degree according to Sydney classification.

					Sydney classification					
Sex	**Age**	**UBT**	**EF**	**Hp**	**Activity**	**Inflam**	**IM**	**Atrophy**	**Dysplasia**	**LF**
M	9yr	+	AN	++	3	3	2	0	0	+
F	12yr	+	AN,ulcer	+	3	1	1	0	0	0

UBT: Urea breath test; EF: Endoscopic finding; AN: Antral nodularity; IM: Intestinal metaplasia; LF: Lymph follicule.

in the body biopsies. Intestinal metaplasia was found in 28.6% and 21.2% of patients in the antrum and body, respectively. In *H.pylori* positive subjects, the prevalences of both atrophic gastritis and intestinal metaplasia increased with age. In a study from Japan, where gastric cancer prevalence is considerably high, the progression of precancerous lesions was strongly related to *H.pylori* infection.[14] The authors found glandular atrophy and intestinal metaplasia in more than half of the *H.pylori* positive patients. Those lesions were low in the *H.pylori* negative patients. The authors suggested that the results confirmed the tight link between *H.pylori* infection, atrophic gastritis and intestinal metaplasia in the stomachs of Japanese patients.

The number of records about gastric atrophy and intestinal metaplasia among children have increased in this decade. Guarner et al. have observed gastric atrophy in 8, intestinal metaplasia in 2 and both in 2 patients out of 19 children.[15] All children were infected with *H.pylori* and all patients with intestinal metaplasia were older than 9 years. Atrophy was seen in 10 patients, all in the antrum, and metaplasia in 4 patients, 3 in the antrum and 1 in the corpus. The authors have characterized inflammatory response using immunohistochemistry for T lymphocytes, B lymphocytes and macrophages and TUNEL assay for apoptosis. The authors have postulated that in *H.pylori* infected patients, increased B lymphocytes and apoptosis of the epithelium and inflammatory cells may predispose to gastric mucosal atrophy and eventually intestinal metaplasia. Ricuarte et al. have examined gastric mucosal biopsies from 173 children in a two-center study from Korea and Colombia. Atrophy was present in 16 children (14% of the patients).[16] All of these children were Colombian and positive for *H.pylori*. Intestinal metaplasia was present in 4 children, and corpus atrophy was manifest by intestinal metaplasia in 6 children. The youngest child with gastric atrophy was 9 years old as in the study by Guarner and collegues.[15] Cohen et al. have studied 79 gastric biopsies from 15 children with gastritis and applied Sydney system, as a result, neither gastric atrophy nor intestinal metaplasia was seen in the biopsies.[17] In a Japanese study, among 131 children infected with *H.pylori* gastric atrophy was seen in 11.4% of the children, and no intestinal metaplasia was found.[18] A recent study investigating the association between gastric atrophy and *H. pylori* infection in 196 children with a mean age of 11 years demonstrated that the prevalence of gastric atrophy in antrum and corpus were 10.7% and 4.3%, respectively, in *H. pylori*-infected children and 0% in *H. pylori*-negative children.[19] In the same study, intestinal metaplasia was found in 4.6% of *H. pylori*-infected cases.

There are 3 studies from Turkey about intestinal metaplasia and gastric atrophy in children. Usta et al. have performed a study from central Anatolia, and found atrophy and/or intestinal metaplasia in 2.8% of children.[20] In a study made among children under 2 years of age who were living in İstanbul, no intestinal metaplasia was seen but gastric atrophy was reported 2.5% in *H.pylori* infected infants. This study also drives attention to early acquisition of *H.pylori* infection in Turkey.[21] The highest ratios of gastric atrophy and intestinal metaplasia are reported in a study as 72.2% and 77.7% respectively, which was made in İzmir.[22] Children with gastric atrophy and intestinal metaplasia were *H.pylori* positive. There was one patient with mild glandular atrophy and none with intestinal metaplasia among *H.pylori* negative children. The authors have attributed these high ratios to the early acquisition of *H.pylori*. In the present study, no gastric atrophy was seen. However 2 children had intestinal metaplasia. Although our study is made in a high seroprevalent area for *H.pylori,* there was 0% gastric atrophy and 0.56% intestinal metaplasia among children undergoing UGE in a 3-year period. Including the present study, there are 4 reports from different regions from Turkey all of them reporting different prevalences of gastric atrophy and intestinal metaplasia.

In the present study, the reported age range of the children with gastric atrophy and/or intestinal metaplasia is narrow. The average age range of children reported in the literature are 9-11 years.[23] This may be because endoscopy for younger children is not performed as frequently as older children, or these precancerous lesions are not taken into ac-

count seriously. Whatever the reason is, our findings are compatible with the literature when the age is concerned.

Another important issue is that there is no validated histological classification for the gastropathies of children. The Updated Sydney classification is widely used for adults and children as well. However, there are some restrictions when it is tried to applied to children. The number and site of the biopsies suggested may not be achieved in all children, particularly in younger children and infants. This condition can lead underestimation of gastric atrophy and intestinal metaplasia. The Updated Sydney classification, although updated, can have interpretational differences, and the quality of the biopsy material may cause the final diagnosis. The place where the biopsies are taken is very important as these lesions are not distributed all over the gastric mucosa, finding these lesion can be suggested to be coincidentally.

CONCLUSION

The reported incidence of gastric atrophy and/or intestinal metaplasia ranges from 0% to 77.7% in children. The distinct different prevalences in the same country as well as among different countries can be attributed to some reasons such as the type of *H.pylori*, genetic factors, host immune response, environmental factors, interpretational variability, the quality of the biopsy material, staining and orientation of the specimen. To evaluate all these issues, pediatric gastroenterologists should pay attention to these precancerous lesions, histopatological classification for childhood gastritis should be defined, and finally additional large multicentric studies are needed.

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Meltem Ugras, performed upper gastrointestinal endoscopies, wrote the manuscript Saadet Alan, did the pathological study, wrote the manuscript.

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