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Original Article

Trends in gastroesophageal reflux disease in Japanese children and adolescents

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Abbreviations: GERD, gastroesophageal reflux disease; EGD, esophagogastroduodenoscopy.

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Abstract

Background: Although the prevalence of gastroesophageal reflux disease (GERD) has been increasing in Japan, little is known concerning the prevalence and severity of GERD in pediatric patients. This study compared the prevalence and severity of endoscopically proven GERD in pediatric patients seen at an endoscopy center in Japan over a 15-year period.

Methods: This was a retrospective chart review of Japanese children between the aged 5 - 18 years undergoing esophagogastroduodenoscopy for upper gastrointestinal symptoms or anemia between 2005 and 2019. The prevalence and severity of reflux esophagitis and endoscopic Barrett's esophagus were compared between 2005-2012 and 2013-2019.

Results: A total of 564 patients were evaluated; 315 from 2005 to 2012 [average age, 13.8 (range, 5-18) years; 147 boys] and 249 from 2013 to 2019 [average age, 14.7 (range, 5-18) years; 108 boys]. Demographics and clinical features were similar between the two groups. The proportion with erosive esophagitis or endoscopic Barrett's esophagus increased significantly between the two periods (9.8% to 18.1% for GERD, $P=0.0045$ and 2.5% to 9.6% for Barrett's, $P=0.0003$). The proportion of GERD patients with endoscopic Barrett's esophagus also significantly increased between the two periods [i.e., 53.3% (24/45) vs. 25.8% (8/31), $P=0.017$].

Conclusion: The prevalence and severity of endoscopically proven GERDs has significantly increased over the past 15 years at an endoscopy center in Japan. Detailed population based studies are needed to assess whether this is occurring throughout Japan.

Key words adolescents , , Barrett's esophagus, children, gastroesophageal reflux disease, reflux esophagitis.

Introduction

Gastroesophageal reflux disease (GERD) is defined as esophageal mucosal injury occurring secondary to reflux of gastro-duodenal contents into the esophagus [1,2]. The predominant symptoms in pediatric patients vary with age. Common GERD symptoms in infants are regurgitation, choking, gagging, irritability, and excessive hiccups whereas GERD symptoms in young children are similar to those experienced by adults and include abdominal pain, vomiting, excessive belching, and dysphagia [3,4,5]. Complications of gastroesophageal reflux include erosive esophagitis that may eventuate in a stricture or development of a columnar-lined mucosa (Barrett's esophagus). Barrett's esophagus is the only recognized precursor lesion of esophageal adenocarcinoma [6]. Typical endoscopic findings for GERD include structural abnormalities such as hiatal hernia and mucosal findings such as erosions, stricture or Barrett's esophagus [6-9].

It has been reported that between 1995 to 2014 the level of gastric acid secretion has increased in healthy young Japanese [10] whereas over the last 40 years, the age-specific severity of gastric atrophy and gastric mucosal intestinal metaplasia has declined remarkably [11]. This trend has been most marked in young adults (20-39 years). It has been suggested that the high-protein diet enhances gastrin secretion stimulated G cells resulted in an increase in acid secretion [12]. Increased acid secretion may also result in an increase in the prevalence and severity of GERD. While the changes in the prevalence of GERD have been amply studied in Japanese adults [13], there is a very limited literature on the trends of reflux esophagitis and endoscopic Barrett's esophagus in Asian pediatric patients. The aim of this study was to examine changes in the prevalence and severity of endoscopically proven GERD at an endoscopy center in Japan during the past 15 years.

Methods

Study design

This was a retrospective analysis of endoscopy results from a single center (the Showa Inan General Hospital in Komagane city, Japan). The Institutional Review Board of the hospital approved the retrospective chart review study protocol (No. 2019-08) on January 15, 2020. All subjects or their guardians had given written informed consent for the original procedures. The study was conducted in accordance with the Declaration of Helsinki.

Subjects

Patients between 5-18 years who had undergone diagnostic esophagogastroduodenoscopy (EGD) at the Digestive Disease Center, Showa Inan General Hospital between January 2005 and December 2019 were retrospectively enrolled. The indications for endoscopy were upper gastrointestinal symptoms including recurrent abdominal pain, vomiting, nausea, regurgitation, and dyspepsia or anemia. Patients with a history of foreign body ingestion or abdominal surgery or repeated upper endoscopies on already-included subjects were excluded. Patients with confounding factors known to increase the risk of developing GERD, such as neuromuscular disorders, hemato-oncological diseases, Down syndrome, and chronic pulmonary conditions were also excluded. Data regarding age, gender, weight, height, indication for EGD and EGD findings were obtained from electronic charts. Weight and height were used to calculate body mass index percentiles.

Procedures

All EGDs were carried out without tracheal intubation. Upon the endoscopists' discretion, propofol or other medications, i.e. midazolam or pentazocine, were also used (prior to or during the procedure). The sum of all medications given during the procedure were recorded. EGD was performed using a small caliber or standard upper endoscope (GIF-XP 240, XP260, or H290; Olympus Optical co. Ltd, Tokyo, Japan) with an endoscopic video

information system (CV 240, CV260, or CV290, Olympus, Tokyo, Japan) by experienced pediatric or adult gastroenterologists. The outer diameter of the instruments used is 7.7 mm, 6.5 mm, or 8.9 mm and the size of biopsy channels are 2.2 mm, 2.0 mm or 2.8mm. The endoscopic images were recorded by both computer image and text reporting system and video tape recorder. All patients had cardiovascular monitoring and continuous oximeter measurement. Respiratory or cardiovascular complications were recorded by the nurse at the time of the procedure, and were entered into the reviewed data. Hypoxia was defined as oxygen saturation below 90% over 30 seconds.

Definitions

Both reflux esophagitis and endoscopic Barrett's esophagus were defined as endoscopically proven GERD (i.e., erosive GERD or Barrett's esophagus). During the procedure, the endoscopists recorded the presence/absence of a hiatal hernia which was defined by displacement of the esophagogastric junction and/or a portion of the upper stomach proximally above the diaphragmatic impression. The severity of erosive esophagitis was graded according to the Los Angeles classification [14].

The normal esophageal squamous mucosal surface appears whitish-pink in color, contrasting sharply with the salmon pink to red appearance of the columnar gastric mucosa. The demarcation line between the two types of mucosa is defined as the squamocolumnar junction or "Z-line". Particular attention was paid to palisade-shaped vessels at the distal end of the esophagus. These vascular structures run superficially in the esophageal lamina propria and are readily detectable on routine endoscopy. At the esophagogastric junction level, the palisade vessels penetrate deeply inside the gastric wall and are no longer endoscopically visible (Fig. 1). The site of 'disappearance' was defined as the esophagogastric junction [13]. The length of columnar-lined esophagus, that is the distance

from the esophagogastric junction to squamocolumnar junction was defined as Endoscopic Barrett's esophagus [13]. The portion extending above the circumferential Barrett segment was defined as a tongue of endoscopic Barrett's esophagus. The extent of endoscopic Barrett's esophagus was graded according to "Prague C & M criteria" assessing the circumferential (C) and maximum (M) extent of metaplasia above the esophagogastric junction in centimeters [15]. The length of endoscopic Barrett's esophagus was estimated using the open-forceps technique (forceps span = 6 mm).

Histopathology

Biopsy specimens were taken for histopathologic examination from the stomach, including the antrum greater curvature, lower corpus lesser curvature, upper corpus greater curvature and esophagogastric junction. Regarding the esophagogastric junction, at least two specimens each were obtained from the most proximal extent of the gastric folds (greater and lesser curvature) and from the distal esophagus with the aim of obtaining tissue samples from both above and below the squamocolumnar junction. The samples were stained with hematoxylin and eosin for the evaluation of gastritis and *H. pylori* status was defined by Giemsa stain. The biopsies obtained from the distal esophagus were examined for the presence or absence of esophagitis according to the extent of basal cell hyperplasia, papillary elongation, dilation of intercellular spaces of the squamous epithelium, as well as the presence of intraepithelial inflammatory cells. In addition, they were examined for the presence of columnar-lined esophagus, defined as hybrid epithelium with characteristics of both squamous and columnar epithelia, characterized by flattened squamoid cells in its basal layers and columnar mucus cells in its superficial layers, respectively. Intestinal metaplasia was diagnosed when goblet cells were present in either the surface or crypt epithelium.

Statistical analyses

Statistical differences were analyzed by Chi-square tests of independence and Fisher's exact test or Student's *t*-test. *P* values <0.05 were considered significant. Statistical analysis was performed using JMP software, version 9.0.2 (SAS Institute Japan Inc., Tokyo, Japan).

Results

Baseline characteristics of enrolled patients

A total of 564 patients were evaluated including 315 from 2005 to 2012 (mean \pm SD) age, 13.8 \pm 3.0 (range, 5-18) years; 147 boys and 249 from 2013 to 2019 (mean \pm SD) age 14.7 \pm 2.8 (range, 5-18) years; 108 boys. None of the children had obesity in either the 2005-2012 group or the 2013-2019 group based on the definition of obesity of World Health Organization (body mass index-SD [5-19 year]: obesity > +2 SD)[16]. The major indications for EGD were the presence of upper gastrointestinal symptoms and/or anemia. The common indication for EGD was upper gastrointestinal symptoms including recurrent abdominal pain, vomiting, nausea, regurgitation, and dyspepsia. Patient demographics and indications were similar between the two periods (Table 1). Antisecretory medications were prescribed for all patients with peptic ulcer and *H. pylori* eradication was performed for all patients with *H. pylori* infection.

The percentages of patients with endoscopic reflux esophagitis or endoscopic Barrett's esophagus were significantly greater in the 2013-2019 period compared to the earlier period (2005-2012) (18.1% vs. 9.8%, *P*=0.0045; 9.6 % vs. 2.5%, *P*=0.0003). Other endoscopic findings such as chronic gastritis, gastric ulcer, duodenal ulcer and esophageal hiatal hernia were also similar between the two periods. The proportion with esophageal hiatal hernias was low in both periods (1.2-1.3%)(Table 1).

Endoscopically proven erosive GERD patients

Seventy-six patients with reflux esophagitis were identified; 31 patients (mean \pm SD) age 13.1 \pm 2.5 (range, 8-18) years; 17 boys from 2005 to 2012 and 45 from 2013 to 2019 (mean \pm SD) age 14.2 \pm 2.3 (range, 7-18) years; 23 boys. Patients demographics, body mass index and the presence of *H. pylori* infection were similar between the two groups (Table 2) as was the proportion of those presenting with upper gastrointestinal symptoms or anemia.

Representative images of reflux esophagitis (Grade A) + endoscopic Barrett's esophagus (C1M1) in the Prague classification are shown in Fig. 1. The proportion of those with GERD presenting with endoscopic Barrett's esophagus significantly increased between the two periods (i.e. 24/45 [53.3%] vs 8/31 [25.8%], P=0.017) (Table 2). In endoscopic Barrett's esophagus, the number of patients with C0M1 and C1M1 Prague classification increased from 3 and 5 (2005-2012) to 17 and 7 (2013-2019), respectively, (P=0.058). Histopathological evaluation from above and below the squamocolumnar junction was performed in 55 (72.4%) of 76 patients with erosive esophagitis. The proportion with histologic reflux esophagitis according to the extent of basal cell hyperplasia, papillary elongation, dilation of intercellular spaces of the squamous epithelium was similar in the two different periods (14/24 [58.3%] vs.17/31[54.8%], P=0.80). Intestinal metaplasia was not found in any biopsy specimens (Table 2).

Discussion

This study shows that the incidence of both reflux erosive esophagitis and endoscopic Barrett's esophagus diagnosed at a single endoscopy center in Japan has increased over the past 15 years. Barrett's esophagus is a preneoplastic condition that develops as a consequence of chronic GERD and predisposes to the development of esophageal

adenocarcinoma [17,18]. Endoscopic Barrett's esophagus is defined as replacement of normal squamous epithelium by columnar epithelium with columnar mucosa extending above the gastroesophageal junction [17,19]. The palisade vessels present at the distal end of the esophagus are considered a reliable landmark of the esophagogastric junction and indispensable for diagnosis of endoscopic Barrett's esophagus on the basis of the Japanese criteria [13].

We found that neither body mass index, the *H. pylori* infection or esophageal hiatal hernia were associated with the increase in reflux esophagitis and endoscopic Barrett's esophagus in our sample of Japanese children and adolescents (Table 2). The increase in GERD identified in this study may reflect the increase in gastric acid secretion associated with the changes in diet and reduction of *H. pylori* in Japan [10,12,20]. An increase in gastric acid secretion could also be responsible for the proportion of GERD patients with endoscopic Barrett's esophagus significantly increasing between the two periods (i.e. 24/45 [53.3%] vs. 8/31 [25.8%], $P=0.017$) (Table 2).

Although endoscopic Barrett's esophagus was limited in extent to only C0M1 and C1M1 in the patients of this study, this may be related to the selection of subjects enrolled which were healthy children and adolescents without obesity, underlying conditions, nor hiatus hernia.

In a previous study, we detected 10 (0.8%) Japanese patients with endoscopically suspected Barrett's esophagus among 1323 pediatric cases; however, none proved to have intestinal metaplasia by histopathological evaluation. The median age of the patients with suspected Barrett's esophagus was 10 years (range 7–14); seven were boys [21]. Although histopathological evaluation was performed in 55 (72.4%) of 76 patients with reflux esophagitis in this study, no case proved to have intestinal metaplasia. Table 3 shows results

of prior reports on the prevalence of endoscopic Barrett's esophagus with and without intestinal metaplasia and among children and adolescents with GERD. Although the prevalence of endoscopic Barrett's esophagus in Japanese children and adolescents has been approaching the prevalence in Canada, Barrett's esophagus with intestinal metaplasia was rarely found at this endoscopy center in Japan. Data from 20 Barrett's esophagus patients (70% male, mean age: 14.9 years) and 17 intestinal metaplasia of the gastroesophageal junction patients (71% male, mean age: 14 years) were retrospectively obtained at a chart review in the United States [27]. A subset of Barrett's esophagus (57%) and intestinal metaplasia of the gastroesophageal junction patients (67%) who underwent EGD prior to initial diagnosis showed non-goblet columnar metaplasia. The natural history of non-goblet cell Barrett's esophagus in Japan is unknown. Seven of the patients in this study had EGD repeated 2 to 4 times over the 15 years of the study and in no case did the endoscopic appearance change; none developed goblet cells.

This study has some limitations. First, it was retrospective and it is not possible to eliminate the influence of the patients' background or any confounding factors such as a change in the indications for EGD over the 15 years. During this period, the technical abilities of the endoscopes have improved and it is not possible to correct for possible different intubation techniques or other pre-existing bias of the endoscopists. Finally, the sample size was small and it was conducted in a single hospital.

In conclusion, the prevalence and severity of both reflux esophagitis and/or endoscopic Barrett's esophagus among children seen at one endoscopy center in Japan has apparently significantly increased over the past 15 years. The dramatic decline in incidence of *H. pylori* in Japanese children with an associated improvement in gastric histology allowing increased acid secretion suggests that the finding in this study may have implications for the

population of Japanese children. These data suggest that further studies on the prevalence of GERD among Japanese children are warranted to test whether the epidemiology of GERD in the Japanese pediatric population is changing. Such studies are required to delineate the development and risk factors for GERD in the Japanese pediatric population and to identify the significance and natural history of endoscopic non-goblet cell Barrett's esophagus.

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Disclosure

The authors declare no conflicts of interest.

Author contributions

M.K and Y.N. designed the study and wrote the manuscript; M.K., Y.N, and A.H. collected and analyzed the data. A.H. and Y.N. revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Table 1. Patients baseline characteristics and their clinical features of 564 patients who underwent esophagogastroduodenoscopy

Group	2005-2012 (N=315)	2013-2019 (N=249)	<i>p</i> Value
Demographics			
Average age [SD] (range)(yr)	13.8[3.0] (5-18)	14.7[2.8] (5-18)	0.53
Gender (male)	147(46.7)	108 (43.4%)	0.44
<i>H. pylori</i> - infected	44/301(14.6%)	25/205(12.2%)	0.41
Indications			
Upper GI symptoms	297	241	0.16
Anemia	18	8	
Endoscopic findings			
Reflux esophagitis	31/315 (9.8%)	45/249 (18.1%)	0.0045
Endoscopic Barrett's esophagus	8/315 (2.5%)	24/249 (9.6%)	0.0003
Chronic gastritis	44(14%)	25(10%)	0.16
Gastric ulcer	5(1.6%)	1(0.4%)	0.17
Duodenal ulcer	12(3.8%)	8(3.2%)	0.70
Esophageal hiatal hernia	4(1.3%)	3(1.2%)	0.94

GI, gastrointestinal.

Table 2. Patients baseline characteristics and their clinical features of 76 patients with reflux esophagitis

Group	2005-2012 (N=31)	2013-2019 (N=45)	<i>p</i> Value
Demographics			
Average age [SD] (range)(yr)	13.1[2.5] (8-18)	14.2[2.3] (7-18)	0.57
Gender (male)	17(55%)	23(51%)	0.75
Average BMI [SD] (kg/m ²)	19.3[3.8]	19.4[4.1]	0.65
<i>H. pylori</i> - infected	1 (3.2%)	3 (6.7%)	0.51
Indications			
Upper GI symptoms	29	44	0.35
Anemia	2	1	
Endoscopic findings and their classification			
Reflux esophagitis Grade A	29 (93.5%)	40 (88.9%)	0.79
Reflux esophagitis Grade B	2 (6.5%)	5 (11.1%)	
Reflux esophagitis Grade C/D	0 (0%)	0 (0%)	
Endoscopic Barrett's esophagus/ erosive esophagitis			
	8/31 (25.8%)	24/45 (53.3%)	0.017
C0M1	3	17	0.058
C1M1	5	7	
Esophageal hiatal hernia	0	0	
Histopathological findings			
Reflux esophagitis	14/24 (58.3%)	17/31(54.8%)	0.80
Intestinal metaplasia	0/24 (0%)	0/31(0%)	

Normal

10/24(41.7%)

14/31(45.2%)

BMI, Body mass index; GI, gastrointestinal.

Table 3. Prevalence of endoscopic Barrett’s esophagus among children and adolescents with gastroesophageal reflux disease

Author (year)	Study design	Study period	Country	No. cases	Endoscopic Barrett’s esophagus (%)	Endoscopic Barrett’s esophagus with IM (%)
El-Serag <i>et al.</i> ²² (2002)	Retrospective study	1996-2000	USA	402	2.7	0
El-Serag <i>et al.</i> ²³ (2006)	Retrospective multicenter study	1999-2002	USA	6731	0.25	0.13
Hassall <i>et al.</i> ²⁴ (2007)	Retrospective study	1989-2004	Canada	166	9.7	4.8
Cohen <i>et al.</i> ²⁵ (2009)	Retrospective study	2000-2007	UK	1453	0.8	0.6
Nguyen <i>et al.</i> ²⁶ (2011)	Prospective multicenter study	2006-2007	USA	840	1.4	0.12
Nakayama <i>et al.</i> ²¹ (2017)	Retrospective study	2005-2015	Japan	1323	0.8	0
Present study	Retrospective study	2005-2012	Japan	315	2.5	0
Present study	Retrospective study	2013-2019	Japan	249	9.6	0

IM, intestinal metaplasia.

Figure legend

Fig. 1 The representative image of reflux esophagitis (Grade A) and endoscopic Barrett's esophagus (C1M1) in Prague classification is shown. White circle shows the esophagogastric junction. Arrow shows erosive esophagitis.

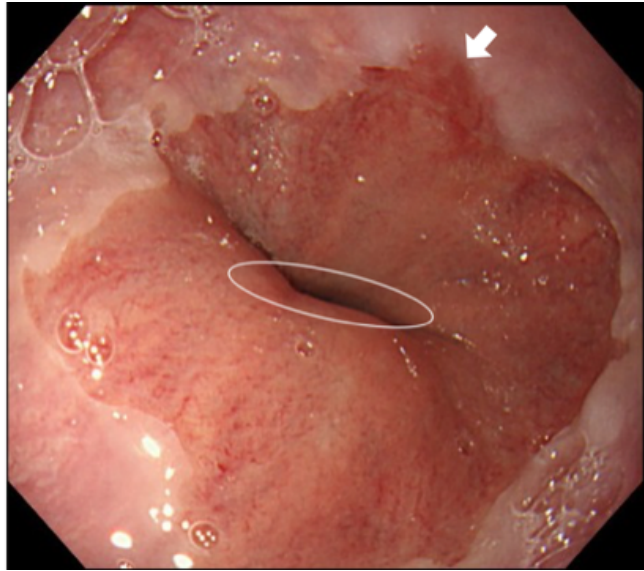


Fig.1