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Original Article

Clinical presentation and disease course of patients with esophagogastric junction outflow obstruction

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SUMMARY. **Esophagogastric junction outflow obstruction, characterized by preserved peristalsis in conjunction with an elevated integrated relaxation pressure, can result from specific anatomic variants or may represent achalasia in evolution. There is limited information on the clinical significance of this diagnosis. The aim of this study is to describe the clinical characteristics and outcomes in our cohort of patients with esophagogastric junction outflow obstruction.**

Consecutive adult patients who had undergone high-resolution esophageal manometry between February 2013 and November 2015 with a diagnosis of esophagogastric junction outflow obstruction were identified. Electronic medical records were reviewed to determine: (1) secondary causes of esophagogastric junction outflow obstruction; (2) treatment; and (3) natural history. Improvement in symptoms noted during follow-up evaluation was considered to be a favorable outcome. Worsening of symptoms or no change in symptoms was considered to be an unfavorable outcome.

Of 874 manometries performed during this time period, 83 met the criteria for esophagogastric junction outflow obstruction. Of these patients, 11 had secondary causes: paraesophageal hernia (4), Nissen fundoplication (2), esophageal stricture (3), prior laparoscopic band placement (1), and diverticulum (1). All of these secondary causes were identified by barium esophagram. The remaining 72 patients were categorized as idiopathic esophagogastric junction outflow obstruction. Two patients developed type II achalasia on follow-up. An additional two patients had no symptoms as testing was performed for preoperative evaluation prior to bariatric surgery, leaving 68 patients for symptom follow-up analysis. Of these, 19 had a favorable outcome, 18 had an unfavorable outcome, and 31 were lost to follow-up. Of those with a favorable outcome, 6 patients underwent treatment: medication (3), botulinum toxin injection followed by laparoscopic Heller myotomy (1), botulinum toxin injection and medication (1), and bougie dilation (1). Of the 18 patients with an unfavorable outcome, 6 patients underwent treatment: botulinum toxin injection (5) and medication (1). Computed tomography scan or endoscopic ultrasound was performed in 40% of patients with available follow-up and none of these studies revealed secondary causes. The overall median follow-up time was 5 months.

Esophagogastric outflow obstruction is a manometric finding of unclear significance. Secondary causes should first be excluded with structural studies. The evolution of esophagogastric junction outflow obstruction to achalasia is rare. Symptoms in patients with esophagogastric junction outflow obstruction do not always require treatment and treatment response is variable. The challenge in managing these patients lies in distinguishing which patients will need intervention. Further studies are needed for consideration of subgrouping this disease or modifying the categorization into clinically relevant entities.

KEY WORDS: **diseases of the esophagus, dysphagia, esophageal dysmotility, esophagogastric junction, hypertensive lower esophageal sphincter.**

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INTRODUCTION

The increasing use of high-resolution esophageal pressure topography in clinical practice has led to the continued refinement of diagnostic categories. The Chicago classification identifies distinct manometric patterns but the clinical significance of patterns other than achalasia (subtyped into three distinct variants) remains unclear. Esophagogastric junction outflow obstruction (EGJOO) is one such topographic pattern that has been of increasing interest in the recent years.[1–3]

EGJOO is characterized by preserved peristalsis in conjunction with an elevated median four-second integrated relaxation pressure (IRP). It is recognized that this topographic diagnosis can be a result of anatomic abnormalities such as a paraesophageal hernia, malignancy, aberrant vasculature, or a gastroesophageal junction (GEJ) stricture.[4] Once secondary causes have been excluded, there is no well-established approach for idiopathic EGJOO. It has been suggested that this abnormality may represent achalasia in evolution although there is no definitive evidence for this. In fact, it appears that most cases of EGJOO do not evolve to achalasia.[2,3,5] There is limited information on the significance of EGJOO to date and the natural history of this abnormality remains unclear.

Achalasia is a disorder with a similar esophagogastric junction pressure topography pattern but it is distinct from EGJOO in that it is characterized by the absence of esophageal peristalsis. Disruption of the lower esophageal sphincter (LES) is the goal of therapy in this disease. Multiple therapeutic modalities including laparoscopic Heller myotomy (LHM), per-oral endoscopic myotomy (POEM), pneumatic dilation (PD), and botulinum toxin injection have been shown to be safe and efficacious for this disorder.[6,7] However, applying this approach to EGJOO has not had the same results to date.[1,5,8]

Our aim is to describe the characteristics and outcomes of our cohort of patients with EGJOO in an attempt to investigate the clinical relevance of this disorder.

MATERIALS AND METHODS

Study design

This is a retrospective case series of consecutive adult patients who underwent high-resolution esophageal manometry (HRM) between February 2013 and November 2015 at the Hospital of the University of Pennsylvania. All manometric studies that met the criteria for EGJOO via the Chicago classification (version 2.0 and version 3.0) were included for analysis.[4,9] The electronic medical records of all patients meeting the diagnosis were reviewed to determine: (1) secondary causes of EGJOO; (2) endoscopic and imaging evaluation; (3) treatment if any; and (4) natural history. Improvement in symptoms described by the patient during follow-up evaluation by the physician was considered to be a favorable outcome. Worsening or no change in symptoms was considered to be an unfavorable outcome.

High-resolution esophageal manometry

An esophageal manometry catheter with 36 pressure sensors (Medtronic, Friedley, Minnesota, USA) was used to perform esophageal pressure topography measurements. After a six-hour fasting period, the catheter was placed transnasally with the distal tip in the stomach at least 5 cm distal to the GEJ. Calibration for landmarks was performed for a minimum of 60 seconds. The patient then swallowed 5 cc of water 10 successive times with at least 30 seconds between swallows, consistent with recently published quality measures.[10] The catheter was subsequently removed and the data were uploaded for analysis.

Manoview analysis software was used to analyze pressure topography plots. Thermal compensation was performed and the following landmarks were manually positioned: upper esophageal sphincter, LES borders, pressure inversion point, and gastric body. The IRP was automatically calculated by the software and each swallow was manually reviewed. Four gastroenterologists with expertise in esophageal disease interpreted all of the manometry studies.

Statistics

The IRP means were compared via the student's t test.

RESULTS

A total of 874 high-resolution esophageal manometries were performed at our center from February 2013 to November 2015. Of these studies, 83 met the criteria for EGJOO. There were 11 patients (13.2%) who had secondary causes for this finding including paraesophageal hernia (4), esophageal stricture (3), Nissen fundoplication (2), prior laparoscopic gastric band placement (1), and an epiphrenic diverticulum (1), as seen in Figure 1. All 11 of these findings were seen on barium esophagram. Of the 72 remaining patients, two patients (2.7%), both of whom presented with dysphagia went on to develop type II achalasia (16 and 22 months after the index manometry). Both index manometries were notable for simultaneous contractions limited to the distal esophagus. The remaining

for intellectual content. All authors have approved the final draft of the manuscript.

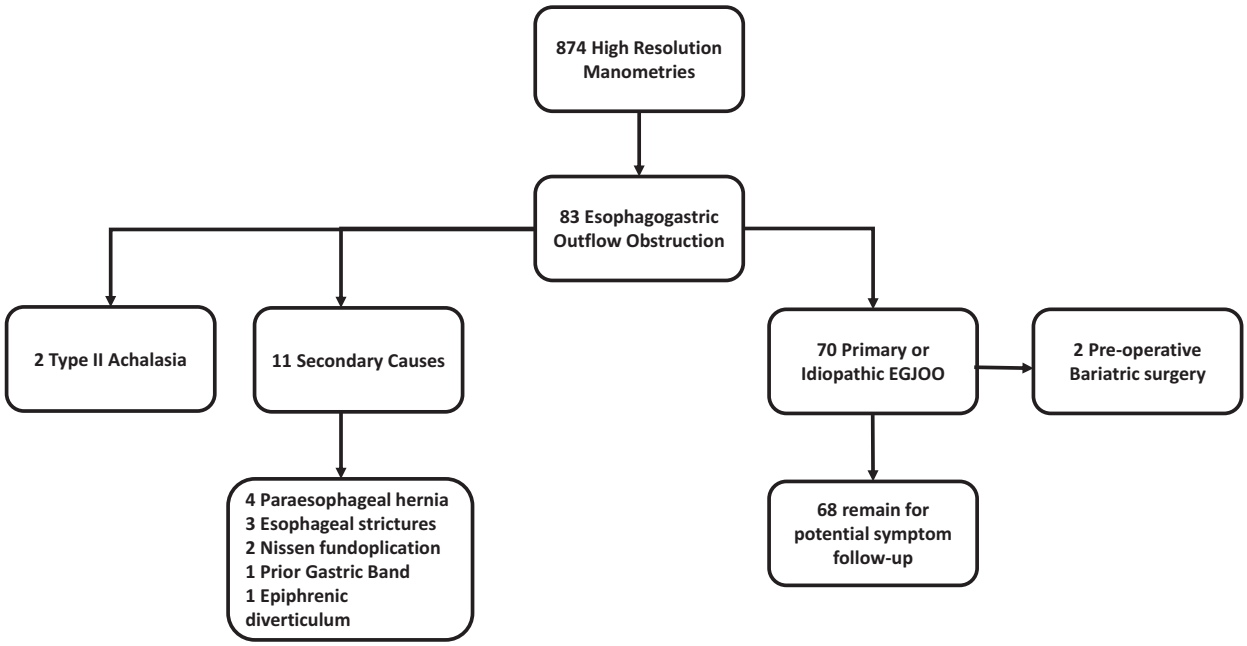

Fig. 1 Flowchart of esophagogastric outflow obstruction patients and secondary causes. There were 68 patients who remained for potential symptom follow-up analysis.

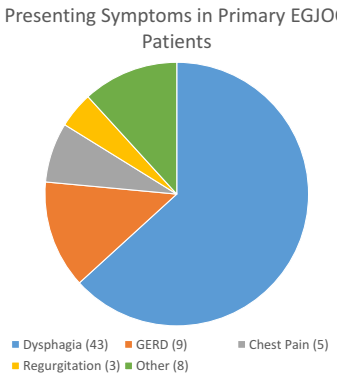

Fig. 2 Presenting symptoms in idiopathic esophagogastric junction outflow obstruction (EGJOO) patients. There were 68 patients with esophagogastric outlet obstruction; the presenting symptoms are seen here. As noted, the majority of patients presented with dysphagia.

Table 1 Characteristics of patients with idiopathic EGJOO

	Favorable response $n = 19$	Unfavorable response $n = 18$
Gender: female *n* (%)	13 (68)	17 (94)
Age: years mean, SD	57 ± 14.6	49 ± 8.2
Dysphagia as presenting symptom: *n* (%)	8 (42)	14 (78)
Integrated relaxation pressure: Mean, SD	19.5 + 6.0†	20.9 + 4.0†
Follow-up time: months, median (IQR)	4 (2–11.5)	6 (2–11)

† $P = 0.34$.
EGJOO, esophagogastric junction outflow obstruction; IQR, interquartile range; SD, standard deviation.

70 patients were categorized as idiopathic EGJOO. Two of the patients were discovered on preoperative testing for bariatric surgery and had no symptoms to evaluate for follow-up.

Indications for esophageal manometry in the remaining 68 patients (Fig. 2) included dysphagia (43), gastroesophageal reflux disease (GERD) (9), chest pain (5), regurgitation (3), cough (2), globus (2), abdominal pain (2), hiccups (1), and cyclic vomiting (1). Further evaluation of these patients was not standardized and varied by provider. Of the patients with available follow-up, 70% (26/37) had a barium esophagram and 40% (15/37) had either computed tomography (CT) or endoscopic ultrasonography (EUS).

Of the 68 patients with idiopathic EGJOO, 19 patients had favorable outcomes, 18 patients had unfavorable outcomes, and 31 patients were lost to follow-up. Characteristics of these patients can be seen in Table 1. Of the 19 patients that had favorable outcomes, the most common presenting symptom was dysphagia (42%). Almost all of these patients had barium esophagrams (11/19). Four of these studies were normal, five reported esophageal dysmotility, 1 revealed aspiration, and 1 revealed a possible narrowing at the GEJ. Of these 19 patients with favorable changes in symptoms, 13 (68%) had spontaneous improvement. Of these 13 patients, 5 patients presented with dysphagia, 2 with GERD, 2 with abdominal pain, 2 with cough, 1 with globus, and 1 with regurgitation. The remaining six patients underwent various treatments. Three patients had pharmacologic therapy; one patient initially presenting with chest pain was treated with amitriptyline, another with dysphagia and was treated with hyoscyamine, and the third presented

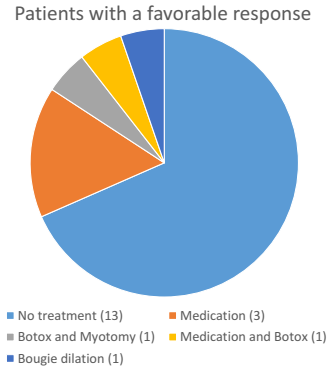

Fig. 3 Patients with a favorable response by treatment type. There were 19 patients who had a favorable response and their treatment selections are seen here.

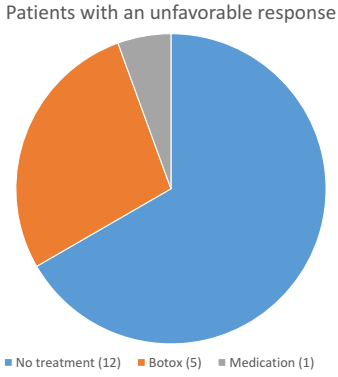

Fig. 4 Patients with an unfavorable response by treatment type. There were 18 patients who had an unfavorable response and their treatment selections are seen here.

with GERD and was treated with a proton pump inhibitor. The remaining patients who underwent treatment presented with dysphagia; 1 patient underwent botulinum toxin injection to the LES followed by a LHM, 1 underwent botulinum toxin injection to the LES and was also started on a calcium channel blocker, and 1 underwent a bougie dilation to 18 mm (Fig. 3). The median follow-up time was 4 months.

Of the 18 patients with an unfavorable outcome, the majority presented with dysphagia (78%). Most of these patients had barium esophagrams that were normal (13/18). Of the abnormal barium esophagrams in this group, 1 reported esophageal dysmotility and 1 revealed possible narrowing at the GEJ. The remaining three patients did not have barium esophagrams. As for treatment selection, 12 patients did not undergo treatment, 5 patients underwent botulinum toxin injection to the LES (4 for dysphagia and 1 for intractable hiccups) and 1 was treated with calcium channel blockers for chest pain (Fig. 4). The median follow-up time was 6 months. The IRP values did not appear to affect outcome. The mean IRP for the favorable outcome group was 19.5 and for the unfavorable outcome group was 20.9 ($P = .34$).

DISCUSSION

EGJOO is a relatively new manometric diagnosis designated as such according to the Chicago Classification of manometric abnormalities and based upon evaluation using high-resolution esophageal manometry.[4] In this study, we found that 11 of 83 patients had secondary causes for this finding. All of the secondary causes were seen on barium esophagram. The majority of our manometries (43/68) of idiopathic EGJOO patients were performed for further investigation of dysphagia. Only 12 patients in our series underwent treatment at our center and the response was highly variable. The modalities of treatment included a variety of medications, botulinum toxin injection, bougie dilation, and LHM reflecting our limited knowledge both of this disorder and how best to treat it. Interestingly, 25 patients did not undergo any treatment at all and over half of them (13/25) had spontaneous resolution or improvement in their symptoms, pointing to considerable heterogeneity in patients with EGJOO.

Prior studies with smaller numbers of patients have shown similar heterogeneity in short-term follow-up. In a series of 16 patients with primary EGJOO, patients were treated with botulinum toxin injection, endoscopic balloon dilation, PD, or LHM. Only the three patients who underwent myotomy responded favorably; follow-up time was 12 months.[8] Additionally, there have been preliminary reports of favorable response to POEM in a small case series described by Okeke and colleagues where all three patients treated by POEM had a favorable response. Our study reports one patient who underwent myotomy and had a favorable outcome.

Another series of 34 idiopathic EGJOO patients described five patients all of whom responded favorably to botulinum toxin injection and 1 of 3 patients who responded favorably to PD. These patients were followed for 6–10 months.[5] A later series in Spain described 28 patients, three of whom responded to botulinum toxin injection and two of whom responded to PD.[1] Our study did not note such a favorable response to botulinum toxin injection as only 2 of the 7 patients treated with this modality had favorable follow-up.

Management of EGJOO with medications has not been extensively described. There are preliminary data that acotiamide may decrease the IRP in EGJOO patients. However, symptom follow-up has not been evaluated as of yet.[11] It is important to note that a considerable number of patients have spontaneous symptom relief, reported as anywhere from 15% to

40%.[1,5] Our study noted that 52% of the patients who elected not to undergo treatment had spontaneous resolution of symptoms. Notably, EGJOO has been described in asymptomatic patients, particularly in controls for a normative HRM data study although secondary causes were not necessarily excluded.[12]

The most recent version of the Chicago classification, published in 2015, recommends further investigation of EGJOO with either EUS or CT scan to potentially clarify the etiology of EGJOO.[4] In our study, 40% of patients with idiopathic EGJOO and available follow-up had EUS or CT scan evaluation. No secondary causes were found on these studies. The limited use of these modalities is likely due to the timing of the most recent publication as our study spanned 2013 to 2015. Eleven of our 83 patients were found to have secondary causes and all of these were seen on barium swallow. This is quite distinct from a recent study published by Delay and colleagues noting 21 of 32 patients with secondary causes for this manometric finding; these findings were seen on upper endoscopy, barium esophagram, endoscopic ultrasound, or CT scan.[3] This discrepancy raises the question of the optimal imaging approach to EGOO. The recent publication of quality measures in esophageal manometry highlights the importance of identifying structural abnormalities prior to the performance of esophageal manometry. That being said, it remains unclear if a standard protocol should be established for cross-sectional imaging in patients found to have esophagogastric outlet obstruction.

We readily acknowledge the limitations of this study. All publications on EGJOO are limited by the rarity of this diagnosis. Our short follow-up may have limited identifying more patients who evolve to achalasia. Additionally, many patients were lost to follow-up. There was no standard method for follow-up evaluation and we did not have a formal scoring system to quantify symptom response. Nevertheless, this is the largest reported series of EGJOO in the medical literature. Our study reflects real world clinical experience with this entity.

From our observations in a sizeable cohort, it appears that symptoms in patients with EGJOO do not always require treatment and that treatment response is variable. On the other hand, the evolution of EGJOO to achalasia is rare but real; two of the patients in our study evolved to type II achalasia. This is consistent with findings on prior studies[2,5] and this possibility needs to be considered by all clinicians who manage patients with esophageal symptoms. The challenge lies in distinguishing which patients need repeat evaluation given the rarity of this entity. It is clearly important to identify these patients as response rates to various achalasia treatments at one year are above 90%.[7] An additional challenge is that in our experience, patients rarely are willing to undergo a repeat manometry due to discomfort of the procedure. We note in our study a median follow-up time of 6 months in the unfavorable outcome group; the achalasia patients were diagnosed at 16 and 22 months of follow-up. As such, the importance of longitudinal follow-up should be recognized as evolution to achalasia, while rare, may still occur in a small subset of these patients.

In summary, we found EGJOO to be a manometric finding within a heterogeneous group of patients. We did not observe a uniform response to management via medications, endoscopic intervention, or avoidance of treatment. We believe that the challenge in managing these patients lies in distinguishing which patients will need intervention. Further studies are needed for consideration of subgrouping this disease or modifying the categorization into clinically relevant entities.

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References

1 Pérez-Fernández M T, Santander C, Marinero A *et al.* Characterization and follow-up of esophagogastric junction outflow obstruction detected by high resolution manometry. Neurogastroenterol Motil 2016; 28: 116–26
2 Clayton S B, Patel R, Richter J E. Functional and Anatomic Esophagogastic Junction Outflow Obstruction: Manometry, Timed Barium Esophagram Findings, and Treatment Outcomes. Clin Gastroenterol Hepatol 2016; 14: 907–11.
3 DeLay K, Austin G L, Menard-Katcher P. Anatomic abnormalities are common potential explanations of manometric esophagogastric junction outflow obstruction. Neurogastroenterol Motil 2016; 28: 1166–71.
4 Kahrilas P J, Bredenoord A J, Fox M *et al.* International High Resolution Manometry Working Group. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015; 27: 160–74.
5 van Hoeij F B, Smout A J, Bredenoord A J. Characterization of idiopathic esophagogastric junction outflow obstruction. Neurogastroenterol Motil 2015; 27: 1310–6
6 Lynch K L, Pandolfino J E, Howden C W, Kahrilas P J. Major complications of pneumatic dilation and Heller myotomy for achalasia: single-center experience and systematic review of the literature. Am J Gastroenterol 2012; 107: 1817–25.
7 Moonen A, Annese V, Belmans A *et al.* Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy. Gut 2016; 65: 732–9.
8 Scherer J R, Kwiatek M A, Soper N J, Pandolfino J E, Kahrilas P J. Functional esophagogastric junction obstruction with intact peristalsis: a heterogeneous syndrome sometimes akin to achalasia. J Gastrointest Surg 2009; 13: 2219–25.
9 Bredenoord A J, Fox M, Kahrilas P J, Pandolfino J E, Schwizer W, Smout A J, International High Resolution Manometry

Working Group . Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. Neurogastroenterol Motil 2012; 24: 57–65.
10 Yadlapati R, Gawron A J, Keswani R N *et al.* Identification of quality measures for performance of and interpretation of data from esophageal manometry. Clin Gastroenterol Hepatol 2016; 14: 526–34.
11 Muta K, Ihara E, Fukaura K, Tsuchida O, Ochiai T, Nakamura K. Effects of acotiamide on the esophageal motility function in patients with esophageal motility disorders: a pilot study. Digestion 2016; 94: 9–16
12 Shi Y, Xiao Y, Peng S, Lin J, Xiong L, Chen M. Normative data of high-resolution impedance manometry in the Chinese population. J Gastroenterol Hepatol 2013; 28: 1611–5.