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EDITORIAL

Overlap Between Gastric and Esophageal Motility Disorders: A Contractual Arrangement?

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Disorders of gut–brain interaction [DGBI, also termed functional gastrointestinal (GI) disorders (FGIDs)] and motility disorders are two common GI conditions in which there is no endoscopic evidence of mucosal disease [1]. Whereas the diagnosis of DGBI is currently based on the Rome IV criteria [1], motility disorders are diagnosed with physiological tests including manometry and scintigraphy. The Chicago classification, which is based on high-resolution manometry (HRM), is applied to diagnose esophageal motility disorders that based on new definitions include achalasia, distal esophageal spasm (DES), esophagogastric junction outflow obstruction (EGJOO), 'jackhammer' esophagus, absent peristalsis, ineffective esophageal motility (IEM), and fragmented peristalsis [2]. In the stomach, motility disorders are categorized based on a standardized radiographic measure, 4-h gastric emptying scintigraphy (GES). More than 60 and 10% retention of the solid egg-based radiolabeled meal at 2 and 4 h, respectively, is considered evidence of gastroparesis (GP), whereas < 35% retention at 1 h and < 20% at 2 h suggest rapid emptying or dumping syndrome [3].

DGBI and motility disorders of the stomach classically manifest as nausea and vomiting, early satiety, excessive postprandial fullness, bloating, and abdominal/epigastric pain. Esophageal dysmotility usually manifests as heartburn, chest pain, dysphagia, nausea, and vomiting. On occasion, overlap between esophageal and gastric-based symptoms is present [4, 5]. Normal HRM with esophageal symptoms is categorized as functional chest pain, functional heartburn, reflux hypersensitivity, functional dysphagia, and globus sensation [4]. In the stomach, normal GES in the presence of chronic nausea and vomiting is considered as chronic unexplained nausea and vomiting (CUNV) or GP-like syndrome, which has been equated with functional dyspepsia as based on Rome IV criteria [5].

In a recently published study on the prevalence of Rome IV-diagnosed FGIDs, Aziz et al. reported that among 2083 subjects meeting Rome IV criteria for FGIDs, 36% had overlapping FGIDs. Gastroduodenal disorders were present in 30% and esophageal disorders in 20%. The overlap between esophageal and gastroduodenal functional disorders was 1.9% [6].

Studies of the overlap between esophageal and gastric motility disorders are limited. Based on an indirect observation in a study sponsored by the Gastroparesis Clinical Research Consortium (GpCRC) using the Patient Assessment of Upper Gastrointestinal Disorders Symptoms Severity Index (PAGI-SYM) questionnaire, 6% of patients with idiopathic GP had gastroesophageal reflux symptoms with overweight patients reporting higher gastroesophageal reflux scores compared to normal weight patients. Patients with severe retention in the GES study had a higher gastroesophageal reflux score [7]. In the GpCRC study, wherein the diagnosis of GP was confirmed based on a GES, the diagnosis of reflux was subjective and symptom-based; thus, combining methods were used in the diagnosis of functional esophageal and motility disorders.

Researchers from Stanford University have gone one step further through looking at HRM and GES data in patients who subjected to both tests [8, 9]. In the current issue of Digestive Diseases and Sciences, Zikos et al. have published an interesting article correlating abnormal GES and HRM. Briefly, after studying 482 patients with normal, delayed, and rapid GES, they found that 53.1, 64.5, and 77.3% had an abnormal HRM, respectively. Abnormal GES was a predictor of abnormal HRM with an adjusted odds ratio of 2.14 (95% CI 1.41–3.26). Moreover, abnormal HRM was a predictor of an abnormal GES with an adjusted odds ratio of 2.11 (95% CI 1.39–3.23). Interestingly, a higher number

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of patients with DES, jackhammer esophagus, ineffective esophageal motility, and fragmented peristalsis had abnormal GES. Compared with 243 patients with normal GES, a significantly higher percentage of patients with delayed and rapid GES had abnormal HRM. Not surprisingly, esophagogastric junction outflow obstruction and absent contractility (which are mainly observed in patients with systemic scleroderma and achalasia) were not associated with an abnormal GES. The presence of nausea, gastroesophageal reflux disease (GERD), atypical chest pain, dyspepsia, and dysphagia were not good predictors for an abnormal GES. Dysphagia was a positive predictor for an HRM abnormality, whereas the presence of nausea and vomiting was a negative predictor of HRM abnormality [8].

Overall, this study supports a common pathophysiology for gastric and esophageal motility disorders. Yet, it is still not clear whether both processes start at the same time or if one triggers the other. Although diseases like diabetes and Parkinson's disease are associated with motility abnormalities throughout the GI tract, one may argue that motility disorders of the stomach, including gastroparesis, produce a large pressure gradient across the gastroesophageal sphincter with reflux of stomach contents into the esophagus. That abnormal GES is not more common in patients with achalasia, and EGJOO supports this hypothesis. Contrariwise, studies of both acid and non-acid reflux events in the setting of delayed gastric emptying had disparate results [9, 10], as only one reported an increase in weakly acidic reflux as well as the prolongation of bolus clearance time in patients with GP [11].

In Zikos et al.'s [8] study, the presence of nausea and vomiting was an inverse predictor of an HRM abnormality, a finding consistent with the observation that only 36.9% of the studied cohort had nausea and emesis, in line with observation that relatively more patients with gastric motility disorders experience nausea and emesis in contrast to the more frequently experienced symptoms such as dysphagia and heartburn in patients with esophageal motility disorders.

Besides the limitations the authors have discussed, other limitations should also be taken into account: This study is a retrospective analysis of HRM and GES data obtained on patients who had both tests results in their medical record, the indications for which were not specified. GES is usually performed on patients who have GP symptoms, not in patients with pure esophageal symptoms such as dysphagia. In other words, performing a test that is not indicated may skew the final conclusion of a study. The large number of normal GES ($n=243$) in this study suggests that the test may not have been indicated in some of these patients. The other interpretation for this large number of normal GES is conversion from delayed toward normal GES during the course of disease; an observation frequently seen in patients with GP, especially if the test was performed while the patient was taking medications such as narcotics. The sample size for some of the analyses was small; since, for example, only 22 patients had rapid GES, the study lacks sufficient power for multiple comparisons.

Despite all the limitations, this study magnifies the cross talk between esophageal and gastric motility disorders, which could occur in the setting of a common background such as in diabetic autonomic neuropathy that affects GI motility through disruption of the enteric nervous system as well as motor and sensory afferent/efferent nerves in the brain–gut axis.

The abnormal HRM findings in this study that were correlated with an abnormal GES support the hypothesis that abnormal gastric emptying may trigger abnormal esophageal motility. This observation should not necessarily be based on gastroesophageal reflux but rather could be due to a retrograde signaling in the ENS, affecting proximal gut segments. How and whether esophageal contractility disorders affect gastric motility need further investigation. Therefore, the whole story is a chicken and egg dilemma in terms of which abnormality is etiological.

Future larger prospective studies should address the following questions:

1. Is abnormal gastric emptying more prevalent in patients with acid/non-acid reflux?
2. Is there any difference between patients with CUNV and GP in terms of having any manometric-/reflux-related abnormality? In the GP group, etiologies including diabetes, idiopathic, and postsurgical/vagotomy should be taken into account.
3. Is the correlation between esophageal/gastric motility disorders triggered by or associated with autonomic dysfunction? This could be obtained by more quantitative measures such as the autonomic nervous system and respiration (ANSAR) test.
4. A multicenter study, possibly organized by the GpCRC, could provide additional data regarding the pattern of esophageal motility as well as acid/non-acid reflux in GP, CUNV, and dumping syndrome. These additional data could provide further insight into the cross talk between motility disorders affecting adjacent GI segments, and could also be expanded by studying the role of small intestinal dysmotility and pyloric dysfunction in the pathophysiology of GP.

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