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Review

Primary and Secondary Causes of Esophageal Dysmotility

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Abstract

Estimates show that abdominal pain is the most commonly diagnosed event in ambulatory settings and gastrointestinal reflux disease (GERD) is the second most common condition. Many etiologies were reported for esophageal dysmotility. Identifying these causes can help understand the pathogenesis of the condition and better assess affected patients. In the present study, we reviewed the primary and secondary causes of esophageal dysmotility based on evidence from the previous studies in the literature. Aberrant esophageal dysmotility usually manifests by non-cardiac chest pain, regurgitation, heartburn, and dysphagia. The pathogenesis of these conditions includes significant muscular changes and degeneration of the inhibitory motor neurons of the myenteric plexus. It has been further shown that all patients with esophageal dysmotility usually exhibit impaired opening and relaxation of the lower esophageal sphincter. Various causes were reported in the literature for esophageal dysmotility, including structural, motility, and neuromuscular disorders. Primary causes are usually due to a pathology confined to the esophagus wall. On the other hand, secondary causes are usually part of a systemic condition that affects other organs in the affected patients.

Keywords: *esophageal dysmotility, motility disorders, etiology, classification, achalasia, gastroesophageal reflux disease.*

Introduction

Aberrant esophageal dysmotility usually manifests by non-cardiac chest pain, regurgitation, heartburn, and dysphagia. Estimates show that abdominal pain is the most commonly diagnosed event in ambulatory settings and gastrointestinal reflux disease (GERD) is the second most common condition (1). Studies from North America show that the latter condition is prevalent in 18-18% of the population (2). In addition, esophageal adenocarcinoma, Barret's esophagus, and strictures are potential complications of GERD. It has been further reported that esophageal disorders have a high economic burden. For instance, a previous report in the United States showed that in 2015, the costs for managing esophageal disorders were $18.1 billion (being the second highest after hepatitis) (1).

It should be noted that these disorders are associated with a low mortality rate and are benign in nature. However, based on the different manifestations and potential complications of esophageal dysmotility, the quality of life of the affected patients can be significantly impaired (3, 4). Accordingly, proper identification and management of these disorders are essential to enhance the outcomes. Many etiologies were reported for esophageal dysmotility (5, 6). Identifying these causes can help understand the pathogenesis of the condition and better assess affected patients. Thus, we aim to discuss esophageal dysmotility's primary and secondary causes based on a literature review.

Pathogenesis

Different symptoms have been reported by patients suffering from esophageal dysmotility. These include regurgitation, heartburn, chest pain, and dysphagia. It has been shown that the severity of these symptoms remarkably depends on the underlying diagnosis and type of esophageal dysmotility. For instance, achalasia is most commonly featured by weight loss and dysphagia. On the other hand, patients with hypercontractile (jackhammer or nutcracker) esophagus and distal esophageal spasms usually present with chest pain (which might be debilitating and imitates cardiac angina). In addition, altered flow patterns of the bolus in the esophagus usually result from reduced relaxation of the distal esophagus or low compliance, which commonly occurs with dysphagia of type 3 achalasia and jackhammer or nutcracker esophagus (7). Accordingly, it has been shown that different surgical and medical approaches (onabotulinumtoxinA injection into the lower esophageal sphincter, Heller's myotomy, and pneumatic dilation), aiming only to ablate the lower esophageal sphincter, might not be good therapeutic approaches in these patients (8, 9). In this context, it has been shown that these patients can be better managed by performing a long myotomy that extends to the aortic arch. Evidence shows that this approach has been widely used in the past to manage patients with diffuse esophageal spasms (10).

Evidence shows that multiple factors are attributed to the development of heartburn and esophageal pain among patients with esophageal dysmotility. For instance, it has been shown that these patients usually have a rigid (low compliance) and hypersensitive esophagus (11). In addition, various factors can influence or stimulate esophageal pain, including cortical hypervigilance, hypersensitivity of the supraspinal and spinal pathways, up-regulation of the nociceptors within the esophageal mucosa, reduced blood flow within the esophageal wall, sustained and prolonged contraction of esophageal muscles, and the presence of reflux disease (12-17). Evidence also shows that a remarkable fibrous tissue replaces myenteric ganglia in type 1 and 2 achalasia cases. On the other hand, the ganglia are present in patients suffering from type 3 achalasia. However, they are usually surrounded by chronic inflammatory cells, including B and T lymphocytes. Moreover, it has been shown that infections usually do autoimmune destruction of myenteric neurons by either human papillomavirus, measles virus, or herpes simplex virus in genetically susceptible patients (18). In addition, routine ultrasound might show significant hypertrophy to the muscular wall of the esophagus and a remarkable increase in mass. In this context, it has been demonstrated that these findings are more prominent with achalasia than a distal esophageal spasm and nutcracker esophagus in a respective order (19). Previous animal studies also showed similar symptoms to achalasia, including loss of inhibitory innervation, inflammatory changes around the mesenteric plexus, muscle hypertrophy, and cork-screw appearance of barium swallow after induction of induction esophageal outflow obstruction (20-22). Based on FLIP investigations, it has been further demonstrated that most patients with primary esophageal dysmotility disorders have reduced distensibility of the lower esophageal sphincter (23). Thus, the primary abnormality observed among patients with primary esophageal motility disorders can be a dysfunctioning esophagogastric junction or lower esophageal sphincter. A dysfunctional lower esophageal sphincter can significantly lead to outflow obstruction by altered myenteric neurons and esophageal muscles in this

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pattern. It has been further suggested that an additional major cause of esophageal dysmotility can be a dysfunctional hiatus. This has been suggested based on previous findings that indicated that the crural diaphragm had been associated with remarkable abnormalities among patients with achalasia (24).

Causes and Types

Many causes and types of esophageal motility disorders were reported in the literature. Overall, evidence shows that these disorders are broadly classified into primary and secondary disorders. The primary disorders are primarily attributed to an apparent esophageal disorder per se. On the other hand, it has been shown that secondary disorders are mainly due to the presence of another global condition that usually affects other parts than the esophagus. These conditions include scleroderma or progressive systemic sclerosis, Chagas disease, and pseudo achalasia (owing to compression or a tumor). The site of the pathology can also be used to classify the different esophageal disorders. For instance, structural causes might include Zenker's diverticulum, thyromegaly, radiotherapy, surgical intervention, carcinoma, proximal esophageal web, osteophytes and spinal disorders, and cervical or pharyngeal infections. In addition, various mechanical disorders include both extrinsic and intrinsic conditions (25). Vascular compression, spinal osteophytes, and mediastinal masses are the most common extrinsic causes. On the other hand, the most common intrinsic causes include medication-induced strictures, benign tumors and carcinomas, foreign body impaction, eosinophilic esophagitis, diverticula, lower esophageal (Schatzki) ring, esophageal rings and webs (other than Schatzki ring), and peptic strictures (6).

Evidence shows that dysmotility can be classified into primary and secondary motility (or neuromuscular) disorders. The primary disorders in this classification might include nutcracker (high-pressure) esophagus, achalasia, hypertensive lower esophageal sphincter, hypercontractile (jackhammer) esophagus, and distal oesophageal spasm. On the other hand, secondary disorders might include relevant rheumatological disorders (scleroderma), reflux-related dysmotility, and Chagas disease. Various neuromuscular disorders can lead to different esophageal dysmotility disorders. These include postpolio syndrome, thyroid dysfunction, stroke, dermatomyositis or polymyositis, muscular dystrophy, Parkinson disease, myasthenia gravis, manometric dysfunction of the upper esophageal sphincter or pharynx, idiopathic upper esophageal sphincter dysfunction, multiple sclerosis, malignant and benign tumors of the central nervous system, and amyotrophic lateral sclerosis (Lou Gehrig disease). It should be noted that manometric dysfunction of the upper esophageal sphincter or pharynx is usually part of a global disorder affecting different parts of the neuromuscular system (26).

Previous studies estimated that the prevalence of esophageal motility disorders among patients with scleroderma is up to 70%. This has been attributed to a remarkable dysfunction in the cholinergic nerve fibers and replacing muscular fibers with fibrous tissues (27, 28). Among patients with scleroderma esophagus, it has been further demonstrated that strictures and severe reflux diseases usually manifest secondary to the hypotensive lower esophageal sphincter, in addition to the significant loss of peristalsis. Esophageal dysmotility was also reported among patients with diabetes. In this context, it has been shown that the multipeaked and hypotensive esophageal peristaltic contractions are owing to autonomic neuropathy involvement in the pathology of the disease. These events have been associated with GERD and mild dysphagia manifestations (29, 30). It has been further shown that secondary achalasia might also result from neoplastic infiltration of the esophageal wall by an ascending adenocarcinoma from the stomach.

Epidemiological data show that the prevalence of primary esophageal dysmotility is higher than that of secondary events. Besides, it has been demonstrated that the pathogenesis of these conditions is not very clear among the different investigations. Accordingly, it has been shown that various novel and advanced diagnostic and management modalities of these disorders have been introduced in the literature for a better understanding and management of these conditions. For instance, it has been shown that the current diagnostic approach for detecting esophageal motility disorders is to perform high-resolution manometric studies. These approaches are usually made with pressures displayed as colored topographic plots and closely placed pressure sensors. In addition, there have been criteria to diagnose primary esophageal dysmotility disorders that have been reported in the literature, especially in the Chicago classification report of these disorders (31). It has been shown that impaired relaxation of the lower esophageal sphincter, shorter latency of distal esophageal contraction, and reduced or increased vigor of esophageal contractions in the distal esophagus are the main findings upon which the primary esophageal dysmotility can be recognized. It

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should be noted that the Chicago classification system of the different esophageal motility disorders is not primarily based on the histological characteristics of these disorders. Accordingly, it has been shown that it is still unknown whether these disorders are part of a general disease condition affecting the esophagus or are a single disease that is confined to the esophagus only. On the other hand, achalasia of the esophagus can be adequately diagnosed by the presence of two criteria. These include the absence of peristalsis and impaired relaxation of the lower esophageal sphincter. Although it is known that the process of emptying in these patients is usually impaired, clinical data show that esophageal emptying can be achieved by the induction of the esophageal peristalsis waves by pressurization via swallowing and not peristalsis. This has been shown among patients suffering from primary esophageal motility disorders (32, 33).

Furthermore, evidence indicates that achalasia is subclassified into additional three types based on the amplitude of pressurization. These include types 1, 2, and 3, which have been reported to help determine the prognosis of the condition. In this context, it has been shown that the amplitude of pressurization is highest in type 3 and lowest in type 1. The worst surgical and medical treatment response has been reported for type 3. On the other hand, the best prognostic evaluation has been estimated for patients with type 2 disorders. Evidence also shows that the jackhammer (or nutcracker) esophagus is usually featured by an exaggerated amplitude of distal esophageal contractions more than peristaltic ones. Moreover, decreased latency of distal esophageal contractions is the main feature of distal esophageal spasm. In the same context, previous evidence shows that reflux disease is usually associated with ineffective esophageal peristalsis (reduced-amplitude esophageal contractions) and reduced pressure over the lower esophageal sphincter. The functional lumen imaging probe (FLIP) system has been described in the literature as a valid novel diagnostic tool. It has been shown that the modality can be performed when upper endoscopy is being conducted to diagnose patients with esophageal motility disorders and during sedation. Evidence shows that the FLIP system is more advantageous than using high-resolution manometry because it has been shown to reduce the discomfort associated with catheter induction. It has been shown that conducting the FLIP system can be used to assess the direction of peristalsis (retrograde or antegrade), the function of the lower esophageal sphincter, and distensibility (compliance and opening) (23). It has been further shown that evaluating the potential tightness of Nissen's fundoplication, and completeness of myotomy in achalasia are additional advantages of using the FLIP in diagnosing the cause of esophageal motility disorders (34, 35).

Conclusion

The pathogenesis of these conditions includes significant muscular changes and degeneration of the inhibitory motor neurons of the myenteric plexus. It has been further shown that all patients with esophageal dysmotility usually exhibit impaired opening and relaxation of the lower esophageal sphincter. Various causes were reported in the literature for esophageal dysmotility, including structural, motility, and neuromuscular disorders. Primary causes are usually due to a pathology confined to the esophagus wall. On the other hand, secondary causes are usually part of a systemic condition that affects other organs in the affected patients.

Disclosure

Conflict of interest

There is no conflict of interest

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Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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