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REVIEW

2011 update on esophageal achalasia

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Abstract

There have been some breakthroughs in the diagnosis and treatment of esophageal achalasia in the past few years. First, the introduction of high-resolution manometry with pressure topography plotting as a new diagnostic tool has made it possible to classify achalasia into three subtypes. The most favorable outcome is predicted for patients receiving treatment for type Ⅱ achalasia (achalasia with compression). Patients with type Ⅰ (classic achalasia) and type Ⅲ achalasia (spastic achalasia) experience a less favorable outcome. Second, the first multicenter randomized controlled trial published by the European Achalasia Trial group reported 2-year follow-up results indicating that laparoscopic Heller myotomy was not superior to endoscopic pneumatic dilation (PD). Although the follow-up period was not long enough to reach a convincing conclusion, it merits the continued use of PD as a generally available technique in gastroenterology. Third, the novel endoscopic technique peroral endoscopic myotomy is a promising option for treating achalasia, but it requires increased experience and cautious evaluation. Despite all this good news, the bottom line is a real breakthrough from the basic studies to identify the actual cause of achalasia that may impede treatment success is still anticipated.

Key words: Esophageal achalasia; High resolution manometry; Endoscopic pneumatic dilations; Minimally invasive surgical procedures; Peroral endoscopic myotomy

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INTRODUCTION

Achalasia is the only primary motor disorder of the esophagus with a well-understood pathophysiology. It affects both sexes and all races equally[1-3]. Achalasia involves the selective loss of inhibitory neurons in the myenteric plexus, leading to the production of vasoactive intestinal polypeptide (VIP), nitric oxide (NO), and inflammatory infiltrate responsible for abnormal lower esophageal sphincter (LES) dysfunction. An unopposed excitation of the LES causes its dysfunction or failure to relax in response to swallowing[3,4].

Clinical presentations include dysphagia for both liquid and solid food, and food regurgitation may be severe enough to produce pulmonary complications such as cough or aspiration pneumonia. Weight loss usually

occurs as a result. The diagnosis of achalasia is made on the basis of the results of barium esophagography, esophageal manometry, and endoscopy. Typical radiological signs are classic "bird-beak" of the gastroesophageal junction, with atonia and a dilated esophageal body observed by barium ingestion and fluoroscopy. Manometry is still the standard diagnostic test for achalasia. The basic criteria required for diagnosis of achalasia include the absence of relaxation of the LES or abnormal swallowing relaxation of the LES and the absence of peristalsis in the esophageal body. However, an endoscopic examination, preferably endoscopic ultrasonography or computed tomography, is always necessary to distinguish primary achalasia from the secondary form[5], in cases of possible malignancy[6]. A greater risk of esophageal squamous cell carcinoma among achalasia patients is well established. Male achalasia patients have substantially greater risks for both squamous cell carcinoma and adenocarcinoma of the esophagus[7]. Recent advances in the diagnosis of esophageal achalasia by using updated high-resolution manometry (HRM) with pressure topography plotting have made it possible to classify achalasia into three subtypes. Furthermore, it is now possible to predict the outcome of each type of achalasia[8-10]. In this paper, the implications of the recent findings in the diagnosis and treatment of esophageal achalasia are reviewed and discussed.

PATHOGENESIS

The mechanisms responsible for the selective loss of inhibitory neurons in the myenteric plexus that produces VIP, NO and inflammatory infiltrate responsible for abnormal LES dysfunction is still not well understood[11]. However, specimens taken from autopsy or myotomy have shown the histological damage of the esophageal myenteric plexus and an inflammatory response consisting of CD3/CD8-positive cytotoxic T lymphocytes, variable numbers of eosinophils and mast cells, loss of ganglion cells, and neurofibrosis[12,13]. These events occur even at the early inflammatory stages of achalasia, and the underlying cause has not yet been identified. Previous studies have implicated hereditary, neurodegenerative, genetic, infectious, and autoimmune mechanisms. The most acceptable hypothesis suggests that achalasia may be caused by viral and autoimmune factors, leading to the inflammatory changes and damage to the myenteric plexus.

Achalasia patients with certain genetic backgrounds are reported to develop an autoimmune reaction and hence the production of autoantibodies that cause chronic inflammation and destruction of inhibitory neurons[12,13]. In addition, infiltration of the myenteric ganglia with CD3/CD8-positive lymphocytes that express activation markers, IgM antibodies, and evidence of complement activation have been observed within the myenteric ganglia[14-16]. Moreover, antibodies against myenteric neurons have been detected in the serum of patients with esophageal achalasia; especially in those with a specific human leukocyte antigen genotype (DQA1 × 0103 and DQB1 × 0603 alleles)[17-19]. The above evidence indicates that an autoimmune mechanism likely plays an important role in achalasia. However, the trigger for the destructive autoimmune events is unknown. So far, viral infection is believed to be the main cause. Some possible causative infections are varicella zoster and measles viruses[16,20-22]. However, some may argue that antineuronal antibodies have also been reported in the serum of gastroesophageal reflux disease patients and even in healthy individuals, suggesting that these antibodies may simply result from tissue damage secondary to inflammation[19]. The other unanswered question is why only neurons in the esophagus and LES are destroyed. The results of some studies have led to the hypothesis that neurotropic viruses, especially those with a predilection for squamous epithelium, could be involved; however, these findings have been inconsistent[16,20-23].

Although there have been many excellent basic studies, the presence of viral antibodies in the serum of patients has been an inconsistent finding. The method to verify the actual cause of achalasia that may impede treatment success is yet to be determined.

DIAGNOSIS

The diagnosis of achalasia is on the basis of the results of gastroscopy, manometry, and timed barium esophagography. Pseudoachalasia is always excluded by either computed tomography or endoscopic ultrasonography. Since the emergence of HRM with pressure topography plotting, esophageal achalasia can be classified into three subtypes[8-10]. In type I achalasia (classic achalasia), impaired LES relaxation but no significant pressurization within the esophageal body is observed. In type Ⅱ achalasia (with compression), swallowing of water causes rapid panesophageal pressurization. This may exceed LES pressure, causing the esophagus to empty. Type Ⅲ achalasia (spastic achalasia) is also associated with rapidly propagated pressurization; however, the pressurization is attributable to an abnormal lumen, obliterating contraction. HRM can be used to predict the outcome of each type of achalasia. Patients in whom HRM shows type Ⅱ achalasia (esophageal pressurization) are more likely to respond to therapies such as pneumatic dilation (PD), heller myotomy (HM), and botulinum toxin (BT) (overall, 70%-100%), compared to those with type I (overall, ⩾ 50%-63.3%) and type Ⅲ (overall, about 30%) achalasia[8,10]. HRM may play an increasingly important role in the diagnosis of esophageal achalasia in the future, especially when the technique becomes more affordable.

CURRENT TREATMENT OPTIONS

Currently, there is no cure for esophageal achalasia. The only available therapeutic options are to loosen the LES and treat the symptoms[24]. However, the advantages of each option must be considered in the patients.

Pharmacological management such as smooth muscle relaxation usually plays a minor role in the treatment of esophageal achalasia[2,24]. Nitrates increase NO concentration in smooth muscle cells, and calcium antagonists block calcium and hence esophageal muscle contractions. By so doing, LES pressure can be reduced, but the efficacy is usually unsatisfactory and incomplete, with intolerable side effects such as headache, dizziness, and pedal edema. This is the same for other drugs such as sildenafil[25].

ENDOSCOPIC TREATMENT

Endoscopic treatment with BT injection at the terminal nerve endings of myoneural junctions prevents the release of acetylcholine from vesicles. This causes chemical denervation, which may last for several months[26]. As a result of its wider safety range and fewer complications, local injection of BT into the LES muscle of patients with achalasia lowers LES tone, and the patient becomes asymptomatic. This treatment yields excellent immediate responses with success rates of > 90%. However, the results last only 6-9 mo on average in most patients, and only half of all the patients benefit for > 1 year[27]. Complications of BT therapy for achalasia are minor because the dosage used is too small to induce serious adverse effects such as generalized paralysis. It is therefore used to treat elderly patients or patients with high surgical risks[28].

The most commonly used endoscopic balloon dilator is the rigiflex dilator. The dilation procedure can be performed under fluoroscopic[29] or endoscopic guidance[30,31]. The number of dilation sessions and the inflation time needed for a successful dilation vary and are operator dependent. Immediate and short-term results have reportedly been good in most series[30-33]. However, large-scale long-term follow-up investigations[28,34,35] have reported unfavorable recurrence in patients who have undergone fluoroscopically guided PD. During a prolonged observation period (median, 13.8 years) in a prospective follow-up investigation study conducted by Eckardt *et al*[29], only 40% of the patients treated using a single PD procedure remained in remission at 5 years. Generally, the response to PD is still determined on the basis of subjective improvement in symptoms, such as dysphagia, regurgitation, and chest pain, by performing structured interviews with validated symptom score methods[29,36]. However, additional radiographic findings could reliably predict clinical remission and strongly suggest the need for further treatment in patients with poor esophageal clearance after each dilation. This could prevent sigmoid-type achalasia[37-39]. It is generally accepted that the predictors of risk factors for relapse after PD include young age (< 40-45 years), male sex, single dilation with a 3.0 cm balloon, post-treatment LES pressure > 10-15 mmHg, poor esophageal emptying after timed barium swallow, and type I and type Ⅲ achalasia pattern on HRM[2,40]. Complications attributable to PD are uncommon. The most severe complication is perforation[41], which was reported to be approximately 2% in a recent analysis by Katzka *et al*[42].

Peroral endoscopic myotomy (POEM) is a novel endoscopic esophagomyotomy for achalasia that was first reported by Pasricha *et al*[43] in porcine models and subsequently by Inoue *et al*[44] in humans. POEM is performed by dissection and division of the inner circular muscle layer of the esophagus through a submucosal tunnel created endoscopically by a small proximal opening in the esophageal mucosa. POEM can be used to perform deeper myotomy incisions in the thoracic esophagus than that performed in surgical myotomy, which is difficult for the surgeon, and is indicated especially for patients with advanced disease and for those with severe fibrosis. Theoretically, injury to the vagus nerve should be less than that with the surgical approach. So far, several centers are using the POEM technique and have achieved good short-term results without serious complications, but long-term follow-up results are required[45]. There is concern that POEM is a sophisticated and demanding technique, even for experienced endoscopists, and serious complications such as purulent mediastinitis may develop. Revisional surgery might be difficult and involve extensive procedures such as esophagectomy because the plane between the submucosal and muscular layers will be inflamed and scarred after the endoluminal approach[46].

A few Chinese studies have reported the utility of self-expanding, 30-mm metallic stents for achalasia at a single center over a 10- to 13-year period, with a long-term clinical success rate > 80%[47-50]. There were no perforations or mortality associated with the treatment, but stent migration occurred in 5% of the patients, reflux in 20%, and chest pain in 38.7%. Overall, the self-expanding, 30-mm metallic stents were associated with better long-term clinical efficacy in the treatment of patients with achalasia than treatment with PD.

SURGICAL TREATMENT

From a surgical point of view, minimally invasive HM has become the gold standard procedure for achalasia in the spectrum of current treatment options[51,52]. Myotomy of the LES is the most direct method used and by far the best treatment modality for satisfactory long-term results with very low mortality. Overall success rates of laparoscopic HM (LHM) were 47%-82% at 10 years[53,54]. Systematic reviews and meta-analysis that have compared existing treatment methods for achalasia have found that surgery is superior to PD[55,56]. However, the major adverse event after surgery is severe reflux. There is much debate on the role of fundoplication with myotomy in the reported literature[57-59]. Intraoperative endoscopy during videoscopic HM is used to guide the extent and adequacy of myotomy by utilizing a focused dissection with preservation of the natural antireflux mechanisms around the gastroesophageal junction and by limiting the extent of myotomy along the cardia. By

so doing, postoperative reflux symptoms are minimized. A concomitant endoscope examination during HM to guide myotomy and routine fundoplication is clinically necessary, despite disagreement about the fundoplication procedure[60,61]. In addition, there is a lot of debate on the choice of laparoscopic cardiomyotomy as the primary treatment for achalasia or as a second-line treatment following the failure of nonsurgical intervention[62]. Some doctors believe that laparoscopic cardiomyotomy can be more technically difficult following PD[63]. However, it has been shown that laparoscopic cardiomyotomy can be as safe and effective as first- or second-line treatment, even after the failure of PD[64]. In general, esophagectomy should be reserved only for those cases in which simpler operations have failed. In summary, as stated in the recent Kagoshima consensus, despite the variations as to the length of the myotomy and the addition of an antireflux procedure, good overall long-term results suggest that these operative variations are not critical[65].

WHICH IS THE BETTER CHOICE: LHM OR PD? THE ONGOING DEBATE

In general, LHM is considered to be superior to PD for treating achalasia. Many experts have regarded LHM as the first choice of treatment for achalasia, at the cost of reflux complications. However, it should be noted that the first randomized controlled multicenter trial published by the European Achalasia Trial group that compared LHM and PD reported that, after 2 years of follow-up, LHM was not associated with superior rates of therapeutic success[66]. The large sample size gathered from 15 European centers and the excellent design of the study gave adequate statistical power for obtaining convincing results for the two treatment groups. Perforation of the esophagus occurred in 4% of the patients during PD, whereas mucosal tears occurred in 12% during LHM. Abnormal exposure to esophageal acid was observed in 15% and 23% of the patients in the PD and LHM groups, respectively. In addition, when considering the cost-effectiveness of treatment strategies for achalasia, laparoscopic myotomy has a higher initial cost, and PD is the most cost-effective treatment option for adults with achalasia. It is unclear how the results of the European Achalasia Trial actual affect the ongoing debate between gastroenterologists and surgeons on the treatment of choice for esophageal achalasia. This study had the following limitations. First, this was only a 2-year cohort study, and the intermediate and long-term remission rates have yet to be proven. Second, the good results for PD may be questioned by the definition of treatment failure in redilation sessions. In fact, all patients in the PD group routinely received at least two sessions of dilation. A maximum of three redilation sessions was allowed. However, this is an ongoing study, and more information will be collected in the future. The debate on which is the better choice between LHM and PD for esophageal achalasia is ongoing; however, it is generally accepted that myotomy is usually suggested for younger patients (age, < 40-45 years), male patients, and those with pulmonary symptoms who failed to respond to one or two initial dilations[2,67].

In summary, despite the ongoing debate and the report of the first randomized control trial, the minimally invasive surgical treatment seems to yield better results than PD with the currently available evidence, despite being less cost-effective and resulting in more reflux symptoms. POEM is a promising technique and is associated with good short-term results without serious complications, but long-term results are not yet available. Despite these advancements, the actual cause of achalasia has not yet been identified, and this knowledge may improve treatment success in the future.

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