



Esophageal Achalasia: An Overview of Current Therapies



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Abstract

Achalasia is a rare disorder of the esophagus that affects the esophagogastric junction's peristalsis and relaxation. It has an incidence of approximately 1.6 per 100,000 individuals. Esophageal achalasia commonly presents with dysphagia, regurgitation, and chest pain. Diagnosis is often challenging and requires a multidisciplinary approach with a combination of clinical presentation, patient history, and diagnostic test findings. Among the most useful diagnostic tools for this condition are upper endoscopy, barium esophagograms, and manometry. Treatment options include medication, endoscopic interventions, and surgery. The most suitable management has to be determined on a case-by-case basis. While current treatments can help improve symptoms and quality of life for many patients with achalasia, further research is still needed to improve the success rates and outcomes for patients. This article provides a narrative review of the role of current therapeutic options for esophageal achalasia, focusing mainly on surgical options.

Keywords: Esophageal achalasia; Achalasia; Surgical management; Laparoscopic Heller myotomy; Peroral Endoscopic Myotomy

Abbreviations: LES: Lower esophageal sphincter, VIP: Vasoactive intestinal peptide, EGJ: Esophagogastric junction, HSV-1: Herpes simplex virus type-1, HPV: Human papillomavirus, POEM: Peroral Endoscopic Myotomy, PD: Pneumatic dilatation, LHM: Laparoscopic Heller myotomy

Background and Aim

Achalasia is a motility disorder of the esophagus that occurs due to a degeneration of the myenteric nerve plexus of the esophageal wall causing a failure of relaxation of the lower esophageal sphincter (LES) [1,2]. Achalasia has an annual incidence of roughly one per 100000 people and a prevalence of

10 per 100000, with equal frequency in both males and females. The disorder typically affects people between the second to the fifth decade of life, with a peak incidence between 30 to 60 years of age. Less than 2% to 5% of cases occur in children younger than 16 [2]. In achalasia, there is a loss of inhibitory neurons containing vasoactive intestinal peptide (VIP) and nitric oxide synthase at the myenteric esophageal plexus. However,

in severe cases, it also involves cholinergic neurons. The exact etiology of this degeneration is unclear, but it is believed to be caused by an autoimmune phenomenon, viral infection, and genetic predisposition. Most cases of achalasia are primary idiopathic achalasia; however, secondary achalasia may be caused by Chagas disease, esophageal infiltration by gastric carcinoma, eosinophilic gastroenteritis, lymphoma, certain viral infections, and neurodegenerative disorders [2]. The symptoms of achalasia are dysphagia for solids and liquids, regurgitation of undigested food, respiratory complications (nocturnal cough and aspiration), chest pain, heartburn, and weight loss [3].

Diagnosis requires a high index of suspicion and exclusion of other causes. Diagnosis is confirmed by manometric, endoscopic, and radiographic investigations. Esophageal manometry is the gold standard in the diagnosis of achalasia [1,2]. Several treatment options can be used to manage achalasia: pharmacological therapy (nifedipine, nitroglycerin, sildenafil), endoscopic therapy (LES pneumatic dilation, botulinum toxin injection), and surgical therapy (Laparoscopic Heller myotomy, peroral endoscopic myotomy, esophagectomy). The purpose of this narrative review is to identify when to use these options, considering the patient's adverse effects, symptoms, and comorbidities.

Etiology, Pathogenesis, and Epidemiology

Achalasia is a disorder of the esophagus which affects the peristalsis and relaxation of the esophagogastric junction (EGJ). It is a considerably rare disorder of the esophagus with an incidence of approximately 1.6 per 100,000 people and affects women and men equally [4]. The incidence is highest among individuals between the ages of 30 to 60 years. Although the prevalence varies in different countries, the prevalence rate of achalasia is between 10 to 15.7 per 100,000 individuals [5]. While the etiology of achalasia is unknown, cases of this disorder have been associated with an autoimmune process directed toward the myenteric plexus [6]. Idiopathic achalasia can potentially be caused by myenteric neuron damage by immune-mediated inflammation, potentially from exposure to antigens from herpes simplex virus type-1 (HSV-1), measles virus, and human papillomavirus (HPV) [4]. The viruses can cause damage to the myenteric neurons by activating immune pathways involving HLA antigen recognition mediated by HLA, cytotoxic T-cell autoantibodies, or direct cytotoxicity [4]. Achalasia can also be secondary to other causes, such as genetic conditions, paraneoplastic syndromes, Chagas Disease, and even opioid use [6].

Clinical Presentation

Esophageal achalasia commonly presents with dysphagia in up to 90% of patients [7]. Although dysphagia may initially be noticed only for solids, 70-97% of patients with achalasia present dysphagia for both liquids and solids [8]. Regurgitation is the second most common symptom (60-75% of patients), occurring

mainly in the postprandial period. Chest pain is another symptom reported by nearly 45% of patients [7,8]. Generally, it appears more commonly in younger patients and tends to diminish over time. Several etiologies have been proposed for chest pain, including esophageal contractions, esophageal distention caused by retained food, gastroesophageal reflux, and enteric-related neuropathic pain. Achalasia is associated with heartburn in about 30% of patients, which is surprising considering achalasia is mechanistically opposed to gastroesophageal reflux disease [9]. As a result of poor esophageal emptying and a reduced or modified diet, approximately 60% of patients with achalasia may experience weight loss at presentation. There is usually a loss of five to ten kilograms of weight before a patient seeks medical attention when they are in the final stages of the disease [10]. Lastly, achalasia may also lead to extraesophageal manifestations, particularly pulmonary complications. Approximately half of all patients present with structural or functional pulmonary abnormalities, which may result from recurrent aspiration or tracheal compression caused by a dilated esophagus [9,10].

In diagnosing achalasia, the clinical presentation alone is insufficient since symptoms may overlap with those of other esophageal disorders, particularly gastroesophageal reflux disease [9]. In addition, manometric findings, degree of esophageal dilation, or prognosis are not related to symptoms' presence or severity. As a result, a complete workup is required in order to determine the most appropriate therapeutic approach [9,11]. An upper endoscopy is often recommended as the first diagnostic test in diagnosing achalasia, and findings include a dilated esophagus with retained food or liquid. Endoscopy, however, appears normal in 44% of patients with achalasia. As a result, a barium esophagogram may assist in the diagnosis, demonstrating esophageal dilatation associated with barium retention and smooth tapered constriction of the gastroesophageal junction [11]. However, these diagnostic modalities might not fully detect achalasia and require further workup. In terms of confirming the presence of achalasia, esophageal manometry has the highest sensitivity, with the characteristics of aperistalsis of the distal esophageal body and incomplete or absent relaxation of the LES being the most distinguishing features [8,9,11]. Corroborating features include a hypertensive LES, low amplitude esophageal contractions, and increased intraesophageal pressure (exceeding intragastric pressure) [11].

Medical Treatment

According to the ISDE Guidelines 2018, the Peroral Endoscopic Myotomy (POEM) and Heller myotomy with partial fundoplication is considered the first-list therapies for Chicago Type I and type II Achalasia, leaving medical options to be considered as "Non-conventional" achalasia treatment modality [12]. For some authors, the medical therapies have been described as "unpractical" with disappointing efficacy

and suggest this rare esophageal motility disorder should be treated by paralyzing, tearing, or cutting the unrelaxing fibers of the lower esophageal sphincter [13]. These medical options encompass certain drugs like beta-agonists, anticholinergics, nitrates, calcium channel blockers, and phosphodiesterase inhibitors, whose final effect is to act as smooth muscle relaxants [12].

Beta-agonist drugs (e.g., Carbuterol) decrease the esophageal sphincter retention pressure by stimulating the functions of catecholamines. Anticholinergic drugs (e.g., Cimetropium, Bromide) currently used for numerous diseases improve peristalsis and reduce sphincter pressure on the LES. Phosphodiesterase inhibitors (e.g., Sildenafil, tadalafil, etc.) primarily used for erectile dysfunction, heart failure, and airway conditions can lower esophageal sphincter tone and the esophageal body's peristaltic forces. Other medical options are Nitrates (e.g., Isosorbide dinitrate, nitroglycerin, etc.), which promote esophageal emptying and lower the LES pressure by acting as smooth muscle relaxants releasing nitric oxide. The calcium channel blockers CCB (e.g., Nifedipine) relax the smooth muscle by inhibiting the influx of calcium through specific *io*-channels in the cell's wall, thus promoting a well-studied reduction of the LES pressure without accelerating the emptying of the esophagus in contrast to other medical therapies. Although all of them have different mechanisms of action and potential side effects, the only possible indications converge on patients with dysphagia who opt for noninvasive procedures and should only be considered individualized case to casa [12]. Benzodiazepines, Opioids, Serotonin, and Norepinephrine Reuptake Inhibitors are drugs with presumable effects on LES relaxation and potential benefits for adults with Esophageal Achalasia. Still, no clinical trials have been addressed to support this, and the administration should be restricted outside well-designed research protocols [14].

Endoscopic Interventions

The most widely used endoscopic therapies in the treatment of achalasia are botulinum toxin injection and pneumatic dilatation (PD). Botulinum toxin is a potent presynaptic inhibitor of acetylcholine release from nerve endings that has proven to be a helpful treatment in achalasia. This botulinum toxin injection is straightforward to administer and is associated with low rates of complications, although rare cases of reflux and mediastinitis may occur. It is the best-studied pharmacotherapy in achalasia, and it is the most effective pharmacological treatment that can be offered; however, its benefits are short-lived, and the medication should not be offered as first-line treatment to patients who are fit for myotomy [15]. The standard technique for botulinum toxin therapy involves the use of 100 units of toxin diluted in normal saline and injected in four quadrants just above the squamocolumnar junction using an injection needle via a standard upper endoscope. This user-friendly technique has a low risk of serious complications [16].

Pneumatic dilation disrupts the LES fibers through intraluminal dilation of a pressurized balloon and is most performed under fluoroscopic guidance [17]. It is an effective option for patients with achalasia. Standard dilators are not effective in disrupting the muscularis propria needed for symptom relief in this group of patients. All patients considered for PD must also be candidates for surgery if esophageal perforation needs repair, which is reported in 1.9% (range 0%–10%) [15]. Therefore, serial PD is an effective treatment option for patients with achalasia for short- and long-term symptoms and physiologic benefits. Predictors of favorable clinical response to PD include the following: older age (>45 years), female sex, narrow (nondilated) esophagus, and LES pressure after PD of < 10 mm Hg [15].

Laparoscopic Heller Myotomy

Laparoscopic Heller myotomy (LHM) is a surgical procedure frequently used as a treatment option for achalasia. The surgery consists of the laparoscopic incision of the LES muscle in order to relieve the muscular spasm and allow food to pass into the stomach. This surgery is typically done under general anesthesia [18]. Recovery time varies depending on the individual, but most people are able to return to normal activities within 2 - 3 weeks [19]. The main indication for LHM is a patient with achalasia who has not responded to other treatments, such as medication, pneumatic dilation of the esophagus, or Botox injections. Additionally, surgery may be recommended for patients who experience severe symptoms that are affecting their quality of life or for those with a high risk of complications from other treatments [19,20]. Other indications include patients with complications due to achalasia (i.e., weight loss, malnutrition, and aspiration pneumonia) and those who are not candidates for endoscopic treatments (i.e., endoscopic myotomy or peroral endoscopic myotomy) [21]. It is important to note that every case must be individualized, and the patient's overall health status, age, the severity of the disease, the risk of complications, and other factors must be considered before performing the procedure. LHM is a relatively safe surgical procedure. However, some of the potential risks include infection (particularly at the surgical site), hemorrhage (during and after the surgery), local organ injury (stomach or spleen), esophageal leakage, post-surgical reflux, difficulty swallowing, and recurrent achalasia [20]. There are certain situations where LHM may not be appropriate or safe due to an increased risk of complications. Some of the contraindications for this procedure include advanced age, obesity (technically more challenging), previous esophageal surgery, active infection, pregnancy, coagulation disorders, and life-threatening illness [19,20].

Laparoscopic Heller myotomy is a highly effective treatment for achalasia, with reported success rates of over 90%. The procedure is designed to relieve the spasm of the lower esophageal sphincter (LES) muscle, which is the primary cause of achalasia symptoms [22]. After the surgery, patients typically

report an improvement in their ability to swallow and a reduction in other symptoms, such as regurgitation and chest pain. Success depends on various factors, including the experience of the surgeon, the patient's overall health, and the severity of the achalasia. The procedure is generally considered most effective for patients with mild to moderate achalasia, although it can also be beneficial for patients with more severe symptoms [20,22]. It's important to note that, even though the procedure is successful in most cases, some patients may experience a recurrence of achalasia symptoms or the development of reflux symptoms after the surgery [21]. These complications can be managed with medications or further treatments, and patients must continue follow-up care with their surgeon to monitor for any potential complications.

Peroral Endoscopic Myotomy

Peroral endoscopic myotomy (POEM) is a recently developed endoscopic technique for treating achalasia [23]. It has been shown to be non-inferior to laparoscopic Heller myotomy in randomized controlled trials [24,25]. It is typically considered for individuals who have failed to respond to other conservative treatments for achalasia, such as lifestyle modifications, medication, or dilation of the LES. It is important to note that POEM indications are determined case-by-case based on the individual's symptoms, medical history, and the results of diagnostic tests [25]. POEM is also an alternative to other surgical treatments for achalasia, such as Laparoscopic Heller Myotomy (LHM) [26]. The main advantage of POEM over LHM is that it is minimally invasive and does not require an incision in the abdominal wall. This makes POEM a less invasive and painful option for patients with achalasia and typically leads to a faster recovery [26,27]. The procedure uses several standard interventional endoscopic techniques, including submucosal lift and endoscopic submucosal dissection, to create a submucosal tunnel, reach the LES, and dissect the circular muscle fibers [27].

POEM has been demonstrated to be effective in the treatment of achalasia. Small-scale studies have demonstrated high success rates of up to 89-98%, even after several previous pneumatic dilatations [27,28]. In several studies, patients who underwent POEM experienced significant improvement in symptoms such as dysphagia, regurgitation, and chest pain [25,26,28]. POEM has also been shown to be a safe and well-tolerated procedure, with low rates of complications and high patient satisfaction [27,29]. Overall, POEM has emerged as a highly effective alternative to traditional surgical treatments for achalasia. However, long-term studies are needed to fully understand the durability and effectiveness of POEM in the management of achalasia.

Esophagectomy

Indication of esophagectomy is reserved for patients with an end-stage disease with recurrent symptoms and prior failure of pneumatic dilation with or without Heller myotomy in the

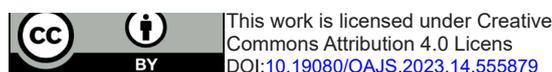
past. It is highly effective, and it has been reported that there is a symptomatic improvement in over 80% of patients [30]. There are many proposed procedures to restore a viable alimentary condition to patients from partial, subtotal, or total resection of the esophagus; each of these procedures confers advantages and specific risks. After failed interventions, subtotal esophagectomy must be indicated for end-stage disease (tortuous or sigmoid esophagus) and persistent dysphagia [31]. Esophagectomies constitute a significant operation, and they can be performed safely through a variety of different types of surgical approaches with varying possibilities for reconstruction of the alimentary tract. This type of esophagectomy can be summarized in three types: The transhiatal esophagectomy removes most of the esophagus and a small amount of the stomach. Then, what is left over between the esophagus and the stomach is joined together near the neck. Ivor Lewis esophagectomy involves incisions in the abdomen and chest. It removes part of the esophagus, makes a tube (conduit) out of part of the stomach and connects the stomach conduit to the esophagus in the chest. The thoracoabdominal incision in the abdomen goes to the left side of the chest, then divides the esophagus in the left chest and brings either the stomach or small intestine up to the left chest to create a new connection. The procedure can last between four to six hours, and patients' recovery can take around eight days, depending on the success of therapy and other metrics. The most important is the relief of symptoms, such as dysphagia or regurgitation [32]. On the other hand, complications can include postoperative dysphagia requiring dilation in up to 50% of patients, mediastinal bleeding, chylothorax, anastomotic leak, and a mortality risk of up to 5.4% [30,33].

Conclusion

Esophageal achalasia is a rare condition characterized by dysphagia, regurgitation, and chest pain. As achieving an accurate diagnosis is often challenging, patients must be evaluated with a comprehensive workup. Symptoms are not sufficient to distinguish achalasia from other esophageal diseases. Furthermore, a detailed and systematic study of these patients allows a fast and correct diagnosis and contributes to therapeutic decision-making and prognosis. Several treatment options are available for this condition, including medications to relax the LES muscle, balloon dilation, endoscopic injection therapy, and surgery. The most appropriate treatment option for achalasia depends on the individual's symptoms, medical history, and diagnostic test results. Patients should discuss the benefits and risks of each treatment option with their healthcare provider to determine the best choice for their specific condition. While current treatments can help improve symptoms and quality of life for many patients with achalasia, further research is still needed to improve the success rates and outcomes for patients. Ongoing studies may lead to new and more effective treatments for achalasia, helping to provide better outcomes for patients with this condition.

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