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EDITORIAL

Current clinical approach to achalasia

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Abstract

Idiopathic achalasia is a rare primary motility disorder of the esophagus. The classical features are incomplete relaxation of a frequently hypertensive lower esophageal sphincter (LES) and a lack of peristalsis in the tubular esophagus. These motor abnormalities lead to dysphagia, stasis, regurgitation, weight loss, or secondary respiratory complications. Although major strides have been made in understanding the pathogenesis of this rare disorder, including a probable autoimmune mediated destruction of inhibitory neurons in response to an unknown insult in genetically susceptible individuals, a definite trigger has not been identified. The diagnosis of achalasia is suggested by clinical features and confirmed by further diagnostic tests, such as esophagogastroduodenoscopy (EGD), manometry or barium swallow. These studies are not only used to exclude pseudoachalasia, but also might help to categorize the disease by severity or clinical subtype. Recent advances in diagnostic methods, including high resolution manometry (HRM), might allow prediction of treatment responses. The primary treatments for achieving long-term symptom relief are surgery and endoscopic methods. Although limited high-quality data exist, it appears that laparoscopic Heller myotomy with partial fundoplication is superior to endoscopic methods in achieving long-term relief of symptoms in the majority of patients. However, the current clinical approach to achalasia will depend not only on patients' characteristics and clinical subtypes of the disease, but also on local expertise and patient preferences.

Key words: Achalasia; Esophageal motility disorder; Dysphagia; Esophagus; Lower esophageal sphincter; Pneumatic dilation; Botulinum toxin; Heller myotomy

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INTRODUCTION

Idiopathic achalasia is a rare primary motility disorder of the esophagus. The classical features are incomplete relaxation of a frequently hypertensive lower esophageal sphincter (LES) and a lack of peristalsis in the tubular esophagus. Although major strides have been made in understanding the pathogenesis of this rare disorder, including a probable autoimmune mediated destruction of inhibitory neurons in response to an unknown insult in genetically susceptible individuals, a definite trigger has not been identified. The motor abnormalities of achalasia are responsible for a number of clinical symptoms with variable response to current treatment options. Current therapies should be based on the results of clinical findings and further diagnostic tests, such as imaging studies, esophagogastroduodenoscopy (EGD), manometry, and possibly high resolution manometry (HRM). This editorial will review the clinical presentation, the latest diagnostic tools and the treatment options for this rare disorder and an individualized therapeutic approach, based on the current evidence, will be suggested.

CLINICAL PRESENTATION

The hallmark of achalasia (Greek: failure to relax) is dysphagia for solids and liquids in up to 100% and 97% of patients, respectively[1-3]. As a result of stasis and retention of food and liquids in the esophagus, patients frequently experience weight loss (30%-91%), chest pain (17%-95%), regurgitation (59%-64%), and nocturnal cough (11%-46%)[1]. Difficulty with belching might result from alteration of the upper esophageal belch reflex[4]. Patients might frequently complain of heartburn. Although heartburn is the cardinal symptom

of gastroesophageal reflux, which is the antithesis of achalasia, it occurred with a frequency of 72% in one study, even after the onset of dysphagia[5]. The sensation of heartburn in patients with achalasia might be explained by retention of acidic or noxious food contents or by lactate production from bacterial fermentation within the esophagus[6]. Hiccups can also occur, and probably result from esophageal distention and stimulation of afferent vagal fibers[7]. The distribution of symptoms can differ in the population studied. Chest pain occurs predominantly in younger patients (mean age 40 years) and appears to improve over time[8]. However, neither manometric, nor radiographic findings predict the occurrence of retrosternal pain. Most symptoms do not appear to have a specific gender distribution, although in Iranian patients, chest pain appeared to be more common among females[9]. Physicians need to be aware of the spectrum of symptoms of achalasia, because diagnostic delays for years after the onset of symptoms appear to be due to misinterpretation of typical findings, rather than atypical presentations[10].

The most common extraesophageal manifestations of achalasia are pulmonary complications. Structural or functional pulmonary abnormalities occur in more than half of patients and might be due to recurrent aspiration or tracheal compression from a dilated esophagus[11]. In cases of extreme dilation and distortion of the cervical esophagus, a "bull frog neck" appearance can develop, leading to tracheal obstruction above the larynx and associated stridor[2]. Although some investigators have observed delayed gastric emptying or gallbladder dysfunction in patients with achalasia[12-14], others were unable to confirm these observations[15], and it still remains elusive whether a selective defect of vagal ganglionic neurons might affect other parts of the gastrointestinal tract as well.

DIAGNOSIS AND CLINICAL VARIANTS

A number of tests are available to confirm the diagnosis of achalasia, once the clinical suspicion arises. Radiographic studies, EGD and esophageal manometry are the primary tools of investigation. Although EGD appears normal in 44% of patients with achalasia[1], it might show esophageal dilatation and retention of food or secretions. During inversion of the endoscope in the stomach, tight adherence of the distal esophagus with downward motion of the gastroesophageal junction upon endoscope advancement can sometimes be visualized. However, despite the commonly elevated LES pressure, the esophagogastric junction can usually be traversed easily, and firm resistance should raise the suspicion of neoplastic infiltration or other causes of pseudoachalasia. Pseudoachalasia can mimic all endoscopic, radiographic and manometric findings of achalasia and has a broad differential diagnosis of neoplastic and non-neoplastic causes, which have been recently reviewed[16,17]. Infiltration of the esophageal myenteric plexus by neoplastic cells or paraneoplastic processes have been suggested in patients with a malignant etiology[16]. A shorter duration of symptoms and older age at presentation should raise a suspicion of pseudoachalasia, which often requires further testing with endoscopic ultrasound or CT scan to rule out malignancy[17]. In our view, a simple and non-invasive initial test to differentiate between primary and secondary achalasia is transabdominal ultrasonography, which often allows a clear visualization of the gastric cardia and its surrounding structures[18]. However, a negative ultrasound does not always exclude pseudoachalasia, and CT or other cross-sectional imaging should be added if clinical suspicion remains strong.

Table 1 Manometric variants of achalasia

Standard Manometry
Vigorous achalasia (high amplitude esophageal body contractions)
A short segment of esophageal body aperistalsis
Retained complete deglutitive LES relaxation with aperistalsis
Intact transient LES relaxation with aperistalsis
High resolution manometry (patients with impaired EGJ relaxation)
Type Ⅰ: Minimal esophageal pressurization
Type Ⅱ: Esophageal pressurization > 30 mmHg
Type Ⅲ: Esophageal spasm

LES: Lower esophageal sphincter; EGJ: Esophagogastroduodenoscopy.

A barium esophagogram (barium swallow) is the most commonly used initial diagnostic study. It classically shows a typical smooth tapering of the distal esophagus ("bird's beak") with proximal dilation of the esophagus and lack of peristalsis during fluoroscopy. The value of obtaining a timed barium esophagogram in patients with achalasia lies in its potential to monitor the success of therapeutic interventions and to detect disease recurrence prior to the development of symptoms[19]. The timed barium swallow is performed by having the patient drink 100-250 mL of barium in an upright position and by taking radiographs one, two and five minutes after the last swallow. The distance from the distal oesophagus to the top of the barium column, as well as the maximal esophageal width, are measured for comparison before and after treatment.

Manometry remains the diagnostic modality with the highest sensitivity and should be part of the diagnostic evaluation in all patients with achalasia. Three cardinal features support the diagnosis of classic achalasia: Aperistalsis of the smooth muscle portion of the esophagus, incomplete LES relaxation and elevated LES resting pressure. As mentioned above, manometric variants of achalasia have been described (Table 1). Vigorous achalasia is a variant characterized by aperistaltic, simultaneous esophageal contractions with higher average amplitudes (> 37 mmHg)[20]. It has been suggested that vigorous achalasia might present an earlier form of achalasia, in which esophageal contractions against the outflow obstruction at the LES are still maintained. However, vigorous achalasia appears to be independent of age of onset and symptom duration, and is not associated with return to normal peristalsis after surgical myotomy[21,22]. Although it has been suggested that patients with vigorous achalasia might show better success with botulinum toxin injection than patients with classic

achalasia[23], this has minor clinical relevance, because other treatment options are superior in most cases. Therefore, it remains unclear whether dividing patients into those with "vigorous achalasia" and "classic achalasia" has any clinical implications. Despite such reservations, physicians need to be aware that achalasia might present with a spectrum of manometric findings that might not meet all of the criteria specified above (Table 1)[24]. Their significance lies in the recognition that these sometimes confusing manometric findings are consistent with achalasia when combined with additional clinical data supportive of the diagnosis. As mentioned for the timed barium swallow, manometry also plays a role in monitoring treatment response and predicting treatment success of pneumatic dilatation, as discussed below.

The recent introduction of HRM with pressure topography plotting into the diagnostic armory has brought a renaissance to the classification of idiopathic achalasia into variants with possible clinical implications. A retrospective study by Pandolfino *et al*[25] described three distinct variants, with type Ⅰ exhibiting minimal esophageal contractility without pressurization, type Ⅱ with absent peristalsis but compartmentalized, pan-esophageal pressurization, and type Ⅲ with lumen obliterating spasm. The authors showed that pan-esophageal pressurization (type Ⅱ) had the best overall treatment response, whereas type Ⅲ predicted a poor treatment response to all types of therapy. Further prospective studies are needed to confirm these interesting early results.

TREATMENT

Treatment of idiopathic achalasia remains strictly palliative. In view of the suspected autoimmune mechanism of the disease, it appears surprising that no study has systematically addressed the use of immunosuppressive therapy in an attempt to prevent disease progression[26]. Therefore, current treatment modalities are primarily directed at relieving distal esophageal obstruction and consist of pharmacologic therapy, endoscopic treatment with pneumatic dilation or botulinum toxin injection, and surgery. The appropriate choice of therapeutic options depends on multiple factors, such as the patient's characteristics, clinical presentation, local expertise and patient preferences, but should be based on the best available evidence.

Pharmacological therapy is directed at achieving a reduction of LES pressure by the use of smooth muscle relaxants, such as calcium channel blockers (e.g. nifedipine 10-30 mg sublingually 30-45 min before meals), nitrates (e.g. isosorbide dinitrate 5 mg sublingually 10-15 min before a meal) or phosphodiesterase 5 inhibitors[27,28]. The main limitations of these agents are their short duration of action, limited improvement of dysphagia despite documented LES relaxation, or the frequent occurrence of side effects, such as peripheral edema, headaches or hypotension, which especially occur with calcium channel blockers and nitrates. Their use is, therefore, limited to symptomatic relief in patients who have very early disease, or as a temporary measure for patients who are awaiting a more definite treatment option, or are high risk for more invasive options[29].

Endoscopic options of treatment include disruption of the LES by pneumatic dilation or botulinum toxin injection. Botulinum toxin is a potent neurotoxin that leads to a blockade of the release of acetylcholine from excitatory motor neurons. In a landmark study, Pasricha *et al*[30] showed that endoscopic injection of botulinum toxin into the area of the LES lead to symptomatic improvement in patients with achalasia, which was accompanied by reduced esophageal retention over a period of 6 mo. One randomized controlled trial (RCT) has shown that the two commercially available formulations of botulinum toxin are equally effective, but need to be given in different dosages because of variable potency[31]. The treatment effect of one of these formulations (Botox® Allergan Inc, Irvine, California, USA) might be maximized when a repeated injection of 100 IU is given one month after the first injection[32]. In contrast, a lack of an initial symptomatic response and residual LES pressure ⩾ 18 mmHg after botulinum toxin are associated with a poor overall response[33].The best results of botulinum toxin have been achieved in patients with vigorous achalasia, older patients and patients whose LES pressures do not exceed ⩾ 50% of the upper limit of normal[23,34]. However, the use of botulinum toxin is limited by its lack of long-term efficacy with recurrence rates of approximately 50% after one year and universal symptomatic relapse at two years[35,36]. Two recent meta-analyses concluded that although botulinum toxin has an excellent safety profile, it seems slightly less effective than pneumatic dilatation in the short-term and is clearly inferior in the long-term for the treatment of achalasia[37,38].

Pneumatic dilatation has been used for the treatment of patients with achalasia for more than half a century and is currently considered the most effective non-surgical treatment for achalasia[39,40]. A number of different pneumatic dilators with variable balloon compliance have been used in clinical trials. Currently, the low-compliance polyethylene pneumatic dilator (Rigiflex®, Boston Scientific, Boston, MA, USA) appears to be the most widely used. Although pneumatic dilators from other manufacturers are available (e.g. Cook Medical, Bloomington, IN; USA or Hobbs Medical, Stafford Springs CT, USA; HCDD, latex balloon, Rüsch Inc, Germany), only limited comparative data exist, which have not shown a difference in efficacy or safety[41,42]. Using a graded approach with the polyethylene balloon dilator, with increasing diameters from 3.0 to 4.0 cm, a 93% response rate was achieved over a mean follow up period of four years with a relatively low complication risk[43]. The most feared complication of pneumatic dilation is perforation, which occurred in 1.6% of patients in a meta-analysis with 1065 patients in experienced hands[39,40]. Studies assessing the long-term efficacy of pneumatic dilation have shown that a permanent treatment success can only be achieved in 40%-60% of patients after a follow up of ⩾ 15 years[44-46]. Although one study showed that "on demand" repeat dilations may again lead to remission in the majority of patients[47], others have shown that longer lasting treatment effects cannot be expected

from such therapy[48].

Predictors of treatment failure with balloon dilation appear to be younger age (< 40 years), male gender, pulmonary symptoms and failed response to one or two initial dilations[49-52]. In contrast older age appears to be associated with favorable outcomes of pneumatic dilation. Manometric findings that predict poor outcome are high initial LES pressures (e.g. > 15-30 mmHg) or a reduction of LES pressure < 50% after the first dilation[50,52,53]. Manometry should, therefore, be routinely performed pre- and post-interventionally.

With the advent of minimally invasive laparoscopic approaches, surgery has evolved from an ancillary procedure, used when pneumatic dilation failed, to the favored primary approach by many surgeons and gastroenterologists in a majority of patients with achalasia[54]. The goal of surgery is to alleviate the esophageal obstruction by myotomy of the LES. To prevent secondary gastroesophageal reflux, the procedure has usually been combined with some type of fundoplication procedure. The superiority of surgical myotomy over pneumatic dilation was suggested by three recent meta-analyses in the English and Chinese literature that mostly considered retrospective cohort studies[38,39,55]. Although both pneumatic dilation and surgical myotomy have a substantial risk of subsequent need of interventions (repeated pneumatic dilation, surgical myotomy or esophagectomy) over a period of 10 years, the probability was significantly smaller in the latter group (56% *vs* 26%, respectively) in one study[56]. To date, only one RCT with data on long-term follow-up has been published by Csendes *et al*[57] comparing myotomy followed by 180° Dor fundoplication to pneumatic dilation with a Mosher bag. Although this study has been criticized because of potentially technique-related suboptimal results in the pneumatic dilation group, it still remains the best available evidence to date. The authors showed good response after a five year follow up period for 95% of surgically treated patients *vs* 65% of patients in the pneumatic dilation group. However, very late results in the surgical group showed that clinical deterioration occurs, reducing the surgical success rate to 75% after a mean follow up of 15.8 years[58]. Of the patients with poor surgical results, 92% resulted from complications of severe reflux disease and not from incomplete myotomy. A number of trials have, therefore, investigated the benefit of anti-reflux procedures in addition to myotomy. In a prospective RCT, reflux symptoms were reduced from 47.6% with laparoscopic Heller myotomy alone to 9.1% when a Dor fundoplication was added[59]. In another RCT, laparoscopic myotomy with Dor fundoplication was equally effective as a myotomy with "floppy" Nissen fundoplication in controlling reflux, but dysphagia rates were significantly higher in the latter group (2.8% *vs* 15%, respectively; $P < 0.001$)[60]. With success rates of 47%-82% at 10 years, laparoscopic Heller myotomy with partial fundoplication appears to have evolved into the surgical procedure of choice[39,61,62]. A recent single center RCT compared laparoscopic cardiomyotomy with partial toupet fundoplication to pneumatic dilation in patients with newly diagnosed achalasia. Similar to the Csendes study, it also showed significantly fewer treatment failures in the surgical arm after a period of 12 mo[63]. Another head to head multicenter RCT has been ongoing for a number of years, but publication is still pending[64].

Predictors of a negative outcome with surgical myotomy were severe preoperative dysphagia, lower preoperative LES pressures of < 30-35 mmHg, progressive esophageal body dilation with flask type or sigmoid esophagus, and preoperative endoscopic treatment in some studies[61,65-68]. However, other studies showed treatment responses even in (selected) patients with dilated esophageal bodies or sigmoid esophagus, and in patients who previously failed pneumatic dilation[48,69,70]. The effect of surgical myotomy on chest pain remains controversial, and patients should be aware that this symptom might not reliably improve after either pneumatic dilation or surgery[8]. Occasionally, a temporary placement of self-expanding metal stents (SEMS) has been suggested as a possible means of dilation or as a bridge to surgery[71,72]. However, because no information with regard to its long-term effectiveness exist and complications might be frequent and potentially severe[73], stent treatment for achalasia cannot be recommended at the present time.

Finally, it should not be forgotten that for patients not responding to any one of the above mentioned therapies, subtotal esophageal resection with gastric pull-up remains as a viable treatment option. Although such therapy is extremely invasive and associated with a high post-operative morbidity, favorable long-term results with significant improvement of symptoms can be achieved, even if endoscopic therapy or surgical myotomy have persistently remained unsuccessful[74].

COMPLICATIONS AND PROGNOSIS

Complications in patients with achalasia might occur from the natural course of the disease (e.g. aspiration, squamous cell carcinoma, and megaesophagus), from iatrogenic interventions (e.g. perforation after balloon dilation, or postoperative complications after myotomy), or from the late consequences of a successful intervention (e.g. reflux related complications, such as strictures or adenocarcinoma).

As a result of the natural course of the disease, structural parenchymal pulmonary disease occurs in 33% of patients with achalasia, probably from chronic microaspiration. Furthermore, delayed diagnosis, or ineffective intervention, might lead to progressive dilation of the esophagus and the development of a megaesophagus. This complication occurs in 10% of patients at a median of 18-21 years after the onset of symptoms and might require esophagectomy in the most severe cases[75,76].

In addition, treatment modalities carry their own inherent risks. As previously mentioned, the main risk of pneumatic dilation is perforation, which occurs at a mean of 1.6% (range from 0%-8%), even in experienced hands[39]. The risk of perforation appears to be highest during initial dilation, as opposed to subsequent

Table 2 Predictors of treatment response in achalasia

Treatment option	Positive predictors	Negative predictors
Botulinum toxin injection	Vigorous achalasia	Initial LES pressure ⩾ 50% of the upper limit of normal
	Older patients	Lack of clinical response or residual LES pressure ⩾ 18 mmHg after initial botulinum toxin treatment
Pneumatic dilatation	Older patients	Male Gender
		Pulmonary symptoms
		Failed response to 1-2 initial dilations
		High initial LES pressure (> 15-30 mmHg)[1]
		Reduction of LES pressure < 50% after the first dilation
Myotomy	Younger patients (< 40 yr)	Severe preoperative dysphagia
		Lower preoperative LES pressures of < 30-35 mmHg[1]
		Esophageal body dilation (flask type or sigmoid esophagus)
		Preoperative endoscopic treatment (in some studies)

[1]Pressure values show considerable inter-study variability, depending on techniques used by different authors. Therefore, the pressure values shown in the table only reflect estimates based on the available literature.

dilations[77]. Although the perforation risk of laparoscopic myotomy is smaller with 0.7% (range 0%-8%), the overall rate of postoperative complications is 6.3%, with a periprocedural mortality of 0.1%[39]. As a result of endoscopic or surgical treatment, reflux esophagitis occurred in approximately 10% of patients in our own prospective cohort, even though 43% of patients received acid suppressing medications[76]. Reflux esophagitis was more commonly observed after surgical myotomy with Dor fundoplication (14%) than after pneumatic dilation (5%), possibly indicating more effective disruption of the LES. Late reflux complications, such as esophageal stricture occurred in half of these patients.

The most feared complication of achalasia is esophageal cancer. A recent review of the available literature reported a mean prevalence of esophageal cancer of 3% in patients with achalasia, indicating a fifty-fold increased risk over the general population[78]. Squamous cell carcinoma appears to occur most commonly, and probably results from stasis, causing bacterial overgrowth and production of nitrosamines, which in turn lead to chronic inflammation, dysplasia and cancer[79]. In addition, adenocarcinoma may result from long-standing reflux after successful treatment[80,81]. Although insufficient data are available to make evidence-based surveillance recommendations, many experts support a strategy of surveillance for cancer or reflux complications. Accordingly, the latest ASGE guideline suggests that it would be reasonable to consider such a strategy after 15 years of symptoms[82]. Annual follow up surveillance intervals have been suggested at least by one author[77]. Patients should be kept on a liquid diet three to four days before the surveillance endoscopy and an esophageal lavage should be considered immediately before the procedure to optimize visualization. Despite the described cancer risk and frequent long-term complications, patients with achalasia do not appear to experience a significant compromise of their overall life expectancy[76].

CONCLUSIONS AND FUTURE PERSPECTIVES

Achalasia is an idiopathic disorder, likely caused by autoimmune mediated destruction of inhibitory neurons in response to an unknown, possibly viral, insult in genetically susceptible individuals. Physicians should be aware of typical and atypical presentations of achalasia to avoid diagnostic delays. Standard diagnostic work-up should include an EGD, timed barium swallow and manometry. Additional testing may become necessary if pseudoachalasia is suspected. The appropriate choice of therapy depends on multiple factors, including local expertise, patient preferences, and known predictors of treatment failures (Table 2). Based on the current evidence, we prefer laparoscopic myotomy in combination with partial fundoplication in young patients (< 40 years) with low surgical risk as the primary treatment option. In older patients, or those who want to avoid surgery, pneumatic dilation produces good long-term results, unless the first one to two dilations are unsuccessful, or LES pressure is not adequately decreased. Botulinum toxin might be especially useful in very old patients, or those with major comorbidities, because of its excellent safety profile. Subsequent treatments should be based on symptom recurrence. Pharmacological therapy should be reserved for patients awaiting a more definite treatment option. For patients not responding to any one of the above mentioned therapies, or patients with megaesophagus, esophageal resection remains a viable option.

In the future, well designed prospective studies are needed to identify optimal treatment options for different subgroups of patients with idiopathic achalasia. The advent of new exciting diagnostic methods, such as HRM, may aid in predicting treatment responses and warrants further investigation. Finally, with growing insight into the pathophysiology of this disease, novel treatment options that aim at preventing the late stages of the disease might evolve.

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