

Achalasia: an Overview of Diagnosis and Treatment

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Abstract

Achalasia is a primary esophageal disorder involving the body of the esophagus and lower esophageal sphincter affecting equally both genders and all ages. While its etiology remains unclear, the pathophysiologic mechanism involves the destruction of the myenteric plexi responsible for esophageal peristalsis. Given the slow, initially oligosymptomatic progression and relative low prevalence of disease, achalasia can remain undiagnosed for years.

In terms of diagnosis, esophageal manometry is the gold standard to diagnose achalasia. Still, its role in post-treatment surveillance remains controversial. Radiological studies support the initial diagnosis of achalasia and have been proposed for detecting pre-clinical symptomatic recurrence. Although endoscopy is considered to have a poor sensitivity and specificity in the diagnosis of achalasia, it has an important role in ruling out secondary causes of achalasia (i.e. pseudoachalasia).

With respect to treatment, laparoscopic myotomy and pneumatic balloon dilatations of the lower esophageal sphincter are considered definitive treatments for achalasia. Both treatment options offer sustained clinical responses, with head-to-head trials being currently underway. Botulinum toxin injection in the lower esophageal sphincter is considered an acceptable alternative in patients who are not candidates for surgery or balloon dilatation or as proof of concept in difficult to diagnose patients. Pharmacologic therapies for achalasia offer mild, transient improvement at best.

In summary, diagnosis achalasia requires shrewd history taking and dedicated esophageal testing. In experienced hands, treatment of achalasia can provide long-term sustained clinical improvement.

Key words

Achalasia - esophageal manometry - barium esophagogram - pneumatic dilatation - Heller myotomy

Introduction

Achalasia is a primary esophageal motility disorder characterized by the absence of esophageal peristalsis and lower esophageal sphincter (LES) relaxation due to damage to the myenteric plexus. The disease was first described in 1674 when Sir Thomas Williams reported on a disease involving food blockage inside the esophagus of unknown origin. He also suggested a treatment option still valid these days – sphincter dilatation with a tool of the time - a fish whalebone (1). The disease was first termed achalasia (Greek for “lack of relaxation”) by Arthur Hurst in early 1927 (2).

In addition to the typical symptom of dysphagia (i.e. difficult swallowing) for both liquids and solids, patients may initially present with chest pain and regurgitation. Due to the low prevalence of the disease, the majority of primary care physicians rarely encounter achalasia patients in their busy daily practice. Still, recognizing the clinical presentation of achalasia is important in order to refer patients for appropriate diagnostic procedures and treatment early in the course of the disease.

The goal of the present review is to highlight epidemiologic, pathophysiological, clinical, diagnostic and treatment aspects of the disease. We reviewed primarily original papers (English language) indexed in Medline from 1964 to 2007 and included some of our experience in diagnosing and treating patients with achalasia.

Epidemiology and physiology

Achalasia is a rare disease affecting both genders with a prevalence of < 1/10.000 and an incidence between 0.03 and 1/100.000 per year (3). It may occur at any age, however incidence peaks in the 3rd and 7th life decade (3, 4).

Primary achalasia, most common anywhere but in South America, is of unknown origin. Pathophysiologically, it is

caused by the degeneration of the plexus myentericus resulting in a lack of inhibitory neurons needed for coordination of lower esophageal sphincter relaxation and peristaltic contractions of the esophagus (5-7). This neurodegenerative insult is believed to be of inflammatory origin with possibly (slow) viral involvement (8). Although arguments have been reported suggesting a genetic, autoimmune or infectious origin of the neural damage, the exact cause remains to be determined.

In secondary achalasia, the cause of neurodegeneration is known. Most cases are associated with Chagas disease caused by *trypanozoma cruzi* endemic to Southern America (9).

Lack of esophageal peristalsis and lower esophageal sphincter relaxation, mimicking achalasia (i.e. "pseudoachalasia") can be the result of other processes. Pseudoachalasia is considered to account for 2-4% of cases of achalasia (10). While adenocarcinoma of the esophago-gastric junction is the most common and most dreaded cause of pseudoachalasia (11) other diseases (i.e. breast cancer, pancreatic cancer, histiocytosis X, amyloidosis etc.) (10, 12) or iatrogenic conditions (13,14) have been implicated as the etiology of this rare condition.

Clinical presentation

Achalasia is a progressive disease that presents with symptoms of dysphagia both for liquid and solid food, regurgitation as well as chest pain with but also long after meals. Regurgitation of indigested foods can often be misinterpreted as gastroesophageal reflux disease leading to delayed diagnosis of the disease. Regurgitation in achalasia occurs during meals, shortly thereafter or hours later when the patient changes into recumbent position and reports regurgitation of undigested foods. More subtle symptoms include the speed of eating (upon questioning,

achalasia patients frequently report being the last to finish their meals, report family or friends teasing them to eat up faster etc.) and stretching or side-to side movement as well as walking around after meals (to accomplish bolus passage through the aperistaltic esophagus and across the lower esophageal sphincter barrier).

In patients with rapid onset of dysphagia (< 6 months), weight loss and age >50 years, pseudoachalasia should be ruled out by endoscopic examination and a CT-scan (15).

Diagnosis of achalasia

Diagnosis of achalasia is primarily symptom based and frequently confused with more common entities such as gastroesophageal reflux disease. Diagnosis is typically delayed 2-3 years from the beginning of symptoms. Typical findings of esophageal manometry, barium esophagogram and endoscopic feature, as well as the clinical utility of these diagnostic techniques are summarized in Table I.

Upper gastrointestinal endoscopy

Comments on esophageal peristalsis and LES during endoscopy are not very accurate. Reports of the lack of peristalsis and LES being difficult to pass are neither sensitive nor specific. Retention of undigested food in the esophagus can be regarded as a more specific parameter in diagnosing achalasia, but it occurs only in patients with advanced disease and severe transit impairment. Candida esophagitis in an immune competent patient should raise the suspicion of esophageal retention.

Radiographic studies

A barium esophagogram is an established test in the evaluation of achalasia. Typical radiographic findings (Fig.1) include the smooth tapering in the distal esophagus with the typical "bird's beak" or "champagne glass" appearance, dilatation of the esophagus above the gastro-esophageal

Table I Diagnostic features of achalasia during esophageal manometry, barium esophagogram and upper GI endoscopy and clinical relevance of using these procedures for initial diagnosis and in the follow-up of patients

	Esophageal manometry	Barium esophagogram	Endoscopy
Features			
Typical	Esophageal aperistalsis + Poorly relaxing LES + Hypertensive LES	Smooth tapering distal esophagus ("bird beak"), dilated esophagus with barium column	Distended esophagus with retained food and "absent peristalsis"
Often in clinical practice	Only aperistalsis is present ± poor LES relaxation	Smooth tapering distal esophagus ("bird beak")	Normal
Clinical relevance			
Initial diagnosis	Required for establishing diagnosis	Supports diagnosis, helps differentiating between achalasia and scleroderma esophagus	Excluding pseudoachalasia; assists balloon dilatation
Clinical follow-up	Limited utility; peristalsis will not return to normal; follow-up LES resting pressure after treatment	Timed barium swallow; identifying pre-clinical disease relapse	Limited utility

junction, lack of primary peristalsis noticed during fluoroscopy and the formation of a contrast column above the LES. While these findings are specific for achalasia, none of them have to be present in the early phase of the disease. Consequently a normal barium esophagogram does not rule out achalasia (16).

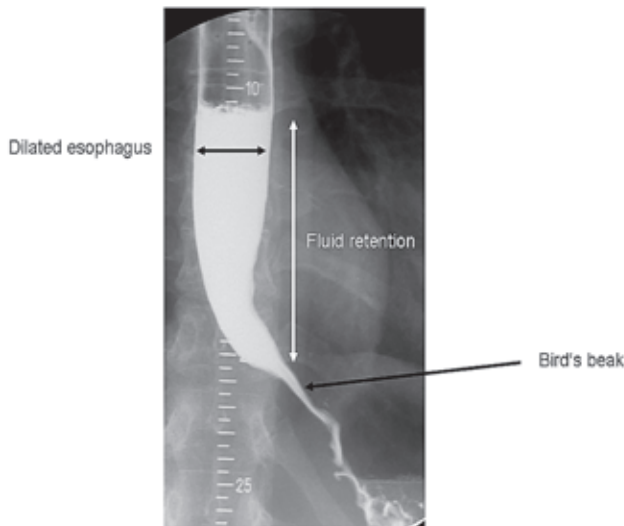


Fig.1 Conventional barium esophagogram in achalasia. Typical for achalasia is the smooth narrowing of the distal esophagus at the level of the lower esophageal sphincter with the characteristic "bird beak" or "champagne glass" appearance. The proximal esophagus may be dilated and frequently a column of barium forms above the LES as a result of the poor relaxation and opening of the sphincter.

Barium studies have also been used to quantify the impairment of bolus transit at the gastro-esophageal junction. Using a standardized approach Vaezi et al proposed the "timed barium swallow" (Fig.2). In contrast to conventional videofluoroscopic evaluation, the timed barium swallow consists of the ingestion of 50-100 ml of barium with plain thoracic radiographs taken at 1, 2 and 5 minutes. Measuring the height of the barium column at this time intervals allows quantifying the degree of esophageal bolus retention. Using

this approach before and at regular intervals after treatment has been proposed to monitor the success of the therapeutic intervention and to detect disease recurrence prior to the development of symptoms (17).

Esophageal manometry

To date, esophageal manometry remains the gold standard in diagnosing achalasia. We require esophageal aperistalsis to be present in order to diagnose achalasia (i.e. "conditio sine qua non"). A poorly or not relaxing LES (i.e. LES pressure above 8mmHg) is frequently observed (18,19). A hypertensive LES (i.e. LES resting pressure >45 mmHg) may be present and occasionally increased intraesophageal basal pressure above the intraabdominal pressure is observed (20). The average esophageal peak pressure during swallowing has been used to distinguish classic from vigorous achalasia. Vigorous achalasia is defined by average contraction amplitudes above 37 mmHg (21,22). The relevance of this subclassification remains unclear as the prognostic and therapeutic value of this separation are controversial (23). Manometric diagnosis is made by conventional or the recently available high resolution manometry (Fig.3) that allows a better pattern recognition of the above mentioned criteria to diagnose achalasia. The extent to which high resolution manometry will improve understanding of this disease is being currently investigated.

Treatment of achalasia

The progression of achalasia is determined primarily by the resistance to the flow of the poorly relaxing and opening LES. Left untreated, most patients will eventually develop a dilated "mega-esophagus" with severe bolus transit impairment, putting them at risk for aspiration pneumonia, esophageal malignoma or organ perforation. Therefore the goal in the management of achalasia is early diagnosis and treatment before reaching this end-stage phase when esophagectomy becomes inevitable. Curing achalasia and restoring esophageal peristalsis implies restoring the

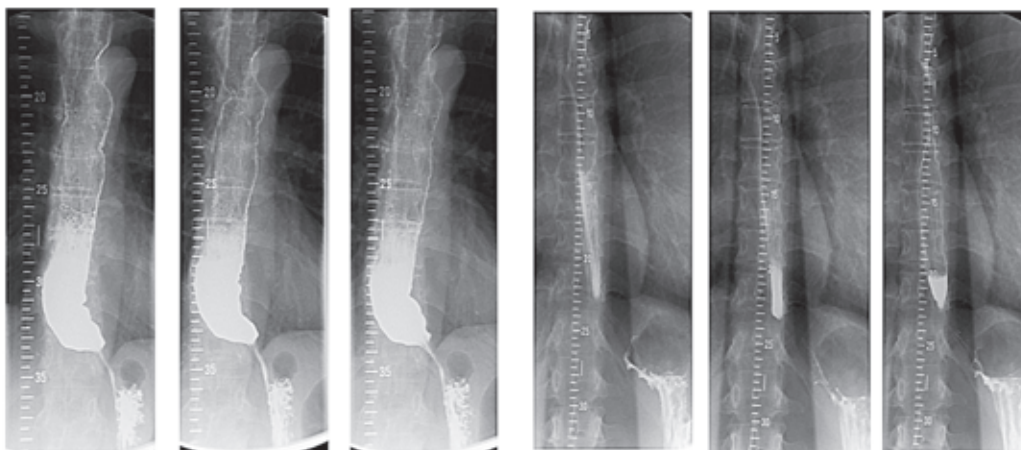


Fig.2 "Timed barium" swallow in achalasia. Images were taken 1, 3 and 5 minutes after ingestion of 50-100ml barium. Some clinicians favor this approach to monitor patients after therapy in order to detect recurring disease before becoming clinically overt. Before (A) and after (B) treatment.

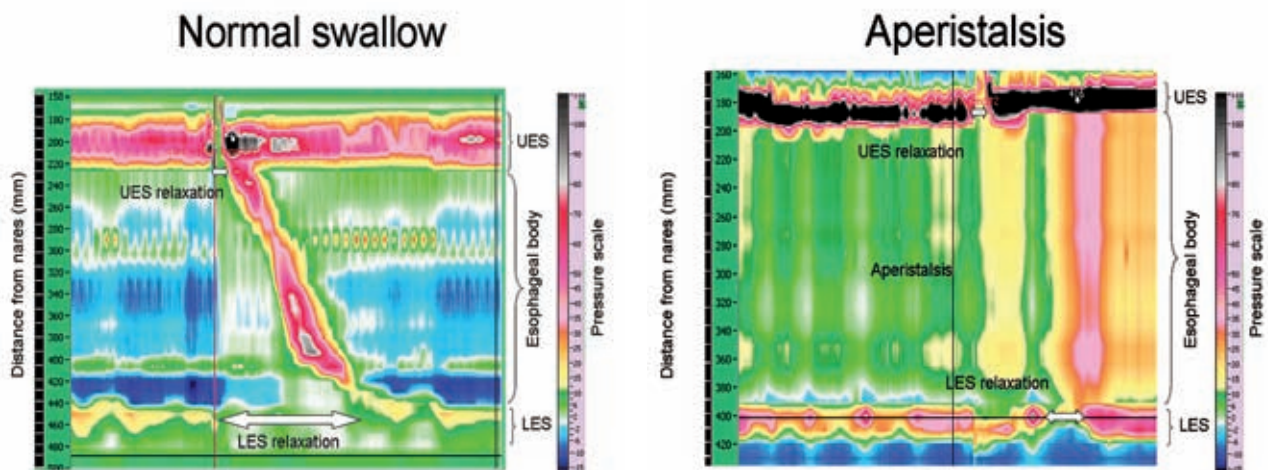


Fig. 3 High resolution manometry recordings in a normal individual (a) and from a patient with achalasia (b). The figures are tempo-spatial representations of pressure data recorded in 32 pressure channels in the esophagus. A distinct color is attributed to a range of pressures as indicated on the scale. At rest the upper and lower esophageal sphincter are identified as two distinct pressure bands. During a normal swallowing sequence (a) the upper esophageal sphincter relaxes and opens. This is followed by the esophageal peristalsis at a time when the LES is relaxed. In patients with achalasia (b) there is only a short if any peristaltic contraction below the upper esophageal sphincter (achalasia does not affect striated muscle peristalsis) and complete aperistalsis in the distal esophagus. The LES has often a poor relaxation (i.e. LES residual pressure >8 mmHg) and may be hypertensive (i.e. LES resting pressure >45 mmHg).

neurons of the myenteric plexi. Until such treatment becomes available all medical interventions currently aim at facilitating bolus transit across the LES. With pharmacologic treatments offering modest, transient improvements at best, endoscopic and surgical treatment options remain the main therapeutic pillars for achalasia.

Oral pharmacologic treatment

Pharmacologic treatment includes smooth muscle relaxants such as calcium channel blockers, nitrates and phosphodiesterase inhibitors aimed at reducing lower esophageal sphincter pressure. Calcium channel blockers (i.e. nifedipine 10-20 mg sublingually prior to meals) have been intensely evaluated with chronic treatment duration up to one year (24-26). Still, a recent meta-analysis regarding the use of nitrates in the treatment of achalasia indicated a low number of controlled studies with heterogeneous data and considerable side effects (27). Smaller studies have reported the use of long-acting nitrates and more recently phosphodiesterase 5 inhibitors (i.e. sildenafil) in the treatment of achalasia.

Clinically available pharmacologic therapies have limited value in the treatment of achalasia. We therefore indicate them only in patients not willing or unable to undergo any other procedure, in patients waiting for a more definitive therapy or as supportive treatment for refractory chest pain in achalasia.

Botulinum toxin injections

Pasricha *et al* reported on the use of botulinum toxin A (Botox) injections in the lower esophageal sphincter to treat achalasia more than 10 years ago. This neurotoxin blocks the release of neurotransmitters at presynaptic cholinergic nerve endings of the terminal plate, resulting in a decreased LES pressure (28). According to the original protocol, 100

IU of botulinum toxin A are injected in 4 quadrants just above the Z-line, an area corresponding to the lower esophageal sphincter. The advantage of this approach is that it carries a much lower risk of perforation and lower morbidity and mortality compared to balloon dilatations and/or surgical interventions (see below). In addition BoTox therapy can be repeated, should the effects wear off. It is however important to recognize that patients not responding to the first set of botox injections are unlikely to profit from further ones. Conversely 3/4 of patients responsive to the first injection will respond to a second one (29).

The best results with BoTox injections have been noticed in patients with vigorous achalasia. The effective duration of BoTox treatment varies according to various studies but it is generally expected to last on average 6-12 months in most patients. The use of a second injection of BoTox irrespective of clinical response especially in older patients one month after the first treatment has been advocated by Dughera *et al* yielding to symptomatic remission of 75% after one year (30).

Further indication to use BoTox injections in the LES include patients with unclear diagnosis. In these patients a "trial" of BoTox could be used to select patients most likely to respond to a more definite treatment (31).

Pneumatic balloon dilatation

Dilating the affected segment is the oldest treatment modality and was first described more than 300 years ago with a tool of the time – a whale fishbone (1). While rigid dilators are effective for esophageal strictures, larger (i.e. 3 cm in diameter and above) balloons are needed that not only stretch but also produce a controlled rupture of the muscle fibers composing the LES. While there is no clear consensus on the technical details of balloon dilatation,

most centers used their own pneumatic dilatation technique passed along from experienced to junior physicians. Inpatient vs. ambulatory treatment, sedated vs. unsedated dilatation, the anesthetics used, the dilator system, initial balloon size, speed, pressure, duration and number of dilatations per endoscopic session and timing of re-dilatations differ from center to center (32-36).

In our practice, we routinely inform patients about other treatment modalities including surgical myotomy and BoTox injection and underscore the risk of perforation during balloon dilatation (i.e. 2-3% of patients). Patients opting for a surgical treatment are referred after complete diagnostic work-up for laparoscopic Heller myotomy with or without fundoplication to experienced surgeons. Patients opting for endoscopic therapy are asked to take liquid diet at least 24 hours prior to the procedure in order to minimize esophageal food retention. Pneumatic balloon dilatation (initially with a 30mm Rigidflex balloon) is performed as an outpatient procedure using intravenous propofol sedation. During endoscopy, the balloon is positioned under fluoroscopic guidance across the LES and inflated slowly to 10 PSI for 15 seconds. After documenting no esophageal leakage in the radiology department, patients are discharged home following 4 hours of observation. The clinical response to treatment is evaluated 1 month after dilatation and, in patients with persistent symptoms (i.e. Eckardt score >3) (37) the procedure is repeated with 35mm and subsequently 40mm balloons.

Long term (i.e. 5-10 years) clinical response rates to balloon dilatations range from 42% to 85% (38, 39). Increased response rates have been reported by investigators closely following up their patients and repeating the procedure when symptoms reoccurred (35, 40). In a recent study, Vela et al reported lower response rates (i.e. 44%) when evaluating esophageal bolus retention, although 85% of patients reported good symptomatic improvement (40).

Surgical lower esophageal myotomy

The goal in surgical myotomy is to relieve the obstruction determined by LES, by the longitudinal transection of the LES. For a good therapeutic outcome the myotomy has to be extended 6-7 cm above the gastroesophageal junction and 3 cm distally to cut also the gastric sling fibers involved in functional formation of the LES (41). As this approach might lead to gastroesophageal reflux in an important proportion of patients, most surgeons advocate combining the myotomy with an antireflux procedure. As there is evidence that extending the distal myotomy and adding an antireflux procedure with a partial wrap results in less postoperative dysphagia while controlling gastroesophageal reflux (42,43) surgeons advocate a partial wrap using the Toupet technique with every myotomy. However, postoperative gastroesophageal reflux symptoms still occur in about 10-30% of patients who will later on require proton pump inhibitor (PPI) therapy (44,45). To date, laparoscopic Heller myotomy has replaced the open procedure, as it leads to comparable results in terms of efficacy and safety while decreasing perioperative morbidity (46).

Symptom improvement after myotomy ranges from 83% to 100% for the first year (47) and long term studies (i.e. >10 years) report sustained remission rates of 67-85% (48,49). One again, more conservative response rates have been reported by studies evaluating esophageal bolus retention. More recently, Vela et al, using prolonged bolus retention time as sign of recurring disease, reported relapse rates of up to 43%, albeit only 15% reporting symptomatic relapse (40).

Balloon dilatation versus surgical myotomy

The debate related to pneumatic vs. surgical myotomy is ongoing (50). There is currently only one prospective randomized controlled trial published favoring the surgical over the endoscopic intervention (92% versus 65% remission 6 years after open myotomy versus pneumatic dilatation) (51). An ongoing head to head multicenter trial comparing laparoscopic Heller myotomy vs. pneumatic balloon dilatation is currently underway (Boeckxstans personal communication UEGW 2006).

In general most studies favor myotomy over pneumatic dilatation given the short- and long-term response rates (52). Recent studies indicate that using an aggressive balloon dilatation, schemes report comparable treatment outcomes (35, 40). In addition, a recent study by Lopushinsky et al found that, although re-treatment is twice more common in patients undergoing pneumatic dilatation, up to 30% of patients undergoing surgical myotomy would require re-treatment within the first 12 years (53). Consequently, we involve our patients strongly in the decision making process by presenting the expected response rates, peri-interventional mortality and morbidity, as well as the need for re-treatment prior to opting for one or the other definitive treatment.

Follow-up after treatment

Recent studies underline the importance of clinical follow-up of patients treated for achalasia. In our outpatient clinic, we schedule an initial, early follow up one month after each procedure. If symptomatic response is not achieved, re-dilatation is offered within weeks after the first dilatation. Patients with sustained clinical response are followed up clinically (Eckardt scores) (37) and radiographically (i.e. timed barium swallow) at yearly intervals. The aim of this surveillance protocol is to recognize relapsing symptoms early in order to avoid the development of end-stage disease requiring esophagectomy (17).

Summary and conclusion

Achalasia, a primary esophageal disease is a rare condition affecting both genders at all ages. The onset of the disease is frequently insidious with dysphagia, chest pain and regurgitation and it is not unusual that the correct diagnosis is delayed 2-3 years from the onset of symptoms. Upper gastrointestinal endoscopy is frequently normal and used mainly to exclude other causes (i.e. pseudoachalasia). A barium esophagogram may show pathognomonic features

and support the manometric diagnosis. Achalasia is diagnosed by the complete absence of esophageal peristalsis on manometric recordings of swallows. Medical therapy is rarely efficient and should be offered at best to bridge the time until a definitive treatment. Patients who are good surgical candidates should be offered either pneumatic balloon dilatation or laparoscopic myotomy and her/his preference should be included in the decision making process as should the local expertise with these procedures. Patients who are not good surgical candidates should be offered endoscopic injection of botulinum toxin in the lower esophageal sphincter, understanding that this procedure has fewer risks but also a lower efficacy compared to balloon dilatation or surgical myotomy. Although the majority of patients notice important improvement after the first treatment, achalasia patients should be followed up regularly in order to identify disease progression early and avoid the development of the end-stage disease when esophagectomy may become the only treatment option.

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