Achalasia: Common Features of an Uncommon Disease

Achalasia is a primary esophageal motility disorder characterized by absence of esophageal peristalsis and poor relaxation of the lower esophageal sphincter (LES). Primary achalasia is a rare worldwide disease with prevalence of eight cases per million population. Absence of peristalsis results from degeneration of nitric oxide releasing inhibitory neurons in the esophageal wall. Dysphagia is the most common symptom of achalasia; however, regurgitation and heartburn are frequently present. Manometry is considered the gold standard for diagnosis. Achalasia is incurable in that no treatment can restore the neuronal degeneration; therefore, therapy is aimed at opening the poorly relaxed LES. Evidence shows that pneumatic dilation (PD) and surgery are equally effective, with PD having a slight edge. We believe that using PD as initial therapy and saving myotomy as a “rescue” approach is the preferred overall approach.

INTRODUCTION

Disorders of esophageal motility are often pursued as an explanation for a variety of upper gastrointestinal symptoms. These include: dysphagia, regurgitation, heartburn and even non-cardiac chest pain. Early radiographic contrast studies demonstrated that many patients with persistent progressively worsening dysphagia showed a classical narrow closure at the esophagogastric junction (EGJ), the so-called “bird beak”. Because of the failure of this segment to relax or open during swallowing the term achalasia (from the Greek; “without relaxation”) was applied.
to the chronic nature of the disease, achalasia apparently has an increasing prevalence with stable incidence with age.4–6

Etiology & Pathogenesis
With the development of accurate intraluminal pressure-sensing probes in the 1950s not only was the pressure defect at the EGJ confirmed but the associated loss of peristalsis was recognized. This helped clarify the pathophysiology underlying the severe and progressive symptoms of dysphagia, regurgitation and weight loss that characterize this entity; worldwide in its occurrence as THE esophageal motility disorder.

More recent manometric technologies with high resolution and colourful 3D pressure displays have expanded awareness of the possibility of 3 distinct subtypes of achalasia.

Esophageal peristalsis and LES relaxation are coordinated by the nitric oxide releasing inhibitory neurons of the myenteric plexus. These neurons are absent in primary achalasia resulting in absent peristalsis and defective LES relaxation. The underlying pathogenesis remains unclear, but recent pathological and genetic studies attributed the disappearance of myenteric inhibitory neurons to chronic ganglionitis resulting from an autoimmune response against these neurons triggered by an environmental factor likely viral (particularly HSV-1) in genetically susceptible individuals. This is supported by observations that found association between achalasia with HLA-DQB1, DQα1 and detection of circulating antibodies to the myenteric neurons. It is worth saying that the end result esophageal pathology is irreversible. Also, an association was found with some genetic syndromes like Down and Allgrove syndrome (also known as triple A syndrome, i.e. alacrima, achalasia, adrenocorticotropic hormone deficiency) suggesting the role of genetic factors.7–11

Clinical Picture
Dysphagia is the most common symptom of achalasia (>90%). Usually, it is for both solid and liquids from the start. On the other hand, mechanical obstruction due to malignancy or stricture also leads to progressive dysphagia, evolving from solids in the beginning to solids and liquids. Regurgitation and heartburn were frequently present. Patients are often treated with acid suppressive medications assuming that these symptoms are due to gastroesophageal reflux disease (GERD). Heartburn in achalasia is explained by stasis and of undigested food in the esophagus secondary to poor esophageal clearance, rather than by real GERD. This misdiagnosis and poor response to acid suppressive medications can lead to the risk that some of these patients may be advised to have a fundoplication. Other symptoms of achalasia include weight loss, cough and chest pain especially in type III achalasia.5,12,13

The Eckardt score14 based on grading of the achalasia symptoms can be used in the initial evaluation of the severity of the condition, as well as in the post-treatment follow up.3 It is calculated by summation of the corresponding score for each symptom of dysphagia, regurgitation, and chest pain (with a score of 0 for absence of symptoms, 1 for occasional symptoms, 2 for daily symptoms, and 3 for symptoms at each meal) and weight loss (with 0 for no weight loss, 1 for a loss of <5 kg, 2 for a loss of 5-10 kg, and 3 for a loss of >10 kg).15

There are other conditions that can mimic achalasia both clinically and on investigations (manometry, endoscopy, and radiological studies). These conditions are called pseudoachalasia or secondary achalasia which is most commonly caused by malignancy at the EGJ either by invading the esophageal neural plexuses directly or by paraneoplastic mechanism. Less common causes are metastatic disease, infection with the protozoan parasite Trypanosoma cruzi (Chagas disease), and iatrogenic like post fundoplication and gastric banding.16,17 Pseudoachalasia should be suspected when some clinical characters are different (short duration of symptoms; advanced age; rapid and marked weight loss; resistance to passing the endoscope through the gastroesophageal junction, and expected treatment outcomes are not achieved. Thus, careful endoscopic assessment of the gastric cardia on retroflexed view to rule out malignancy should be done.12

Investigations
Manometry is considered the gold standard for diagnosis of achalasia. EGD and barium esophagram are complimentary methods to support the diagnosis of achalasia and for exclusion of structural lesions.1,18 Achalasia can be diagnosed using conventional or high resolution (HRM) manometry systems. According to conventional manometry 2 types of achalasia have been identified, classic and vigorous. The manometric criteria of classic achalasia are: (1) absent peristalsis in the body of the esophagus characterised either by
simultaneous esophageal contractions with amplitudes <40 mm Hg or by no apparent esophageal contractions and (2) incomplete relaxation of the LES. Vigorous achalasia is characterised by simultaneous esophageal contractions with amplitudes >40 mm Hg. 17

In HRM: achalasia is classified according to the latest version of the Chicago classification19 into: types I, II and III. Table 1 shows the diagnostic criteria of the 3 types in comparison to the corresponding description of the previous conventional classification.

Also, the use of multichannel intraluminal impedance with esophageal manometry (MII-EM) allows functional esophageal assessment and identifies chronic fluid retention. 20

Endoscopy and barium esophagram are essentially used for exclusion of mechanical obstruction and pseudoachalasia due to tumours at the EGJ. EGD findings in achalasia are non-specific; it might show dilated esophagus and food retention in advanced cases. Barium swallow can show these features: (1) dilated esophagus; (2) air-fluid level in the mid-esophagus; and (3) narrowed EGJ giving the classic “bird-beak” appearance. Occasionnally, barium study can demonstrate an extreme cork screw appearance indicating esophageal spasm associated with type III (vigorous) achalasia. 5,15,21

Computed tomography (CT) and endoscopic ultrasound (EUS): In cases of suspected pseudoachalasia for detection of masses, esophageal mural thickening or infiltrating lesion. 16,22

Table 1. Manometric Criteria of Achalasia in Conventional and High Resolution manometry.1,17,19

<table>
<thead>
<tr>
<th>Conventional Manometry</th>
<th>High Resolution Manometry</th>
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<tr>
<td><strong>LES</strong></td>
<td>The median value of the &quot;IRP &gt; 15mm/Hg.</td>
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<tr>
<td>Mean nadir relaxation pressure &gt; 8mm/Hg above the gastric pressure.</td>
<td>Type I: 100 % failed peristalsis (**DCI &lt; 100 or &lt; 450 with ***DL &lt; 4.5 seconds). Type II: same as type I but with panesophageal pressurization in ≥ 20 % of swallows irrespective of the IRP.</td>
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<td>Short relaxation duration &lt; 6 sec.</td>
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<td>Resting pressure &gt; 45 mm/Hg.</td>
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<td><strong>Esophageal Peristalsis</strong></td>
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<tr>
<td>Absent peristalsis with either no apparent contractions or presence of simultaneous contractions &lt; 40 mm/Hg.</td>
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<td><strong>Atypical/ Variants</strong></td>
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<tr>
<td>Vigorous achalasia: Simultaneous contractions with amplitude &gt; 40 mm/Hg.</td>
<td>Type III: same as type I, but with premature contractions (DL &lt; 4.5 sec) with DCI &gt; 450 in ≥ 20 % of swallows.</td>
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* IRP: integrated relaxation pressure ** DCI: distal contractile integral *** DL: distal latency

Treatment
Achalasia is an incurable disease in that no treatment can restore the neuronal degeneration of the esophageal wall. Therefore, therapy is aimed at opening the poorly relaxed LES. This will improve the esophageal clearance and emptying in the upright position by gravity, leading to symptom relief. 23 The treatment options available are:

1. Pharmacological Therapy
Nitrates (isosorbide mononitrate) and calcium channel blockers (nifedipine) are the most common drugs used for temporary decrease of the LES pressure. Both causes smooth muscle relaxation either by increasing the nitric oxide levels or by blocking the calcium necessary for smooth muscle contraction. They can achieve short-term relief of symptoms, however the clinical response is partial and with decreased efficacy over time. 24

Both drugs can cause dizziness, headaches and pedal edema. These side effects in addition to short duration of action and decreased efficacy over time are the primary causes limiting their use to high risk patient in favor of more effective treatment options (endoscopic or surgical). 25

Some studies showed that phosphodiesterase inhibitors (Sildenafil) causes significant decrease in the LES pressure suggesting its use in clinical practice, nevertheless, comparative studies are lacking. 26

2. Botulinum Toxin (Botox)
Botox (BTX) is a potent toxin that inhibits the release of
Acetyl choline from nerve endings leading to paralysis of the innervated muscle. It is injected endoscopically using a sclerotherapy needle in all four quadrants of the LES 1-2 cm above the Z-line. The total dose injected is from 80 – 100 U.27, 28

76% of achalasia patients will respond to one Botox injection with 50% recurrence of symptoms within 6 months. These studies suggest consideration of a trial of another injection since 75% of patients can respond to the second injection.25 Because of this high recurrence rate; our practice is to use BTX in high risk patients or in patients refusing or fearing to have pneumatic dilation or surgical myotomy.

BTX can be tried before proceeding to pneumatic dilation and also can be given in cases of failed dilation. Some studies in the surgical literature indicate that BTX injection before myotomy can lead to increased rate of surgical failure because of the scarring produced by the toxin on the LES muscle layer, however evidence shows that it can be used in cases of surgery failure.29 Contraindications of Botulinum toxin include egg allergy and Lambert Eaton syndrome. Also it should be used cautiously in patients receiving aminoglycoside antibiotics as it can potentiate the toxin effect.30

3. Pneumatic Dilation (PD)

This endoscopic technique aims to produce a controlled tear in the muscular layer of the LES by forceful stretching using an air-filled balloon. This method improves esophageal emptying and so relieves the symptoms. The most common balloon used for this purpose is the Rigiflex balloon dilator (Boston Scientific Corporation, Boston, MA, USA). It is a 10 cm long balloon made of polyethylene polymer and comes in 3 diameters (30, 35 and 40 mm). The balloon has 4 radiopaque markers helping in identifying the balloon borders under fluoroscopic guidance; radiopaque markers at each end of the balloon, and another 2 markers identifying the middle.2,5,31

The technique involves careful endoscopic examination of the esophagus and to determine the location and gross appearance of the LES. It may show puckering and opens by gentle pressure with the endoscope. If forceful pressure is needed, one should suspect pseudoachalasia. The EGJ should be examined carefully with retroflexion inspection of the cardia to exclude pseudoachalasia. The findings expected to be in the esophagus are: esophageal dilation and retained fluid/food residues. The mucosa may show redness, friability and cracked appearance due to prolonged stasis.31

After endoscopic examination, we withdraw the scope and insert the balloon blindly over a Savary wire. The key of a successful dilation is to accurately place the balloon across the EGJ while the patient is in the supine position.25

Our practice is to inflate the balloon to 10 psi. The duration of inflation is less than 15 seconds, however it is not as important as observing that the “waist” is obliterated during fluoroscopy.32

Figures 1 and 2 show fluoroscopy images during PD procedure.

Then we withdraw the balloon (blood on it indicates mucosal tear but not necessarily a successful dilation), and place a NG tube to perform a gastrographin study under fluoroscopy to detect early perforation.31

Afterwards we put the patient under observation for 2 hours before discharge. We reassess the patient after one month using the clinical response and the Eckardt symptom score. If the patient has a score of 3 or less, we consider this a success; otherwise, we proceed with dilation using the next larger diameter balloon until achieving clinical remission.

This approach of graded dilations has a documented initial clinical remission rate in 90% of patients, and probability of remaining in remission without further dilations at 5 and 10 years is 67% and 52%, respectively. Also, performing repeated dilations on demand of symptom recurrence increases the 5 and 10 year remission rate to 97% and 93% respectively. It is our belief that PD is the most cost-effective treatment for achalasia over a 5–10-year follow up period with an overall perforation rate of less than 2%.2, 25, 33

Surgical Cardiomyotomy (Open or Laparoscopic)

Open surgical myotomy was first described by the German surgeon Ernest Heller.34 Now, it is widely replaced by the laparoscopic approach which was first performed by Cuschieri et al.35 Laparoscopic Heller myotomy (LHM) has the advantages of being less invasive, lower morbidity and shorter hospital stay than the open approach. To curtail the resulting reflux, addition of a partial fundoplication (Dor or Toupet) rather than a full Nissen fundoplication as an anti-reflux procedure shows good results with less postoperative GERD and dysphagia.36

Successful esophageal myotomy lowers LES...
pressure by up to 75%, markedly improves esophageal emptying and decreases the esophageal diameter.\textsuperscript{25}

The overall complication rate of LHM is about 6\% with reported mortality of 0.1\%, hence LHM combined with partial fundoplication is considered a safe operation.\textsuperscript{5}

Data are lacking to demonstrate how many operations are needed to ensure competency of the surgeon performing LHM. Sharp et al. reported that in a series of 100 operations, most of the complications occurred in the first 50.\textsuperscript{25, 37}

Early recurrence of dysphagia can develop in up to 31\% of cases within 12–18 months after surgery and is usually caused by incomplete myotomy, excessive scarring or tight anti-reflux wrap. Management of LHM failure can usually be done conservatively by pneumatic dilation.\textsuperscript{25, 38, 39}

### Esophagectomy

This may be necessary in cases of megaesophagus with esophageal diameter >6 cm or if tortuosity (sigmoid esophagus) is hindering emptying. The reconstruction options after esophageal resection are gastric pull-up or long segment colonic interposition. Most surgeons prefer the gastric pull-up because it requires only one anastomosis to be done.\textsuperscript{40}

Figure 3. Barium esophagram showing sigmoid configuration of the esophagus.

### Per Oral Endoscopic Myotomy (POEM)

It seems that even as we appear to have settled some age-old questions the equation is being changed by the new kid on the block, per oral endoscopic myotomy, or POEM.

Both PD and LHM are considered the “standard of care” of achalasia treatment. Recently, POEM is emerging as an alternative to LHM. POEM has the advantages of minimal invasiveness of an endoscopic procedure and the precision of a surgical myotomy.\textsuperscript{41, 42}

The standard POEM steps as described by Inoue et al are (1) creation of a submucosal tunnel from 12 cm proximal to the LES to about 2-4 cm into the stomach. The submucosal tunnel is usually created on the anterior esophageal wall except in post-Heller patients in whom it is created on the posterior esophageal wall; (2) myotomy of the circular muscle fibers starting 3-4 cm distally from the first incision and 2-4 cm into the stomach wall; and (3) closure of the entry site by using endoscopic clips.\textsuperscript{42}
Since POEM is relatively new, only short- and intermediate-term treatment success rates are available. There were several studies that showed objective improvement in esophageal function assessed by manometry and timed barium esophagram findings after POEM (even comparable to LHM).\(^4\)

One of the main concerns with POEM, compared with laparoscopic Heller myotomy (LHM), is that an anti-reflux procedure is not performed concurrently. The reported incidence of reflux following POEM reaches higher than 50% in America and Western Europe.\(^4\)

**PD vs. LHM**
Over the years management of achalasia has revolved around discussion of preference for a “medical” or surgical approach as a definitive therapy; i.e. large balloon pneumatic dilatation (PD) versus myotomy as the means to disrupt the dysfunctional circular muscle of the LES. Each has its champions and its naysayers; for years there has been no high level RCT to direct treatment preference beyond opinion and “local expertise”. The recent publication in the New England Journal of a large multicenter prospectively randomized trial from across Europe has shown convincingly that the two widely used approaches are equally effective with PD having a slight edge. Maybe the popular approach of using PD as initial therapy and saving myotomy as a “rescue” approach is the best. The European experience also reminded us that PD should be performed with step-wise balloon sizes and that repeated dilations for recurring symptoms, even years apart should be considered; not the “one and done” approach of a myotomy.\(^2\)

As most practicing gastroenterologists are unlikely to see patients with achalasia very often, it is difficult for them to maintain a level of appropriate expertise with pneumatic dilatation as a treatment option and patients are thus often referred for a myotomy.

Whether the inclination is for treatment of achalasia with pneumatic dilatation or LHM it is our belief that these patients should be referred to a specialist center (center of excellence) where an individual or a team actively treats patients with achalasia regularly.

The results of the European trial strongly reinforces the suggestion that the real decision should be based on what local expertise is available; that is, whether there is an individual in the vicinity who has the experience and knowledge to treat achalasia, be it by surgical or balloon dilation.

Interestingly, the rapidly evolving technique of high-resolution manometry has brought to light the concept of three subtypes of achalasia. Although no difference in outcome between Heller myotomy and PD has been noted for patients with type I and II achalasia, patients with type III disease seem to respond better to Heller myotomy than to PD.\(^4\)

To the neophyte, this observation is often considered as new. To the experienced esophagologist, however, subtyping of achalasia is just a new vision of a well-known concept. Interestingly, the European study was performed at a group of medical centers, none of which used high-resolution manometry to establish the diagnoses. Therefore, one could argue definitively that this old disease is well recognized and appropriately staged for therapy on the basis of good-quality manometry of any kind, and is not a new disease recently discovered by a new technology. Use of subtyping, perhaps made easier by the technique of high-resolution manometry, should continue to guide therapy decisions for patients with achalasia.

**CONCLUSION**
The European multicentre study comparing pneumatic dilatation with laparoscopic Heller myotomy, along with the author’s experience of greater than 40 years as an “esophagologist”, established PD as the preferred approach for initial treatment of achalasia. We think it is appropriate to consider a referral to an esophageal expert, for either a PD or a myotomy.
References


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