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REVIEW

Achalasia: investigation and management

Naim Slim[1]

James ML Williamson[1]

Author details can be found at the end of this article

Correspondence to:
Naim Slim;
naimslim@doctors.org.uk

Abstract

Achalasia, characterised by the absence of peristalsis and failure of relaxation of the lower oesophageal sphincter, is an uncommon degenerative condition that results in dysphagia. If left untreated it can lead to aspiration, oesophageal perforation, oesophagitis and malnutrition. It has a range of immune, allergic, viral and genetic aetiological causes. Successful diagnosis relies on the use of oesophagogastroduodenoscopy, barium swallow and oesophageal manometry to characterise the severity of the disease and to rule out underlying malignancy. Although no treatment can reverse the degenerative process, therapeutic strategies including lifestyle modification, medication, endoscopic and operative intervention can help to reduce symptoms. This article reviews the latest methods used to investigate and manage achalasia.

Key words: Achalasia; Barium swallow; Dysphagia; Eckardt score; Manometry; Oesphagogastroduodenoscopy

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Introduction

Dysphagia (difficulty in swallowing) is common and affects approximately one in seventeen people (World Gastroenterology Organisation, 2014). This is higher in older people (Holland et al, 2011) and those with concurrent neurological disease (Roden and Altman, 2013), who have a significant risk of aspiration and malnutrition (Sura et al, 2012). Dysphagia is an indication for oesophagogastroduodenoscopy, as it is a prevalent feature of oesophageal cancer (Taylor Ripley et al, 2016). However, only 1–4% of patients referred for oesophagogastroduodenoscopy with dysphagia have associated malignancy (Kapoor et al, 2005; Krishnamurthy et al, 2012). Therefore, it is important to investigate for any underlying motility disorder that may account for the patient's symptoms.

Achalasia is characterised by the absence of peristalsis and failure of relaxation of the lower oesophageal sphincter (Vaezi et al, 2013). It is uncommon in the UK, with a prevalence of 27 in 100 000 individuals and annual incidence of 1.5–2 per 100 000 (Harvey et al, 2019). Dysphagia is a highly typical feature of those affected (Fisichella et al, 2008), as a result of stasis of both solids and liquids. Achalasia results from the degeneration of enteric neurons within the oesophageal wall, but the causative mechanisms are unclear; autoimmune, viral and genetic factors are thought to be implicated (Gyawali, 2016).

History and examination

Patients with achalasia tend to complain of difficulty in swallowing; the symptoms are progressive and more prevalent with drier, bulkier foods (Fisichella et al, 2008). Associated symptoms include retrosternal chest pain, reflux, weight loss and regurgitation. If left untreated, the disease can progress to include aspiration, oesophageal perforation, oesophagitis and malnutrition. Examination tends to be unremarkable, but signs of complications or underlying malignancy may be detected.

The severity of symptoms can be graded using the Eckardt score (Table 1) (Eckardt et al, 1992), which can also be used to evaluate the efficiency of a treatment during follow up. An Eckardt score of two or lower is considered as evidence of remission of disease.

Pathology

Degeneration of inhibitory ganglionic cells in the oesophagus and lower oesophageal sphincter, and the resultant loss of secretion of vasoactive intestinal peptide and nitric oxide, is hypothesised

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Table 1. Eckardt severity and scoring criteria

Score	Weight loss (kg)	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5–10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

From Eckardt et al (1992)

to be the cause of loss of oesophageal peristalsis and hypertonia of the lower oesophageal sphincter (Lecea et al, 2011). This degenerative process is thought to be both immune mediated (with eosinophilic infiltration, and consequent cytokine and other cytotoxic protein release contributing to oesophageal smooth muscle contractility) (Spechler et al, 2018), and to have an allergy-driven component (as a result of mast cell degranulation) (Nelson et al, 2021). Viral triggers include the herpes family of viruses, which are highly neurotrophic and more readily infect squamous epithelium (which is exclusively located in the oesophageal segment of the gastrointestinal tract) (Kanda et al, 2021). In addition, there is growing evidence that achalasia is associated with other autoimmune diseases (Romero-Hernández et al, 2018), and that genetic factors, particularly the presence of risk genes HLA-DQB1 (Becker et al, 2016) and HLA-DRB1 (Furuzawa-Carballeda et al, 2018), increase the susceptibility of developing achalasia.

Investigations

Three investigative modalities are crucial and complementary in confirming a diagnosis of achalasia: oesophagogastroduodenoscopy, barium swallow and oesophageal manometry.

Oesphagogastroduodenoscopy

Endoscopy tends to be the initial investigation for patients with dysphagia (Figure 1), principally to exclude malignancy or eosinophilic oesophagitis. Suspicions of an underlying oesophageal motility disorder may be raised with direct visualisation of a dilated or tortuous oesophagus, with the presence of retained food or fluids, particularly in advanced achalasia (Vaezi et al, 2013), but its usefulness is limited in the diagnosis of early disease. An obstructing gastro-oesophageal junctional malignancy can lead to a similar constellation of clinical symptoms and manometric observations – termed ‘pseudoachalasia’ – and strong resistance to gastric intubation through the gastro-oesophageal junction during oesophagogastroduodenoscopy can raise suspicion (Ponds et al, 2017). A gastro-oesophageal junctional adenocarcinoma that involves the muscularis layer and Auerbach’s plexus while avoiding the inner mucosal or submucosal layers can result in a falsely negative oesophagogastroduodenoscopy (Moonka et al, 1999). Pseudoachalasia secondary to a gastro-oesophageal junctional tumour should be considered in older patients with a short duration of symptoms and substantial weight loss; these patients should undergo computed tomography (Figure 2) or endoscopic ultrasound (Ponds et al, 2017).

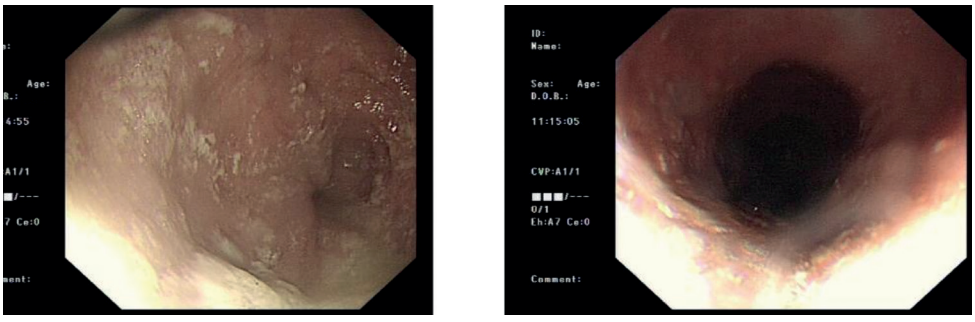

Figure 1. Oesophagogastroduodenoscopy showing a dilated oesophagus and tight lower oesophageal sphincter in a patient with achalasia.

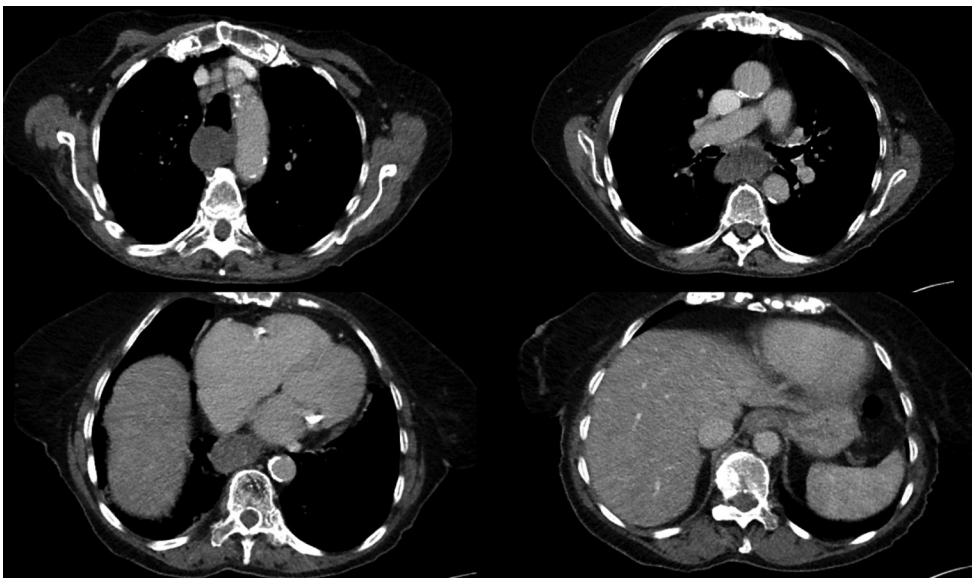

Figure 2. Computed tomography scan showing a dilated oesophagus that tapers down at the gastro-oesophageal junction.

Barium swallow

The characteristic 'bird beak' sign (Figure 3), with narrowing at the gastro-oesophageal junction and proximal oesophageal dilatation, is diagnostic for achalasia, but is only present in 50–70% of cases (Fisichella et al, 2008); this may reflect early referral, rather than a radiological shortfall.

Oesophageal manometry

Oesophageal manometry is the most accurate investigation for achalasia: an immotile oesophageal body with a hypertensive lower oesophageal sphincter confirms the diagnosis (Kahrilas and Boeckxstaens, 2013). The 'conventional' method involves the use of a device graduated with pressure sensors at 3–5 cm intervals used to capture the changes in

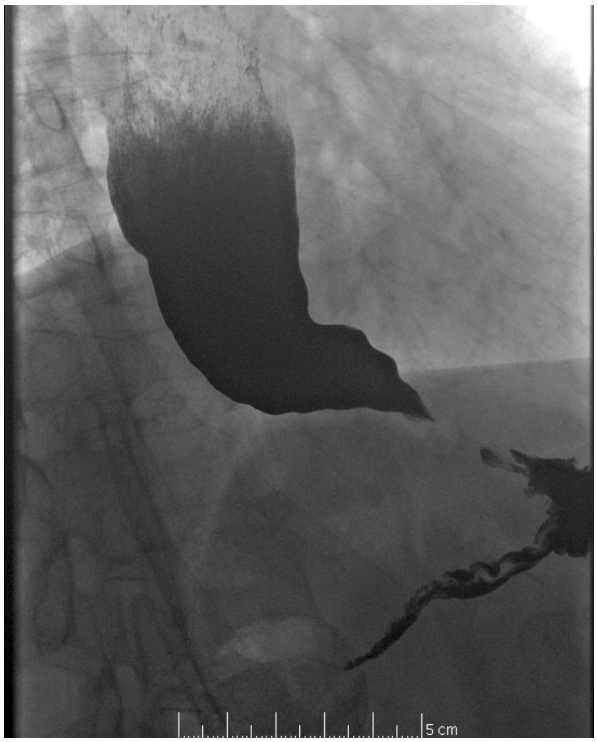

Figure 3. Contrast swallow with the characteristic 'bird beak' sign.

pressure along the length of the oesophagus, and the detection of aperistalsis and lower oesophageal sphincter hypertension following five wet swallows is considered diagnostic (Müller, 2015). The development of high-resolution manometry has substantially improved understanding and allowed greater characterisation of the various disorders of oesophageal motility (Pandolfino et al, 2008).

The development of the Chicago classification (Kahrilas et al, 2015) allowed stratification of three distinct subtypes of achalasia – types I, II and III. Type I, or 'classical' achalasia, is defined as the absence of peristalsis causing passive transit of food boluses down the oesophagus using gravity alone. Type II achalasia consists of panoesophageal pressurisation, whereby the entire oesophageal lumen enclosed between the upper and lower oesophageal sphincters is highly pressurised as a result of the simultaneous contraction of these sphincters and the oesophageal longitudinal muscle (Bredenoord et al, 2012). Type III, or 'spastic' achalasia, consists of premature distal oesophageal contractions (Kim et al, 2016).

A meta-analysis of nine studies involving 727 patients with achalasia undergoing either endoscopic or surgical treatment (Ou et al, 2016) suggested that type II has the most favourable prognosis after treatment, and type III the worst prognosis. However, the meta-analysis only used retrospective observational studies that specifically classified achalasia as per the Chicago classification, with variations in the definition of success – in particular, differences in length of treatment-free time – with or without the use of the Eckardt score as an objective qualifier of dysphagia-related symptoms. Nevertheless, the study supports use of the classification as a useful prognosticator of disease.

The superiority of high-resolution manometry over conventional manometry in the detection of achalasia remains uncertain. A multicentre randomised controlled trial by Roman et al (2016), involving 247 patients with dysphagia, showed that while a manometric diagnosis of achalasia was achieved in significantly more patients with high-resolution manometry, the initial manometric diagnosis was confirmed to be correct at 6 months post initial diagnosis in both arms and in similar proportion (89% high-resolution manometry vs 81% conventional, P=0.07). The multicentre nature of the study may yield inter-observer variability, which is often the case with conventional manometry (Fox et al, 2015). The higher detection rate of achalasia in the high-resolution manometry arm may be a result of greater randomisation of patients with achalasia in the high-resolution manometry arm, and it is thus unclear, despite the authors' claims, to what extent high-resolution manometry improves 'detection' of achalasia.

Treatment

There are no treatments that reverse the degeneration of the enteric nervous system that causes achalasia, and current treatments aim to reduce hypertonicity of the lower oesophageal sphincter (Krill et al, 2016) and provide symptomatic relief without pathological reflux. Patients should be advised that they are unlikely to be asymptomatic despite successful treatment. Therapeutic options fall into four main groups: lifestyle modification, medication, endoscopic intervention and operative intervention. Patients should be counselled about these strategies of ongoing management. The traditional idea of operative intervention being the mainstay of treatment has been questioned in recent years following randomised controlled trials.

Lifestyle modification

Patients should be informed and educated about their diagnosis so that they understand that they have a chronic health condition (Kalantari et al, 2021). Dietary modification, including chewing foods well, drinking with meals and eating frequent smaller meals, should be advocated. Patients should also be advised to have a softer diet and avoid spicy and acidic foods. Avoiding caffeine can also be considered, and patients should wait for 4 hours after their evening meal before sleeping.

Medication

Nitrates and calcium-channel blockers can be used to relax the lower oesophageal sphincter and assist in oesophageal emptying (Vaezi et al, 2013), although there is limited evidence of their efficacy. There is a dearth of good quality randomised controlled trials, and any demonstrated effect in non-randomised studies is accompanied with side effects such

as headache, peripheral oedema and hypotension (Wen et al, 2004). Their suboptimal therapeutic profiles mean that these are mainly used for patients unfit for any other definitive intervention. Antacid medication has no direct therapeutic benefit in patients with achalasia, but can be used to improve symptoms.

Endoscopic intervention

Endoscopic treatments for achalasia involve injecting botulinum toxin directly in the lower oesophageal sphincter, and forceful pneumatic dilatation of the cardia. Botulinum toxin can relax the lower oesophageal sphincter by inhibiting acetylcholine release from presynaptic nerve terminals in Auerbach's plexus (Qureshi, 2002) A multicentre randomised controlled trial by Annese et al (2000) involving 118 patients with achalasia demonstrated that injection of 100 units was sufficient to exhibit a therapeutic effect in 84% of patients, but almost 20% of these patients relapsed at 12 months, as might be expected as the effect of botulinum toxin wears off over time. A multicentre retrospective analysis (van Hoeij et al, 2017) of 657 procedures in 386 patients, 196 of whom had achalasia, found symptoms of chest pain and heartburn were the most common side effect at 6.6% of the cohort with achalasia. Acute mediastinitis was a rare (0.2%) but fatal consequence of treatment.

Pneumatic dilatation involves the use of polyethylene balloons to dilate the oesophagus at the lower oesophageal sphincter under fluoroscopic guidance, resulting in intentional impairment of the competence of the lower oesophageal sphincter (Arora et al, 2017). Pneumatic dilatation has been reported to be successful in 90% of cases in the initial phase (Vela et al, 2006) but these patients may relapse and require repeated procedures to remain in remission. The perforation rate is around 2% following pneumatic dilatation (Katzka and Castell, 2011) and this has implications for patient selection; pneumatic dilatation should be reserved for patients who are otherwise fit for surgery (in the event of perforation) who opt for an initial endoscopic approach. Pneumatic dilatation also increases the risk of reflux disease in up to 35% of patients and requires the use of a proton-pump inhibitor (Richter, 2008).

Leyden et al (2014) conducted a Cochrane review comparing the efficacy of both endoscopic treatments (pneumatic dilatation vs botulinum toxin), involving 178 patients across seven randomised controlled trials, and found that patients undergoing pneumatic dilatation were significantly more likely to be in remission longer (at 6 and 12 months) than patients undergoing botulinum toxin injection. It is arguable that the studies included in the review were underpowered, with the largest trial involving only sixty participants (Zhu et al, 2009), although this may be a consequence of the low prevalence of the condition. There was also heterogeneity in the definition of remission (differing between quantitative manometric measurement and the use of symptom scores), which makes comparison difficult. These findings suggest that pneumatic dilatation is the best non-surgical option, but patients who undergo surgical treatment having had previous endoscopic treatment are at greater risk of treatment failure and complications (Smith et al, 2006).

Operative intervention

Laparoscopic Heller's myotomy

Laparoscopic Heller's myotomy involves dividing the circumferential muscular layers of the lower oesophageal sphincter to lower the pressure at the cardia (Kahrilas et al, 2018). It has been reported to be successful in up to 94% of patients (Arora et al, 2017). The key complication is gastro-oesophageal reflux disease, but an anti-reflux procedure can reduce its incidence. A review of two meta-analyses, three randomised controlled trials and three prospective series studies by Mayo et al (2012) concluded that any fundoplication resulted in reduced reflux, but no specific fundoplication type was significantly superior, and those undergoing a total (Nissen's) fundoplication were more likely to report increased postoperative dysphagia (Mayo et al, 2012).

Laparoscopic Heller's myotomy was perceived to be better than endoscopic approaches in terms of longer remission and fewer relapses (Campos et al, 2009), but its superiority over pneumatic dilatation has been questioned. Operative intervention has been considered to be more complicated following endoscopic intervention, leading some centres to advocating surgery as the interventional treatment of choice. The European achalasia trial

showed no difference in Eckardt score, lower oesophageal pressure or quality of life in 201 patients randomised to either pneumatic dilatation or laparoscopic Heller's myotomy after 2 years' follow up (Boeckxstaens et al, 2011). A meta-analysis including four randomised controlled trials with 404 patients measuring the same outcomes also found no significant difference in either group (Bonifácio et al, 2019). However, the European trial and the studies in the meta-analysis predate the Chicago classification, thus the heterogeneity of the achalasia phenotype of patients in these studies may account for the reported lack of difference. Rohof et al (2013) found that when the Chicago classification was applied to patients enrolled in the European trial, type II patients had a more successful outcome with pneumatic dilatation and type III with laparoscopic Heller's myotomy. The sample size discrepancy between the two arms of the study (114 type II vs 18 type III) means that one should interpret the benefits of laparoscopic Heller's myotomy in people with type III achalasia with caution, and greater powered randomised controlled trials are needed to define the optimal treatment strategy.

Per-oral endoscopic oesophageal myotomy

Despite the safety of laparoscopic Heller's myotomy, a new endoscopic method has been used as a treatment alternative, or as an option in treatment failure, which occurs in up to 20% of patients undergoing laparoscopic Heller's myotomy (Fernández-Ananín et al, 2018). Per-oral endoscopic oesophageal myotomy involves intraluminal dissection of the lower oesophageal sphincter using an endoscopic approach (Barbieri et al, 2015). An advantage of this over laparoscopic Heller's myotomy is its minimally invasive nature, which may make it an attractive option for patients unfit for surgery. A meta-analysis by Barbieri et al (2015), including 551 patients across 16 studies, demonstrated a 93% success rate with a serious (requiring surgery) complication rate of 0.2%. This was echoed in a more recent meta-analysis of four randomised controlled trials by Rodríguez de Santiago et al (2019), who concluded that anterior and posterior myotomy were equivocal in terms of success rate, but with a lower incidence of complications and shorter incision closure time for posterior myotomy.

However, when compared to laparoscopic Heller's myotomy as definitive treatment, pathological gastro-oesophageal reflux disease is a greater concern following per-oral endoscopic oesophageal myotomy. Schlottmann et al (2018) conducted a meta-analysis analysing resolution of dysphagia and incidence of gastro-oesophageal reflux disease across 53 studies detailing laparoscopic Heller's myotomy and 21 detailing per-oral endoscopic oesophageal myotomy and found the incidence of postoperative gastro-oesophageal reflux disease was significantly higher with per-oral endoscopic oesophageal myotomy. The meta-analysis is flawed by the extraction of data from separate retrospective studies, which can make direct comparison difficult, but the absence of an anti-reflux procedure in patients undergoing per-oral endoscopic oesophageal myotomy is a plausible explanation for the increased incidence of gastro-oesophageal reflux disease.

Oesphagectomy

About 5% of patients progress to end-stage disease despite failed surgical myotomy and multiple endoscopic dilatations. In these patients, oesophagectomy (with either a gastric pull-up or colonic interposition) should be considered for definitive treatment (Aiolfi et al, 2018). The studies included in the meta-analysis by Aiolfi et al (2018) reported resolution of a normal diet in 75–100% cases postoperatively, but there remains a significant risk of postoperative morbidity, with complications including pneumonia and anastomotic leak.

Conclusions

Achalasia is an uncommon condition characterised by the absence of peristalsis and failure of relaxation of the lower oesophageal sphincter. Symptoms range in severity and can be classified using the Eckardt classification. Achalasia is caused by degeneration of enteric neurons within the oesophageal wall and tends to result in dysphagia. Investigation typically includes oesophagogastroduodenoscopy, barium swallow and oesophageal manometry, with the latter the investigation of choice for diagnosis.

Key points

- Achalasia is an uncommon condition characterised by the absence of oesophageal peristalsis combined with failure of relaxation of the lower oesophageal sphincter.
- Causative factors are poorly understood, but include immune, allergic, viral and genetic aetiological components.
- Diagnosis is dependent on oesphagogastroduodenoscopy, barium swallow and oesophageal manometry, with the latter considered most definitive.
- Treatment aims to reduce the severity of symptoms and includes lifestyle modification, medicine and both endoscopic and operative intervention.

Treatment includes lifestyle medication, medical management and both endoscopic and operative interventions: there has been a shift away from operative management as long-term outcomes from endoscopic and operative intervention seem equivocal. Patients should be fully informed of their condition and counselled as to any intervention. Treatments focus on the effects of the disease (hypertensive lower oesophageal sphincter) rather than the underlying aetiology, which remains an area of continued research. The resolution of symptoms and overall prognosis appears to depend on the distinct achalasia subtype.

Author details

[1]Department of General Surgery, The Great Western Hospital, Swindon, UK

Conflicts of interest

The authors declare that there are no conflicts of interest.

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