Section A-Research paper

Achalasia; Overview Pathophysiology, and Management

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Abstract

Background: Achalasia is defined as the presence of esophageal outflow obstruction due to impaired relaxation of the LES with absent or spastic contractions in the esophageal body in the absence of structural obstruction in the esophageal body or esophagogastric junction (EGJ). The clinical manifestations of achalasia are a consequence of obstruction in esophageal transit owing to abnormal swallow-induced LES relaxation. Incomplete LES relaxation and abnormal esophageal body peristalsis can also be seen in pseudoachalasia, which needs to be distinguished from achalasia. Diagnosis of achalasia requires recognition of presenting symptoms as well as appropriate use and interpretation of diagnostic testing. The treatment of achalasia is palliative, and its main goal is to eliminate the functional obstruction caused by the non-relaxing and often hypertensive LES, thus improving the emptying of the esophagus into the stomach. Treatment modalities are Endoscopic (PD, botulinum toxin injection [BTI] of the LES, POEM) and Surgical (LHM with partial fundoplication). Medications are of very limited value.

Keywords: Achalasia

Introduction

Achalasia is defined as the presence of esophageal outflow obstruction due to impaired relaxation of the LES with absent or spastic contractions in the esophageal body in the absence of structural obstruction in the esophageal body or esophagogastric junction (EGJ) ***(Vaezi M. et al., 2020).***

The clinical manifestations of achalasia are a consequence of obstruction in esophageal transit owing to abnormal swallow-induced LES relaxation. Incomplete LES relaxation and abnormal esophageal body peristalsis can also be seen in pseudoachalasia, which needs to be distinguished from achalasia ***(Gergely M. et al, 2021).***

Epidemiology

Achalasia has been regarded as an uncommon disorder with an annual incidence of approximately 1.6 cases per 100,000 individuals and prevalence of 10 cases per 100,000 individuals ***(Sadowski D. et al., 2010).*** Although epidemiologic data on achalasia are limited, its frequency appears to be rising, with one study suggesting that, from 2004 to 2014, the incidence and prevalence of achalasia in central Chicago were two- to threefold greater than estimates from earlier years would have predicted ***(Samo S. et al, 2017).***

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A 2021 US study suggested that incidence and prevalence could be higher than previously thought, with incidence of 10 and 26 per 100,000 individuals, and prevalence of 18 and 162 per 100,000 individuals in ***(Gaber C. et al., 2022).***

Achalasia can occur at any age, but incidence and prevalence increase with age, and the mean age at diagnosis is >50 years. Incidence (and prevalence in men and women are similar ***(Van Hoeij F. et al., 2018).***

Pathophysiology

In achalasia, the pharyngeal swallow effort and proximal esophageal peristalsis are generally normal, as the disease primarily affects LES relaxation, with compromising consequences on coordination and strength of

distal esophageal circular muscle function and impaired contractility of longitudinal muscle layers. Thus, swallowed boluses traverse the pharynx and upper part of the esophagus without difficulty, arriving in the non-functioning lower two-thirds of the esophagus, which dilates and retains content because of insufficient contractile emptying force and an obstructing non-relaxing LES. In early achalasia, retained esophageal muscle tone and hydrostatic forces generated by the ingested bolus can overcome the sphincteric resistance such that LES obstruction is incomplete and adequate nutrition is maintained; however, the esophagus never completely empties. In later disease stages, emptying comprises only a small stream of fluid seeping through the obstructed, closed sphincter ***(Gregersen, H. & Lo K. 2018).***

The core patho-physiological abnormality in achalasia is loss of predominantly inhibitory nerve control of the esophagus, leading to esophageal outflow obstruction from loss of swallow-induced relaxation of LES, and loss of or abnormal esophageal body peristalsis. Symptoms are a consequence of this obstructive effect, which leads to progressive dilation of the esophageal lumen over time. Histopathological analysis shows inflammation and depletion of esophageal ganglia and neurons in early achalasia and replacement with fibrosis in later stages of achalasia. End-stage achalasia results in a dilated, sigmoid-shaped esophagus that may not empty even if the LES is open from adequate therapeutic disruption ***(Savarino E. et al, 2022).***

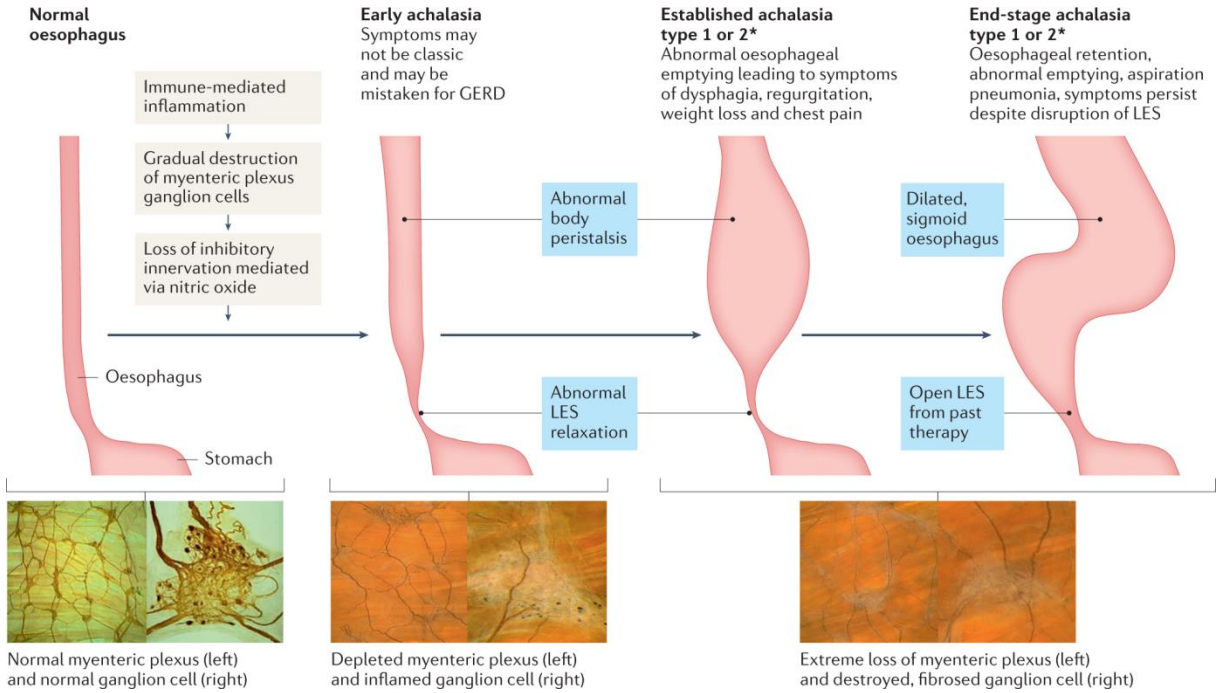


Fig (1): Pathophysiological abnormality in achalasia *(Savarino E. et al, 2022).*

Ganglion cell loss

The enteric nervous system is distributed along the gastrointestinal tract, including the esophagus. The myenteric plexus is situated between the circular and longitudinal smooth muscle layers of the gut and consists of postganglionic neurons that differentiate into excitatory cholinergic neurons and inhibitory nitrogenic neurons. While the excitatory neurons release acetylcholine, the inhibitory neurons release the free radical NO and the neurotransmitter/anti-inflammatory cytokine VIP; the coordinated release creates the balance of relaxation and contraction that is vital for normal esophageal peristalsis ***(Patel D. et al., 2015).***

Achalasia is known to be caused by the reduction of interstitial cells of Cajal, but most importantly to a selective loss of inhibitory ganglion in the myenteric plexus of the esophagus, which is associated with a decrease of NO and VIP. Human studies have suggested a significantly decreased or absent NO innervation

in the myenteric plexus of patients with achalasia. Immunohistochemical studies of biopsies from patients with achalasia who underwent surgical treatment showed that levels of the VIP, nNOS, neural proteins, S-100, substance P and protein gene product 9.5 (PGP9.5) were significantly lower than in healthy individual ***(Gockel I. et al., 2008).***

Esophageal myenteric neurons degeneration is attributed to confirmed cell-mediated and possible antibody-mediated mechanisms, thus achalasia is considered an autoimmune disease. Autoimmune disorders, including Sjögren syndrome, type 1 diabetes mellitus and hypothyroidism, are frequently encountered in patients with achalasia, supporting autoimmune mechanisms in achalasia pathophysiology ***(Sara C. et al, 2021).***

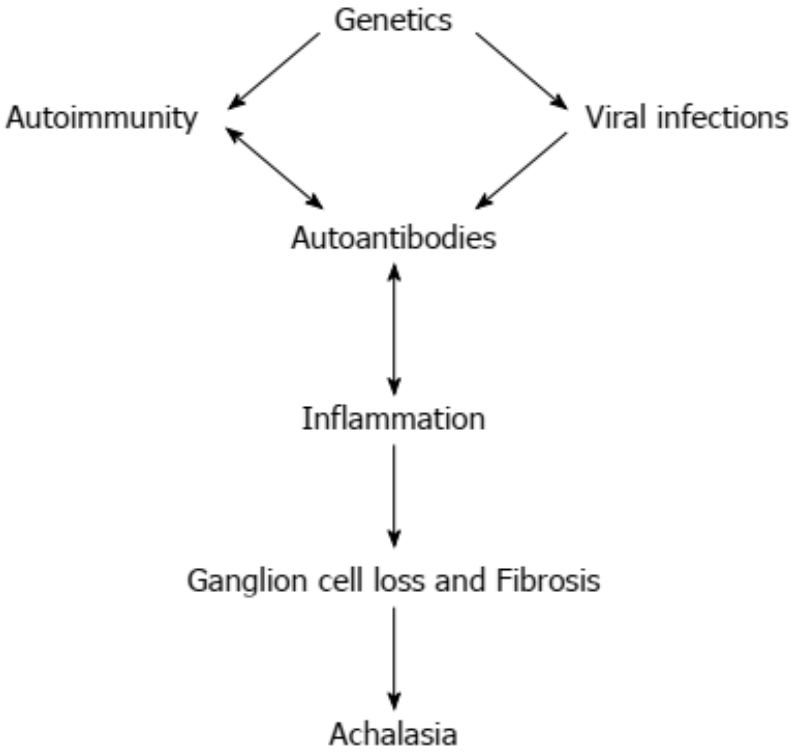


Fig (2): Main mechanisms in the etiopathogenesis of achalasia *(Furuzawa-Carballeda, J. et al., 2016).*

In a large European cohort of patients with idiopathic achalasia, comorbid allergic and autoimmune disorders, as well as viral infections (in particular with varicella zoster virus) before symptom onset, were observed ***(Becker J. et al., 2016).***

Genetic predisposition also has a role, as an eight-amino-acid insertion in the cytoplasmic tail of HLA-DQβ1 is a risk factor for achalasia ***(Furuzawa-Carballeda, J. et al., 2018).*** Thus, loss of myenteric plexus neurons involves **autoimmunity**, **viral infection** and **genetic predisposition** ***(Savarino E. et al, 2022).***

Genetic factors

Many studies implemented on immunogenetics underlying achalasia and revealed presence of specific alleles on the human leukocyte antigen (HLA) complex predisposing to achalasia. Reports on HLA mainly show an association between HLA-DQ, including HLA-DQw1, HLA-DQA1, and HLA-DQB1 and achalasia, including HLA-DQw1, HLA-DQA1, and HLA-DQB1. Among them, HLA-DQB1 is the most commonly reported ***(Wu X. et al., 2021).***

A specific study in 2014 performed Immunochip genotyping in 1 068 cases with achalasia and 4 242 controls from Europe, covering 196 524 single nucleotide polymorphisms (SNPs). The authors reported an

8-residue insertion in the HLA-DQB1 gene (encoded by HLA-DQB1*05:03 and HLA-DQB1*06:01) presenting the strongest risk for achalasia. HLA-DQB1*03:01 and HLADQB1*03:04 may independently be related to the risk of achalasia ***(Gockel I. et al, 2014).***

Autoimmunity

When autoimmune disease occurs the immune system releases proteins called autoantibodies that mistakenly attack healthy cells. Studies conducted on autoantibodies in patients with achalasia have led the researchers to doubt its possibility of being an autoimmune disease. Autoantibodies against M2-muscarinic acetylcholine receptors (M2 mAChR) have been reported in achalasia patients with chronic Chagas disease. The results showed a strong connection between the prevalence of circulating anti-M2 mAChR antibodies and the presence of achalasia in such patients. Thus, the test for autoantibodies was further narrowed down to patients with achalasia ***(Goin J. et al, 1999).***

Recently, a study demonstrated the significant prevalence of antiganglionic acetylcholine receptor (anti-gAChR) antibodies in patients with achalasia ***(Mukaino A. et al, 2018).*** In another study, ***Latiano et al*** reported that serum anti-neuronal autoantibodies were positive in 24.4% of the patients with achalasia by indirect immunofluorescence ***(Latiano A. et al, 2006).***

Other studies have investigated the relationship between autoimmune diseases and achalasia, showing that autoimmune diseases such as hyperthyroidism and rheumatoid arthritis are more prevalent in those with achalasia ***(Romero‐Hernández F. et al., 2018).***

Viral infection

It is still not known what factor triggers the T cell-mediated infiltration and attacks on these neurons. Viral infection has been speculated to be the main cause based on preliminary clues ***(Pressman A. & Behar J., 2017).***

Unfortunately, determinate evidence still lacks although a potential role of viral infection in other motility disorders has been reported. The possible mechanism is that antibody-mediated demyelination caused by viral infection damages peripheral and autonomic nerves, which suggests that viruses can trigger the autoimmune reactivity. Based on existing evidence, potential achalasia-related viruses mainly include herpes simplex virus (HSV)-1, varicella-zoster virus (VZV), measles, mumps, and humanimmunodeficiency virus (HIV). Chagas disease, caused by an infection of Trypanosoma cruzi, is similar to the pathophysiological progression of achalasia ***(Wu X. et al., 2021).***

Clinical Presentation

Achalasia can initially present with a variety of symptoms (Table 1) that impair a patient's quality of life, work productivity, and functional status ***(Patel D. & Vaezi M., 2016).***

Table 1: Frequency of Achalasia symptoms *(Patel D. & Vaezi M., 2016)*

Presenting Symptom	Frequency
Dysphagia	**82%-100%**
Regurgitation	**76%-91%**
Weight loss	**35%-91%**
Chest pain	**25%-64%**
Heartburn	**27%-42%**
Nocturnal cough	**37%**
Aspiration	**8%**

Classically, achalasia presents as progressive dysphagia to solids and liquids. Heartburn may present in 27% to 42% of patients with achalasia, and, thus, patients are frequently misdiagnosed with gastroesophageal reflux disease (GERD) and treated with proton pump inhibitor (PPI) therapy. An incorrect GERD diagnosis often leads to a significant delay in diagnosing achalasia, until patients have persistent symptoms that eventually lead to the correct diagnostic studies ***(Patel D. et al, 2017).***

The exact mechanism underlying chest pain remains unclear but could include fermentation of food retained in the esophagus to acidic by products that stimulate chemoreceptors, stasis-related esophageal

inflammation, spastic and discoordinated smooth muscle contraction and/or esophageal hypersensitivity ***(Vaezi M. et al., 2020).***

The Eckardt score quantifies the four cardinal achalasia symptoms (dysphagia, regurgitation, chest pain and weight loss) using a 4-point grading system (Table 2), in which a score of ≤ 3 quantifies adequate treatment outcome. It is useful to record the Eckardt score at initial achalasia diagnosis as a measure of symptom severity ***(Patel D. et al., 2017).***

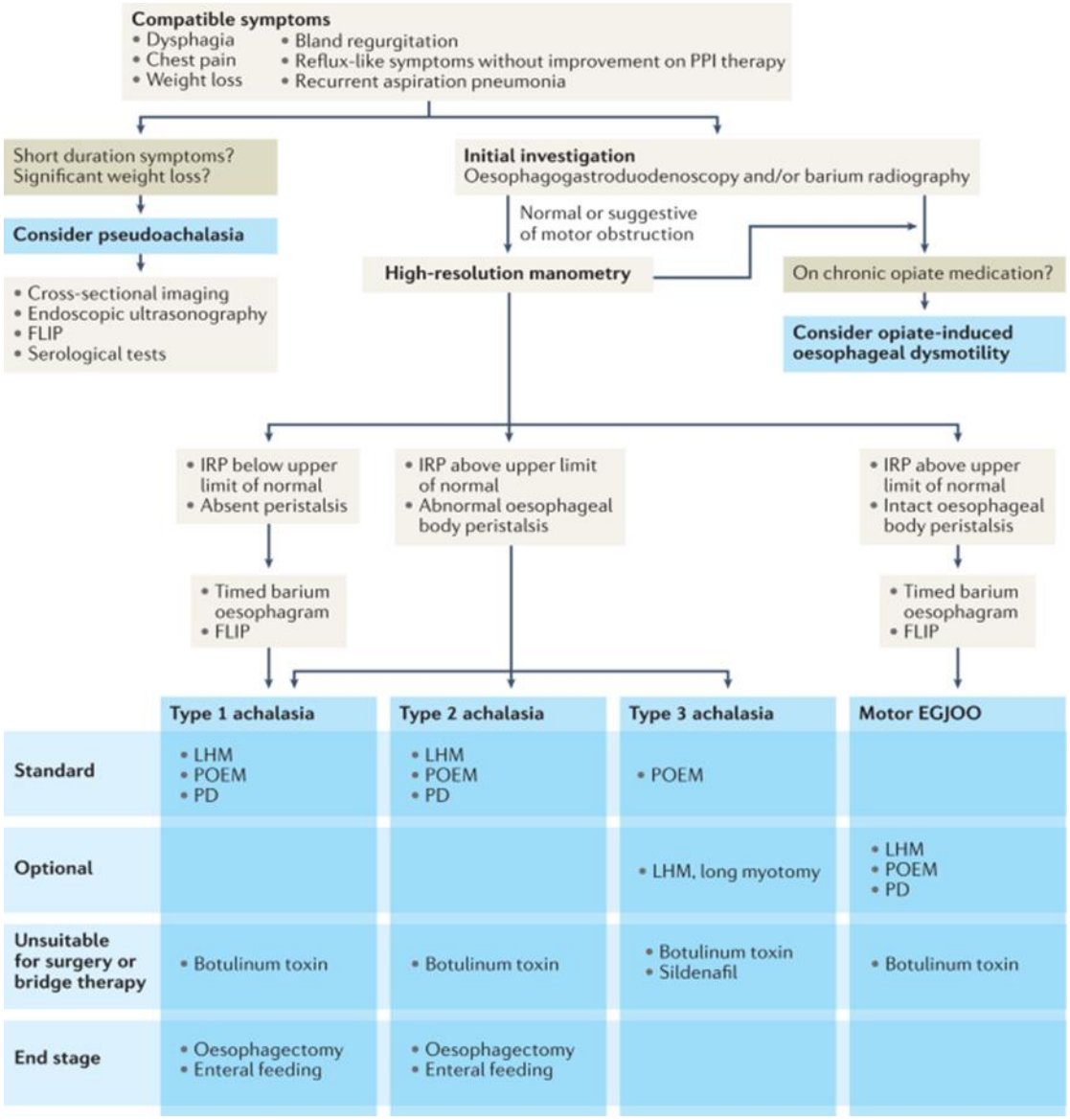
Table 2: The Eckardt score (Eckardt, V. et al., 1992)

Symptoms	**Score**			
	0	**1**	**2**	**3**
Dysphagia	None	Occasional	Daily	Every meal
Regurgitation	None	Occasional	Daily	Every meal
Chest pain	None	Occasional	Daily	Every meal
Weight loss (kg)	None	Less than 5	5-10	More than 10

Diagnostic modalities

Diagnosis of achalasia requires recognition of presenting symptoms as well as appropriate use and interpretation of diagnostic testing ***(Savarino E. et el., 2022).***

Table 3: Diagnostic and management algorithm for achalasia *(Savarino E. et el., 2022)*



The integrated relaxation pressure (IRP), Functional lumen imaging probe (FLIP), Pneumatic Dilation (PD)) or myotomy (laparoscopic Heller myotomy (LHM) or per-oral endoscopic myotomy (POEM))

Upper endoscopy

Dysphagia is considered an alarm symptom that mandates theperformance of esophago-gastro-duodenoscopy (EGD) as an initial diagnostic modality to exclude structural or mucosal lesions in the esophagus or the stomach cardia. Examples of these include tumors, inflammation, esophageal rings, strictures, and other pathologies that can mimic achalasia, a condition traditionally named pseudochalasia. A clinical suspicion of pseudo-achalasia should be sought in patients older than 55 years of age with a prompt onset of solid dysphagia that proceeds to liquid dysphagia and weight loss ***(Mari A. et al, 2019).***

Classic endoscopic findings of achalasia present in about half of the cases include widening of the esophagus, residue in the esophageal lumen, and obstructed EGJ ***(Mari A. et al., 2021).***

Barium Swallows

Barium esophagography has commonly been used to evaluate esophageal morphology prior to surgery. Recently, the timed barium swallow (TBS) has been used to assess treatment success by evaluating esophageal emptying. Measurement of the retained barium column at several time points after the swallow has been accepted as a reliable tool to objectively assess the level of obstruction at the esophagogastric junction. Moreover, barium emptying studies have gained special popularity in the post treatment period, and they correlate well with treatment response ***(Rohof W. et al., 2013).***

TBS has several advantages: it is simple, practical, reproducible, economic, non-invasive and well-tolerated by patients. A latest work by Sanagapali et al. that aimed to study the role of barium surface area compared with the traditional barium column as an indicator of treatment response revealed that barium surface area decrease predicted a more precise treatment response ***(Sanagapalli S. et al., 2020).***

Manometry

Achalasia is diagnosed on the basis of manometric demonstration of abnormal LES relaxation and aperistalsis. HRM is the modern standard for this assessment and is easier to perform than conventional manometry.HRM uses a classification scheme termed the Chicago classification to define disorders of EGJ function and oesophageal peristalsis, which was revised and updated in 2021, as mentioned in chapter 1***(Yadlapati R. et al., 2021).***

Whenever possible, HRM should be performed in the absence of opioid or other medications that may alter oesophageal motility. The key metric for adequacy of LES relaxation is the integrated relaxation pressure (IRP), which describes nadir LES pressures over 4 s during a 10 s window that includes swallow-induced LES relaxation. The sensitivity of the IRP over the upper limit of normal was 98% for a diagnosis of abnormal LES relaxation, with a specificity of 96% ***(Ghosh, S. et al., 2007).***

In addition to abnormal LES relaxation, oesophageal smooth muscle contraction is considerably altered in achalasia, including absence of peristaltic contractions, although premature or spastic contractions can also occur. The pattern of pressurization or contraction within the smooth muscle oesophageal body determines achalasia subtypes, which has implications for disease management ***(Pandolfino J. et al., 2008).***

Absence of peristalsis without pressurization is seen in type 1 achalasia, in which the IRP may be manometrically normal in some instances, and alternative tests are needed to confirm achalasia in the presence of compatible symptoms ***(Ponds F. et al., 2017).***

Pan-oesophageal pressurization in ≥20% of supine water swallows defines type 2 achalasia, which has the best management outcomes among all achalasia subtypes ***(Rohof W. et al., 2013).***

Contractility is retained in type 3 achalasia, but peristalsis is not normal; premature and/or spastic contractions are seen in ≥20% of the swallows ***(Yadlapati R. et al., 2021).***

Functional lumen imaging probe (FLIP)

In the past 5 years, the FLIP, an endoscopic device consisting of a distensible balloon containing a catheter with several pairs of electrodes and a pressure sensor that simultaneously measures the cross-sectional area and pressure within a hollow viscus, has become a valuable complementary tool in the diagnosis of EGJ obstruction ***(Savarino E. et al, 2020).***

This advanced imaging system is able to study the biomechanical properties of luminal organs, in particular, the oesophagus and the EGJ. EGJ distensibility measured using FLIP can reliably diagnose achalasia even when EGJ relaxation is manometrically normal ***(Carlson, D. et al., 2016).***

Achalasia types

CCv4.0 continued upon prior versions by subtyping achalasia into type I, type II, and type III on HRM. **Type I achalasia** having 100% failed peristalsis without panesophageal pressurization (PEP), **Type II achalasia** with PEP in at least 20% of swallows, and **Type III achalasia** having at least 20% of swallows premature with no appreciable peristalsis .Table 4 concluded the conclusive and in conclusive diagnosis of achalasia ***(Khan A. et al, 2021).***

Type I achalasia has historically been termed the classic presentation of achalasia, and is typically a later state of disease progression than type II achalasia, with progressive functional neuronal cell loss of both the myenteric ganglion cells of the distal esophagus and LES, leading to moderate to severe esophageal dilation of the esophageal body on barium studies ***(Pandolfino J. & Gawron A., 2015).***

Type II achalasia is considered an earlier stage of disease than type I achalasia, and continues to be the most common subtype seen on HRM. Pathophysiologic studies have shown that the simultaneous pressurization in type II achalasia is due to a cavity pressure in which there is an absence of luminal contact during the pressure deflection. Further evidence details that this cavity pressure may be from non-lumen obliterating

circular muscle contraction and possibly longitudinal muscle contraction that cause reduction in lumen size and/or volume, as opposed to sole pressure from bolus trapping ***(Park S. et al.,2018).***

Type III achalasia is the least common subtype of the disease, and may reflect a different pathophysiologic consequence than the other subtypes, with less evidence of progressive neuronal cell loss of the myenteric ganglion cells of the distal esophagus and LES ***(Rieder E et al., 2020).*** There is pathophysiologic evidence that these spastic contractions in type III achalasia are not always truly simultaneous, but the motor pattern in the distal esophagus still results in early luminal closure and resistance to passage of bolus flow ***(Kim, T. et al., 2016).***

Table 4: conclusive and in conclusive diagnosis of achalasia *(Khan A. et al, 2021).*

Type I achalasia	A conclusive diagnosis is : an abnormal median IRP and absent contractility (100% failed peristalsis)
	An inconclusive diagnosis includes absent contractility with no appreciable peristalsis in the setting of IRP values at the upper limit of normal in both positions, with or without panesophageal pressurization in 20% or more swallows
Type II achalasia	A conclusive diagnosis is : an abnormal median IRP and absent contractility (100% failed peristalsis) with panesophageal pressurization in 20% or more swallows
	An inconclusive diagnosis includes absent contractility with no appreciable peristalsis in the setting of IRP values at the upper limit of normal in both positions, with or without panesophageal pressurization in 20% or more swallows
Type III achalasia	A conclusive diagnosis is : an abnormal IRP and evidence of spasm (20% or more swallows with premature contraction) with no evidence of peristalsis
	An inconclusive diagnosis of type III achalasia includes an abnormal IRP with evidence of spasm and evidence of peristalsis. If these cases fulfill strict criteria for EGJOO (as detailed in the EGJOO section) these patients should be classified as EGJOO with spastic features, which may represent an achalasia variant.

Treatment of achalasia

The treatment of achalasia is palliative, and its main goal is to eliminate the functional obstruction caused by the non-relaxing and often hypertensive LES, thus improving the emptying of the esophagus into the stomach. Treatment modalities are **Endoscopic** (PD, botulinum toxin injection [BTI] of the LES, POEM) and **Surgical** (LHM with partial fundoplication). **Medications** are of very limited value ***(Schlottmann F. & Patti M., 2018).***

Endoscopy

POEM

In 2010, Dr. Inohue published the first report of a new and revolutionary endoscopic technique for the treatment of achalasia –POEM. The outcome in the first 17 patients was outstanding, as every patient experienced a significant improvement of the dysphagia. This report opened a new era in the treatment of achalasia ***(Inoue H. et al., 2010).***

Pneumatic Dilation (PD)

The goal of PD is to eliminate the functional obstruction at the level of the gastroesophageal junction by disrupting the circular muscle fibers of the LES. PD is typically an outpatient procedure. Patients are asked to stay on a liquid diet for 2 days prior to the procedure and to take nothing by mouth for 12 h before the endoscopy.The balloon is positioned under fluoroscopic guidance

over a wire so that the 'waist' caused by the non-relaxing LES applies pressure on the centerof the distending balloon. When the correct position of the balloon is confirmed, the balloon is progressively inflated, aiming at obtaining a progressive and controlled tearing of the muscle fibers, which usually occurs with distention pressures of 8–15 psi. The first PD session should be performed by using a 30-mm Rigiflex balloon. Larger balloons – 35 and 40 mm in diameter – should be used 2–4 weeks later if symptoms persist. If dysphagia recurs after a PD with a 40- mm balloon, the response to further PDs is unlikely ***(Schlottmann F. & Patti M., 2018).***

After the procedure, patients should be observed for a few hours, to monitor for chest pain, fever, shortness of breath, and signs of a perforation such as subcutaneous emphysema. If a perforation is suspected, a gastrografin study eventually followed by a barium esophagogram should be performed. If the recovery is uneventful, the patient is given liquids and eventually is discharged home. Significant predictors of a favorable outcome are LES pressure after dilatation, older age, female gender, and type II achalasia according to the Chicago classification. Post-dilatation LES pressure has been considered the single most important factor for predicting the long-term clinical response.The goal of PD is to achieve a LES pressure of less than 10 mmHg. Young males have a worse outcome than females. In addition, age younger than 40 years, irrespective of gender, also predicts a poor response to PD ***(Vaezi M. et al, 2013).***

Botulinum toxin injection

Injection of botulinum toxin into the LES is a short-term option for symptom relief or until more-durable therapies can be administered ***(Weusten B. et al., 2020).***

Botulinum toxin impairs acetylcholine release, leading to inhibition of contraction of LES smooth muscle fibres, thereby lowering LES tone. A statistically significant decrease in average LES pressure from 38.23 mmHg (range 34.40–42.06 mmHg) before the procedure to 23.30 mmHg (range 20.79–25.81 mmHg) after botulinum toxin injection ($P < 0.01$) has been demonstrated. Botulinum toxin injection can improve achalasia symptoms by decreasing LES pressure and improving oesophageal emptying, but the duration of benefit is short (median 6–9 months), necessitating repeated injection to maintain benefits. ***(Khashab M. et al., 2020).***

Surgical

Laparoscopic Heller myotomy

Heller myotomy was introduced as an open surgery more than a century ago, but the procedure has evolved to laparoscopic Heller myotomy (LHM), which comprises an anterior cardiomyotomy that disrupts both circular and longitudinal muscle fibres up to 5–7 cm proximally from the EGJ and at least 2 cm onto the gastric cardia ***(Savarino E. et al., 2022).***

Of note, a partial anterior or partial posterior fundoplication is routinely performed as part of LHM, primarily because a randomized controlled study found objective reflux in 48% of patients without a fundoplication compared with 9% with a partial fundoplication at LHM after 3–5 months of follow-up***(Richards W. et al., 2004).***

LHM has excellent efficacy, with an improvement in symptom scores in >90% and high satisfaction in >90% of patients for up to 5 years after the procedure ***(Ortiz A. et al., 2008).***

The procedure has a high safety profile in carefully selected patients. Potential complications include mucosal perforation, splenic injury, pneumothorax and incisional bleeding. A large single-centre series of 400 patients reported morbidity and mortality rates of 2% and 0%, respectively, and an initial failure rate of 10% ***(Zaninotto G. et al., 2008).***

Medical therapy

Oral pharmacological therapy

Calcium channel blockers, nitrates, anticholinergics and phosphodiesterase inhibitors have been used for treating achalasia in small number of patients. Although these agents can reduce LES pressure and temporarily relieve dysphagia, they do not improve oesophageal peristalsis or enhance LES relaxation ***(Oude Nijhuis, R. et al., 2020).***

Conflicts of Interest: The authors declare no conflict of interest.

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