

Achalasia: A Review of Etiology, Pathophysiology, and Treatment

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ABSTRACT

Achalasia was a condition marked by peristaltic movement absent in lower esophageal sphincter and segment that hypertonic result in imperfect relaxation during food ingestion. Achalasia incidence did not differ between men and women, account for 1 in 100,000 people every year with prevalence of 10 in 100,000 people, unrelated specifically with ethnic, and has its highest incidence on 30-60 age group.

Based on its etiology, it was divided into primary and secondary Achalasia, while based on its motility, it was into hypermotil, hypomotil, and amotil achalasia. Until present, several therapeutic modalities were available to treat Achalasia, among them was pharmacology therapy, botulinum toxin injection via endoscopy, pneumatic dilatation, Heller myotomy surgery, and per oral endoscopy myotomy (POEM).

Keywords : *achalasia, patophysiology, therapy*

ABSTRAK

Akalasia merupakan suatu keadaan yang ditandai dengan tidak adanya peristaltik di esofagus bagian bawah dengan spingter esofagus bagian bawah (LES) yang hipertonic sehingga tidak terjadi relaksasi sempurna saat menelan makanan. Angka kejadian akalasia pada perempuan dan laki laki adalah sama, yaitu 1 dari 100.000 orang per tahun dengan prevalensi 10 pada 100.000 orang, tidak didapatkan pada ras khusus dan angka kejadian tertinggi pada usia 30-60 tahun.

Berdasarkan etiologi terdapat dua jenis akalasia, yaitu primer dan sekunder sedangkan berdasarkan motilitas terdapat tiga jenis akalasia, yaitu akalasia hipermotil, akalasia hipomotil, dan akalasia amotil. Hingga saat ini, terdapat beberapa modalitas terapi akalasia, antara lain intervensi farmakologi, injeksi toksin botulinum per endoskopi, dilatasi pneumatik, bedah Heller myotomy, dan Per Oral Endoscopy Myotomy (POEM).

Kata kunci : *akalasia, patafisiologi, terapi*

INTRODUCTION

Achalasia was firstly describe by Sir Thomas Willis in 1674 after he use whale bone to dilate his patients esophagus because of lower esophageal sphincter relaxation failure. Achalasia was progressive idiopathic neural degeneration of Auerbach myenteric plexus,

result in food static during ingestion and esophagus dilatation. This condition will lead to several symptoms and complication, depend on its severity and duration.^{1,2} Some Literatures said that Achalasia was a primary disorder of esophagus with relaxation insufficiency of lower esophageal sphincter as its etiology, with

radiographic findings of aperistaltic esophagus with minimal openings, called bird-beak sign.³

Incidence of Achalasia in men and women was similar, account for 1 from 100,000 people every year with prevalence of 10 in 100,000 people, did not specific for some ethnics, and highest incidence was found in 30-60 age groups. In US, 2000 cases of Achalasia was reported every year, mostly at 25-60 age groups, and rarely found in children. Otherwise, in Gastroentero-hepatology division, Internal Medicine Department, Faculty of Medicine, University of Indonesia/Dr. Cipto Mangunkusumo Hospital, 48 cases was found during 5 years period (1984-1988), mostly with the same age groups.^{2,3} Achalasia was not a rare condition. This could be seen in middle-aged population, clinically marked with dysphagia, regurgitation, and epigastric discomfort. Clinically, Achalasia was divided into primary and secondary, based on its etiology.^{2,3}

American collage Gastroenterology Clinical Guideline in Diagnosis and Management of Achalasia in 2013 recommended barium esophagogram to assess esophageal emptying, esophagogastric junction morphology both during gastric emptying and to evaluate its motility. Endoscopy procedure to see gastroesophageal junction and gastric cardia was recommended in all patients with Achalasia to eliminate the possibility of pseudoachalasia.³ If irreveribe functiona disorder happened, the main therapy for Achalasia was palliative treatment. Dominant symptoms of this disorder was progressive dysphagia, regurgitation, chest pain, and weight loss.³

ETIOLOGY

Achalasia was divided into primary and secondary Achalasia. In primary Achalasia, the exact etiology is unknown, probably caused by neutropic virus infection result in dorsal vagal nucleus lesion in brainstem and mesenteric ganglia in esophagus. Hereditary factor also has a role in this disorder. Otherwise, secondary Achalasia was caused by infection, intraluminal tumor such as cardia tumor, extraluminal pressure from pancreatic pseudocyst, anticholinergic drugs, or post vagotomi operation.²

PATHOPHYSIOLOGY

Esophagus main function is to deliver food ingested from faring to stomach by peristaltic movement ranged from 5-15 seconds. In upper and lower part of esophagus, a sphincter was important for gastric

acid reflux barrier to esophagus, and normaly in tonic or constriction state, except during food ingestion. Esophagus mucosa was base and not suitable for acid from gastric secretion. Submucosal layer has secretory cells which produce mucus in order to help food movement during ingestion process.⁴

At normal state, esophagus shown two types of peristaltic: primary peristaltic and secondary peristaltic. Primary peristaltic was only a movement following previous peristaltic movement in faring and continuing to esophagus during ingestion process. This movement period start from faring to stomach was estimated for 8 to 10 seconds. But, food ingestion durin erect position result in faster food movement, about 5-8 seconds, because of gravity effect. If primary peristaltic movement fail to push all the food into stomach, secondary peristaltic movement than started. This movement start from mienteric nerve and several reflexes from afferent vagal nerve, from esophagus to medulla than back to esophagus.⁴

In the lower part of esophagus, about towo to five centimeter above stomach, esophageal circular muscle functioned as gastroesophageal sphincter. Anatomically, this sphincter was not differ to other esophagus parts. Physiologically, sphincter will have tonic constriction (with intraluminal pressure of 30 mmHg), differ from middle esophagus which in normal condition was in relaxation state. When peristaltic movement during ingestion process pass esophagus, receptive relaxation process will relax lower esophageal sphincter before peristaltic movement and allow food to enter stomach. Rarely, sphincter does not relax, so that the condition called Achalasia happened.⁴

CLINICAL MANIFESTATION

Dysphagia of both solid and liquid food was the most common symptoms of achalasia, followed by regurgitation, chest pain, nausea, vomiting, weight loss, and night cough. Otherwise, chest pain was the main symptoms of gastroesophageal reflux disease (GERD) caused by esophagus irritation from gastric acid. In patients with Achalasia, this symptoms could be caused by gastric acid retention or toxin produced by fermented lactate by bacteria in esophagus.³

Achalasia was divided into three types (Figure 1) based on its motility. First type is hypermotile Achalasia, a vigorous Achaalasia, with pain dysphagia and regurgitation symptoms. Second type is hypomotile Achalasia with dysphagia, pain, and regurgitation as its symptoms. The last type was amotile Achalasia with

dysphagia and regurgitation symptoms. In amotile Achalasia, there were failure of normal peristaltic so that esophagus was widely dilated in chronic Achalasia.^{5,6}

There were several diagnostic modalities to evaluate

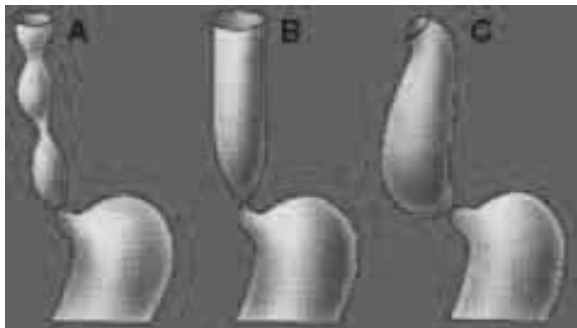


Figure 1. Types of Achalasia⁵

Achalasia, such as manometry, barium esophagogram, esophagoduodenoscopy, and esophagus CT-scan.⁶

TREATMENT

Since 17th century, achalasia therapy was started. Surgeons have made significant improvement in Achalasia therapy.¹ Otherwise, until now, none of achalasia therapy could change its pathology and all treatment was just a palliative of its clinical manifestation³

Pharmacology

Based on Society of American Gastrointestinal and Endoscopic Surgeons in Guidelines for the Surgical Treatment of Esophageal Akalasiain 2009, the goal of pharmacotherapy was to help obstruction reduction and improve lower esophageal sphincter relaxation function. Several pharmacological agents such as

calcium channel blocker and long acting nitrate was effective to lower pressure in LES and sometimes reduce dysphagia, but did not improve its relaxation ability or peristaltic movement of LES.⁷

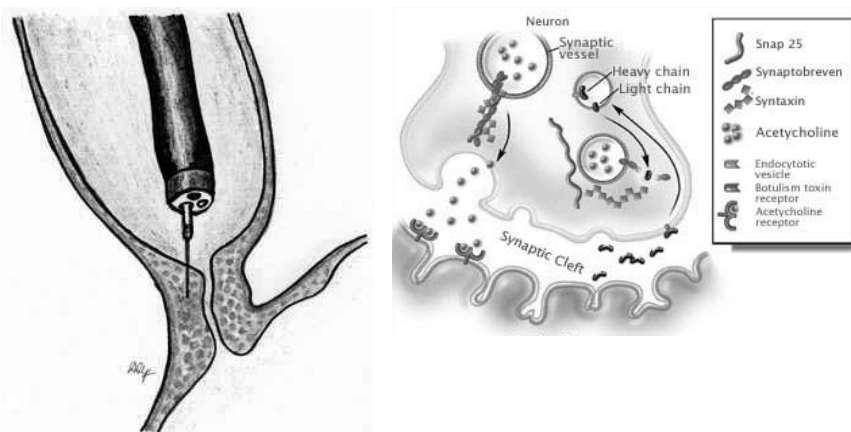
Because of longer transit time and delayed in esophagus emptying, which was a characteristic of Achalasia, absorption and effectivity of any oral drugs cannot be calculated. Those drugs was better used via sublingual route, such as nifedipine 10-30 mg sublingual for 30-45 minutes before meals and ISDN 5 mg sublingual 10-15 minutes before meals. Those drugs reduce pressure in LES for about 50%. Ong acting nitrate has a shorter time of action, 3-27 minutes, and showed a better clinical improvement in 53-87% case compared to nifedipine that works for 30-120 minutes with 0-75% effectivity.⁷

The main limit in those drugs is its short duration of action that only reduce some symptoms and reduce its efficacy in long term use. Besides, its side effect like peripheral edema, headache, and hypotension could be found in 30% patients.⁷

Drugs were used limited to patient in early condition without esophageal dilatation, or in patients waiting for definitive treatment, or patient in high risk that refuse to undergo invasive procedures. Drugs were also indicated in severe Achalasia with chest pain symptoms. Pharmacotherapy in this condition was highly recommended.⁷

Endoscopic Botolium Toxin Injection

Toxin botulinum is a neuro toxin works to inhibit neurotransmitter in terminal cholinergic receptor. Botulinum toxin-A that used for Achalasia therapy works by breaks SNAP-25 protein molecule in presynaptic membrane, so that acetylcholine relese



Botox injection into LES

Figure 2. Botulinum toxin mechanism of action and injection location^{9,10}

was blocked and inhibit acetylcholine exocytosis to synaptic area. This will result in transient muscle weakness by blocking cholinergic stimulation in LES (Figure 2).¹

Botulinum toxin injection locally could reduce LES pressure and increase esophagus passive emptying. Toxin injected via sclerotherapy during endoscopy. In normal condition, 80 to 100 unit of Botulinum toxin-A was injected in each LES quadrant to reduce its pressure, increase esophageal opening, and improve esophageal emptying.^{1,8}

Clinical effect from single injection was short term effect with relaps incidence more than 50% in 6 months. Otherwise, repeated injection could give more effect in 70-90% patients. A report showed that 21% of newly diagnosed Achalasia patients was treated using botulinum toxin as early modalities with injection duration of 6 months. Good response from botulinum toxin injection was found in patients aged less than 50 years old and patients with severe Achalasia.^{1,8}

This therapy was safe, only 10% complained chest pain after injection, but mostly did not require specific therapy. But, repeated injection could make myotomy procedure during surgery seems harder because of adhesion of muscular layer and increase perforation possibility in mucosa. Regarding to patient safety, botulinum toxin injection could be given if no other choice present or if surgery correction contraindicated, and in patients with survival rate of 2 years.¹

Pneumonic Dilatation

Dilatation procedure was firstly done to treat achalasia. This principle of therapy is to weaken LES by tearing its muscle fiber radially from inside esophagus. Endoscopic dilatation was believed as the most safe no surgical therapy for achalasia. Pneumatic dilator were preferred than stiff dilator in achalasia therapy because of its effect that widening and break muscle fibre in LES. Several pneumatic dilator available today have the same efficacy and safety, but only few data could support it.¹

Dilatation treatment was slowly reduce its symptoms. The most simple treatment to done is Hurst plugging procedure, made from mercury-contained rubber, have four different size in F (French) scale. It works principally based on gravitation using the smallest radius plug to the biggest. Its effectivity only 50% with no relaps case, 35% with relaps, and 15% failure to respond.²

The most recommended procedure was LES dilatation using pneumatic dilator. This procedure

was used in recent 30 years with the most successful rate of 75-85% after repeated dilatation. Complication such as esophageal reflux or esophageal perforation were rarely found. This special technique was not only based on its size, but also based on its duration of LES dilatation, range from seconds to 5 minutes. Balloon

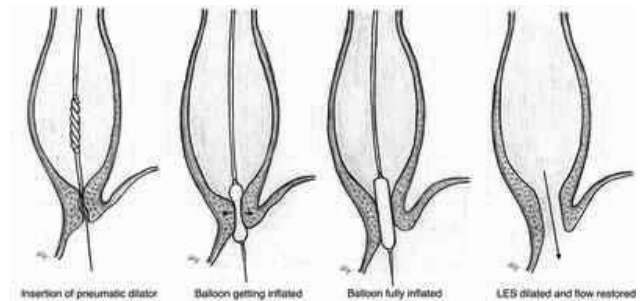


Figure 3. Pneumatic dilatation⁹

was dilated perfectly in short time to get optimum LES dilatation. In 60 seconds, balloon was reexpanded in several minutes, and in each procedure was using maximum two balloons (Figure 3).²

The use of dilator made from polyethylene has a successful rate of 93% with lower complication during 4 years follow up. Fluoroscopy guided endoscopy was effective to dilate balloon. Pneumatic dilatation was done using endoscopy in sedated patients, result in 60% reduce in LES pressure and 79% symptoms resolution. A report from Cleveland showed that 41% of new cases was treated with pneumatic therapy, result in clinical response of 86% and 54% esophagus emptying.^{1,11}

Pneumatic Dilatation vs. Botulinum Toxin Injection

In randomized study involving 42 patients, botulinum injection and pneumatic dilatation was happened in 70% and 32%, respectively, in 12 months. A Cochrane database review in six studies involving 178 patients showed statistically indifferent after four weeks of intervention. Three research, including reviewer, showed a remission of about 33 cc per 47cc after pneumatic injection. This also happened in 11 of 43 patients after both botulinum injection and pneumatic dilatation. Relative risk was 2.67. This showed that pneumatic dilatation was more effective than botulinum injection in long term Achalasia³

Laparoscopic Heller Myotomy (LHM)

Surgical therapy in Achalasia was known as Heller myotomy, a procedure where muscle surrounding esophagus was exposed and cut. Conventional surgery was using long incision in thorax. Recent years, laparoscopic approach have been use as minimal

invasive concept similar to open-surgery concept. This method was having lot of benefit because of its shorter length of stay in hospital, less pain, smaller operation scar, and faster recovery time. Laparoscopic approach was safe and effective in achalasia therapy, although sometimes anatomical variation made it slight difficult.¹⁰

A meta-analysis that compare short term and long term effect of LHM and balloon dilatation via endoscopic was done. From 16 studies consist of 590 LHM procedure and balloon dilatation via endoscopy with follow up in 12, 24, and 60 months, it can be concluded an OR of 2,2 in 12 months, 5,06 in 24 months, and 29,83 in 60 months of LHM superiority as the main choice of therapy. Besides, only 18 patients reported having redilatation after LHM procedure, while 110 patients in balloon dilatation, even 36 among them should undergo myotomy as its retreatmen.¹²

LHM was found to be effective with long term outcome. Most of its risk came from general anesthesia procedure. Esophageal perforation is one of the complication, but could be detected during operation and repaired without serious further complication.⁹

Peroral Endoscopy Myotomy (POEM)

POEM is a technique involving tunneling between esophageal muscle to treat achalasia, especially with Chagas disease. This procedure was done via endoscopy so that no exterior incision was made. POEM was effective to cure dysphagia symptom in Achalasia. After this procedures, achalasia was have Eckardt score 0 or 1. In a study using barium intake showed a complete emptying in 90% and found to have lower esophageal pressure. Sphincter pressure were reduced after this procedure, but not as dramatically as patients undergo LHM procedure. This procedure was done via endoscopy in general anesthesia. A tunnel was made below esophageal deeper layer until reach LES. Esophageal muscle fiber and gastric cardia then resected during endoscopy. Early result of this procedure was promising. But, esophageal damage risk still possible and there were no long term experience result of this therapy. GERD risk after procedure which needed a lifetime antacid was happened in 32% patients. POEM does not cure Achalasia, but this was a palliative procedure.¹³

POEM was firstly done in September 2008 in our institution. POEM with the longest follow up, 2 years, was firstly reported in October 2010. All over the world, there have been 900 case that successfully treated with POEM. One of its contraindication was general anesthesia intolerance.¹³

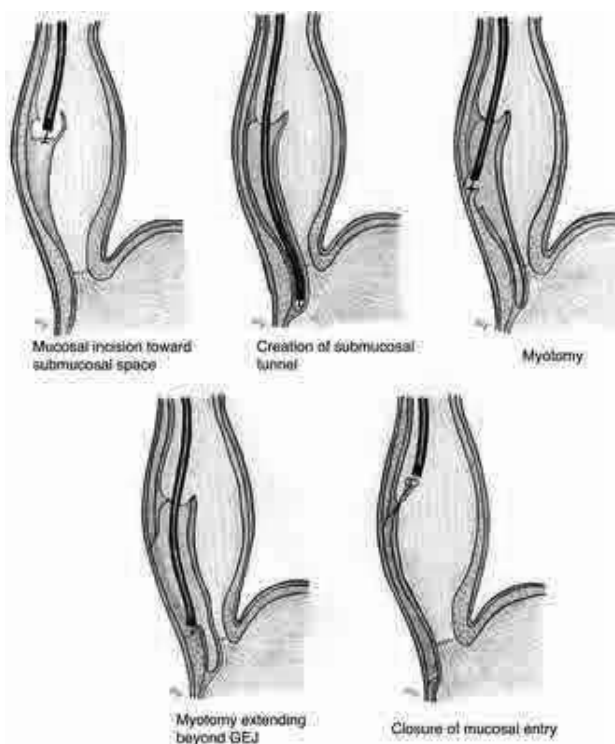


Figure 4. POEM procedure¹³

CONCLUSION

There were several types of Achalasia based on its etiology and motility. Modality choices to treat Achalasia was more various in recent years. But, there were no therapy yet to change its pathology, so that those therapies were just palliative therapies.

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