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Achalasia In The Elderly.

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ABSTRACT

Achalasia is derived from the Greek *khalasis*, translated as "not loosening or relaxing" Achalasia is a primary motor disorder of the esophagus characterized by insufficient lower esophageal sphincter relaxation and loss of esophageal peristalsis. This results in patients' complaints of dysphagia to solids and liquids, regurgitation, and occasional chest pain with or without weight loss. Historically, annual achalasia incidence rates were believed to be low, approximately 0.5-1.2 per 100,000. More recent reports suggest that annual incidence rates have risen to 1.6 per 100,000 in some populations.The etiology of achalasia is still unclear but is likely to be multifactorial. Suggested causes include environmental or viral exposures resulting in inflammation of the esophageal myenteric plexus, which elicits an autoimmune response. Risk of achalasia may be elevated in a sub-group of genetically susceptible people.Although achalasia is a relatively rare condition, it carries a risk of complications, including aspiration pneumonia and esophageal cancer. The risk of both squamous cell carcinoma and adenocarcinoma of the oesophagus is believed to be significantly increased in patients with achalasia, however the absolute excess risk is small.Elderly patients with achalasia have a lower esophageal sphincter pressure than the young, even when we exclude patients with Chagas disease but, as a group, they are less symptomatic.Recents studies brings that minimally invasive Heller myotomy can be performed safely in achalasia patients 70 years of age or older and that it should be considered as primary therapy in centers with significant experience in laparoscopic foregut surgery.

Keywords: esophageal achalasia, esophageal dysmotilities, myotomy, heller's myotomy, endoscopic surgical procedures, elderly.

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INTRODUCTION

Achalasia is a primary esophageal motor disorder of unknown etiology characterized manometrically by insu cient relaxation of the lower esophageal sphincter (LES) and loss of esophageal peristalsis; radiographically by aperistalsis, esophageal dilation, with minimal LES opening, “bird-beak” appearance, poor emptying of barium; and endoscopically by dilated esophagus with retained saliva, liquid, and undigested food particles in the absence of mucosal stricturing or tumor [1]. It is an uncommon but quintessential esophageal motility disorder de ned traditionally by manometric criteria in the classic setting of dysphagia [1,2]. It is an incurable disease characterized by incomplete or absent relaxation of the LES and aperistalsis of the esophageal body. The symptomatic consequence of this motility disorder is the classic presentation of dysphagia to solids and liquids associated with regurgitation of bland undigested food or saliva [1].

METHODS

We reviewed the literature inPubmed, Scopus, Web of Science and EMBASE, using the descriptors below keywords, selecting the main scientific evidence chosen by peers and oriented by professionals in the field, involving randomized clinical studies, systematic reviews, meta-analyses and the main guidelines found in literature over the last thirty years, for the construction of the present revision.

EPIDEMIOLOGY

Achalasia occurs equally in men and women with an incidence of 1 in 100,000 individuals annually and prevalence of 10 in 100,000[1,2]. The peak incidence occurs between 30 and 60 years of age. In the United States, rates of hospitalization for achalasia depend on patient age, ranging from 0.25/100,000 (<18 years) to a high of 37/100,000 (>85 years). Although the incidence is low, the chronicity of achalasia significantly affects patients health-related quality of life, work productivity, and functional status compared with the general US population

RISK FACTORS

Since the 1960's a few studies have investigated the effect of age on esophageal motility. Alterations demonstrated in older individuals include a reduction in amplitude of esophageal contraction, reduction the pressure of the upper and lower sphincters, as well as in the relaxation of the lower esophageal sphincter[2-6]. Autopsy studies have also shown that the elderly had a significant and asymptomatic reduction in the number of ganglion cells in the esophageal myenteric plexus[7,8]. These findings suggest that in elderly people asymptomatic, manometric findings may look like those of patients with achalasia.

ETIOLOGY

The etiology is autoimmune, viral immune, or neurodegenerative[1,2]. Infection by Trypanosoma cruzi, also known as Chagas disease, can also result in achalasia[9].

Genetic predisposition

The genetic basis for achalasia has not been widely investigated due to its low prevalence. One syndrome, known as the triple “A” syndrome, which consists of a triad of achalasia, alacrima and adrenocorticotrophic hormone resistant adrenal insufficiency is a known autosomal recessive disorder caused by gene mutations on chromosome 12. This syndrome, together with the prevalence of cases within children of consanguineous couples[8], suggests the possibility for a genetic component to the aetiology of achalasia. There have been associations with other genetic diseases including Parkinson’s disease, Downs syndrome and MEN2B syndrome[10]. One recent suggested the possibility of involvement of the rearranged during transfection gene, which is a major susceptibility gene for Hirschprung’s disease (also linked with Down’s syndrome)[11]. Mayberry et al. conducted a study of first degree relatives of achalasia patients but concluded that inheritance was unlikely to be a significant causative factor due to the rarity of familial casesand exposure to common environmental and social factors within a family group may explain the presence of familial cases of achalasia[12]. It has been postulated that achalasia may incorporate a multifactorial etiology with an initiating event such as a viral or environmental insult resulting in esophageal myenteric plexus inflammation.

This inflammatory reaction may then initiate an autoimmune response in a susceptible group of genetically predisposed people, causing destruction of inhibitory neurons[13].

Auto-immune causes

One recent study observed that patients with achalasia were 3,6 times more likely to suffer an autoimmune condition, compared with the general population[14]. Sjogren's syndrome, Systemic Lupus Erythematosus and uveitis were all significantly more prevalent in achalasia patients. The study also found the presence of a T-cell infiltrate and antibodies within the myenteric plexus of many patients with achalasia and an increased presence of human leukocyte antigen class II antigens[14]. Another study noted an overall higher prevalence of neural autoantibodies in patients with achalasia in comparison with a healthy control group[15]. Although no specific autoantibody was identified, this further supports the theory that achalasia has an autoimmune basis[15].

Infectious agentes

The role of an infectious agent in the development of achalasia has been widely debated with several viral agents being implicated. For example, Chagas disease has a known infectious etiology, and exhibits many similarities with achalasia[16]. In addition, there are several reports of varicella zoster virus and Guillain-Barre syndrome preceding the onset of achalasia[16]. Antibody studies have demonstrated increased titres to herpes and measles viruses in patients with achalasia in comparison to healthy control groups[17,18]. One study looking specifically at the link between the herpes simplex virus (HSV) and primary achalasia indicated the presence of HSV-1 reactive immune cells in the lower esophageal sphincter of achalasia patients, suggesting that HSV-1 may be involved in the neuronal damage to the myenteric plexus leading to achalasia[19].

A further study of peripheral blood immune cells found that patients with achalasia showed an enhanced response to HSV-1 antigens[18]. In contrast, another investigation using PCR on myotomy specimens did not find any association between herpes, measles or human papilloma viruses and achalasia[20,21]. The current evidence for a causative infectious agent is contradictory and no clear causal relationship has yet been established[18-20].

Diagnosis

Dysphagia is the cardinal symptom of achalasia. Diagnosis requires a high index of suspicion and exclusion of other causes. Diagnosis is confirmed by manometric, endoscopic and radiographic investigations. Esophageal manometry is regarded as the gold standard in the diagnosis of achalasia, classically showing aperistalsis and failure of relaxation of the lower esophageal sphincter[21]. Endoscopy is not accurate in the diagnosis of achalasia. However, it is still necessary to exclude a carcinoma at the lower end of the oesophagus[22].

Barium esophagogram can often show the pathognomonic "bird's beak" appearance of the distal oesophagus with dilatation of the oesophagus proximally. However, this is often a finding in established disease and therefore a normal barium swallow does not rule out the diagnosis of achalasia. With the introduction of high resolution manometry, together with pressure topography, plotting the diagnosis of achalasia can now be classified into three subtypes; type 1 - classic achalasia, type 2 - achalasia with compression and pressurisation effects, and type 3 - spastic achalasia[23]. This classification process can aid treatment decisions, with type 2 achalasia being the most responsive to pneumatic dilatation, Heller´s myotomy and botulinum toxin and therefore having the best outcome[24].

Esophageal emptying is determined by the distensibility of the oesophago-gastric junction. This can be assessed using an endoscopic functional luminal imaging probe (EndoFLIP). Recently, Dutch and American groups have demonstrated that this novel technique is a better predictor than lower esophageal sphincter pressure for assessing response to treatment in achalasia, both symptomatically and when measured by gastric emptying by o esophageal emptying[25,26].

Esophagogastroduodenoscopy with mucosal biopsy should be performed in most patients presenting with solid food dysphagia, liquid food dysphagia, or both. This is done to rule out erosive gastroesophageal reflux disease, eosinophilic esophagitis, structural lesions (strictures, webs or rings), and esophageal cancer or "pseudoachalasia"[24]. Endoscopic features of an esophageal motility disorder include a dilated or tortuous esophagus, food impactions and fluid pooling in the esophagus, and resistance to intubation of the gastroesophageal junction[23]. Patients with achalasia may also develop candidiasis attributable to esophageal stasis, and evidence of candidiasis in the context of intact immune function should prompt an evaluation for esophageal dysmotility. Although endoscopy may suggest achalasia, other testing must be performed to confirm the diagnosis[26].

Esophageal manometry to assess esophageal pressures and contractions along the length of a flexible catheter has become the standard for diagnosing and classifying achalasia. Major technological advances have occurred during the last decade, wherein conventional water-perfused or strain gauge systems with a line tracing output have been replaced by more reproducible 43 and accurate 44 high-resolution manometry systems that present pressure data in the context of esophageal pressure topography plots[23-25]. One important advantage of esophageal pressure topography has been the ability to further refine conventional diagnoses, such as achalasia, into clinically relevant phenotypes. The diagnosis of achalasia is classically made by demonstrating impaired relaxation of the lower esophageal sphincter and absent peristalsis in the absence of esophageal obstruction near the lower esophageal sphincter attributable to a stricture, tumor, vascular structure, implanted device, or infiltrating process[27]. Three distinct subtypes of achalasia (types I, II, and III) are defined with high-resolution manometry that have both prognostic and potential therapeutic implications[28]. If criteria for achalasia subtypes are not met, a validated hierarchical analysis is used to determine if patients have non achalasia motor disorders. However, a possible diagnosis of achalasia should be considered when patients present with an esophagogastric junction outflow obstruction, because this may represent an incomplete or early form of the disease. Similarly, it is also important to consider achalasia in patients with absent contractility, as these cases may be confused with scleroderma owing to the complexities of measuring relaxation of the lower esophageal sphincter[27-29]. Equivocal cases may require further workup with endoscopic ultrasound in the case of EGJ outflow obstruction to rule out a subtle obstruction and a barium esophagram in the case of absent contractility to document bolus retention, which would favor a diagnosis of achalasia[29,30].

Differential diagnosis

When patients primarily present with dysphagia, a careful history and evaluation of swallowing by watching the patient drink water can be helpful in distinguishing between oropharyngeal dysphagia and esophageal dysphagia[2,3]. Patients with oropharyngeal dysphagia will typically struggle to move the bolus into the esophagus during water swallows and will often have coughing and immediate regurgitation. Primary oropharyngeal symptoms should first prompt an evaluation for oropharyngeal etiologies, with a modified barium cookie swallow study performed by speech pathology[1,5-6]. Patients with intact oropharyngeal swallowing and dysphagia should be evaluated for esophageal causes, and the differential should focus on distinguishing between a structural mechanical obstruction and a motility disorder. Mechanical obstruction should be ruled out first, via either upper gastrointestinal tract endoscopy or radiologic imaging, prior to evaluation for abnormal motility[31].

These are include esophageal and stomach tumors, strictures (caused by scar tissue or inflammation), and narrowing caused by aberrant blood vessel position (dysphagia lusoria), for example[10,11].

Treatment

This review aims to identify and collaborate relevant literature detailing the management options available to treat achalasia.

The mainstay of treatment for achalasia is either pneumatic balloon dilatation or laparoscopic myotomy. In pneumatic balloon dilatation, a balloon is positioned across the lower esophageal sphincter and inflated, effectively rupturing the muscle of the affected segment[30].

Surgical myotomy can be performed as either an open or laparoscopic procedure. The laparoscopic technique is now the most commonly performed. The procedure involves making a longitudinal division of the circular muscle of the lower esophageal sphincter, extending this both proximally and distally into the cardia[31]. Many surgeons advise the use of an anti-reflux procedure together with surgical myotomy, as these patients at are an increased risk of reflux following surgery[32].

The best comparative study between pneumatic dilatation and surgery to date has demonstrated remarkably similar outcomes in matched patients over a three year follow up period[6]. Therapeutic success at two years was noted in 86% of those treated by pneumatic dilatation and 90% of those who had laparoscopic Heller's myotomy. The regimen for pneumatic dilatation was rigorous with the option of multiple dilatations. A new endoscopic esophagomyotomy technique has been recently introduced: peroral endoscopic myotomy involves dividing the inner circular muscle of the oesophagus. This requires sophisticated expertise and remains experimental[33]. In patients for whom invasive procedures are not suitable, alternative treatment options may be considered including pharmacological intervention using long-acting nitrates and calcium channel blockers. However, these are of limited benefit[34].

Clinical treatment

Oral calcium channel blockers or nitrates cause a prompt reduction in lower esophageal sphincter pressure of up to 47% to 64%, with mild benefit for dysphagia[35]. These medications can have limiting adverse effects (headache, orthostatic hypotension, or edema) and do not halt disease progression. Consequently, they are poor longterm treatment options and should be reserved for patients who are poor candidates for surgical or endoscopic therapy. Nifedipine (10-30mg, 30-45 minutes before meals) or isorbide dinitrate (5-10mg, 15 minutes before meals) may be useful as shortacting temporizing treatments. Absorption and effect of oral medications can be unpredictable in achalasia[34,35].

5′-Phosphodiesterase inhibitors, such as sildenafil, have also been used (off-label) to treat achalasia and spastic disorders of the esophagus[36]. Sildenafil lowers esophagogastric junction pressure and attenuates distal esophageal contractions by blocking the enzyme that degrades cyclic guanosine monophosphate induced by nitric oxide. Sildenafil is a viable alternative in patients not responding to or proving intolerant of calcium channel blockers or nitrates. However,minimal long-term treatment data exist pertinent to using 5′-phosphodiesterase inhibitors to treat achalasia[34-36]. Other less commonly used medications include anticholinergics (atropine, dicyclomine, cimetropium bromide), β -adrenergic agonists (terbutaline), and theophylline[37].

Pharmacologic therapy via endoscopy

Botulinum toxin (Botox) is a potent presynaptic inhibitor of acetylcholine release from nerve endings that has proven to be a useful treatment in achalasia[38]. The toxin cleaves the protein (SNAP-25) involved infusing presynaptic vesicles containing acetycholine with the neuronal plasma membrane in contact with the target muscle. The is, in turn, inhibits exocytosis of acetycholine into the synaptic area and causes a short-term paralysis of the muscle by blocking the unopposed cholinergic stimulation of the lower esophageal sphincter (LES), which is devoid of inhibitory influence in achalasia[39-41]. This effect interrupts the neurogenic component of the sphincter; however, it has no effect on the myogenic influence maintaining basal LES tone[42,43]. Thus, the treatment is limited and most treatment effects are associated with an 50 % reduction in the basal LES pressure. This reduction may be sufficient to allow esophageal emptying when esophageal pressure rises to a level where it can overwhelm the partially paralyzed LES[44].

Using this technique, Pasricha et al. reported improved dysphagia in 66% of patients with achalasia for 6 months[45]. No increase inefficacy has been demonstrated with greater doses[46]. The effectis temporary and is eventually reversed by axonal regeneration; subsequent clinical series report minimal continued efficacy after 1 year[47].Most patients relapse and require re-treatment within 12 months[48,49].

In addition, there is some evidence that injection of botulinum toxin into the LES may increase the diffi culty in subsequent surgical myotomy[41]. Given these limitations, the utilization of botulinum toxin is restricted to specifi c circumstances where PD and surgical myotomy are not considered appropriate because of inherent patient-related risks[46]. Alternatively, botulinum toxin can be considered as an adjunct treatment

in patients with residual spastic contractions above the myotomy site or LES; however, outcome-related data are lacking[50].

Pneumatic Dilation

A pneumatic dilator is a noncompliant, cylindrical balloon that is positioned fluoroscopically across the lower esophageal sphincter and inflated with air using a handheld manometer. Patients with a poor result or rapid recurrence of dysphagia are unlikely to respond to additional dilations, but subsequent response to myotomy is not influenced[50,51]. Although the reported incidence of perforation from pneumatic dilation ranges from 0% to 16%, a recent systematic review on the topic concluded that using modern technique the risk was less than 1%, comparable to the risk of unrecognized perforation during Heller myotomy. Pneumatic dilation should be performed by experienced physicians, and surgical backup is required[51].

Studies using pneumatic dilation as the initial treatment of achalasia have reported excellent long-term symptom control. A third of patients will relapse in 4 to 6 years and may require repeat dilation. Response to therapy may be related to preprocedural clinical parameters, such as age (favorable if >45 years), sex (more favorable among females than males),70 esophageal diameter (inversely related to response), and achalasia subtype (type II better than I and III)[52,53]. Although surgical myotomy has a greater response rate than a single pneumatic dilation, it appears that a series of dilations is a reasonable alternative to surgery. A recent randomized trial compared this type of graded strategy with surgical myotomy and found it to be noninferior in efficacy[54]. Addition of botulinum toxin injection does not appear to improve outcomes[55].

Surgical myotomy

The original approach to surgical myotomy involved division of the muscle fibers of the LES (circular layer without disruption of the mucosa) through a thoracotomy[56]. This achieved good-toexcellent results in 60-94 % of patients followed for 1-36 years, and it remained the surgery of choice for many years[57]. The technique evolved initially with a laparotomy approach, which was subsequently supplanted by minimally invasive techniques. A thoracoscopic approach was developed and used with success, but laparoscopic myotomy has become the preferred method because of decreased morbidity and faster recovery[55-57].

Laparoscopic Heller myotomy is superior to a single pneumatic dilation in terms of efficacy and durability, with reported efficacy rates in the 88% to 95% range[39,58-60].However, the superiority of surgical myotomy over pneumatic dilation is less evident when compared with a graded approach to pneumatic dilation using repeat dila tions as mandated by the clinical response[55,61]. An antireflux repair has been shown to significantly decrease gastroesophageal reflux disease, and this can range from an anterior 180° fundoplasty (Dor) to a 270° partial fundoplication (Toupet)[62,63]. There is general agreement that a full 360° Nissen fundoplication is contraindicated, as 1 randomized trial showed that 15% of patients had recurrent dysphagia[64].

Per-Oral Endoscopic Myotomy

Per-oral endoscopic myotomy (POEM) is the newest treatment for achalasia[40,65].The procedure requires making a small mucosal incision in the mid-esophagus and creating a submucosal tunnel all the way to the gastric cardia using a forward-viewing endoscope, transparent distal cap, and submucosal dissection knife[66]. Selective myotomy of the circular muscle is accomplished with electrocautery for a minimum length of 6 cm up the esophagus and 2 cm distal to the squamocolumnar junction onto the gastric cardia. Initial success rates of the POEM procedure in prospective cohorts of patients with achalasia have been greaterthan 90%, comparable with those of laparoscopic Heller´s myotomy[66,67].A recent prospective, single-center study found that symptoms and postmyotomy integrated relaxation pressures were not different between patients undergoing laparoscopic Heller myotomy or POEM[68]. Preliminary results comparing more than 30 POEM cases with laparoscopic Heller myotomy suggest comparable perioperative outcomes[69].A recent retrospective multicenter study reported a greater than 90% response rate in patients with type III achalasia, perhaps due to longermyotomy length with the endoscopic approach[70].There have been no randomized trials comparing POEM to laparoscopic myotomy or pneumatic dilation, and its relative efficacy in terms of long-term dysphagia control, progression of esophageal dilatation, and postprocedure reflux remains to be established.

Esophagectomy

Some patients may develop "end-stage" achalasia characterized by megaesophagus or sigmoid esophagus and significant esophageal dilation and tortuosity. In this group of patients, Pneumatic Dilation (PD) may be less effective but a surgical myotomy may be a reasonable initial approach before consideration for esophagectomy. Two recent studies documented symptomatic improvement after myotomy in 92 % and 72 % of patients with megaesophagus[71,72]. However, in those unresponsive to therapy, esophageal resection is frequently required[73]. Esophagectomy is associated with a greater morbidity / mortality than laparoscopic Heller´s myotomy, and should be reserved for patients who have failed PD and / or myotomy and who are good candidates for surgery. Dysphagia requiring dilation may occur in up to 50 % of patients after esophagectomy[74]. Data from uncontrolled studies show generally good response to esophagectomy, with symptom improvement in over 80 % of patients with end-stage achalasia; mortality ranges between 0 and 5.4 %[75]. There is a paucity of studies comparing the two main approaches to esophagectomy, that is, gastric or colonic interposition. However, a recent extensive review on this topic found that gastric interposition is the first choice of therapy in the majority of patients undergoing esophagectomy[76].

In addition to clinical presentation, the choice of treatment may differ with age of the achalasia patient. In younger individuals (< 50 years old), minimally invasive Heller myotomy (MIM) is the gold standard as the response rate to either Botox injection or pneumatic dilatation (PD) is significantly lower[77,78]. The optimal treatment in older patients, however, is a matter of controversy. Botox is usually reserved for physiologically compromised individuals who cannot undergo PD or MIM, as most patients relapse within 6–12 months of initial injection[79,80]. PD is recommended by many gastroenterologists as it is associated with a success rate of 70–90%, although it has been demonstrated that approximately 50% of patients experience symptom recurrence with extended follow-up[81]. The outcomes of MIM specifically in the older population are not well published, thus limiting comparisons with other treatment modalities in this subset of patients[82].

CONCLUSION

In conclusion, achalasia remains a relatively under-researched condition with many details on etiology, true incidence, and risk of complications still unknown. There has been some progress over the past years into the etiology of the condition but there is a need for further research to be carried out into this eld to establish causative agents. Furthermore, in relation to the need for an endoscopic screening program in patients with achalasia to detect the development of oesophageal cancer is required.

Achalasia should be diagnosed as early as possible, so that complications can be prevented. A lot of improvements have been made on the understanding of the etiology, pathophysiology and treatment of achalasia in the last two decades. Although different treatment options are available definitive cure is lacking. The choice of treatment involves the consideration of several clinical and economic factors.

Traditionally, gastroenterologists treating achalasia have preferred dilation due to the risks associated with open myotomy, especially in vulnerable populations such as the elderly. With the introduction of minimally invasive techniques, these patients experience less postoperative pain, lower morbidity and mortality, and therefore can tolerate even relatively complex procedures. Older individuals who were unable to undergo open surgery for achalasia seem to have particularly benefited from the maturation of MIM over the past 15 years.

Importantly, even with all the results, more studies are needed, so we can clarify unequivocally the relationship between age, esophageal function and treatment.

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