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EDUCATION PRACTICE

A Young Man With a New Diagnosis of Achalasia

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Clinical Scenario

A 32-year-old man began to experience food sticking intermittently in the midchest about 2 years ago. By the time he presents to the gastroenterology clinic, he is complaining of dysphagia at every meal for most hard, solid foods (ie, bread, meats, uncooked vegetables), and for the past 4 months he has noted dysphagia for liquids, especially cold beverages. Once or twice a week, after his large evening meal, he experiences regurgitation of recently eaten food with a nonacidic taste. His wife complains he "gurgles" at night and sometimes awakes her with coughing. He denies chest pain, but does complain of "heartburn," improving with over-the-counter Prilosec (Proctor & Gamble, Cincinnati, OH). His weight is down 10 lb.

The complaints of dysphagia for both solids and liquids raise the suspicion of achalasia. A barium esophagram shows a mildly dilated esophagus with a column of barium maintained just below the clavicles with no emptying in the upright position over a 5-minute period. The distal esophagus has narrowed, with a small amount of barium intermittently streaming into the stomach. No orderly peristalsis is seen on fluoroscopy. Esophageal manometry confirms the diagnosis, finding a high lower esophageal sphincter (LES) pressure (56 mm Hg) with incomplete relaxation and low-amplitude, simultaneous mirror image waves after all swallows of water.

The patient and his wife return to your office after completing his tests. They have read extensively about achalasia on the Internet. They have many questions: Will I ever be able to eat normally? Can you cure this disease? What is the best treatment—pneumatic dilation, surgical myotomy, or botulinum toxin injections? What are the side effects and which one will give me the most relief for a long time?

The Problem

Achalasia is the most recognized motor disorder of the esophagus and the only primary motility disorder with an established pathology. The term means *failure to relax*, describing the predominate feature of this disorder—a poorly relaxing LES. The cause of achalasia is unknown. Available data suggest that hereditary, degenerative, autoimmune, and infectious factors are possible causes—the latter two being the most commonly accepted. Pathologic changes are seen in the esophageal myenteric (Auerbach's) plexus, and include prominent inflammatory response consisting of CD3- and CD8-positive cytotoxic T lymphocytes, variable numbers of eosinophils and mast cells, loss of ganglion cells, and some degree of myenteric neural fibrosis. The end result of these inflammatory changes is a selective loss of postganglionic inhibitory neurons containing nitric oxide and vasoactive intestinal polypeptide. Because postganglionic excitory neurons are spared, cholinergic stimulation continues unopposed, leading to increased LES pressures. The loss of inhibitory input results in incomplete LES relaxation. Sequential peristalsis along the esophageal body, a process mediated by nitric oxide, is lost, resulting in aperistalsis. The combination of aperistalsis and incomplete LES relaxation produces poor esophageal emptying, gradual esophageal dilation, and, in some patients, a tortuous megaesophagus.

Achalasia occurs with equal frequency in men and women, with the peak incidence between 30 and 60 years. There is no racial predilection. The disease prevalence is approximately 10 cases per 100,000 population, with an incidence of about 0.5 cases per 100,000 population per year. Most gastroenterologists will encounter at least 1 case yearly; esophageal specialists may see 10 or more cases yearly.

Achalasia should be suspected in patients complaining of dysphagia for solids and liquids with regurgitation of bland food and saliva. The onset of the dysphagia usually is gradual, being described initially as an infrequent "fullness in the chest" or "sticking sensation," but usually occurs daily or with every meal by the time the patient sees a physician. Initially, the dysphagia is primarily for solids, but by the time of clinical presentation nearly all patients complain of dysphagia for liquids, especially cold beverages. Various maneuvers, including power swallows and carbonated beverages, both of which increase intraesophageal pressure, may be used to improve esophageal emptying. Regurgitation of bland, undigested, retained food or accumulated saliva occurs postprandially and at night, often awaking the patient with coughing and choking. Chest pain occurs in some patients, especially in milder disease with a minimally dilated esophagus. Heartburn is a frequent complaint, despite achalasia not being associated with increased episodes of acid reflux by pH monitoring. The cause is speculative but probably related to retention of acid beverages, such as carbonated or fruit drinks, and in some cases the production of lactic acid from retained food in a markedly dilated esophagus. Most achalasia patients have some degree of weight loss, usually only 5 to 20 pounds.

In most cases, the diagnosis of achalasia is made easily by using a combination of tests including barium esophagram, esophageal manometry, and endoscopy.

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; PD, pneumatic dilation.

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Table 1. Long-Term Efficacy and Complications of Rigiflex Balloon Dilation Versus Laparoscopic Heller Myotomy for Achalasia

	Rigiflex balloon	Laparoscopic
Myotomy		
Number of studies	22	33
Number of patients	1212	1812
% With excellent/good response	78%	85%
Follow-up period, mo	36	32
Complications	2.0% (perforation)	17% (GERD)

Management Strategies and Supporting Evidence

No treatment can restore muscular activity to the denervated esophagus in achalasia. Esophageal aperistalsis and impaired LES relaxation are rarely, if ever, reversed by any treatment. Therefore, every therapy for achalasia is directed to reducing the pressure gradient across the LES with the following 3 goals: (1) relieving patients' symptoms, especially dysphagia and bland regurgitation; (2) improving esophageal emptying by disrupting the poorly relaxing LES; and (3) preventing the development of megaesophagus.

This disruption of the LES gradient is best accomplished with pneumatic dilation (PD) or surgical myotomy and less effectively by pharmacologic agents. Regurgitation and dysphagia are the easiest symptoms to treat, but chest pain can be problematic in some patients. Overall, by using single or multiple modalities of treatment, more than 90% of achalasia patients will do well with a return to near-normal swallowing and minimal dietary restrictions. However, achalasia is never cured and touch-up therapies after PD or Heller myotomy often are needed. All achalasia patients should be followed-up every year or two by a gastroenterologist or surgeon familiar with the disease. The timed barium swallow to assess esophageal emptying over a 5-minute period is very helpful in following up patients, thereby reserving manometry, pH testing, and endoscopy for those who are not doing well.

Pneumatic Dilation

PD has become much easier and more standardized with the development of the Rigiflex balloon system (Boston Scientific Corp, Boston, MA). These are noncompliant polyethylene balloons that come in 3 sizes (3.0, 3.5, and 4.0 cm) on a flexible catheter placed over a guidewire at endoscopy. The catheter within the balloon has radio-opaque markers that help with location at fluoroscopy. Unfortunately, there is no consensus on the PD protocol for achalasia. The author's technique over the past 25 years is described elsewhere.

Table 1 summarizes the good-to-excellent symptom relief with the Rigiflex dilators in more than 1200 patients. These studies found the clinical response improves in a graded fashion with increasing size of the balloon diameter: good-to-excellent response in 74%, 86%, and 90% with the 3.0-, 3.5-, and 4.0-cm balloon. More than a third of achalasia patients treated with PD will experience symptom recurrence during a 4-year period. Long-term remission can be achieved in virtually all of these patients treated by repeat PD according to an on-demand strategy based on symptom recurrence. PD is the most cost-effective method for treating achalasia when compared with Heller myotomy or Botox (Allergan, Irvine, CA), over a time period of 5 years.

Recently, we and others have begun to refine our technique of PD with the Rigiflex balloons. Risk factors for relapse are mainly young age (<40 y), male sex, single dilation with a 3.0-cm balloon, posttreatment LES pressure greater than 10 mm Hg, and poor esophageal emptying on a timed barium esophagram. The relationship between age and sex is particularly interesting. Using an older balloon system, Eckardt et al showed a 5-year remission rate of 16% for patients younger than 40 years, compared with 58% for those older than 40 years. In a study of 126 patients, Ghoshal et al found that male sex but not age was associated independently with poor outcome after PD. A large study from the Cleveland Clinic (106 patients, 51 women) confirmed the importance of age, but also found sex to be an equally important variable (Figure 1). Men, up to age 50 years, did poorly with a single 3.0-cm Rigiflex PD. However, most women (≥30 y) did well over at least 5 years with a single PD. Approximately 10% to 15% of patients do poorly with PD; these patients usually are defined within the first year of initiating treatment. They do well with Heller myotomy with success similar to initial treatment with surgery.

The most serious complication for PD is esophageal perforation, with an overall rate in experienced hands of 1.0% to 3.0%. Other minor complications include chest pain (15%), aspiration pneumonia, hematemesis, fever, esophageal mucosal tear, and hematoma. Severe complications of gastroesophageal reflux disease (GERD) (esophagitis, peptic stricture) are rare after PD, but 15% to 35% of patients have heartburn, responding to proton pump inhibitors.

Laparoscopic Heller Myotomy

The first successful surgery for achalasia was performed in 1913 by the German surgeon Ernest Heller, consisting of an anterior and posterior (double) lower esopha-

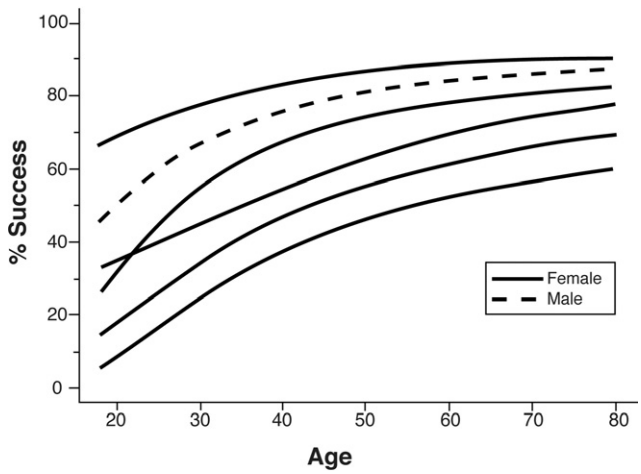

Figure 1. Effect of age and sex on the early phase (within 6 months) outcome of a single PD with a 3.0-cm Rigiflex balloon. The 95% confidence intervals are shown for each curve. Younger patients, especially men, have a higher likelihood of early failure. – – –, Female; —, male. Reprinted with permission from Vela et al (2006).

geal myotomy through a laparotomy. Later, the surgery was modified to a single anterior myotomy performed usually through a left posterior thoracotomy. This was the primary surgery for achalasia until the mid-1990s with a reported good success rate, but high postoperative morbidity, making this treatment much less attractive. This dramatically changed with the introduction of the minimally invasive myotomy by Pellegrini et al in 1992. Initially performed through the chest, the overall success of the laparoscopic surgery is superior to the thorascopic approach. Patients usually are hospitalized for less than 48 hours and can return to work in 1 to 2 weeks. Recent improvements have included extending the myotomy 2 to 3 cm onto the proximal stomach to cut the gastric sling fibers, further decreasing LES pressure and improving dysphagia. This more aggressive myotomy accentuates the risk for postoperative GER, therefore, the consensus now is to add an incomplete fundoplication, usually an anterior Dor, to prevent this complication.

Table 1 summarizes the good-to-excellent relief with laparoscopic Heller myotomy in more than 1800 patients. Younger patients, especially men, and patients with higher LES pressure benefit most from primary surgery. Importantly, patients who failed PD or Botox treatment can be treated successfully with surgical myotomy. However, repeated Botox injections significantly hinder the dissection of the submucosal plane, leading to mucosal perforations in up to 15% of surgeries. Although these perforations usually are recognized and repaired at the initial surgery, recent studies have suggested a negative effect on long-term results. Surgical expertise is key, with most complications occurring in the first 50 surgeries. Surgery is the most costly treatment for achalasia. However, it may be cost effective, but only if its efficacy reliably lasts at least 10 years.

Although the short-term results of laparoscopic Heller myotomy are excellent, it remains to be seen if the long-term results are as favorable. Three groups recently reported the long-term outcome of laparoscopic Heller myotomy (mean follow-up period, 5.3–11.2 y) in 179 patients. Deterioration over time occurs with striking consistency across studies: 18% required PD, 5% required Botox injections, and 5% to 10% required repeat myotomy or esophagectomy.

Complications of laparoscopic myotomy include death (0.1%) and esophageal perforation (7%–15%). The most common problem is chronic GERD and its sequelae, occurring overall in 17% of patients (range, 5%–55%). Barrett's esophagus and secondary adenocarcinoma are reported after Heller myotomy. The addition of an incomplete fundoplication decreases, but does not eliminate, the risk of GERD. A recent study by Csendes et al illustrated the potential for GERD complications, especially among patients followed up for more than 10 years. The investigators reported on 67 patients with Heller myotomy and Dor fundoplication with a mean follow-up period of nearly 16 years (range, 6.6–30 y). Overall, 31% of patients developed GERD and 55% had abnormal pH studies 20 years after their myotomy. Nine patients (13.4%) developed Barrett's esophagus (6 short- and 3 long-segment) with the frequency increasing over time, reaching 30% after 20 years. In this series, poor or failed results were seen in 22.4% of patients, but only 1 was caused by an incomplete myotomy, with the remaining 14 being caused by complications of severe GERD.

Drug Therapy

Smooth Muscle Relaxants

Nitrates and calcium channel blockers decrease LES pressure in a dose-dependent manner with a maximum effect of approximately 50%, thereby temporarily relieving dysphagia. These drugs are taken 15 to 30 minutes before meals, the improvement in dysphagia usually is incomplete and short-lived, efficacy decreases with time, and side effects (headache, dizziness, pedal edema) are common. As a result, smooth muscle relaxants are used infrequently, with most authorities preferring Botox injections for achalasia patients requiring drug therapy.

Botulinum Toxin

Botulinum toxin (Botox) is a potent inhibitor of acetylcholine release from nerve endings. The inactive form is synthesized by the *Clostridium botulinum* bacteria. Botox cleaves SNAP-25, a cytoplasmic protein involved in the fusion of acetylcholine containing presymptomatic vesicles with the neuronal plasma membrane. Exocytosis of acetylcholine is inhibited and paralysis of the innervated muscle occurs. Botox counteracts the unopposed LES stimulation by cholinergic neurons, helping to restore the LES to a lower resting pressure. On average, Botox injection decreases LES pressure by 50% while partially improving esophageal emptying. Usually, a total dose of 100 U is injected endoscopically into the LES in divided 25-U aliquots, 1 in each quadrant of the sphincter. Increasing the dose to 200 U does not improve the success rate, but repeated 100 U may improve efficacy. The drug is contraindicated in patients with allergy to egg proteins. The most common side effect of Botox injections is chest pain in 16% to 25% of patients.

Based on numerous studies (some placebo-controlled), Botox markedly improves symptoms in approximately 75% of achalasia patients. However, symptoms recur in more than 50% of patients within 6 months, possibly because of regeneration of the affected receptors. In those responding to the first Botox injection, 75% respond to a second injection, but the response decreases with further injections, probably from antibody production to the foreign protein. Patients older than 60 years and those with vigorous achalasia are more likely to get a sustained Botox response (up to 1.5–2 y). Serial Botox injections are required to give sustained relief, and comparison studies show its long-term efficacy is inferior to PD or myotomy. Botox injections are more expensive than PD, but this treatment may have a cost advantage for patients living less than 2 years.

Areas of Uncertainty

Ideally, the choice between 2 treatment options should be based on prospective randomized studies. Unfortunately, there is only 1 older study addressing this issue. Csendes et al performed a randomized prospective study comparing open Heller myotomy and an older single (Mosher) balloon bag, both procedures performed by the same individual. After 5 years, 95% of the 41 patients treated with myotomy were improved compared with 65% improvement in the 39 patients undergoing PD. Two more recent studies failed to show a difference in outcome between the 2 procedures, both for short- and long-term follow-up evaluation. Our study from the Cleveland Clinic

compared 106 patients treated with PD using Rigiflex balloons by a single gastroenterologist and 73 patients undergoing Heller myotomy (20 had failed PD and crossed over to surgery) by a single esophageal surgeon. The success of PD and myotomy, defined as dysphagia/regurgitation less than 3 times per week or freedom from alternative treatment, was similar: 90% versus 89% at 6 months and 44% versus 57% at 6 years. Causes of symptom recurrence were incompletely treated achalasia (96% after PD vs 64% after myotomy) and complications of GERD (4% after PD vs 36% after myotomy).

Another method to address this issue is to investigate large population-based databases comparing outcomes of PD and Heller myotomy in typical practice settings. This was reported recently by Lopushinskey and Urbach in a retrospective longitudinal study using linked administrative health data in Ontario, Canada, from July 1991 to December 2002. A total of 1461 persons aged 18 years or older received treatment for achalasia: 1181 (80.8%) had PD and 280 (19.2%) had surgical myotomy as their first procedure. The cumulative risk of any subsequent intervention (PD, myotomy, or esophagectomy) after 1, 5, and 10 years, respectively, was 36.8%, 56.2%, and 63.5% after initial PD treatment, and 16.4%, 30.3%, and 37.5% after initial Heller myotomy (hazard risk, 2.37; 95% confidence interval, 1.86–3.02; $P < .001$). The risk differences were observed only when subsequent PD was included as an adverse outcome. Because on-demand PD treatment is an accepted treatment for achalasia, this cannot clinically be viewed as failure of this treatment modality. Interestingly, the 33% need for subsequent PD and the 18% risk of repeat surgery after Heller myotomy are much higher than the current literature suggests, probably defining the more realistic frequency in the clinical community.

Obviously, a large study with acceptable statistical power is required to address which of these techniques is superior to the other, or to determine which therapy should be reserved for a certain subset of patients. To this end, a large prospective randomized study is ongoing in Europe to address these issues with the plan to include 200 patients.

Published Guidelines

The only practice guidelines for the diagnosis and management of achalasia were published from the American College of Gastroenterology in 1999. Input was obtained from gastroenterologists and surgeons familiar with achalasia, as well as an extensive literature review. However, current evidence-based criteria were not used. The guidelines concluded that "the two most effective treatment options are pneumatic dilation or surgical myotomy" with Botox or pharmacologic treatments reserved for patients who are "poor candidates for surgery." The investigators suggested the choice between the 2 procedures should depend on institutional preference and experience. Guidelines were not based on age, sex, or physiologic/radiographic parameters.

Recommendations

This young man should be counseled that achalasia can never be cured, but most patients will return to near-normal swallowing. Botox should not be offered because of its short duration of symptom relief and need for repeated injections. Rather, the 2 best treatments are PD and Heller myotomy. My algorithm for treating achalasia is summarized in Figure 2.

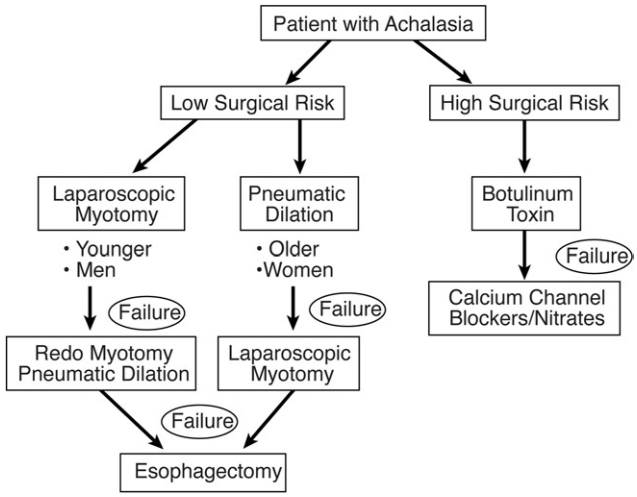

Figure 2. Algorithm for the treatment of achalasia. The healthy patient with low risk of surgery can be offered potentially definitive therapy with either PD or laparoscopic myotomy. High surgical risk patients, primarily the elderly, are best treated with botulinum toxin injections.

Rarely will a single treatment give lasting relief and many patients may cross over from one treatment to another. Some patients eventually may require an esophagectomy for end-stage achalasia.

This young man should be encouraged to have a laparoscopic Heller myotomy with a Dor fundoplication performed by an experienced surgeon. He should be advised that about a third of patients may require touch-up therapy for recurrent dysphagia over the next 10 years. All my patients are placed on a single-dose AM proton pump inhibitor after surgery, regardless of symptoms, to hopefully prevent reflux complications after surgery. We do not perform pH testing after surgery, although some recommend this routinely. Surgical myotomy is my preferred treatment for men younger than 50 years of age and teenagers of both sexes.

If the patient chose PD, I would initiate therapy with a 3.5-cm diameter balloon, based on my Cleveland Clinic experience illustrated in Figure 1. A second dilation with a 4.0-cm balloon may be required and the patient has a better than 60% chance of needing a repeat PD within the next 10 years. If at any time PD does not give long-term relief, he can undergo surgical myotomy with results similar to choosing surgery as initial treatment. On the other hand, PD beginning with a 3.0-cm balloon is my treatment of choice for women, especially those 30 years of age or older. Reasons for these age and sex differences are not known, although variations in LES muscle characteristics are postulated.

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