The Kagoshima consensus on esophageal achalasia

G. Triadafilopoulos,1 G. E. Boeckxstaens,4 R. Gullo,2 M. G. Patti,2 J. E. Pandolfino,3 P. J. Kahrilas,3 A. Duranceau,5 G. Jamieson,6 G. Zaninotto7

1Division of Gastroenterology, Stanford University School of Medicine, Stanford, California, 2Department of Surgery, University of Chicago, and 3Division of Gastroenterology, Northwestern University, Chicago, Illinois, USA; 4Department of Gastroenterology, Catholic University of Leuven, Leuven, Belgium; 5Department of Surgery, University of Montreal, Montreal, Quebec, Canada; 6Department of Surgery, University of Adelaide, Adelaide, South Australia, Australia; and 7Department of Surgery, University of Padua, Padova, Italy

SUMMARY. Esophageal achalasia is a primary esophageal motility disorder characterized by lack of peristalsis and a lower esophageal sphincter that fails to relax appropriately in response to swallowing. This article summarizes the most salient issues in the diagnosis and management of achalasia as discussed in a symposium that took place in Kagoshima, Japan, in September 2010 under the auspices of the International Society for Diseases of the Esophagus.

KEY WORDS: achalasia, high resolution manometry, Heller myotomy, BoTox injection, myotomy.

INTRODUCTION

Esophageal achalasia is a primary esophageal motility disorder characterized by lack of peristalsis and a lower esophageal sphincter (LES) that fails to relax appropriately in response to swallowing. The LES is hypertensive in less than 50% of patients.1 Herein, we summarize the most salient issues in the diagnosis and management of achalasia, as discussed in a symposium that took place in Kagoshima, Japan, in September 2010 under the auspices of the International Society for Diseases of the Esophagus.

PATHOPHYSIOLOGY

Under normal conditions, swallowing results in a well-coordinated peristaltic wave with relaxation of the LES. It is now well established that enteric inhibitory neurons located in the esophageal wall are responsible for both the timing of the peristaltic contractions and LES relaxation.2 In achalasia, however, esophageal manometry reveals absence of peristalsis and impaired swallow-induced LES relaxation. Similarly, when LES muscle strips obtained during surgery from patients with achalasia are mounted in organ baths and electrically stimulated, no relaxations can be evoked. This strongly contrasts with control tissues where electrical stimuli result in frequency-dependent relaxations mediated by the inhibitory neurotransmitter nitric oxide. To date, we know that lack of relaxation in achalasia is due to the loss of the enteric neurons3 but why the esophageal enteric neurons gradually disappear in such patients remains unclear. However, evidence is accumulating that an autoimmune response targeted against these neurons, most likely triggered by an infectious agent, may be involved.4,5 This hypothesis fits with previous studies showing that similar to autoimmune diseases, the risk to develop achalasia is associated with
a certain genetic background, rendering individuals susceptible to develop an ‘abnormal’ immune response to an infectious event. Genes that are associated with MHC genes, in particular class II MHC genes, are linked to autoimmunity. Several previous reports have indicated a significant association of HLA-DR and -DQ alleles with achalasia, and have even shown that antineuronal antibodies were especially found in patients carrying the DQA1*0103 and DQB1*0603 alleles. Recently, Facco et al. provided evidence that after herpes simplex virus -1 (HSV-1) infection, the virus or some virus-related antigens persist in the neurons of the esophagus triggering a persistent immune activation, consisting of infiltration of the ganglia with cytotoxic CD8+ T cells and circulating antineuronal antibodies. Interestingly, when T cells were isolated from esophageal tissues obtained during surgery, only T cells from achalasia patients were activated, as demonstrated by proliferation and cytokine production, when they were incubated with HSV-1. Clearly, these data need to be confirmed but would suggest that an aberrant response to a viral infection or to self-antigens triggered by the infection leads to an immune response against esophageal enteric neurons. The observation that enteric ganglia are infiltrated by T cells in early achalasia progressing to a total loss of neurons and fibrosis further supports the autoimmune-mediated disease hypothesis.

DIAGNOSIS

The diagnosis of achalasia is based on a careful clinical history and the results of barium swallow, endoscopy, and esophageal manometry.

Clinical

Among 145 patients with untreated achalasia, dysphagia was present in 94% of patients, regurgitation in 76%, heartburn in 52%, and chest pain in 41%. Weight loss was reported by 35% of patients. The average body mass index was 25 (range, 15–41). Symptoms alone do not distinguish achalasia from gastroesophageal reflux disease (GERD). In one study, 65 of the 145 patients (45%) had been initially treated by acid-reducing medications on the assumption that GERD was the cause of their symptoms.

Barium swallow

Barium swallow in achalasia usually shows narrowing at the level of the gastroesophageal junction (‘bird beak’) due to the functional obstruction caused by the nonrelaxing LES, and associated variable degrees of esophageal dilation (Fig. 1). Compared to esophageal manometry, the diagnostic sensitivity of barium swallow is 60%; in the remaining 40%, the study is either considered normal, suggestive of GERD, nonspecific esophageal motility disorder, or peptic stricture. Barium swallow is of key importance in defining the morphology of the esophagus (diameter and axis) and associated conditions, such as epiphenic diverticulae or cancer. When seen later in the course of achalasia, some patients may present with a dilated and sigmoid-shaped esophagus (Fig. 2) that leads to important preoperative technical considerations. In other circumstances, the barium swallow shows associated pathology, such as an epiphenic diverticulum (Fig. 3). In such instances, the distance of the diverticular neck from the gastroesophageal junction and the side of origin in the esophageal wall are important in allowing adequate preoperative planning. Most diverticula originate from the right side of the esophagus and can be resected through a laparoscopic approach that allows easy orientation of the stapler for transection of the diverticular neck, and the performance of a myotomy and partial fundoplication.

Endoscopy

Although endoscopy may suggest the presence of achalasia, it is diagnostic only in 50% of patients. It may identify esophageal dilation, atony, chaotic spasticity of the esophageal body, food or fluid retention,
or resistance to the passage of the endoscope into the stomach; esophageal candidiasis is often seen (Fig. 4). The main reason to perform endoscopy is to exclude the presence of other pathology, such as cancer. Patients with achalasia have an increased risk of developing stasis-related squamous cell cancer; if they have undergone previous treatment that has allowed abnormal reflux to occur, they are mostly at risk for adenocarcinoma. In addition, it is important to exclude pseudoachalasia (or secondary achalasia), often caused by a neoplasm of the gastroesophageal junction that leads to dysphagia not necessarily only by luminal obstruction.12,13 The clinical presentation can be identical to that of idiopathic achalasia, often resulting in a substantial delay in diagnosis and treatment. This syndrome should be suspected in elderly patients who have had a significant weight loss but a short duration of symptoms. When the clinical presentation suggests a malignancy that cannot be identified by routine evaluation, an endoscopic ultrasound and a fine cut CT scan should be performed.

High-resolution manometry

High-resolution manometry (HRM), capable of monitoring pressure from the pharynx to the stomach together with esophageal pressure topography (EPT) plotting represents an unquestionable evolution in the diagnosis and management of achalasia.14,15 The algorithm begins with a stepwise algorithm that analyzes each swallow for the morphology of the esophagogastric junction (EGJ), the extent of EGJ relaxation, the contractile front velocity of peristalsis, the vigor of the peristaltic contraction, and abnormalities of intrabolus pressure. The resultant classification objectifies the identification of three unique subtypes of achalasia. Additionally, it also provides enhanced detail in the description of EGJ obstruction and thus, may be helpful in defining achalasia variants. Figure 5 depicts the typical high-resolution esophageal pressure topography of both sphincters and the intervening esophageal body during a normal swallow; the relative timing of sphincter relaxation and segmental contraction as well as the position of the transition zone are all readily demonstrated.

The diagnosis of achalasia is focused primarily on defining patients based on the presence of EGJ outflow obstruction while the subtypes are determined by the contractile and pressurization pattern. The prerequisite pattern should lack ordered propagating peristalsis (aperistalsis) and can range from complete failure of peristalsis to spastic contractions. However, it is possible that some variant patients may have intact or partially retained propagating contractile activity and these variants could potentially be an achalasia motor disorder in evolution or a pseudoachalasia/EGJ obstruction related to a secondary cause that would require further evaluation to rule out mechanical obstruction (Fig. 6).16 The pressurization pattern is also an important qualifier as
this metric will signify the level of esophageal dilation and the pressure target for EGJ disruption for flow to occur. Combining these parameters allows for a mechanistically driven classification with a focus on predicting clinical outcome.\textsuperscript{17}

The diagnosis of achalasia requires both aperistalsis and impaired deglutitive EGJ relaxation. In its most obvious form this occurs in the setting of esophageal dilatation with negligible pressurization within the esophagus (Fig. 7a). However, despite there being no peristalsis, there can still be substantial pressurization within the esophagus. In fact, a very common pattern encountered is achalasia with esophageal compression and pan-esophageal pressurization (Fig. 7b). The other, less common pattern is of spastic achalasia in which there is a spastic contraction within the distal esophageal segment (Fig. 7c). In a series of 99 consecutive patients with newly diagnosed achalasia, 21 had the pattern in Figure 7a, 49 the pattern of Figure 7b, and 29 the pattern of 7c.\textsuperscript{16} Logistic regression analysis found pan-esophageal pressurization (Fig. 7b) to be a predictor of positive treatment response while spastic achalasia (Fig. 7c) and pretreatment esophageal dilatation were predictive of negative treatment response. Adopting these subclassifications will likely strengthen future prospective studies of achalasia management.\textsuperscript{17,18}
Pneumatic dilation (PD) weakens the LES by bluntly tearing its fibers. It is currently performed using a Rigiflex balloon (Boston Scientific Corp, Boston, MA, USA), passed over a guidewire, filled with radiographic contrast and positioned using fluoroscopy to straddle the LES. There are three commercially available balloons with different diameters (3.0, 4.0, and 6.0 cm). The procedure is typically performed under conscious sedation, and patients are monitored closely for complications such as perforation or stricture formation.
3.5, and 4.0 cm). Typically the graded approach is used, one dilation per session, starting with the smallest balloon: if symptoms persist, the procedure can be repeated with incrementally larger balloons.

A gastrografin esophagogram is usually performed shortly postprocedure to rule out perforation that occurs at a rate of 3–5% (range 0–20%) and carries a favorable outcome if detected early. Some perforations can be managed nonoperatively, but free perforation needs urgent laparotomy or thoracotomy. Patients are referred to surgery if three consecutive dilations do not provide symptom resolution. PD provides long-term relief of dysphagia in 65–89% of cases but has little effect on chest pain that is present in 40–60% of patients. The likelihood of GERD after PD is 2–4%. Reliable predictors of response to PD are a post-dilation decrease in lower esophageal sphincter pressure (LESP) to <10 mmHg, age >40 years and female gender. Symptom duration, initial LESP, nuclear emptying scan, size of the balloon dilators and post-dilation barium swallow are not reliable in predicting the clinical response. PD after BoTox injection is safe and feasible but there is no added benefit to combination therapy of BoTox injection before pneumatic dilation.

In a long-term study of 77 patients, 69 achieved stable remission and were followed for 5.6 years; six patients had myotomy and two perforated. Twelve patients relapsed after 2.6 years and 9 of them had 1–2 PD. Six-year remission rates were 82% after first PD and 96% after all PD. Continuous proton-pump inhibitor (PPI) was clinically needed in 16%, esophagitis in 7%, and pathological reflux by pH was seen in 28%. The effects of PD on esophageal motility and diameter were maintained. Overall, retrospective studies on PD show good to excellent response in 70% of patients while prospective studies show that 50% of patients relapse over 5 years, requiring at least one additional dilation, or surgery. Patients who stay well in the first 5 years are likely to continue to do well; in contrast, nonresponders to a single pneumatic dilation, particularly younger patients, should be offered early surgery.

A randomized controlled trial of endoscopic pneumatic dilation and laparoscopic Heller myotomy (LHM) has been recently reported. In this multicenter trial, 204 newly diagnosed achalasia patients (117 males; ages 19–74 mean 46) were randomized to either PD (n = 94; using Rigiflex balloon, 30 and 35 mm) or LHM (+ Dor antireflux procedure) (n = 106). Patients were re-evaluated at 1, 3, 6, 12 months after treatment, followed by a yearly visit; treatment was considered unsuccessful if their Eckardt score was >3. The authors concluded that after 2 years, PD and LHM have a comparable success rate of 92–87%, lower esophageal sphincter pressure is higher in PD after 1 year, and that either approach can be proposed as initial treatment. Further follow-up will be required to evaluate long-term outcome.

Botulinum toxin (BoTox) injection

Figure 8 shows three different applications of BoTox, a potent inhibitor of acetylcholine release from nerve endings, in patients with achalasia: intra-sphinetic, at the level of LES, in the esophageal body (for vigorous achalasia) and intra-pyloric, for achalasia-associated gastroparesis. The only one that has been formally studied, endoscopic intra-sphinetic injection of BoTox, carries an initial clinical response of 90%, a 32% response at 12 months, and a 3% response at 2 years. Its efficacy decreases with repeat injections, possibly as a result of antibody formation. Because of its safety, BoTox injection is a good
option for elderly patients with comorbidities but it carries an increase in risk of subsequent myotomy, due to fibrosis at the injection sites. The BoTox injection technique is shown in Figure 9. In a randomized controlled comparison of myotomy to BoTox injection, 88% of myotomy patients were symptom-free at 2 years in contrast to only 34% of the BoTox-treated patients. Prior BoTox or PD may have significant impact on the outcomes of subsequent myotomy with twice the number of complications, dysphagia, and failure rates seen.

**Per oral endoscopic myotomy**

Per oral endoscopic myotomy is a new endoscopic procedure for the treatment of achalasia. In a series of 20 consecutive cases (four with sigmoid esophagus), a submucosal tunnel was made, followed by a circular myotomy, 7 cm in the distal esophagus and 2 cm into the cardia, without complications. Although symptom reduction or elimination was reported in all cases and mean LESP decreased from 52.5 mmHg to 19.8 mmHg, the follow-up has been short (months).

**Other**

Several other endoscopic therapies may be used in patients with achalasia, depending on their clinical condition and are shown in (Fig. 10).

In summary, several endoscopic procedures are available to patients with achalasia, depending on the indication. PD and BoTox are similar in improving symptoms over 1–2 years, although most patients treated with BoTox will require additional treatment. Myotomy is more likely to lead to long-term symptom control than PD or BoTox, but at the cost of GERD.

**SURGICAL THERAPY**

To some extent, endoscopic balloon dilation and Heller myotomy of the lower esophagus have always been alternative therapies in the treatment of achalasia. Nevertheless, the introduction of laparoscopic surgery has led to a swing toward the surgical treatment for this condition. Surgery has the advantage of a more precise disruption of the lower esophageal
musculature and probably a more prolonged relief of dysphagia, but the disadvantage of requiring general anesthesia (Figs. 11 and 12). Randomized studies of the two procedures have tended to favor the surgical treatment also, although the largest trial mounted to date at very early follow-up suggests there is not a lot to choose between the two therapies.

The principle underlying the lower esophageal myotomy is for all the muscle fibers of the lower esophageal sphincter to be divided, therefore diminishing the resistance to esophageal outflow and allowing food to pass through into the stomach under gravity. Although regarded as one of the more challenging laparoscopic esophagogastric operations, with appropriate mentoring the learning curve for the procedure is probably in the range of 10–20 operations. A majority of surgeons today add some form of antireflux procedure (vide infra) to prevent the reflux that might be expected to occur after destroying the lower esophageal sphincter.

The major difference of opinion among surgeons today is in two areas: (i) the length of the myotomy. There are no very scientifically hard data on how long the myotomy should be. Observational studies have led to the conclusion that the myotomy should extend 4 or 5 cm onto the esophagus and 2 to 3 cm onto the stomach, and this length is probably utilized by most surgeons today. Some surgeons use intraoperative endoscopic monitoring to determine the length of the myotomy, terminating the division of muscle when the lower esophagus has been rendered patulous. Using endoscopy like this means that the myotomy is usually shorter, extending about 4 cm onto the esophagus and for 1 cm or less onto the gastric wall. (ii) The addition of an antireflux procedure. There are now several randomized controlled trials showing that the addition of an antireflux procedure to a myotomy substantially diminishes the amount of pathological reflux that occurs following the procedure (Fig. 12). The clinical importance of this reflux has not been certainly determined, particularly since it can usually be successfully treated with PPI. Nevertheless, the majority of surgeons today advocate the use of an antireflux procedure, usually either an anterior (Dor) or posterior partial fundoplication. The higher incidence of dysphagia after a 360° fundoplication compared to a partial fundoplication in achalasia has led to the steady decline of the former being performed following a myotomy.

There are several reports on the long-term outcomes of the treatment of achalasia with a laparoscopic myotomy combined with an antireflux procedure. One study of 155 patients followed for a minimum of 5 years showed that about a quarter of
the patients still experience difficulty in swallowing on a daily basis and another quarter have problems on a weekly basis. In spite of this, 90% of the patients rated their procedure as successful. These findings undoubtedly reflect the fact that surgery does not alter the adynamic nature of the achalasic esophagus. Similarly, other studies show good results with the maintenance of patient satisfaction above 80% at 5 years and beyond.

In summary, despite the variations as to the length of the myotomy and the addition or not of an antireflux procedure, good overall long-term results suggest that these operative variations are not too important. The different types of achalasia that are now detected using HRM may lead to further fine tuning of surgery, but this remains to be demonstrated.

**MANAGEMENT OF ‘END-STAGE’ ACHALASIA**

The current therapies for esophageal achalasia achieve good results in the majority of patients: surgical myotomy, if performed when the esophagus shows a straight axis, results in a 90–95% early success rate, while pneumatic dilation improves symptoms and esophageal emptying in 70% of patients. However, over time, these success rates decrease: 10–15% of treated patients will undergo progressive deterioration of their esophageal function and up to 5% may eventually end up with an ‘end-stage’ achalasia requiring esophagectomy. The achalasic esophagus should be considered at an ‘end stage’ when massive dilation and retention have occurred despite an appropriate initial treatment. Incomplete esophageal emptying with mucosal damage from unresponsive reflux disease or despite multiple attempts of treatment are also part of the ‘end stage’ definition. Stasis of luminal contents induces diffuse squamous hyperplasia with papillomatosis, basal cell hyperplasia, an increased number of intraepithelial lymphocytes, and extensive basal and supra-basilar cell p53 immunoreactivity.

Despite a consensus on the need for esophagectomy in end-stage achalasia, most surgeons emphasize that a modified Heller myotomy should be attempted initially, even in patients with a dilated and sigmoid-shaped esophagus, reserving esophagectomy for the failures (Fig. 13). More recently, Peters, reporting the experience of the University of Southern California, proposes the following indications for esophageal resection: (i) massive esophageal dilation with failed previous myotomy; (ii) multiple previous operations; and (iii) reflux complications. In the last case, however, the need for a more radical treatment as an esophagectomy has to be weighted against long-term acid suppression using PPI and H2 receptor antagonists. When the esophagus has been rendered unusable either by natural disease evolution or from complications of therapy, resection may become necessary. However, the ideal method of reconstruction has not been yet established.

Gastric interposition after esophagectomy has the advantage of a single anastomosis when not counting or adding a pyloroplasty and has good to excellent results in 70–81% of patients but significant morbidity. The vascular supply to the proximal stomach is rarely perfect contributing to anastomotic complications at the neck, while reflux-related mucosal damage is virtually always present on the esophageal remnant, making this reconstruction an ideal clinical model for

---

**Fig. 12** The operation is complete after constructing a partial fundoplication; in general, the Dor anterior hemi-fundoplication is preferred. Two rows of stitches suture the anterior part of the fundus to the left and right muscular edges of the myotomy.
reflux. This is particularly evident if a distal (partial) esophagectomy and esophagogastrostomy are performed and the reconstruction is on an achalasic esophagus that typically cannot regain function. Antrectomy and a Roux-en-Y reconstruction may offer a solution, but there is little objective information on the functional response after this operation in achalasia patients. If the Roux-en-Y is added primarily to a gastric interposition with a reconstruction high in the chest or in the neck, the operative complexity might be compared to that of a long limb colon interposition. Adding antrectomy and bile diversion to an already performed gastric interposition has its own complexity although the endoscopic results on the esophageal remnant are excellent.

Esophagectomy followed by colon interposition is more complex because of the vascular anatomy of the transplant and because of the three anastomoses required. Once again, objective functional assessment, endoscopic, as well as histologic evaluation of the transplant over time will be still needed. A short colon interposition may represent a good choice for the achalasia patients; the achalasic esophagus as well as the transplanted colon need close follow-up, however, for their respective long-term results and evolution of complications. Jeyasingham reported in 1999 the Bristol series with 365 colon interpositions. Sixty-nine of these reconstructions were long, while 296 were short interpositions between the subaortic esophagus and the posterior stomach. For the long ones, ischemia at the distal extremity of the transplant is perceived as a risk for fistula and stricture formation at the cervical anastomosis while redundancy at the supraaortic, supradiaphragmatic, and subdiaphragmatic levels become responsible for functional and mechanical dysfunction that may require reintervention. The short segment colonic transplant is an iso-peristaltic colon replacement based on either the middle colic or the left colic arterial supply and is generally perceived as an excellent operation, with minimal and mostly preventable morbidity.

Jejunal interposition (Merendino’s technique) was initially reported to give satisfactory results, but mostly in patients with idiopathic reflux strictures. In achalasia patients, its results are comparable with that of colon interposition. The vascular supply, however, is less reliable and limits the reconstruction to the distal esophagus, unless microvascular revascularization is added.

References


