Techniques in Gastrointestinal Endoscopy 16 (2014) 10–19

Contents lists available at ScienceDirect

Techniques in Gastrointestinal Endoscopy

journal homepage: www.techgiendoscopy.com/locate/tgie

Botulinum toxin and pneumatic dilation in the treatment of achalasia

Anand R. Kumar, MD, MPH[a], Felice H. Schnoll-Sussman, MD, FACG[b], Philip O. Katz, MD, FACG[a,*]

[a] Einstein Medical Center, Philadelphia, Pennsylvania
[b] New York Presbyterian Hospital/Weill Medical College of Cornell University, New York, New York

ARTICLE INFO

Article history:
Received 19 July 2013
Received in revised form
12 August 2013
Accepted 5 October 2013

Keywords:
Botox
PD
Endoscopy
Technique
Efficacy
Manometry
HRM
Treatment choice

ABSTRACT

Achalasia is an esophageal motility disorder characterized by complete absence of peristalsis in the esophageal smooth muscle and a functional esophagogastric junction outflow obstruction. Treatment is directed at improving this outflow obstruction with the goal of improving symptoms in an incurable disease. Multiple treatment options are available to meet this goal. Long-term success can be achieved with effective use of endoscopic pneumatic dilation. In the appropriate patient, botulinum toxin injection can afford short-term relief. This review addresses the use of and techniques for performing these therapies as treatment for achalasia.

1. Introduction

Achalasia is an esophageal motility disorder characterized by absence of peristalsis in the smooth muscle along with incomplete lower esophageal sphincter (LES) relaxation. Achalasia, a word derived from Greek and New Latin, literally means failure of a ring of muscle to relax. The primary cause of symptoms in patients with achalasia is functional outflow obstruction in the distal esophagus secondary to incomplete (or failed) LES relaxation. The most common presenting symptom is dysphagia to both solids and liquids, with the former predominating. Additional common symptoms include heartburn and chest pain. Cough is rare, as is pneumonia secondary to aspiration. The disease can present at any age and appears equally in men and women. Diagnosis is based on clinical suspicion, findings seen on barium swallow, and endoscopy and should always be confirmed by esophageal manometry. Currently, the only required finding on manometry is the complete absence of peristalsis in the smooth muscle of the esophagus. In addition, esophagogastric junction (EGJ) outflow obstruction is seen on high-resolution manometry or incomplete LES relaxation on traditional solid-state manometry (Figure 1). Barium esophagram can show a dilated esophagus with air-fluid level, bird beaking of the lower end of the esophagus, and lack of air-bubble in the gastric fundus (Figure 2). High-resolution manometry (HRM) with pressure topography has allowed for perhaps a more precise classification of achalasia into 3 subtypes using the new Chicago classification [1].

Achalasia is caused by a loss of myenteric plexus ganglion cells in the smooth muscle portion of the esophagus and LES. The exact factors responsible for the ganglion cell degeneration are poorly understood [2-7], therefore achalasia should be considered idiopathic. Nitric oxide is a key inhibitory neurotransmitter involved in esophageal sphincter relaxation. Less nitric oxide synthase in the LES of patients with achalasia has been reported [7]. There are conflicting studies implicating a variety of viral agents including herpes simplex, varicella, and measles [2]. Some evidence supports a genetic basis for achalasia, including polymorphisms identified in VIPR1, IL 23 receptor, and PTPN22 [3,7]. Involvement of the esophagus by Chagas disease, which is caused by infestation with the parasite *Trypanosoma cruzi*, is associated with the classic manometric pattern seen in achalasia. However, unlike the selective involvement of the esophagus in idiopathic achalasia, Chagas disease involves other organs as well, resulting in cardiomyopathy, megaduodenum, megacolon, and megaureter [5].

2. General principles of treatment

There are several important considerations for the clinician offering treatment options to the patient with achalasia. First, there is no treatment option that would reverse the pathologic changes in the sphincter or restore peristalsis in the body of the esophagus. Therefore, treatment is palliative, aimed at

* Corresponding author.
E-mail addresses: KatzP@einstein.edu, philipokatz@gmail.com (P.O. Katz).

0049-0172/$ - see front matter © 2014 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.tgie.2013.10.002

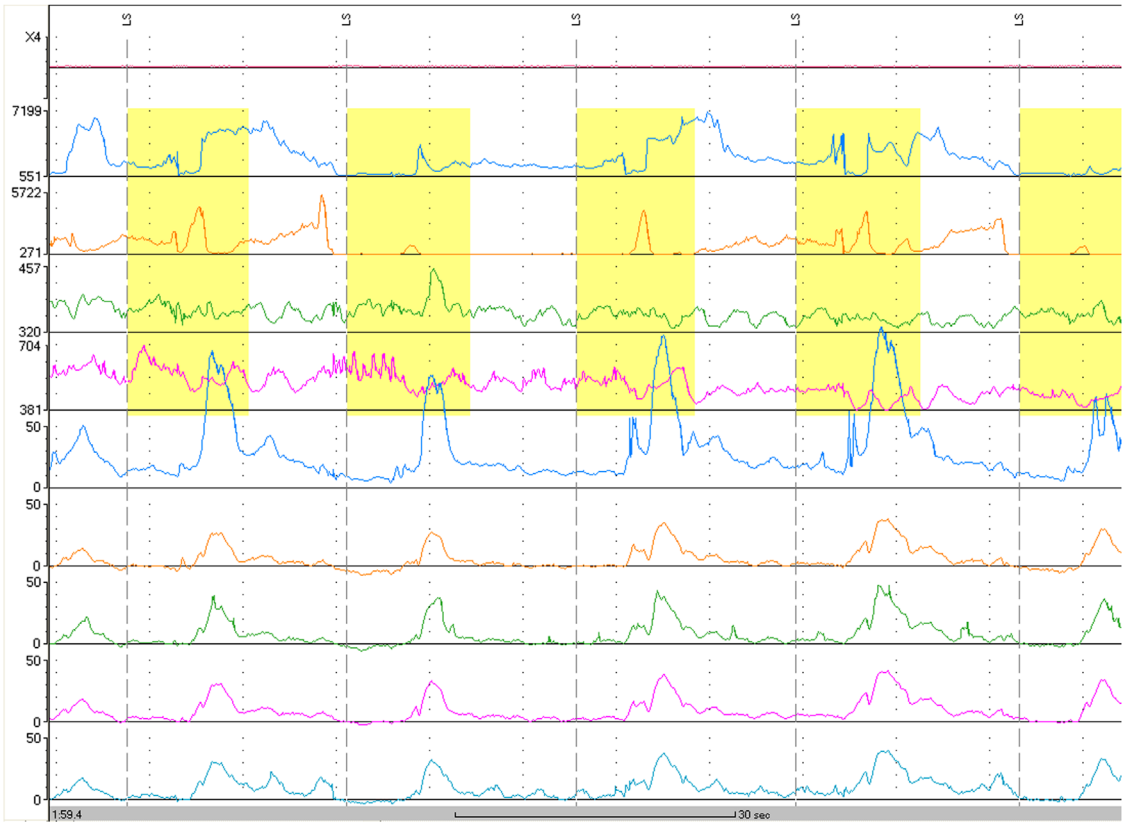

Fig. 1. Achalasia as seen on standard manometry tracing. "Mirror images" of contractions seen in the smooth muscle portion of the esophagus, indicating absence of peristalsis. (Color version of the figure is available online.)

improving symptoms and enhancing quality of life as best as our treatment can. Available data suggest strongly that achalasia does not result in shortened life span and is unlikely a major risk for development to cancer. Although routine surveillance is not supported by national Gastroenterology society guidelines, achalasia has long been held as a potential risk factor for the development of esophageal squamous cell carcinoma [8]. Although studies are small and potentially flawed, the clinician taking care of a patient with a history of achalasia should discuss surveillance and promptly work up any red flag symptoms suggestive of an esophageal malignancy. Symptoms are improved by relieving the outflow obstruction at the LES; thus, dysphagia and heartburn are the symptoms most readily and consistently relieved. Chest pain is traditionally harder to treat. Treatment, therefore, must balance the relief of symptoms against complications (procedure risk) and the production of gastroesophageal reflux after either pneumatic dilation or surgical myotomy. Patients must be informed that no treatment is universally successful and that additional treatment beyond the initial intervention may be required over a lifetime.

Recent analysis of the pressure topography patterns recognized on HRM allows achalasia to be divided into 3 subtypes. All 3 have EGJ outflow obstruction and absence of peristalsis (Figure 3). Division into these subtypes has been shown by retrospective and post hoc analysis to have prognostic significance, with type 2 having the best response and type 3 the worst [7,9-13]. Early evidence suggests that knowing the subtype may be useful in planning the initial treatment.

There are 2 effective "long-term" treatments for achalasia: esophageal myotomy and endoscopic pneumatic balloon dilation. Endoscopic botulinum toxin injection and medical therapy with calcium channel blockers, nitrates, and more recently sildenafil are treatment options that typically offer only short-term symptom improvement. The type of intervention chosen largely depends on the patient's overall surgical tolerance and well-being, in addition to the center's expertise and individual patient's preference. The remainder of this review focuses on the endoscopic treatment modalities, botulinum toxin injection, and pneumatic dilatation.

3. Botulinum toxin

Elegant studies in pigs demonstrated that botulinum toxin (Botox) injection into the LES region reduced LES pressure; findings were confirmed in subsequent human studies. Botox acts on presynaptic nerve terminals in the neuromuscular junction by blocking the release of acetylcholine through inhibition of the SNAP-25 protein, which is essential for the exocytosis of neurotransmitters [14]. The toxin's action on postganglionic cholinergic nerve terminals of the myenteric plexus was first described in 1980 [15]. Successful outcomes after the injection of Botox into the LES were first reported over a decade later by Pasricha and colleagues [16-19]. Subsequently, numerous other investigators have reported successful outcomes with Botox injection using various techniques [20-52].

In the initial studies [16-19], the LES was identified as a rosette, seen typically at the squamocolumnar junction. The toxin (80 U in 4 ml saline) was injected using 5-mm sclerotherapy needle in 1-ml aliquots (20 U each) into the LES in a 4-quadrant fashion. Symptom improvement was reported in about two-thirds of patients, most commonly in those older than 50 years [19]. Objective testing showed some decrease in LES pressure but improvement in only esophageal emptying as measured by nuclear radiology, with little improvement in barium emptying. This discrepancy leaves the rationale for symptom improvement unclear. Little to no side effects were reported in this and subsequent studies (chest pain in 10%). Overall, injection of Botox achieves improvement of dysphagia in