P. Marco Fisichella
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Editors

Achalasia

Diagnosis and Treatment

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ISBN 978-3-319-13568-7 ISBN 978-3-319-13569-4 (eBook)
DOI 10.1007/978-3-319-13569-4

Library of Congress Control Number: 2015951963

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

To Dr. Melina R. Kibbe, inspiration and role model for those who have committed their lives to academic surgery.

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Introduction

Esophageal achalasia is motility disorder characterized by the absence of esophageal peristalsis and failure of the lower esophageal sphincter to relax in response to swallowing. These abnormalities lead to impaired emptying of food from the esophagus into the stomach with resulting food stasis. Most patients experience severe dysphagia, and regurgitation can lead to aspiration and respiratory problems. As a consequence, the quality of life of patients affected by this disease is severely affected.

The last 25 years have witnessed a significant improvement in the understanding of the pathophysiology of achalasia, and our ability to diagnose it and treat it. Today the results of treatment are significantly better than they were in the past.

This book represents a joint effort of experts who have focused their career on the treatment of this disease. The reader will find an excellent presentation of the pathophysiology of the disease and its diagnostic approach. In addition, the treatment is carefully described, from dilatation to per oral endoscopic myotomy (POEM), from a laparoscopic Heller myotomy to esophageal resection. Special emphasis is given to new techniques such as POEM, and to special situations such as the treatment of pediatric patients, patients with achalasia and epiphrenic diverticulum, patients with achalasia and obesity, and those with recurrent dysphagia after prior treatment.

This is an important contribution for residents, fellows, and practicing gastroenterologists and surgeons who have an interest in helping patients with esophageal achalasia.

A One Hundred Year Journey: The History of Surgery for Esophageal Achalasia

1

P. Marco Fisichella and Marco G. Patti

Introduction

> There is probably no disease that responds more satisfactorily to proper treatment than cardiospasm. Herman J. Moersch, Mayo Clinic, 1933 [1]

Dr. Moersch could not have been more accurate. Today, like in 1933, operations for achalasia are very gratifying for the patients, as their quality of life is often dramatically improved. How did we get here today, from 1933? The history of treatment of achalasia is mesmerizing, and is deeply intertwined with the thought processes involved in trying to identify its etiology and determine its pathophysiology. What is striking today is the evolution of the concept of this disease which takes place at the beginning of the twentieth century, a time when only post mortem examinations could shed light on indirect evidence of actual pathophysiologic theories. Giants of surgery, like Maingot, Wangesteen, Ochsner, and Plummer and Vinson, clearly understood the importance of recognizing the pathophysiology of this obscure disease and used this knowledge as a guide for the best form of treatment. Therefore, by reading the original accounts of those days early in 1900 the modern surgeon is definitely fascinated by the great wisdom and surgical acumen of the fathers of modern surgery. Our goal is to revisit those early accounts faithfully to understand the lessons learned over a journey that has lasted 100 years since the first report of Dr. Heller. We also aim to continue our journey to modern days to describe the development of fundoplications and other endoscopic treatments to finally illustrate the modern surgical approach of patients with achalasia.

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Early Accounts and First Attempts to Propose a Pathophysiologic Mechanism of an Elusive Disease. The Term: "Achalasia" Is Coined

Early accounts of dysphagia relieved by mechanical anterograde dilatation with a whalebone date back to 1674 [2]. In more modern times, Purton in 1821 reported the first case of cardiospasm treated by dilatation, while Zenker and Von Ziemssen in 1878 reported 17 cases [3].

The origin of the disease remained elusive and many theories were proposed. Crossan Clark from Hamilton, Canada, enumerated in detail

P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_1

those theories most in vogue at the beginning of the century. Clark illustrated how Flainer, Zenker, and Sievers theorized that esophageal dilatation resulted from congenital muscular irritability; how Martin considered primary esophagitis the most important factor; how Kraus claimed that there was paralysis of the circular musculature of the esophagus; and how Golden and Mosher thought that "*the upper border of the liver*" exerted outflow obstruction at the distal esophagus [3]. During the same time, Jackson also proposed that the diaphragmatic pinchcock action could provoke an outflow obstruction to the food bolus by incoordination or spasm of the diaphragm during the act of swallowing [4].

Pathophysiologic theories in the early 1900 were based on anecdotal evidence at its best. However, in 1914 Dr. Arthur Hertz, while commenting a paper form F. Parker Weber proposed that the disease was not due to a spasm of the cardia, like most at that time believed [5]. As a proof of his thesis Hertz brought the results of his studies done in 1909 at the Guy's Hospital on extensive post mortem examination of cases thought to be caused by cardiospasm. Hertz argued against a cardiospasm because "*the symptoms were often present for many years before death and it was quite unconceivable that a spasm of such long duration should not lead to any hypertrophy of the cardiac sphincter… The condition was really due to the absence of the normal relaxation, which should occur when each peristaltic wave, travelling down the oesophagus, reached the cardiac sphincter. It had been experimentally shown that section of the vagi … prevented this relaxation, and led to accumulation of food in the oesophagus, which consequently became dilated*" [5]. Intrigued by Hertz's logic, F. Parker Weber replied that "*such state of affairs might almost be compared to what occurred in cases of "heart-block"*" [5]. It was the first time that an unknown abnormality of peripheral nervous system was implicated in the pathophysiology of the disease. Later studies from Rake would confirm this simple intuition.

In 1915, Dr. Hertz reiterated formally his theory to which he gave the name of "*achalasia of the cardia*". In fact, in his paper "Case of Achalasia of the Cardia (so-called cardiospasm)" Hertz writes that "*the term "achalasia" (a, not; χαλαω, I relax) was coined for me by Sir Cooper Perry to replace the term "spasm", which is incorrect*" [6]. The arguments of Hertz were subsequently substantiated by Rake who is credited to have been the first to show a degeneration of the Auerbach plexus in patients with non-organic dysphagia [7]. Rake, in fact, in post-mortem examinations of specimens demonstrated that the Auerbach plexus in those with cardiospasm was twice its normal size and infiltrated with small round cells, which Hertz attributed to "*primary*" inflammation of the esophageal epithelium [7].

Hertz's theory was later accepted by Plummer and Mikulicz who believed (based on the experiments done by Rake and the observation by Hertz that symptoms could be alleviated by atropine and worsened by transection of both vagi) that there was some sort of "*neuromuscular disturbance*" responsible for the esophageal dilatation [3]. Clark also added to the argument that: "*No other lesion in the oesophagus causes such marked dilatation above the point of constriction, and therefore the factor of loss of tone is as much as considered as stenosis"* [3].

From Ineffective Esophageal Plications and Retrograde Dilatations to the Successful Cardiomyotomy: The Golden Era of Heller and Zaaijer

Hertz's theory was not widely accepted right away. To summarize the sentiment at that time, Greenwood recites in the British Medical Journal in 1928: "*The term "achalasia" is a premature attempt at generalization, facile and tempting, but quite unjustified by the present state of our knowledge*" [8]. Those who disagreed with Hertz hypothesized that the esophageal dilatation was responsible for the cardiospasm and that an operation should aim to treat the former rather than the latter. The logic was proven fault. The operation of plication consisted in invaginating the upper segment of the dilated and sigmoid esophagus into the lower one, without opening its lumen,

"*thus restoring the proper length and longitudinal tension*" (Dr. Leonard Freeman, 1923) [9]. Also, by Freeman's accounts: "*A number of similar operations also have been done, with more or less success, by various other surgeons (Sencert, Oettinger, Caballero, Sauerbruck, Exner, Tuffier, etc.) having the common objective of straightening out the oesophaus by pulling its redundant portion down into the abdominal cavity and perhaps anastomosing it to the stomach or to the duodenum*" [9]. These operations soon fell out of favor because of their dismal results. Similar fate attended the operation devised by Mikulicz in 1904. Mikulicz devised the technique of retrograde dilatation in which after a gastrotomy was done, he introduced a clamp with rubber covers and used it to stretch the cardia [10].

It was 1910 when Wendel reported the first cardioplasty performed through a vertical incision onto the anterior wall of the cardia and sutured it transversally [11]. Then, in 1914 Heller first described a transabdominal extramucosal cardioplasty performed onto the anterior and posterior walls of the cardia [12]. Heller presented his excellent results at the German Surgical Congress in 1921 [13]. Heller's operation (a modified Ramsted procedure used to treat pyloric stenosis in infants) was a real revolution at that time. As Watts put it in 1923: *"…it would seem that the simplest operative measure is stretching the cardia… but this may be followed by a recurrence. The extramucous cardioplasty of Heller is probably the simplest and best radical operation, if it is as easy and efficient as the reports would lead us to believe"* [14].

The operation devised by Heller had such a success that it was readily adopted and simplified by surgeons in Holland. Dr. J.H Zaaijer from Leiden, in 1923 reported that the Heller operation was a great operative intervention in those cases in which antegrade dilatation was not possible (he cited data from by Plummer and Porter that reported a 25 % failure rate in treating dysphagia with a hydrostatic dilator) [15]. Zaaijer in fact treated eight cases without mortality and with excellent outcomes. As to the details of the operation Zaaijer highlighted that: "*It does not appear to make any difference relative to the subsequent findings whether the incision is made on the anterior side and one on the posterior side as Heller did, or one incision only on the anterior side as has been employed by de Bruine, Groeneveldt and myself*" [16]. Zaaijer continues: "*Heller points out that he considers it necessary to lengthen the incision particularly downwards, whereas it needs only to be carried upwards as far as the beginning of the dilatation"* [16].

Early Attempts to Approach Megaesophagus: The Rise and Fall of Esophagogastrostomy

At the beginning of the 1940s the operations of esophagogastrostomy (side-to-side, Finney type, or Heyrovsky-Grondahl – 1912–1916) still performed by Ochsner and DeBakey fell out of favor mainly because their major side effects. Dr. Rodney Maingot in 1944 recite that "*Although the technical beauty (ndr. esophagogastostomy) has nevertheless one flaw – regurgitation"* [17]. In fact, in those who had an esophagogastrostomy the regurgitation of gastric contents was particularly severe, especially in the supine position, and caused severe esophagitis. Conversely, Maingot noted, "*Oesophagocardiomyotomy is, in my opinion, worthy of a more general adoption, as it is a simple and safe operation, the technique is readily mastered, and the immediate and late results are most gratifying"…"It is associated with negligible mortality and a stay in the hospital which does not in the average case exceed eight days, there is no regurgitation of gastric contents into the oesophagus or mouth and there are no teasing complications such as peptic ulceration. The patient can furthermore enjoy hearty meals without the slightest restraint or discomfort* [17]. Curiously, Maingot's myotomy was "*10 to 15 cm in length… curving slightly upwards towards the fundus, until the oesophageal mucosa and the gastric mucosa bulge boldly outwards without restraint*" [17]. Finally, Maingot claimed that Gottstein in 1901 first suggested the operation later popularized by Heller. Maingot further explained: "*We name certain operations after certain well-known surgeons*

merely because it is customary and more convenient; but it is often the best known sponsor rather than the originator of a particular operation who receives all the praise and credit" [17].

Importantly, it was evident in the 1940s and 1950s that a transabdominal approach was considered the best approach, even though many still preferred a transthoracic approach. Earle B. Kay from Cleveland noted in 1948: "*Most opinions have favored the transabdominal approach, in that this was felt to be associated with less risk*" [18]. Indeed, in 1951 Owen Wangesteen preferred a transabdominal cardiomyotomy, even though this was performed under digital control through a finger inserted into esophagus through a gastrotomy [19].

The Advent of the Partial Fundoplication to Prevent Gastroesophageal Reflux

Up until the late 1960s there is no mention in the literature about the necessity to control or prevent gastroesophageal reflux that arises after the cardiomyotomy. Rudolph Nissen popularized a fundoplication the bears his name in 1956, but it was in 1962 that J. Dor from Marseille, France, proposed an operation that he called "*technique de Heller-Nissen modifiee*" for the treatment of reflux with esophagitis associated with cardiospasm [20]. This operation was performed though a transabdominal approach and involved the performance of a single longitudinal anterior extramucosal cardiomyotomy 10 cm long, extending 5 cm onto the anterior wall of the stomach, below the level of the angle of His. Then, the left side of the myotomy was sutured to the anterior wall of the stomach, which was then folded anteriorly and secured to the right edge of the myotomy with another row of sutures. This is the technique used today in most centers. Of note, Dor never transected the short gastric vessels to facilitate the anterior rotation of the fundus of the stomach to cover the myotomy. In 1967, Dor published a modification of the technique best suited for those who had their gastroesophageal region shaped like a "*hotte de cheminee*", or "the flue of a chimney" (with a very wide angle of His, which Dor aimed at reconstructing to avoid reflux) [21]. This modification still involved a 10 cm extramucosal cardiomyotomy which was then encircled with a sling and pulled down to allow the greater curvature to be folded upwards thus recreating a new angle of His. The edges of the myotomy were then suturing together to form a modified, side-to-side, Finney type, cardioplasty [21].

The new technique was able to provide relief of dysphagia while limiting gastroesophageal reflux. Also at the same time, Andre' Toupet in 1963 devised the posterior fundoplication that bears his name; however, this technique was not implemented until 1976 and only in children [22, 23]. These techniques of fundoplication were not readily incorporated into the surgical treatment as a few still considered a fundoplication unnecessary. Results from the Mayo Clinic confirmed the tendency of not adding a fundoplication during a myotomy. Ellis and Olsen in fact favored a transthoracic short esophagomyotomy, ("*a 3 cm anterior extramucosal esophagomyotomy which extended only a few millimiters onto the stomach*") over a long one "*extending 3 cm onto the anterior wall of the esophagogastric region* [24]". Backed up by manometric data and a review of the outcomes of their 269 patients, Ellis and Olsen argued that a short esophagomyotomy relieved dysphagia and controlled reflux better than the "classic" Heller and "long" Heller. Ellis attributed the good results of the short myotomy in preventing significant gastroesophageal reflux to the preservation of the gastric sling fibers (Willis' loop or collar of Helvitius, or "*sphincteric remnant*"), which contributed to the continent mechanism of the cardial region [24].

Nevertheless, the Heller myotomy and Dor fundoplication become widely implemented, probably because many were not able to reproduce the results of the Mayo Clinic. In 1988, the first long term results of the Heller myotomy and Dor fundoplication on a large case series started to appear in the literature. Csendes et al. performed on 100 patients "*an anterior esophagomyotomy 6 cm long, not extending into the stomach more than 5–10 mm, with the*

addition of an anterior hemi-Nissen or Dor procedure, similar to the Thal serosal patch" and reported, at a mean follow-up of 6.8 years, excellent and good outcomes in 92 of the 94 patients followed-up and objective reflux in 19 % of patients [25]. Subsequently, Bonavina et al. published in 1992, the long-term outcome (median follow-up 64.5 months) on 206 patients operated on from 1976 to 1989 with a cardiomyotomy "*10 cm long (8 cm on the esophagus and 2 cm on the stomach)*" and Dor fundoplication, and reported clinical results excellent or good in 93.8 % and fair in 2.6 % of patients. Similarly, 24-four-hour esophageal pH monitoring showed an abnormal acid exposure in seven (8.6 %) of 81 patients tested [26].

From Thoracoscopic to Laparoscopic Cardiomyotomy

At the beginning of the 1990s minimally invasive techniques were introduced in the clinical treatments of foregut diseases. Because of their advantages in minimizing pain and shortening length of stay, these approaches gained widespread popularity. Therefore, it seemed natural at that time to reproduce the well-known operations with the new minimally invasive approaches. Dr. Cuschieri first performed a laparoscopic cardiomyotomy in 1991 [27]. In 1992, Dr. Pellegrini, aiming to reproduce the technique of Ellis, described the results of 17 patients who underwent a thoracoscopic short myotomy onto the left side of the esophagus extending only 5 mm onto the gastric wall, with the goal to balance the relief of dysphagia with the prevention of reflux [28]. Dr. Pellegrini is also credited to be the first to perform the first two cases of laparoscopic myotomies in United States. These were patients in whom a thoracoscopic myotomy proved to be too short and a second myotomy was then performed laparoscopically [28]. Although the short and long term outcomes proved to be excellent in about 90 % cases, it soon become evident that the thoracoscopic approach had some drawbacks: it required lung exclusion intraoperatively and a chest tube postoperatively, and when reflux was objectively measured by pH-monitoring 60 % of patients had abnormal acid exposure [29]. In 1995, Bonavina et al. first adopted the new minimally invasive techniques to the treatment of patients with achalasia, when they reported a laparoscopic esophageal myotomy combined with a Dor fundoplication that was performed uneventfully in 33 patients [30]. In another study on the same year, the group of Padua concluded that outcome of the laparoscopic approach was as good as that of the open approach, and concluded that because of lesser surgical trauma with consequent reduced postoperative pain and fast return to work the laparoscopic approach was preferable [31]. The laparoscopic approach therefore became at the end of the 1990s the standard of care and relegated the thoracoscopic approach in patients with a hostile abdomen and previous complex abdominal surgery. A few questions remained open, though: (1) How long the myotomy should be? (2) Which fundoplication should be done?

Modern Era: Standardization of the Surgical Technique

Today, it is generally believed that a laparoscopic short myotomy, usually associated with an inadequate extension onto the gastric wall, is often associated with persistent or recurrent dysphagia. Wright et al. compared 52 consecutive patients with achalasia who underwent a Heller myotomy extending for 1–2 cm onto the gastric wall and Dor fundoplication to 63 patients who underwent an extended myotomy (3 cm onto the gastric wall) with a Toupet fundoplication, and found that an extended myotomy gave better relief of dysphagia [32]. Therefore, today most surgeons perform a long myotomy which extends for 2–3 cm onto the gastric wall, as originally described by Heller. A fundoplication is also today routinely performed to prevent postoperative reflux. In fact, a randomized trial by Richards et al. showed that when a fundoplication is not performed, the incidence of abnormal postoperative reflux was 48 %, whereas it was 9.5 % only when a Dor fundoplication was added

to the myotomy [33]. As far as the type of fundoplication, Rawlings et al. in 2012 compared a Dor fundoplication to a Toupet fundoplication after myotomy for achalasia, and found no significant difference in terms of relief of dysphagia and reflux control [34]. On the other hand, a Nissen, 360° fundoplication, is contraindicated as it causes too much of an outflow obstruction in patients without peristalsis. In 2008, Rebecchi et al. in a prospective randomized trial comparing the outcome of a Heller/Dor and floppy Heller/Nissen demonstrated that while reflux was controlled in all cases, the incidences of dysphagia were 2.8 and 15 %, respectively [35]. Therefore, the current recommendation from the Society of American Gastrointestinal and Endoscopic Surgeons is that only a partial fundoplication to prevent reflux should be always done together with a cardiomyotomy [36].

Robotic Surgery, Single Site Surgery, and POEM: The Future?

A few groups have tried to apply the robotic techniques to perform the Heller myotomy arguing that the absence of tremor and magnified 3-D view can reduce the incidence of esophageal perforation. Horgan et al. in 2005 showed that the incidence of perforation was 0 % in the robotic group vs. 16 % in the laparoscopic group [37]. Later, in 2007, Huffman et al. showed similar findings (perforation rate: 0 % in the robotic group vs. 8 % in the laparoscopic group) [38]. Non-superiority of robotic surgery in terms of clinical outcomes when compared to laparoscopic surgery and significant cost and operating room times might raise concerns about the cost-benefit of this approach.

Notably, in the last few years there has been an impetus towards a more minimal approach to achalasia. Single-site surgery has been used to mimic the laparoscopic operation using only one port and short-term results have been promising. Barry et al. compared the short-term outcomes of 66 patients who underwent conventional multi-port Heller myotomy and Dor fundoplication with 66 patients who underwent single site Heller myotomy and Dor fundoplication [39]. They found that the single site operation took longer, but was as safe and effective in relieving dysphagia when compared to conventional surgery. However, their follow-up was short and no data were provided on the postoperative incidence of reflux [39].

In 2010, Inoue developed the Per-Oral Esophageal Myotomy (POEM) with overall initial good patient satisfaction and relief of dysphagia [40]. However, subsequent larger studies showed that this endoscopic surgical technique was frown by a high incidence of pneumothorax, pleural effusions, and heartburn [41]. Since 2010, then, many centers started performing POEM to evaluate objectively the efficacy and safety of this innovative technique. In 2013, Dr. Swanstrom reported his initial results on 18 patients. Although the clinical outcomes were good, 28 % of patients had esophagitis, the residual esophageal sphincter pressure after the procedure was still high (16.8 mmHg), and 46 % of patients had pathologic gastroesophageal reflux on pH- monitoring [42]. At the same time, 70 patients with Type II achalasia were recruited for POEM in five centers in Europe and North America. Again, the clinical outcomes were good but intraoperative complications were substantial (full thickness dissection in the mediastinum was 69 % and perforation into the peritoneal cavity was, 57 %). Also 42 % of patients in this series had esophagitis on follow-up endoscopy and no data on pH monitoring were available [43]. Finally, the most recent comparative study published in 2013 comparing objective outcomes of laparoscopic Heller myotomy with POEM for achalasia showed at a follow up 6 months a disturbing high persistent dysphagia in 76 % of patients who laparoscopic Heller myotomy compared to none in the POEM group [44].

In summary, time will test the outcomes of POEM against the long-term results benchmarked by those of laparoscopic myotomy with partial fundoplication and will assign POEM a defined and very specific role in the treatment of patient with achalasia.

Conclusions

The 100-year journey through the history of surgery for achalasia has identified through its successes and failures what constitutes today the "*proper treatment*" imagined by Moersch

in 1933 and Maingot in 1944. The cardiomyotomy, as envisioned by Heller exactly a century ago, performed laparoscopically together with a partial fundoplication is today the surgical treatment of choice. Longer follow-up and objective assessments of newer endoscopic techniques will characterize their role in the management of patients with achalasia.

Conflicts of Interest The authors have no conflicts of interest to declare.

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Pathophysiology of Achalasia

2

Wai-Kit Lo and Hiroshi Mashimo

Achalasia is a motility disorder of the esophagus with a prevalence of 1:100,000 [1]. The most common primary presenting symptom is dysphagia to both solids and liquids, with gradual symptom progression. Other non-specific symptoms may include regurgitation, chest pain (predominantly in younger patients), heartburn, and halitosis. In advanced cases, patients may also report weight loss, nocturnal cough, and finding regurgitated food or mucous on the pillow upon waking from sleep.

Normally, the lower esophageal sphincter (LES) has myogenic tone, i.e., remains intrinsically contracted in the absence of neural input or hormones, to prevent reflux of gastric contents. It relaxes in response to swallowing and esophageal or gastric distention. This muscle is also under neurogenic control involving the myenteric plexus, which contain both excitatory (acetylcholine-producing) and inhibitory (nitric oxide- and vasoactive intestinal peptide-producing) motor neurons. In contrast, the smooth muscle of the esophageal body lacks demonstrable tone, likely owing to differences in contractile proteins and isoforms compared to smooth muscle of the LES [2]. Unlike contraction in the skeletal muscles controlled by central sequential activation of motor neurons, primary peristalsis along the smooth muscle portion (approximate distal two-thirds) of the esophageal body is initiated by non-sequential simultaneous central activation, and is believed to be propagated largely by peripheral mechanisms to produce a deglutitive inhibition followed by excitation. There is an intrinsic gradient of decreasing cholinergic and increasing nitrergic innervation distally in the esophagus [3, 4].

Pathophysiology involves the selective degeneration of inhibitory neurons in the esophagus, which are needed for peristalsis of the smooth muscle of the esophageal body, as well as relaxation of the tonic LES [5]. The etiology of primary achalasia remains largely unknown. Based on viral antigen reactivity in some patients with achalasia, such viruses as varicella-zoster, human papilloma and herpes have been implicated in initiating an inflammatory reaction [6, 7]. The preference of herpes virus for squamous rather than columnar epithelium could explain predominant esophageal involvement in achalasia while largely sparing the rest of the gastrointestinal tract, and increased risk for esophageal squamous carcinoma. However, polymerase chain reaction

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_2

amplification failed to detect such viruses in myotomy specimens from achalasic patients [8]. Nonetheless, this negative finding does not rule out the role of other viruses, or an earlier viral assault that is cleared by the time symptoms arise. There are also known familial cases of achalasia, including a case report of siblings with coexistent Hirschsprung's disease [9]. Albeit extremely rare, such cases raise the possibility of a genetic basis of the disease [10]. An autoimmune etiology has been suggested, with evidence of circulating autoantibodies [11], and antibodies against myenteric neurons in the serum of approximately a third of achalasic patients [12], as well as association with Class II histocompatibility antigen [13]; however, antibody detection had low specificity for the disease, suggesting the likelihood of epiphenomenon rather than true causation [14]. Neurodegeneration may be a primary etiology given the detection in one study of Lewy bodies, as found in Parkinson's disease [15], or secondary to the aforementioned viral or autoimmune processes, but no central neurologic lesion has ever been implicated [16].

Secondary achalasia, or pseudoachalasia, is considered when achalasia arises secondary to other known causes. For example, Chagas' disease is a tropical parasitic disease found in South America, in which infection by the protozoan *Trypanosoma cruzi* results in systemic invasion of internal organs, thereby disrupting normal functions of structures including the heart, brain, and gastrointestinal system [17]. Malignancy is also an important cause of secondary achalasia, and must be excluded before proceeding with treatment for primary achalasia [18]. Invasive disease, such as esophageal cancer, or extrinsic compression from lung or gastric cancer, can result in achalasia-like symptoms with suggestive findings on testing modalities. Additionally, several malignancies, including breast and small cell lung cancer, have been associated with a paraneoplastic phenomenon of dysmotility based on elaboration of humoral factors, neuronal degeneration, and possibly abnormal neurotransmission [5, 19]. Type 1 antineuronal nuclear autoantibodies (ANNA-1, also called anti-Hu) react with both small cell lung cancer cells and with various nerve cells, and has been found in patients with achalasia, gastroparesis, and pseudobstruction, even before overt diagnosis of cancer [20]. Allgrove's syndrome, consisting of achalasia, alacrima, and adrenal insufficiency, is another secondary cause of achalasia with autosomal recessive inheritance that has been linked to 12q13 chromosome with features also of mental retardation and peripheral and autonomic neuropathy [21].

Whether primary or secondary, the resulting esophageal aperistalsis and incomplete relaxation of the LES impede passage of the swallowed food bolus into the stomach, leading to accumulation of undigested material in the esophagus. Over time, this may result in permanent dilation of the body of the esophagus. In most cases, histologic examination confirms evidence of decreased neurons in the myenteric plexi, with significant inflammatory infiltration including lymphocytosis [22]. The nitric oxide-producing, inhibitory neurons are preferentially affected [23], while cholinergic neurons are largely preserved [24]. As such, the acetylcholinesterase inhibitor edrophonium choline produces enhanced contraction in achalasia. Specific targeted deletion of the neuronal nitric oxide synthase gene in an animal model produces the phenotype of achalasia [25]. Exceptions to this pathological finding include secondary achalasia from multiple endocrine neoplasia (MEN) type 2B and von Recklinghausen's disease (neurofibromatosis), which are characterized not by dropout, but by hyperganglionosis or dysplasia of the myenteric plexus. A mutation in the RET protooncogene, associated with Hirschsprung's disease, was also identified in 90 % of patients with MEN type2, which may explain improper neural crest migration and differentiation [26]. However, other hereditary forms of achalasia require further genetic characterization. Achalasia is also described in patients with autoimmune polyglandular syndrome [27].

Many of the treatments applied for achalasia address and add clarity to these pathophysiologic pathways. The goal of treatment is symptom improvement by decreasing the LES resting

pressure to enhance esophageal clearance, and to minimize the effects of esophageal stasis leading to progressive esophageal dilation. However, no treatments to date have shown restoration of peristalsis in the esophageal body. The non-relaxing LES can be treated by mechanical methods (pneumatic dilation or surgical myotomy), or biochemical means (endoscopic botulinum toxin injection (EBTI) and oral medications). While mechanical methods treat the anatomic obstruction resulting from incomplete LES relaxation, biochemical methods are targeted at specific portions of the proposed pathway. In EBTI, botulinum neurotoxin type A is endoscopically injected into the LES. Botulinum toxin inhibits acetylcholine release to reduce the unopposed excitation of the LES seen in achalasia, thereby allowing the LES to function as normal [28].

Oral medications such as calcium channel blockers (nifedipine 10–30 mg SL, 30–45 min before meals) [29] and nitrates (isosorbide dinitrate 5 mg SL, 10–15 min before meals) [30] can also induce relaxation of the smooth muscle of the LES to enhance esophageal transit in achalasia. The efficacy of these medications, though limited, suggest that the underlying function of the LES remains preserved. More interesting, sildenafil has also been investigated for treatment of achalasia in a smaller study with some success [31]. Sildenafil is a phosphodiesterase inhibitor used in functional impotence, and results in enhancement of inhibitory pathway induced by nitric oxide. Its application in achalasic patients results in improved LES relaxation, further supporting the importance of the above pathophysiologic pathway in achalasia.

Complications of achalasia may include esophageal candidiasis or frank esophagitis, due to retention of food matter in the esophagus. This can contribute to symptoms of dysphagia or odynophagia. There have also been reports of esophageal diverticula, developing as a result of slowed esophageal transit with alteration in bolus flow [32].

The diagnosis of achalasia is usually made with a combination of three testing modalities, which demonstrate evidence of the pathophysiologic process. Esophagogastroduodenoscopy (EGD) may often reveal esophageal dilation with retained foodstuff, as well as complications of esophagitis or candidiasis (Fig. 2.1). Endoscopy is also helpful to exclude other findings such as esophageal or gastric malignancy that can result in secondary achalasia. Barium swallow radiography will often reveal the characteristic finding of smooth tapering or "bird-beaking" in the distal esophagus, which suggests lack of overt mucosal pathology but represents poor LES relaxation (Fig. 2.2). Finally, esophageal manometry is key to the diagnosis of achalasia by revealing evidence of aperistalsis, poor LES relaxation, and often an elevation in baseline LES pressure.

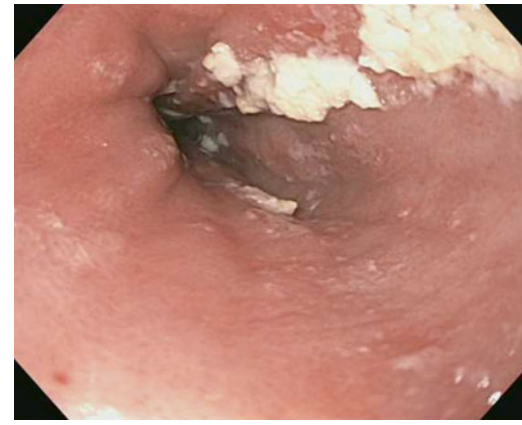

Fig. 2.1 Esophagogastroduodenoscopy (EGD) is used in the assessment of dysphagia, and to evaluate for complications of achalasia. Here, EGD demonstrated evidence of white plaques in the esophagus, signifying a diagnosis of esophageal candidiasis, in a patient with achalasia

As a result of advances in high resolution esophageal manometry (HREM), the diagnosis of achalasia can be further divided into manometric subtypes, with impact on treatment response [33, 34]. Although esophageal aperistalsis, poor LES relaxation, and elevation in basal LES pressure are seen commonly across subtypes, distinguishing manometric characteristics allows for further sub-classification. Type 1 is the classic subtype, with absent esophageal pressurization (Fig. 2.3). Type 2 is the esophageal compression subtype, with pan-esophageal pressurization of the esophagus in greater than 20 % of swallows (Fig. 2.4). Type 3 is the spastic subtype, with high amplitude spastic contractions of the esophagus

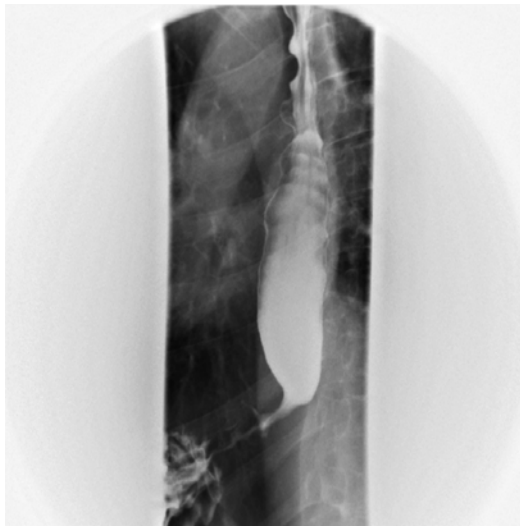

Fig. 2.2 Barium swallow radiography will often demonstrate the classic "bird-beaking" finding in the distal esophagus, signaling poor relaxation of the lower esophageal sphincter

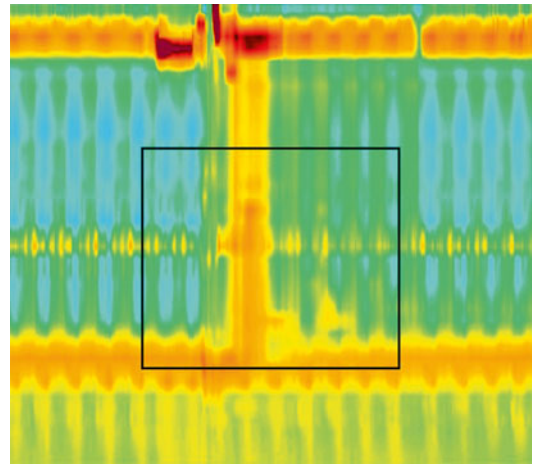

Fig. 2.4 A representative swallow in high resolution esophageal manometry from a patient with Type 2 achalasia, or the esophageal compression subtype, in which panesophageal pressurization is seen in greater than 20 % of swallows. This subtype is most responsive to treatment

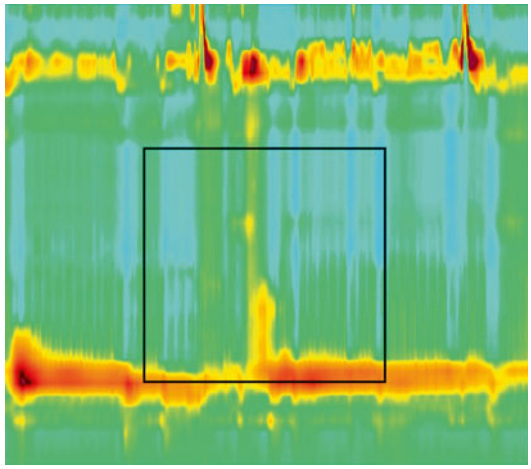

Fig. 2.3 A representative swallow in high resolution esophageal manometry from a patient with Type 1 achalasia, or the classic subtype. Esophageal pressurization is absent. This subtype is moderately responsive to treatment

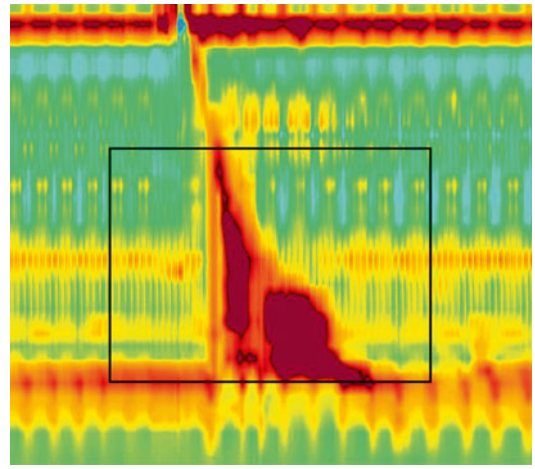

Fig. 2.5 A representative swallow in high resolution esophageal manometry from a patient with Type 3 achalasia, or the spastic subtype, in which high amplitude spastic contractions are seen in greater than 20 % of swallows. This subtype is least responsive to treatment

in greater than 20 % of swallows (Fig. 2.5). Distal esophageal peristalsis may be preserved in this subtype, but proximal peristalsis remains absent. A normal esophageal manometric swallow is included for reference (Fig. 2.6).

In candidates with suggestive history or risk factors, chest imaging such as x-ray or CT scan may assist in excluding etiologies of secondary achalasia, including lung cancer, which cannot be identified on the aforementioned testing modalities.

The natural disease course of patients with achalasia that do not receive treatment includes progressive esophageal dilation and tortuosity. In late-stage achalasia, megaesophagus is irreversible

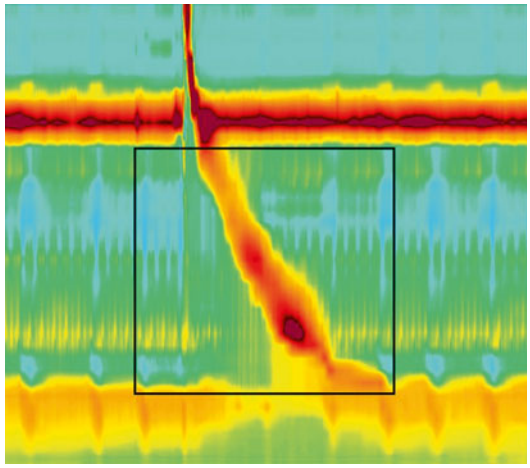

Fig. 2.6 A normal swallow in high resolution esophageal manometry for comparison

and may require esophagectomy [35]. Additionally, an increased risk of squamous cell esophageal cancer has been identified in patients with achalasia, but as the absolute risk is low (with annual incidence of 0.34 %) [36], endoscopic surveillance is not routinely recommended. An association with esophageal adenocarcinoma has also been reported [37]. The pathway has not been elucidated, though it has been proposed that chronic stasis may result in bacterial overgrowth and mucosal dysplasia, leading to the increased cancer risk [38].

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Clinical Presentation and Diagnostic Evaluation

3

Marco E. Allaix, Mauricio Ramirez, and Marco G. Patti

Introduction

Esophageal achalasia is a primary esophageal motility disorder with a peak incidence occurring between 30 and 60 years of age. It is characterized by absence of esophageal peristalsis and by impaired lower esophageal sphincter (LES) relaxation in response to swallowing. As a consequence, there is abnormal emptying of food from the esophagus into the stomach with consequent stasis.

The diagnosis of achalasia is challenging since it is a rare disease and symptoms are nonspecific: dysphagia, regurgitation of undigested food, aspiration, heartburn, and chest pain. As a consequence, there is often a long delay between the onset of symptoms and the diagnosis [1].

Since a diagnosis based on symptoms only is uncertain, a proper work-up is necessary to make the diagnosis of achalasia. The diagnostic work-up includes symptom evaluation, upper endoscopy, barium esophagram, esophageal manometry and ambulatory 24-h pH monitoring [2].

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This chapter reviews the clinical presentation and the diagnostic evaluation of achalasia.

Symptom Evaluation

Dysphagia

Dysphagia is the most frequently reported symptom, being present in about 95 % of achalasia patients. It occurs often for both liquids and solids. It may be associated with weight loss; however, most patients are able to maintain a stable weight thanks to changes made in their diet.

Regurgitation and Aspiration

Regurgitation of undigested food is the second most frequent symptom and is present in about 60–70 % of patients. It occurs more often in the supine position, and may lead to aspiration. Aspiration can cause respiratory symptoms, such as cough, hoarseness, wheezing, and episodes of pneumonia.

Heartburn

Heartburn is present in about 40 % of patients. It is due to stasis and fermentation of undigested food in the distal esophagus, rather than to gastroesophageal reflux. Since heartburn is

P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_3

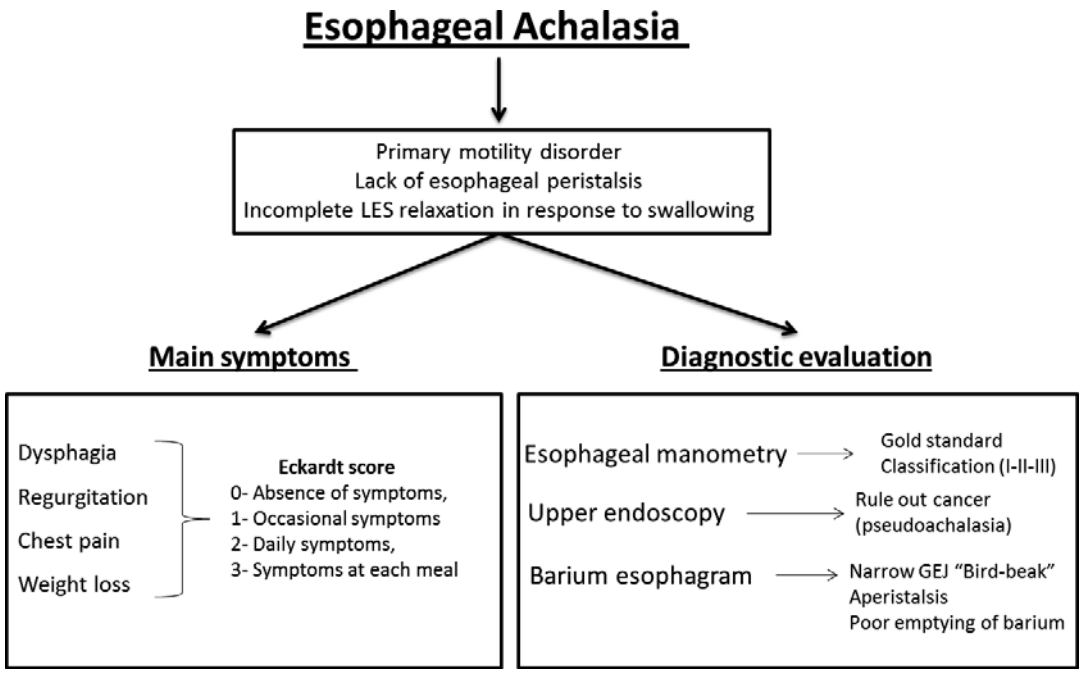

Fig. 3.1 Eckardt's score

frequently reported, misdiagnosis of achalasia as gastroesophageal reflux disease (GERD) can occur, particularly in the early stages of the disease. Because endoscopy is frequently normal and barium esophagram does not show the typical radiological findings of long-lasting achalasia, 24-h pH monitoring is necessary in addition to esophageal manometry to make the diagnosis.

Chest Pain

Some achalasia patients also experience chest pain, usually exacerbated by eating. The cause of chest pain is still unknown. In the past, it was thought that chest pain predominantly affected young patients with a shorter duration of symptoms than patients with no chest pain, and that it was associated to the presence of vigorous achalasia [3]. In untreated patients, chest pain frequency tends to diminish spontaneously with advancing age [4].

More recently, some large studies evaluating the prevalence of chest pain, the clinical and manometric features of patients with chest pain in the setting of achalasia, have challenged these concepts. For instance, Perretta et al. [5] analyzed 211 achalasia patients. Chest pain was present in 117 patients (55 %) at the time of presentation. It was felt in the retrosternal area in most cases, and it was experienced mainly during the day. No differences were observed in age, duration of symptoms or manometric profile between patients with or without chest pain. With a median follow-up of 24 months, chest pain resolved in 84 % and improved in 11 % of patients after laparoscopic Heller myotomy. These data suggest that the relief or improvement of chest pain is due to the improved esophageal emptying.

Symptom Scores

The Eckardt score is the most commonly used score system. It is the sum of the scores for dysphagia, regurgitation, and chest pain (a score of 0 indicates the absence of symptoms, 1 indicates occasional symptoms, 2 indicates daily symptoms, and 3 indicates symptoms at each meal) and weight loss (a score of 0 indicates no weight loss, 1 indicates a loss of less than 5 kg, 2 indicates a loss of 5–10 kg, and 3 indicates a loss of more than 10 kg) (Fig. 3.1). The maximum score on the Eckardt scale is 12 [6].

Diagnostic Evaluation

A thorough evaluation to establish the diagnosis should be performed in all patients with symptoms suggestive for achalasia [2].

Upper Endoscopy

It is usually the first test performed in patients with dysphagia to rule out the presence of a mechanical obstruction secondary to a peptic stricture or cancer. An infiltrating tumor of the gastroesophageal junction can mimic the clinical, radiological, and manometric findings of achalasia, resulting in impaired LES relaxation, esophageal dilatation and absence of peristalsis. This condition, defined as "secondary achalasia" or "pseudo-achalasia," should be suspected and ruled out in patients older than 60 years of age, with rapidly progressing dysphagia and excessive weight loss. However, these symptoms are not sensitive or specific [7]. When a malignancy is suspected, additional imaging including a CT scan or endoscopic ultrasound should be obtained [8–11].

The endoscopic findings in achalasia patients widely range from a normal exam (in about 33–40 % of patients) [2, 12] to tortuous and dilated esophagus with food retention (Fig. 3.2). The esophageal mucosa can be normal or can present signs of esophagitis (secondary to food stasis or to Candida infection).

Finally, upper endoscopy helps making correct diagnosis of achalasia in patients with a previous erroneous diagnosis of GERD if esophageal dilatation and retention of food and saliva are found.

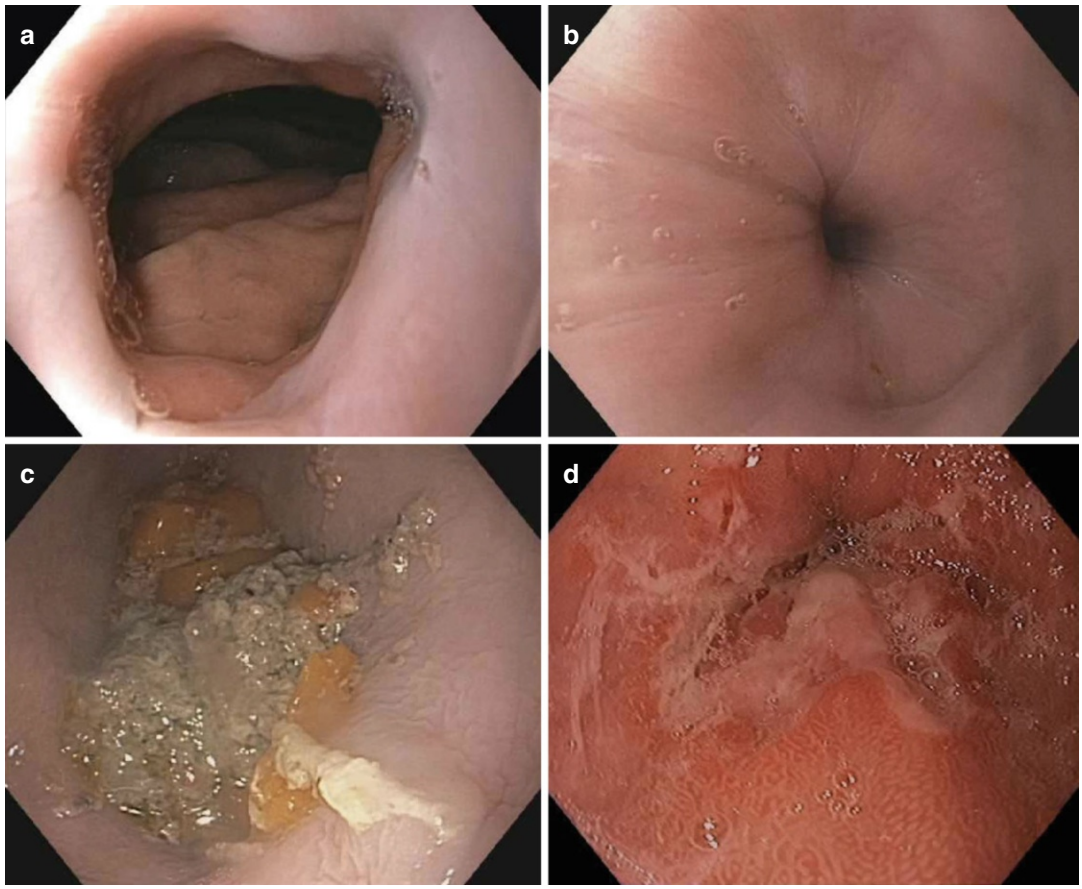

Fig. 3.2 Upper endoscopy. (**a**) Dilated esophagus; (**b**) Puckered esophagogastric junction; (**c**) Retained food; (**d**) Adenocarcinoma – pseudo achalasia

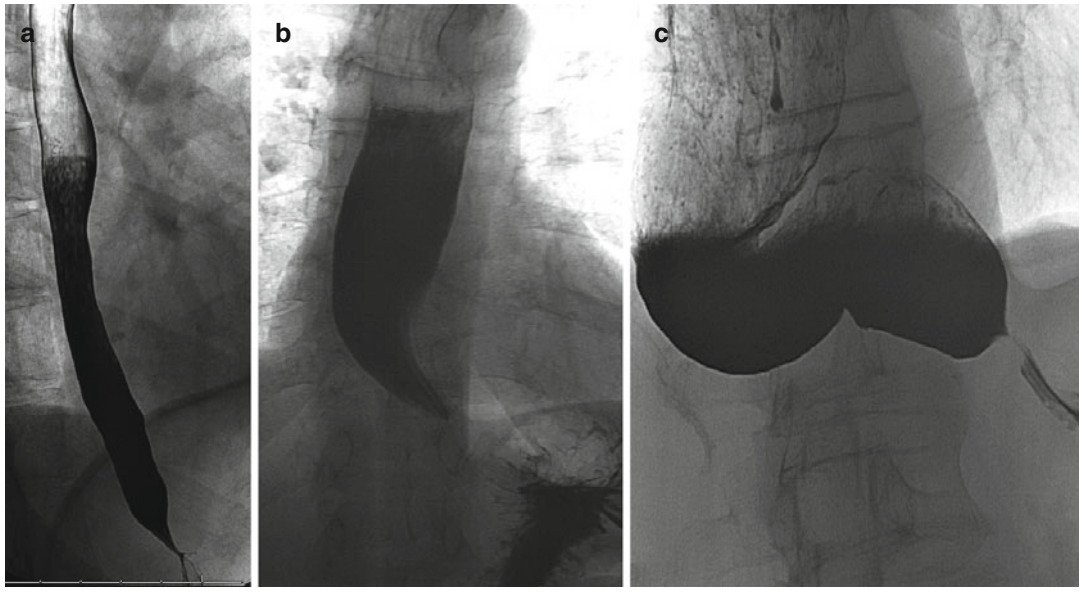

Fig. 3.3 Barium swallow.(**a**) Normal esophageal diameter; (**b**) Dilated esophagus, straight axis; (**c**) Dilated esophagus, sigmoid shape

Barium Swallow

This test provides information regarding anatomy and emptying of the esophagus. Typical radiologic findings are a narrowing at the level of the gastroesophageal junction, (the so-called *bird beak*), slow esophageal emptying of contrast with an air- fluid level, and tertiary contractions of the esophageal wall. The diameter, the shape and the axis of the esophagus (dilated and sigmoid in longstanding achalasia), and associated pathology, such as an epiphrenic diverticulum are also defined (Fig. 3.3). All this information is necessary to plan the most tailored approach to the patient with achalasia.

However, the barium swallow may be without abnormalities in about 30 % of cases, particularly in the early stages of the disease. In addition, the expertise of the radiologist with this rare condition is key for a proper interpretation of the radiologic features [12].

Esophageal Manometry

Esophageal manometry is the gold standard for the diagnosis of achalasia. Lack of peristalsis and absent or incomplete LES relaxation in response to swallowing are the key criteria for the diagnosis. The LES is hypertensive in about 50 % of patients [2, 13]. However, substantial heterogeneity in terms of peristaltic abnormalities, LES relaxation and esophageal pressure dynamics in patients with achalasia is well known [14, 15].

To date, high-resolution manometry (HRM) is widely used and has superseded in most centers conventional manometry. Briefly, HRM is performed after an overnight fast using a solid-state catheter with 36 circumferential sensors spaced at 1-cm intervals. The probe is inserted trans-nasally, and positioned in order to record from the pharynx to the stomach. Pressure, length, and relaxation of the LES, as well as the pressure of the upper esophageal sphincter (UES) are measured. Esophageal body motility is assessed starting with a basal period without swallowing, followed by 10 wet swallows of 5 ml of water at 30-s intervals. Amplitude, duration and velocity of the peristaltic waves are recorded. When the esophagus is dilated and sigmoid, it may be difficult to pass the catheter through the gastroesophageal junction into the

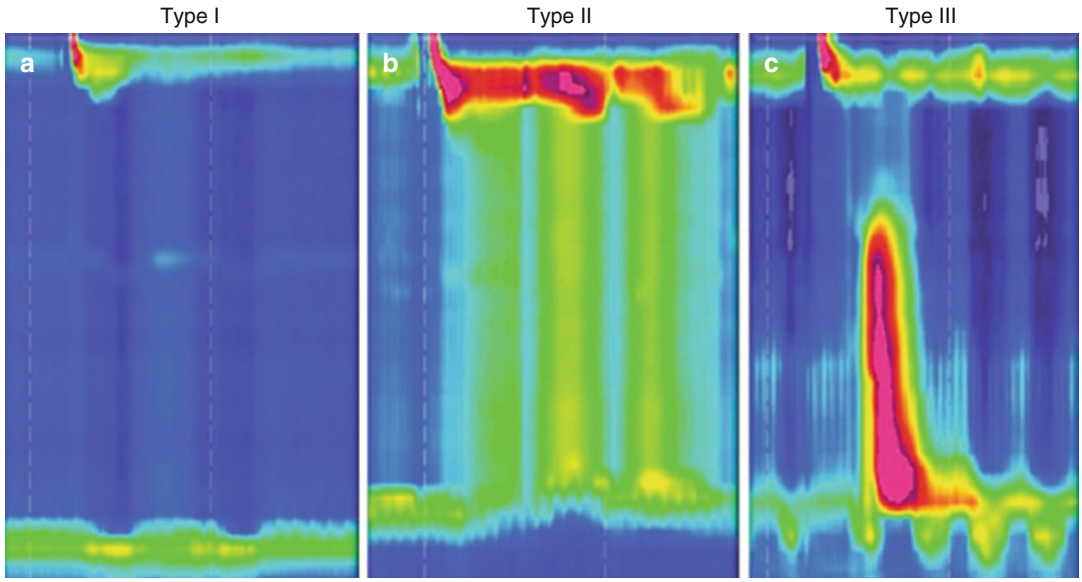

Fig. 3.4 Chicago classification of esophageal achalasia

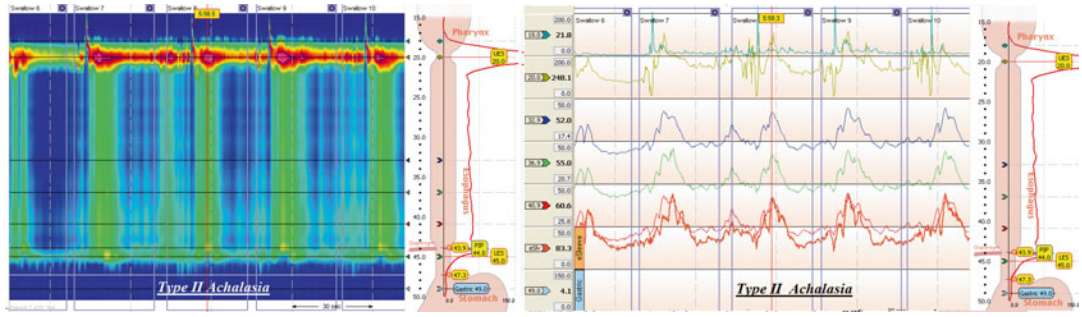

Fig. 3.5 Chicago classification, type II achalasia

stomach, and fluoroscopic or endoscopic guidance may be necessary.

Pandolfino et al. [16–18] proposed in 2008 a new classification of achalasia according to the manometric patterns of esophageal body contractility by high-resolution manometry: type 1, classic, with minimal esophageal pressurization; type 2, achalasia with pan-esophageal pressurization; and type 3, achalasia with spasm (Figs. 3.4 and 3.5). Type 2 achalasia patients are significantly more likely to respond to any form of treatment than type I or type 3 patients [17, 19]. At logistic regression analysis type 2 was found to be a predictor of positive treatment response, whereas type 3 was predictive of negative treatment response [17].

Ambulatory 24-h pH Monitoring

This test is recommended in selected untreated patients when the diagnosis is uncertain, in order to distinguish between GERD and achalasia.

Briefly, the pH probe is calibrated in a buffer solution at pH 7 and 1 before and after the test. The monitoring is performed after discontinuing acid-suppressing medications 10 days (proton pump inhibitors) or 3 days (histamine-2 receptor antagonists) before the study. The dual-channel pH catheter with two sensors located 15 cm apart is placed trans-nasally so that the distal and the proximal sensors are positioned respectively 5 cm and 20 cm above the upper border of the

manometrically determined LES. Patients are encouraged to consume an unrestricted diet during the study, but to avoid snacks and carbonated beverages in between meals. Gastroesophageal reflux is evaluated in terms of (1) number of reflux episodes; (2) number of episodes longer than 5 min; (3) duration of the longest reflux episode; (4) acid exposure (percentage of time with pH less than 4); and (5) esophageal acid clearance (mean duration of a reflux episode) in total, in the distal and proximal esophagus, in the supine and upright position. Data are integrated into the DeMeester score, with a value greater than 14.7 set as abnormal [20].

The examination of the pH monitoring tracing is mandatory. In both GERD and achalasia, the pH monitoring score is abnormal, but the tracing is different. While in GERD patients, the tracing is characterized by intermittent drops of the pH below 3 with subsequent return of the pH values above 5, in achalasia patients there is a slow and progressive drift of the pH below 4 with no return to higher values (pseudo GERD).

The 24-h pH monitoring should be obtained also in patients who had undergone a previous endoscopic balloon dilatation for two reasons: (1) reflux is often asymptomatic and exposes untreated patients to a higher risk of Barrett's esophagus or cancer; and (2) in case of persistent or recurrent dysphagia, further endoscopic dilatations should be avoided and a Heller myotomy with antireflux surgery should be considered [21].

Postoperatively, ambulatory pH monitoring should be routinely performed even in asymptomatic patients to rule out reflux, which is present in roughly 10–30 % of cases after Heller myotomy [22].

In conclusion, the American College of Gastroenterology has recently published the recommendations for the diagnosis of achalasia according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system for grading evidence and strength of recommendations [23]:

1. Esophageal manometry should be obtained in all patients with suspected achalasia who do not have evidence of a mechanical obstruction on endoscopy or esophagram to confirm the diagnosis of achalasia (strong recommendation, low-quality evidence).
2. Upper endoscopy is recommended in all achalasia patients to rule out pseudoachalasia (strong recommendation, moderate-quality evidence).
3. Barium esophagram is recommended to evaluate esophageal emptying and esophagogastric junction morphology in those with equivocal motility testing (strong recommendation, low-quality evidence).
4. Radiologic findings such as dilated esophagus, a narrow esophagogastric junction with "bird-beak" appearance, aperistalsis, and poor emptying of barium support the diagnosis of achalasia (strong recommendation, moderate-quality evidence).

Conflict of Interest The authors have no conflicts of interest to declare.

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Achalasia and Chagas' Disease

4

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Introduction

Chagas' disease (CD) is a tropical infectious disease first described in 1909 by the Brazilian physician Carlos Chagas (Fig. 4.1) [1, 2]. CD is highly prevalent in Latin America with 8–10 million infected people, with an annual death toll of about 14,000. During the last years, while the prevalence of CD in Latin America has been reduced, the United States and a number of non-endemic countries in Europe and Western Pacific Region have experienced a considerable increase in number of *T. cruzi*-infected individuals, especially due to migration of people from endemic countries. The total estimated number of Chagas patients outside Latin America is more than 400,000 with the USA as the most affected country accounting for three-fourths of all cases [3].

The disease is caused by the protozoan *Trypanossoma cruzy* (Fig. 4.2), a flagellated protozoan that is transmitted to humans by a blood-sucking insect (Fig. 4.3). Humans and a large number of species of domestic and wild animals constitute the reservoir, and the vector insect infests houses with thatched walls and roofs (Fig. 4.4). Non-vectorial mechanism of transmis-

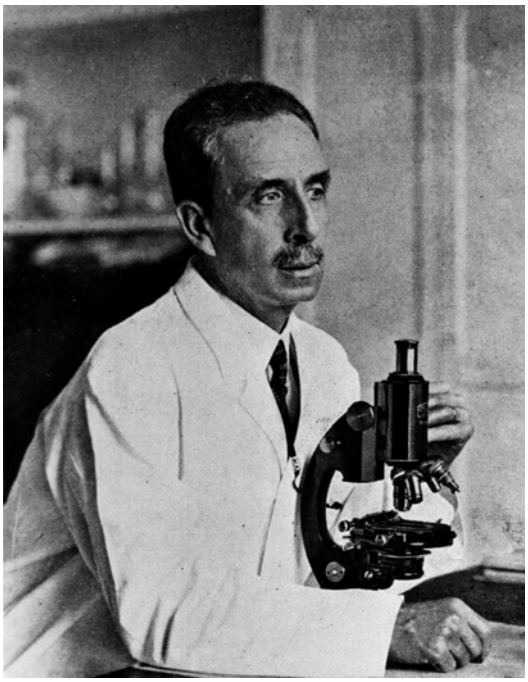

Fig. 4.1 Carlos Chagas (Source: National Library of Medicine)

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_4

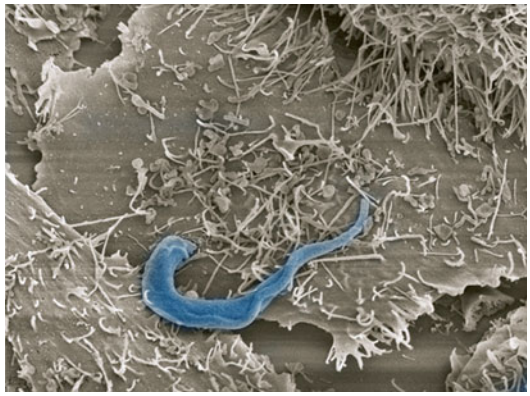

Fig. 4.2 Trypanossoma cruzy. Chagas disease causative parasite (Courtesy: Dr. Clara Lúcia Barbiéri Mestriner. Chair, Department of Parasitology, Federal University of São Paulo, São Paulo, Brazil)

Fig. 4.3 Triatoma infestans. Chagas disease insect vector

sion such as blood transfusion, solid organ and bone marrow donation, ingestion of infected food and vertical transmission also play important role in CD's spread nowadays. Insects of the subfamily Triatomidea act as vectors of protozoan, sheltering trypomastigotes in their digestive system. Humans contract trypanossomiasis when bitten by vector species. The protozoan present in the insect's stools infiltrates man's scratched skin or permissive mucosa, where a lymphoreticular response occurs. This local inflammatory response may be clinically apparent as an inoculation *chagoma*. Circulating forms (trypomastigotes) (Fig. 4.5) are taken to peripheral tissues, such as liver, spleen, lymphatic ganglia, skeletal and heart muscle, where they form pseudocysts of amastigotes (Fig. 4.6). Pseudocysts rupture triggers inflammatory reaction with muscle and neuron cell damage. The inflammatory reaction and cell destruction are maintained by the presence of *Trypanossoma cruzy* or its fragments and by the DNA of the parasite, with a late hypersensitivity reaction that results in esophageal aperistalsis and dilation [3].

CD is characterized by an acute phase, which is assymptomatic in most cases. The majority (60–70 %) of infected individuals will never manifest the disease (indeterminate form). In about one-third of infected cases, a chronic form develops some 10–20-years later, causing irreversible damage to heart, esophagus and/or colon. Injury to these organs is characterized by:

1. dilated cardiomiopathy and conduction system abnormalities, most frequently right bundle branch block or left anterior fascicular block (Fig. 4.7)
2. Achalasia-like esophagopathy with marked esophageal dilatation (Fig. 4.8)
3. megacolon, particularly of the sigmoid segment, usually complicated by fecal impaction or sigmoid volvulus (Fig. 4.9)

The heart is the most commonly affected organ (60 %). The colon and the esophagus are affected in approximately 20 % of cases, with 60 % of the patients developing concomitant cardiopathy [4]. There is neither vaccine nor recommended drug available to prevent

Fig. 4.4 A typical thatched house that lodges the insect vector

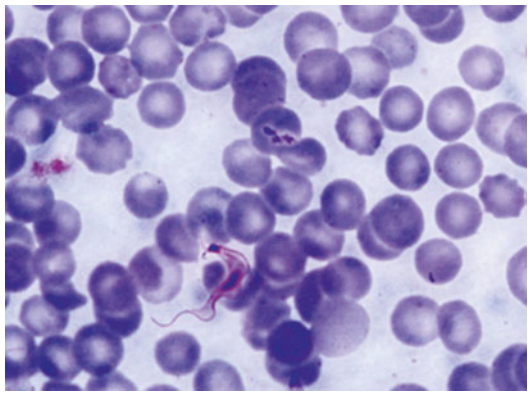

Fig. 4.5 Circulating blood forms (trypomastigotes) of Trypanossoma cruzy. Chagas disease causative parasite (Courtesy: Dr. Clara Lúcia Barbiéri Mestriner. Chair, Department of Parasitology, Federal University of São Paulo, São Paulo, Brazil)

CD. Also specific treatment for chronic phase of the disease is non-existent. In Chagas Disease Esophagopathy (CDE) there is always some degree of destruction of the autonomic nervous system, which is presumed to precede the changes in esophageal motility. CDE leads to slow esophageal emptying due to nonrelaxing of the lower esophageal sphincter (LES) and absence of peristalsis of the esophageal body, similar to Idiopathic Achalasia (IA). Table 4.1 shows the characteristics of those with IA and CDE [5, 6].

Clinical Presentation

CDE and IA have a similar clinical presentation. Dysphagia is the most frequent symptom in both situations (almost 100 % of cases). Other symptoms such as regurgitation, weight loss, heartburn, chest pain and cough are also very common for the two diseases. The duration of symptoms ranges from 8.5 to 18 years in CDE series versus 9 months to 8 years in IA series, probably as a result of the poor conditions of underdeveloped countries, where CD is endemic, with insufficient medical assistance and delay in diagnosis and treatment [5].

Esophageal Motility

Esophageal Body

Aperistalsis is the common manometrical abnormality found in CDE and IA (Fig. 4.10). According to the Chicago high resolution manometry classification for achalasia, Type III is a very rare finding in CDE. Moreover, when patients with positive serological tests for CD are studied, an undetermined form with multi-peaked peristaltic contractions, spontaneous and repetitive contraction waves can be also found that may represent a pre-disease [7, 8].

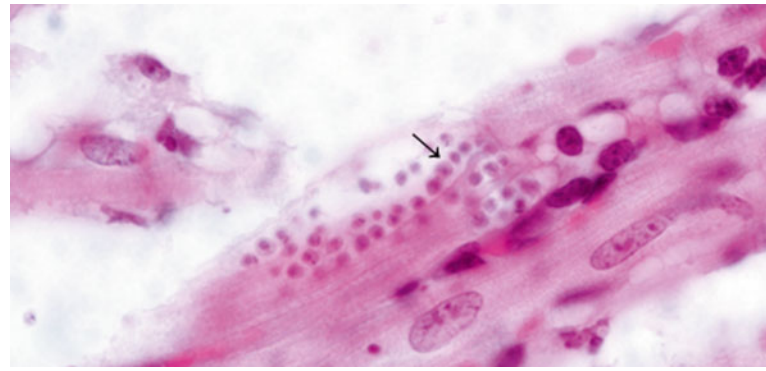

Fig. 4.6 Trypanossoma cruzy amastigotes (Courtesy: Dr. Clara Lúcia Barbiéri Mestriner. Chair, Department of Parasitology, Federal University of São Paulo, São Paulo, Brazil)

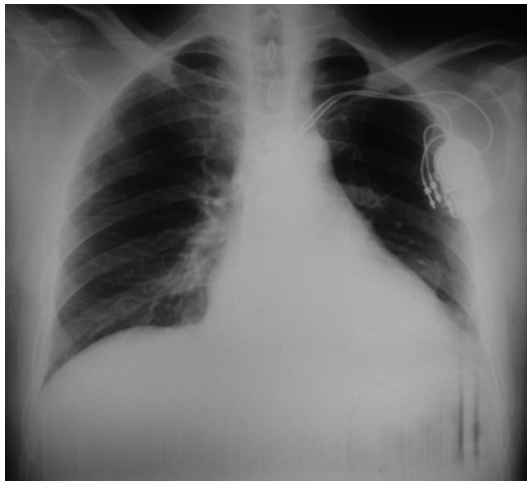

Fig. 4.7 Cardiomegaly due to Chagas' disease with a pacemaker due to Chagas' disease arrhythmia

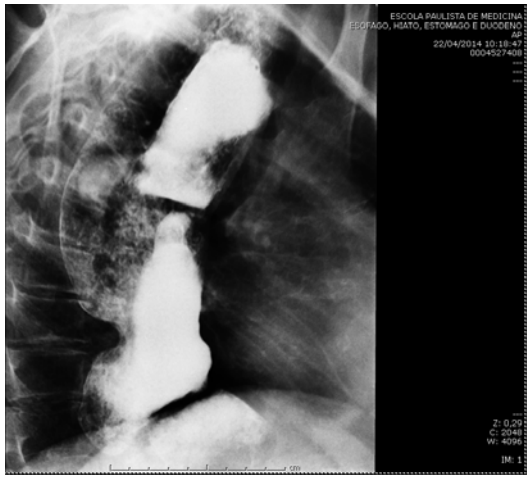

Fig. 4.8 Megaesophagus due to Chagas' disease

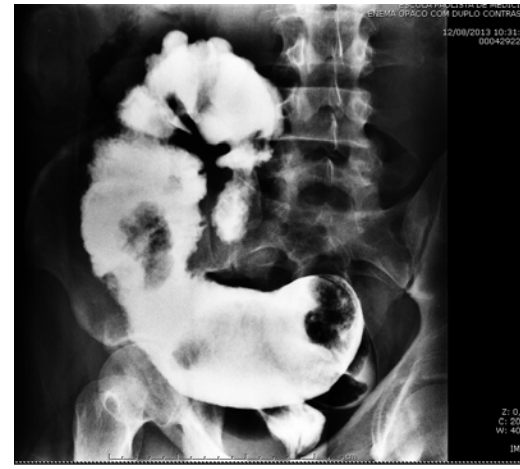

Fig. 4.9 Megacolon due to Chagas' disease

Table 4.1 Putative differences between Idiopathic Achalasia (IA) and Chagas' Disease Esophagopathy (CDE)

	CDE	IA
Clinical presentation	Longer duration of complaints	Shorter duration of complaints
Age at appearance of symptoms (years)	30–50	40–60
Upper sphincter	?	?
Esophageal body	Aperistalsis Chicago type III rare	Aperistalsis
Lower sphincter	Variable	Hypertonic
Esophageal dilation	Pronounced	Rare
Diverticulum formation (%)	?	4–8 %
Cancer prevalence (%)	1–10 %	0–7 %

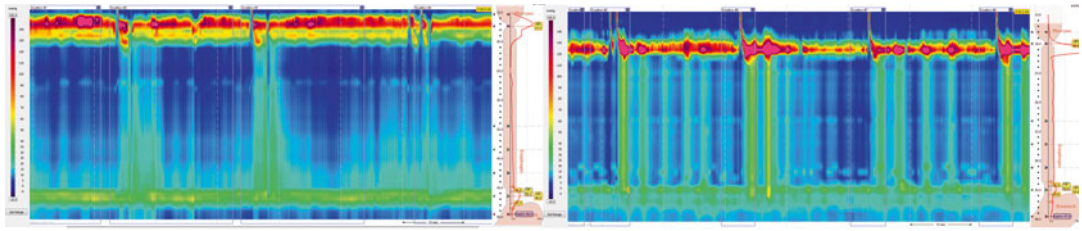

Fig. 4.10 High resolution manometry tracings for patients with Chagas' disease esophagopathy (*left*) and idiopathic achalasia (*right*)

Lower Esophageal Sphincter

Partially relaxing or nonrelaxing LES is a common characteristic of both diseases. In CDE, basal pressure of the LES can be low, normal, or high. Mean LES basal pressure in CDE series ranges from 12.6 to 39.1 mmHg. In IA, basal pressure of the LES is supposed to be hypertonic; however, it also can bellow, normal, or high. Mean LES basal pressure varies in different series from 22.3 to 43 mmHg, with a wide range (7–208 mmHg) [7, 8].

Esophageal Dilation

Esophageal dilation is a common feature of CDE. Radiological dilation of the esophageal body (more than 4 cm) is found in 70–100 % of cases of CDE in various series. Large dilations (more than 10 cm) are found in from 10 to 37 % of cases. In IA, esophageal dilation is not pronounced, with esophageal caliber not exceeding 6 cm. Dilations larger than 6 cm was found in only 10–33 % of cases in IA series. In both conditions, the caliber of the esophagus increases with the time of symptoms, and it is significantly reduced after treatment. The delay to treatment in CDE can be a factor in the degree of dilation in these patients.

Mucosal Abnormalities

Although CDE and IA are primary motor diseases, mucosal abnormalities can be present secondarily. Stasis esophagitis is the most common finding. It has been found in from 2.5 to 33.8 % of cases of CDE and from 25 to 39 % of case of IA. Leukoplasia is the second most common finding. It is present in 0.1–9.2 % of cases of CDE and not frequently reported in IA.

Pathology

Studies carried out in esophagectomy specimens, autopsy cases, and muscular biopsies of surgical myotomy showed, similarly in their diseases, decreased or absence of neurons in myenteric plexus (Auerbach). In both cases, myenteric inflammation and replacement of neural structures by fibrosis are found. Secondary features due to obstruction, stasis, and previous treatment have also been noted in both conditions.

Diverticulum Formation

Epiphrenic diverticula are commonly associated with esophageal motor disorders, especially achalasia. IA has been associated with diverticular formation in from 4 to 8 % of cases, while the real prevalence in CDE is not known.

Cancer Risk

Both diseases are considered at risk for esophageal cancer. The prevalence of cancer ranges from 1 to 10 % of cases in CDE and from 0 to 7 % in IA. The duration of dysphagia is considered a risk factor. Esophageal dilation and long lasting symptoms may explain the higher prevalence of cancer in CDE.

Treatment

Preoperative Evaluation

Some clinical characteristics should be taken into account in the surgical preparation of patients with CD. Due to late presentation to medical care, most of the patients with CDE are undernourished. For the same reason, a significant number of patients present also with subclinical pulmonary complications of the disease as a result of chronic aspiration. The disease may affect, apart from the esophagus, the heart and the colon. For this reason, different from idiopathic achalasia, a cardiac and colonic workup is also ever necessary.

Barium esophagram must be performed in all patients to guide therapy that is based on the grade of the esophageal dilatation.

Upper endoscopy is always performed to rule out malignancy or premalignant lesions of the esophagus and concomitant gastroduodenal disease.

Esophageal manometry is not performed routinely, since the frequent finding of massive dilatation makes the diagnosis of the disease not difficult. Moreover, there is still a lack of evidence if manometric parameters are prognostic for CDE.

Endoscopic Treatment

Dilatation

Endoscopic forceful balloon dilatation of the lower esophageal sphincter was traditionally indicated as the initial treatment for patients with absent or minimal dilatation of the esophagus. However, at the present time, dilatation is rarely used as a primary and definitive treatment. Currently, indications for endoscopic dilatation include:

(a) Primary treatment in patients unfit or unwilling for surgery
(b) Recurrence of symptoms after myotomy
(c) To improve nutrition status before a major operation

Botulinum Toxin

Botulinum toxin injection is rarely used for the treatment of CDE. To date, only one representative series has been published regarding botulinum toxin in CDE. Twenty-four patients were randomically assigned to botulinum toxin injection or placebo injection. Most patients (58 %) had clinical improvement of dysphagia in a 6 months follow-up. Interestingly, gender, age and lower esophageal sphincter pressure did not influence outcomes, contrary to the results obtained in IA series [9].

Surgical Treatment

Heller's Myotomy

As for IA, Heller's myotomy is the most performed operation also for CDE with excellent and good results exceeding 90 % in most series. Brazilian surgeons and some European centers always performed extended myotomies onto the stomach (2 cm) with better results for dysphagia. Not until Oelschlager et al. [10] published improved outcome after extended myotomy was the practice widely accepted in North America. Few centers perform a myectomy (resection of a strip of muscular layer) instead of a myotomy. They claim that the technique decreases the risk of healing or scaring of the myotomy. In Brazil, most surgeons associate a posterior fundoplication to the myotomy. However, an anterolateral fundoplication incorporates the advantages of covering the exposed mucosa and a better reflux control due to a more ample wrapping of the esophagus [9].

Other Conservative Techniques

Some authors propose other esophagus-preserving techniques than myotomy [11], as an alternative to esophagectomy in patients with end-stage dilated esophagus or recurrent disease after previous myotomy [9].

Cardioplasty, Vagotomy and Roux-en-Y Gastrectomy

Cardioplasty, vagotomy and Roux-en-Y gastrectomy (CVG) was first described by Holt and Large and popularized in Brazil by Serra Dória,

as the operation is known in South America. It consists of a Gröndahl cardioplasty, truncal vagotomy and Roux-en-Y partial gastrectomy (antrectomy). Proposed advantages of this procedure (CVG) are:

(a) Ample permeability of the esophagogastric junction
(b) Prevention of acid and alkaline reflux
(c) May be used after previous gastric operations
(d) Decreased hospitalization and recovery period compared to esophagectomy
(e) Decreased morbidity and mortality compared to esophagectomy

Published series reported low morbidity (0–25 %) and low mortality (0–2 %) associated to this procedure.

Esophagectomy

A significant number of patients with CDE present with end-stage disease. Thus, esophagectomy became popular in Brazil in the 1970s and 1980s. Satisfactory results with this approach have been found not only by Brazilians surgeons but also by others. Due to significant rates of morbidity and mortality, however, a decrease in the number of esophagectomies for achalasia was noticed in the 1990s with several groups choosing for less invasive procedures, such as Heller's myotomy. Contrary to this tendency, minimally invasive approach made esophagectomy more appealing, making the procedure, recently, well liked again among some centers. Currently, the indications for esophageal resection are:

(a) end-stage disease, as the initial treatment according to some groups or after failure of conservative operations according to others
(b) Concomitant premalignant or malignant lesions of the esophagus
(c) Esophageal perforation unsuitable for repair during diagnostic tests, therapeutic endoscopy or intraoperatively

Brazilian surgeons adopt a transhiatal approach to the thoracic esophagus. Medial incision of the diaphragm is routinely used. It must be emphasized that esophagectomy for achalasia may be more technically challenging compared to operation for cancer due to the larger diameter of the esophagus and inflammatory adhesions to mediastinal structures. The stomach is the first choice to replace the esophagus due to the frequent association of chagasic megacolon.

Esophageal Mucosectomy and Endomuscular Pull-Through

Esophageal mucosectomy and endomuscular pull-through is an attractive alternative to conventional esophagectomy. The technique of resection of the esophageal mucosa with preservation of the muscular layer and transposition of the stomach through the muscular tunnel has the advantages of:

(a) Decreased bleeding
(b) Decreased pleural lesion
(c) Preservation of mediastinal lymphatic system
(d) Preservation of vagus nerve if a vagal sparing esophagectomy is indicated

The operative technique follows the principle of transhiatal esophagectomy. Major steps of the operation include:

1. Abdominal and neck incisions
2. Dissection of the abdominal and cervical esophagus
3. Opening of the anterior muscular layer at the abdominal and cervical esophagus, similarly to a Heller myotomy
4. Circumferential dissection of the esophageal mucosa at the areas of myotomy in an extension of 5 cm
5. Small esophagotomy at the level of the abdominal myotomy and passage of a large diameter rectal tube that is exposed in the neck through a esophagotomy at the level of the cervical myotomy
6. The esophageal mucosa at the neck is excised, tied to the tube and removed inverted by downward traction of the tube.

Careful inspection of the mucosa must be done, since retained islands of mucosa in the mediastinum preclude the procedure. Reconstruction is

performed with the stomach pulled through the muscular tunnel.

Conclusions

CD is decreasing in incidence but immigration is spreading the disease worldwide. Treatment for CDE is not different from IA. However, the frequent presence of massive dilatation and the involvement of other target organs impose a more detailed study and therapeutic planning in these patients.

Conflicts of Interest There are no conflicts of interest.

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Botulinum Toxin for Achalasia

5

Hiroshi Mashimo

Introduction

Botulinum neurotoxin (BoNT) is one of the most potent toxins known, with a median human lethal dose of 1–2 ng when injected. However, its effect as a neurotoxin has been employed to treat spasms, hyperhidrosis, migraine, and various pain syndromes. It is also widely used for cosmetic treatments. Off-label gastrointestinal uses include treatment of gastroparesis, anal fissures, anismus, sphincter of Oddi dysfunction, and esophageal dysmotility. Local injection of BoNT in the lower esophageal sphincter (LES) has been used to treat dysphagia syndromes, including achalasia [1]. Other agents for local injection have been used, including ethanolamine oleate with comparable efficacy and reduced cost [2]. But this chapter will focus on the chemistry, mechanism, endoscopic administration, and clinical evidence supporting BoNT use in the treatment of achalasia.

History

BoNT was first described as a "sausage poison" (i.e., Latin *botulus* means "sausage"), in the early 1800s by a German poet and medical officer, Kerner, who traced the outbreak of deaths to improper handling of meat products. He also postulated a potential medical use for the toxin, but the agent producing the toxin was not isolated until 80 years later in 1897, by van Ermegem at the University of Ghent, who named the bacterium *Clostridium botulinum* [3]. A method to purify the toxin was first described by Snipe and Sommer in 1928 [4]. BoNT mode of action in blocking cholinergic neuromuscular transmission was described by Burgen's group in 1949 [5].

Chemistry

There are eight known serotypes of BoNT (A, B, C1, C2, D, E, F and G), which all share a common structure consisting of one Heavy Chain of 100 kD and one Light Chain of 50 kD (toxifying chain) linked by a single disulfide bond. There are also various toxin subtypes, but human botulism is caused mainly by A, B and E serotypes [6]. Currently in the United States there are two main serotypes used medically, A and B, which have the longest *in vivo* activity (weeks to months): BoNT-A is available as onabotulinumtoxinA (marketed as Botox by Allergan), abobotulinumtoxin (marketed as Dysport by Ipsen) and incobotulinumtoxinA (marketed as Xeomin by Merz), and BoNT-B is available as rimabotulinumtoxin B

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_5

(marketed as NeuroBloc/Myobloc by Solstice Neurosciences). There are various other formulations of BoNT-A manufactured and marketed outside the US, including Neuronox/Siax (Medytox), Botulax (HuGel) and ChinaTox (Lanzhou/China).

BoNT-A is derived from fermentation of Hall strain *Clostridium botulinum* type A by dialysis and series of acid precipitations then dissolved in normal saline with human albumin prior to vacuum drying. This needs to be reconstituted in normal saline without preservatives prior to use.

BoNT-B is derived from fermentation of *Clostridium botulinum* type B (Bean strain) by a series of precipitation and chromatography steps. It is non-covalently associated with hemagglutinin and non-hemagglutinin proteins. Each single-use vial comes with 5000 units/ml of botulinum toxin B in a sterile solution, and is generally diluted in saline without preservatives prior to use.

A unit for these preparations is defined as medial lethal dose in mice, but FDA emphasizes that these various preparations and activity assays are not equivalent, and the doses should not be considered equivalent between the various forms of BoNT.

Mechanism of Action

These various BoNT serotypes inhibit acetylcholine release at the neuromuscular junction by binding to neurons via the Heavy Chain, entering the cell by receptor-mediated endocytosis, then translocating the Light Chain into the cytoplasm via an ATP- and pH-dependent mechanism where it acts as a zinc-dependent endoprotease to cleave a specific protein essential for neurotransmitter release (Fig. 5.1). BoNT-A cleaves SNAP-25, which is essential for vesicular docking to release acetylcholine from nerve terminals. BoNT-B cleaves synaptic Vesicle Associated Membrane Protein 1 (VAMP, also known as synaptobrevin), which is also a component of the docking complex essential for neurotransmitter release. This mechanism of inhibiting vesicular release may also affect the release of other neurotransmitters. Indeed, an antinociceptive effect has been attributed to inhibiting the release of Substance P [9] and the release of glutamate [10]. BoNT has not been found to block the relaxatory neurotransmitter nitric oxide, but there is rather an induction of proinflammatory mediators including nitric oxide and tumor necrosis factor alpha, which may have further and indirect relaxatory effects at the site of injection [11].

BoNT has been shown to have additional effects on the muscle spindle organ of skeletal

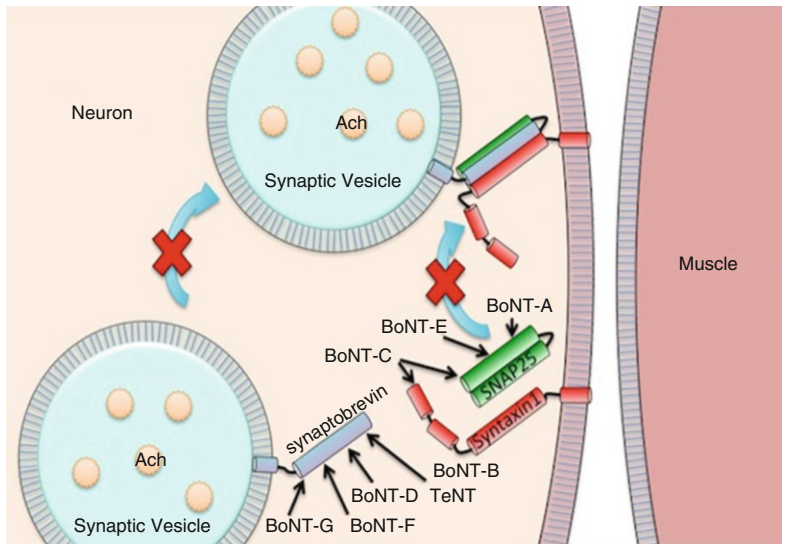

Fig. 5.1 Molecular targets of botulinum toxin serotypes (Modified from Lacy et al. [7] and Barr et al. [8] Ach (Acetyl Choline), TeNT (Tetanus Neurotoxin). Drawn by Gabriel Gonzalez

muscles. BoNT also has many indirect effects on the central nervous system [12], although none are evidenced after intramuscular injections. There is also increasing evidence that these neurotoxins have direct inhibitory effects on the smooth muscle, particularly at higher concentrations, as evidenced by reduced muscular contraction to acetylcholine [13, 14]

One of the limitations of BoNT therapy is that the effects are short-lived. In part, this can be explained by increased presynaptic membrane regeneration following the decrease in acetylcholinesterase, upregulation of acetylcholinesterase receptors, and increased lysosomal and endocytic activity [15]. Investigators using gene microarray have shown that upregulation of the insulin-like growth factor-1 pathway plays a central role in this neuromuscular junction stabilization, remodeling, myogenesis and eventual muscle functional recovery after BoNT injection [16]. A sprouting network of neurons may bypass the BoNT-inhibited neuromuscular junction. However, this new network is known to regress as the inhibited nerve terminals recover their function [17]. Indeed, age-dependent decline in such presynaptic regenerative capacity may explain the generally more prolonged effect of BoNT in elderly patients [18].

Another mechanism underlying the poor durability of BoNT effect is the common formation of neutralizing antibodies despite therapeutic doses of BoNT being deemed too low to mount any immune reaction. Such neutralizing antibodies can persist beyond a decade and generally necessitate stopping therapy or possibly switching to another BoNT serotype [19]. Clearly, further studies uncovering these fundamental mechanisms of BoNT action and of transience would help optimize or create newer therapies in the future.

Medical Use

The various preparations are used on- and off-label for various conditions including upper motor neuron syndrome, hyperhidrosis, various spastic disorders including blepharospasm, hemifacial spasm, neurogenic detrusor over-activity, focal dystonias, strabismus, and vaginismus. BoNT is also used for chronic migraine, benign prostatic hyperplasia, and bruxism, and widely used in cosmetic treatments. Emerging uses for botulinum toxin type A include chronic musculoskeletal pain, vocal cord dysfunction, and allergic rhinitis.

Neither BoNT-A nor BoNT-B has been approved by the US Food and Drug Administration for any gastrointestinal disorder, including achalasia. However, besides achalasia, various other potential off-label uses have been described, including obesity (by purportedly delaying gastric emptying time) [20], and conversely gastroparesis (by improving gastric emptying time), gastric cancer (by possible vagal denervation) [21], sphincter of Oddi dysfunction [22], and anal fissure [23].

Side Effects and Contraindications

The profile of adverse effects for the various available preparations is similar, although BoNT-B may have additional reported systemic autonomic adverse effects. Long-term use did not show additive adverse effects [24]. Serious and/or immediate hypersensitivity reactions have been reported, which include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BoNT should be discontinued and appropriate medical therapy should be given immediately. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, thus the causal agent could not be reliably determined. Side effects of BoNT may be seen beyond the site of injection, and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties, depending also on site of injection. These side effects have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin and its effects. The risk of symptoms is probably greatest in children

treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions. BoNT injection is relatively contraindicated in patients with disorders of neuromuscular transmission or with bleeding, and significant risk of side effects has been reported in patients with mitochondrial cytopathies, for example [25]. While various BoNT preparations contain human albumin, their risk for transmitting viral diseases is deemed extremely remote owing to careful screening of donors and manufacturing processes. The potential transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote for the FDA-approved formulations, and no known cases of transmission of viral diseases or CJD have ever been identified.

Side effects specifically after intraesophageal injections include transient non-cardiac chest pain and reflux. Severe complications are rare, and only in isolated case reports. These complications include gastroparesis, mediastinitis, and fatal arrhythmia, which were largely attributed to technical difficulties [26].

Contraindications for use of BoNT include history of allergy/sensitivity, and those with infections at the proposed site of injection. No formal drug interaction studies have been conducted with BoNT for injection. Co-administration of BoNT and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution because the effect of the toxin may be potentiated. Likewise, the use of anticholinergic drugs after administration of BoNT may potentiate systemic anticholinergic effects. The safety is unknown for using different BoNT products at the same time or within several months of each other before resolution of known effects, but may lead to excessive neuromuscular weakness. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BoNT.

No long-term carcinogenicity studies in animals have been performed, and safety and effectiveness in pediatric patients have not been established. Various preparations of BoNT remain FDA Pregnancy Category C, and animal reproduction studies have not been conducted; it is not known whether BoNT can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Also studies have not established whether BoNT is excreted in human milk after various sites of administration, thus caution should be exercised when BoNT is administered to a nursing woman.

While most patients continue to respond to repeated BoNT treatments, some become unresponsive possibly as a result of forming neutralizing or blocking antibodies, particularly to the heavy chain of either BoNT-A or -B [27, 28]. Risk factors leading to blocking antibodies is unknown, but is thought to increase with increased dose and frequency. Formation of neutralizing antibodies seems to be a higher risk in younger patients receiving higher doses intramuscularly, as in patients with neuromuscular diseases [29].

Method for Treating Achalasia

Generally, 100 units of BoNT-A marketed as BoTox is used for treatment of achalasia. Although there are reports of similar efficacy using BoNT-B, animal studies generally show longer duration of action for BoNT-A [24]. There are also differences even between preparations of BoNT-A, and a review of head-to-head, randomized controlled trials of onabotulinumtoxinA vs. abobotulinumtoxin suggested that the latter tends to have higher efficacy, longer duration, and higher frequency of adverse effects, albeit depending on use. The actual conversion factor between the two preparations varies in such studies and remains controversial, but a Botox:Dysport conversion ratio of 1:3 may be clinically appropriate, consistent with animal studies, which suggest a conversion ratio of approximately 1:2.5–3.0 [30]. Specifically in treatment of achalasia, however, there were no differences in response rates between onabotulinumtoxinA and abobotulinumtoxin [31].

Botox is diluted in 10 ml preservative-free normal saline just prior to use. Rehydration should be done gently, first by releasing the vac-

uum from the bottle, slowly introducing 10 ml of preservative-free normal saline, then rotating rather than shaking the vial. Once reconstituted, the solution should be used within a couple hours.

For the injection, a Carr-Locke (US Endoscopy) or equivalent sclerotherapy injection needle is introduced through the accessory channel of the endoscope, and approximately 20–25 units of BoNT-A is injected in four quadrants at or just above (within 1 cm) the squamocolumnar junction just above the z-line under direct visualization. The angle of the needle should be approximately 45 degrees to the surface and care must be taken to confirm that there is significant resistance at the syringe during the injection consistent with intramuscular injection in order to avoid injection outside the esophageal wall or into the superficial layers, which may create a bleb. Use of ultrasound guidance has been proposed, but has not become standard practice [32]. The overall method for injecting BoNT has essentially not changed with different studies, although there is some variation in doses and procedures. For example, one study advocates not a single, but two injections of 100 U of BoNT-A 30 days apart as the most effective therapeutic schedule [33].

Clinical Evidence

The clinical response rate for BoNT is approximately 90 % at 1 month after BoNT treatment, but approximately 30–50 % at 1 year and <5 % at 2 years, according to some studies. However, other observational studies looking particularly at long-term efficacy of BoNT have shown better remission rates of approximately 70–80 % at 1 year, and 50 % at 2 years [18, 34].

Nevertheless, most studies comparing BoNT to pneumatic dilation (PD), show superiority of the latter. For example, one non-randomized study showed that global symptom scores and LES pressures improved significantly in both BoNT (n = 23) and PD (n = 14) groups at 12 months, but at 24 months there was significantly superior response rate of a single PD over BoNT treatment, and at 48 months all BoNT patients had symptomatic relapse while 35 % of patients treated by dilation (and 45 % of patients treated successfully by dilation) remained symptom-free [35]. Similarly, another study looking at response rates particularly in the elderly (>65 years of age) showed that the relief of symptoms was shorter-lived for BoNT compared to dilation: symptom alleviation was 13.8 ± 9.5 months for BoNT and was 48 ± 33 months for myotomy [36]. A Cochrane collaborative meta-analysis compared BoNT to Rigiflex balloon dilation in patients with primary achalasia. In the six reviewed studies involving 178 patients, there was no significant difference in short term (within 4 weeks of injection) responses, but the 6- and 12-month responses were significantly better with dilation, with 74 % failure by BoNT compared to 30 % by dilation at 1 year follow-up [37]. Similarly a large systematic review and meta-analysis of 105 articles involving 7855 patients showed better symptomatic relief with laparoscopic myotomy combined with antireflux procedure than BoNT injection [38]. One randomized control study studied the effect of injecting BoNT 1 month prior to PD, and showed a tendency towards a greater response with pre-dilation BoNT (77 % in remission) compared to dilation alone (62 %) at 1 year follow-up, but this did not reach statistical significance. However, a second dilation upon relapse of symptoms increased the remission rate to 100 % in the BoNT-PD group compared to 85 % for PD alone [39].

An early non-randomized study comparing BoNT to laparoscopic Heller myotomy showed that both BoNT and myotomy improved dysphagia score and reduced LES nadir pressure at 2 months post BoNT and 6 months post myotomy, but only myotomy significantly reduced LES basal pressure and improved esophageal barium clearance [40]. Subsequently, a randomized control trial comparing BoNT to laparoscopic myotomy showed similar response rates at 6-month follow-up, but marked difference at 1-year follow-up (i.e., 53 % remission in BoNT vs. 90 % remission in myotomy group) [41].

A review of randomized controlled trials comparing different treatment options concluded that endoscopic BoNT should be considered mainly

when other treatments are contraindicated [32]. Similarly, guidelines from both the American College of Gastroenterology [42] and the American Gastroenterology Association [43] emphasized that BoNT should not be used as first line treatment for patients who would otherwise be candidates for either PD or surgical/endoscopic myotomy. One concern is that BoNT may increase inflammation in the mucosa and muscle planes, and lead to greater difficulty for subsequent myotomy. Studies in pigs showed fibrotic changes in the LES after BoNT injection [44]. However, most histological studies in humans show that there are no significant changes in muscle [45], and post-surgical studies show no significant differences in outcome after BoNT treatment [46]. One abstract with limited number of cases suggests that a prior BoNT may increase perforation risk of subsequent PD [47]. Other reports suggest that prior BoNT may make surgical myotomy more difficult [48, 49]. While the factors explaining these observational differences remain unclear, BoNT should be reserved for those with significant co-morbidities, and for those who would poorly tolerate medical therapy, dilation, or complication of dilation. However, repeated BoNT treatments can approximate the short-term (2-year) response rates of PD [50].

Which BoNT Patients Do Better?

When patients are given treatment choices upon diagnosis of achalasia, almost a third of patients in one study chose to have no treatment for the first year, and only a minority of these patients underwent treatment ultimately, although these patients generally showed worsening symptom score [51]. Clearly there are no definitive treatments for achalasia, and current therapy options are aimed to improve symptoms and relieve the LES functional obstruction. While most patients prefer non-surgical means, attempts to identify patients who have better response to BoNT injections have had varying results. In general, several studies have shown that elderly patients [52, 53] and those with vigorous achalasia had better responses [33, 54, 55]. There is no specific study addressing which patients are more likely to respond to BoNT injection based on the Chicago Classification of subtypes, although generally type II (with at least 20 % of liquid swallows with a body pressurization > 30 mmHg) has better symptom response to other treatments compared to "classic achalasia" (Type I) and "spastic achalasia" (type III). However, one report finds that no response was seen in patients with IRP <15 mmHg [56].

Summary

In light of oral pharmacologic agents falling out of use because of poor efficacy and frequent side effects, BoNT injection offers an appealing alternative to surgery based on ease and safety. However, there is wide variation in reported durability of response, and further studies are required to determine the optimal injection protocol and the best patients for BoNT therapy. The repeatedly demonstrated durability of response with PD and myotomy over BoNT makes the latter reserved largely for frail or elderly patients. However, the role of BoNT or similar injectable agents as treatment for patients who failed PD or myotomy, or as adjuvant therapy to re-dilation remains unclear. Future agents for local injection may include depot formulations of BoNT, other inhibitors of neurotransmission, long-acting nitric oxide donors, and cell-based therapies including engineered stem cells.

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Pneumatic Dilation

6

Vijaya Rao and Robert Kavitt

History

Achalasia is caused by the selective loss of inhibitory neurons in the myenteric plexus resulting in failure of the lower esophageal sphincter (LES) to relax. Currently there are no treatments to reverse the underlying neurologic dysfunction and restore normal esophageal motor function. Existing therapies aim to palliate symptoms via reduction of LES pressure to allow esophageal emptying by gravity and improve bolus transit through the cardia. The primary therapeutic options for achalasia are pneumatic dilation (PD), laparoscopic Heller myotomy (LHM), botulinum toxin injections, and pharmacotherapy.

PD leads to stretching and controlled mechanical disruption of the circular smooth muscle fibers of the LES and resultant fracture of the muscularis propria. Forceful dilation of the LES dates back to 1674 when Sir Thomas Willis used a carved whalebone with a sponge affixed to the distal end as a prototypic bougie to accomplish distraction of the muscular fibers at the gastroesophageal junction (GEJ) [1]. Willis first described achalasia as a "spasm of the lower esophageal sphincter". In 1937, Frederick Lendrum proposed the modern-day concept that the syndrome is caused by incomplete relaxation of the LES. He branded the disease process *achalasia*, a word of Greek origin with the literal translation being "without loosening" [2].

The technique of PD has evolved through several models of balloon dilators, many of which are no longer manufactured. Standard balloon dilators or bougienage are ineffective in the degree of disruption of the LES muscle fibers needed for symptomatic relief [3].

Early metal dilators (Starck) were modified in the early 1990s so that expanding balloons were incorporated onto flexible shafts so that they could be placed at the LES to forcefully dilate. The first balloon, called the Plummer hydrostatic dilator, utilized water as an expander. Subsequent dilators replaced water with air and were therefore referred to as pneumatic dilators [4, 5].

The Browne-McHardy and Hurst-Tucker pneumatic dilators consisted of mercury-filled tubes with a rubber covered silk bag at the distal end. The Mosher bag contained barium strips embedded within the wall of the bag to facilitate fluoroscopic visualization. The Rider-Mueller

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_6

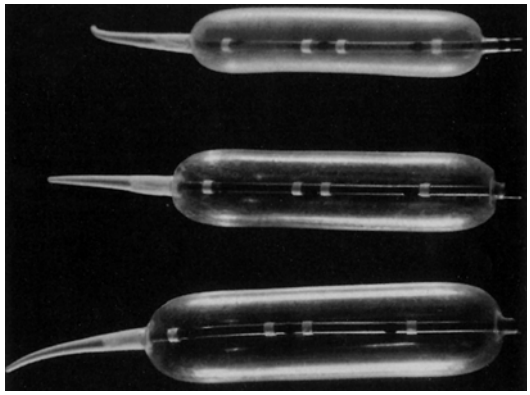

Fig. 6.1 Rigiflex pneumatic balloon dilators with three diameter sizes: 3.0, 3.5, and 4.0 cm (Adapted by permission from Richter and Roberts [6])

dilator was the first dilator to be available in a number of sizes and consisted of a dumbbell-shaped bag that could be positioned across the GEJ via guidewire placement. The Sippy pneumatic dilator employed two latex balloons covered by a nylon bag to limit expansion of the balloon. Each of the aforementioned dilators required fluoroscopy for proper positioning before dilation and ranged from 2.5 to 4.5 cm [6].

Currently, the most commonly employed balloon dilator in the United States is a non-radiopaque, non-compliant air-filled polyethylene balloon, known as the Rigiflex balloon (Boston Scientific, Marlborough, MA, USA) [3] (Fig. 6.1)

Technique of Pneumatic Dilation

PD is typically an outpatient procedure [7]. The patient is required to take nothing by mouth for 12 h preceding endoscopy with recommended adherence to a liquid diet for at least 1–2 days prior. In those with clinical or radiographic evidence of severe food retention and resultant dilation of the esophagus, a lavage with a large bore tube may be necessary [8]. All patients should be appropriate candidates for surgical intervention if an esophageal perforation were to arise.

The balloon system should first be inflated and checked for leaks or signs of malfunction. A comprehensive endoscopic evaluation should be performed prior to dilation with special attention to the gastric cardia during the retroflexed exam, to rule out mechanical obstruction or pseudoachalasia which can mimic achalasia [3]. Landmarks should also be determined, particularly the distance between the incisors and the gastroesophageal junction.

A guidewire is placed into the stomach via the working channel on the endoscope. The endoscope should be carefully removed to preserve the position of the guidewire in the stomach. The balloon and tip of the catheter are then lubricated and passed over the guidewire.

The previously noted distance between the gastroesophageal junction and incisors should be measured from the center of the balloon to ensure that the center will be across the LES. The position of the balloon should be so that the "waist" caused by the non-relaxing LES applies pressure on the center of the distending balloon [8].

This position is usually at or above the level of the diaphragm, except in patients after Heller myotomy, when the narrowing may be below the diaphragm. Minor re-adjustments in positioning may have to be made to ensure proper location, with deflation of the balloon with each adjustment. If performed under fluoroscopic guidance, a small volume of dilute contrast can be injected into the balloon to assist in radiographic visualization [9].

After proper positioning, the balloon is then connected to an external pressure gauge and is inflated until the pressure reaches 7–15 pounds per square inch (psi) of pressure (approximately 120 mL of air) and held for 6–60 s. Balloon distension time is variable, but studies have shown distension times as short as 6–15 s are as effective as longer distension times up 60 s [10, 11].

If a second inflation is necessary, the pressure will typically be at least 3 psi less than the initial pressure. A precipitous decrease of the intraballoon pressure signifies successful disruption of LES muscle fibers. After this is achieved, the balloon is then deflated and carefully removed.

Post-procedurally, it is recommended that patients routinely undergo a Gastrografin study followed by a barium esophogram to exclude perforation, however, in clinical practice, this is often only done if suspicious signs or symptoms

are present [12, 13]. Observation of the patient is generally recommended for 5–8 h to monitor for chest pain, fevers, and signs of perforation [14]. The patient is subsequently discharged if tolerating fluids without difficulty and the recovery was otherwise uneventful.

There is no clear consensus on the optimal method for performing PD with regard to balloon diameter and the amount and rate of inflation pressure. However, a 30 mm Rigiflex balloon is typically used for the initial dilation in most adults [8]. The standard approach is to perform one dilation per session, with repeat dilations being performed according to symptomatic recurrence.

Summary of Data Regarding Efficacy

Pneumatic dilation is considered to be the most cost-effective first-line therapy for achalasia over a 5–10 year post-procedure period [15–17]. The graded approach to dilation is effective in achieving symptom relief. The 3 year success rate for a single dilation with a 30-mm balloon is 37 % in comparison with 86 % for the graded dilation protocol [18].

Other studies estimate that with a graded dilation approach, symptomatic relief is achieved in 50–93 % of patients [19]. The 2013 American College of Gastroenterology guidelines regarding the diagnosis and management of achalasia cite that PD with 30, 35, and 40 mm balloon diameters result in symptomatic relief in 74, 86, and 90 % of patients, respectively, with an average follow-up of 1.6 years (range: 0.1–6 years) [3, 20].

Variability in these results is likely secondary to both inconsistent follow-up times as well as lack of consensus regarding a distension protocol. Data from retrospective studies are more limited by lack of follow-up, while prospective studies may be more accurate in predicting efficacy. One recent prospective study reported that 70 % of patients who underwent PD maintained control of symptoms after a median of 5.6 years of follow-up [21]. A prospective randomized controlled trial comparing PD to LHM found that there was no significant difference in rates of therapeutic success. In patients who underwent PD, clinical remission was reported in 90 % and 86 % after 1 and 2 years of follow up, respectively [22].

Persistent symptoms, especially in conjunction with impaired esophageal emptying or an LES pressure above 10 mmHg warrants repeat dilation with incrementally larger balloons. Generally, if symptom relief is not achieved with a 40 mm balloon or with three consecutive dilations, surgical intervention is then pursued [8].

While symptom-free periods at shorter term follow up times have been reported, approximately one-third of treated patients are expected to experience symptom relapse over 4–6 years of follow up, despite adherence to a graded pneumatic dilation approach [3, 23].

The lack of strong long-term data makes the efficacy of repeated dilations after relapse of symptoms difficult to definitively assess. However, existing studies suggest that patients who remain in clinical remission for 5 years are likely to benefit from the longstanding treatment effect of PD [24].

As there is no definitive cure for achalasia, the proportion of patients who remain in remission after successful graded PD or surgical myotomy declines over time and repeat intervention is typically warranted in 23–33 % of patients within 5–7 years [25].

Predictors of Success

Significant predictors of favorable clinical outcomes after PD include LES pressure after dilation of less than 10 mmHg, older age, female gender, and type II achalasia pattern on high resolution manometry [3].

Post-dilation LES pressure has been considered the single most valuable factor for predicting the long-term clinical response [26]. A post-dilation LES pressure to approximately 10 mmHg has been suggested as a goal of PD. Prospective studies of patients over 10 years also found that those patients with a post-dilation

LES pressure of less than 10–15 mmHg were more likely to achieve sustainable clinical response compared to those with higher LES pressures [24, 27].

Young males, aged less than 45 years, have a greater failure after 30 mm PD as well as after graded PD as compared to older men or women in general, which may be secondary to thicker LES musculature [28]. Age younger than 40 years, irrespective of gender, also predicts a poor response to pneumatic dilation [24, 26, 29].

Females have a better clinical outcome after PD when compared to males [30]. Young men initially treated with a 30 mm balloon were found to require repeat dilations more often than young women [28]. For this reason, initial PD with a 35 mm balloon or surgical myotomy is often considered as first-line therapy in young male patients [8].

The use of high-resolution esophageal manometry has stratified achalasia into three main subtypes which influence the response to therapeutic interventions. While each subtype is unified by the presence of impaired LES relaxation and aperistalsis, each has a distinct manometric finding. Type I, known as classic achalasia, is defined as no pressure generation in the esophageal body. Type II patients exhibit rapidly propagated compartmentalized pressurization, localized to the distal esophagus or present across the entire esophagus. In Type III, or spastic achalasia, patients have lumen-obliterating contractions in the distal esophagus, causing a functional obstruction. A study investigating clinical response to botulinum toxin injections, LHM, and PD found that Type II patients are most likely to respond to any therapy (botulinum toxin injections [71 %], PD [91 %], or LHM [100 %]) than type I (56 % overall) or type III (29 % overall) patients [31]. Severe esophageal dilation associated with any subtype of achalasia also is associated with a decreased response to therapeutic attempts.

Several other variables, such as pre-treatment LES pressure, duration of symptoms, size of balloon dilators utilized, and results of post-dilation barium esophograms have been studied but not found to significantly affect therapeutic response to PD [28, 30, 32].

Complications

The overall PD-associated complication rate is estimated to be lower than 10 % and most commonly include perforation, chest pain, bleeding, fever, aspiration pneumonia, and formation of diverticula [33, 34].

The most important and serious complication of PD is esophageal perforation, with an overall reported rate of 1.9 % (range 0–21 %) [3, 18, 35]. Perforations are typically small and located above the cardia along the left side of the esophagus, where there is an anatomic area of weakness and usually occur during the first dilation session.

Age greater than 60 years and initial dilation performed with 35 mm balloon compared with 30 mm balloon have been identified as risk factors in predisposing to perforation [17, 22]. Other risk factors for transmural perforation have been identified and include inappropriate positioning and distension of the balloon, balloon instability, higher dilation pressures, minimal weight loss, malnutrition, longer duration of symptoms, high-amplitude contractions, and pre-existing esophageal diverticula [17]. Incidence of perforation is generally considered to be lower with the serial, graded balloon dilation approach.

Prompt recognition of possible perforation is crucial either by routinely performing a post-dilation radiograph of the esophagus using water-soluble contrast or by recognizing signs and symptoms of perforation such as persistent chest pain or tachycardia [36]. Assessment of pain evoked by ingestion of water 1–2 h after the procedure can also be diagnostic. Should perforation arise, broad-spectrum antibiotics should be initiated and immediate surgical consultation should be sought. In some clinical situations, conservative management with antibiotics and initiation of parenteral nutrition may be sufficient [17].

PD-induced disruption of the LES, which is the principal barrier to acid reflux, commonly results in resultant gastroesophageal reflux disease (GERD). This has been reported in 15–35 % of patients post-dilation, the majority of which respond to proton-pump inhibitors [18].

Other minor complications have been reported including post-procedural chest pain, intramural

hematomas, and new diverticula, particularly at the gastric cardia. When bleeding does occur, there is usually not an associated drop in hemoglobin [37].

It is recommended that patients should undergo PD only at high-volume centers [3].

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Peroral Endoscopic Myotomy

7

Marc A. Ward and Michael B. Ujiki

Introduction

The idea of conducting an endoscopic myotomy for the treatment of esophageal motility disorders was first described by Ortega in 1980 [1]. Due to concerns of mediastinal leaks and the development of subsequent mediastinitis, this technique was not widely adopted. As technology improved, with the development of high-definition endoscopes, endosurgical tools, and endoluminal suturing devices, the idea of an endoscopic myotomy was revisited especially with the growing interest in natural orifice transluminal endoscopic surgery or NOTES in the early 2000s. Through NOTES, endoscopic surgeons developed a submucosal tunneling technique that was instrumental in the development of an endoscopic myotomy, because it leaves a protective mucosal flap that can be closed using standard endoscopic clips [2]. In 2009, Haruhiro Inoue used this technique to perform a Peroral Endoscopic Myotomy or POEM, in which he divided the circular muscle of the lower esophageal sphincter (LES), while leaving the longitudinal muscle alone [3]. This, coupled with the submucosal tunneling technique, provided a margin of safety as well as the benefit of treating only the dysfunctioning mechanics of the disease, thereby limiting the possibility of mediastinal leaks and mediastinitis. Although POEM is a relatively young procedure, it is gaining popularity around the world as an alternative to the laparoscopic Heller myotomy (LHM) or pneumatic dilation (PD) in the treatment of esophageal motility disorders.

Indications

POEM was originally designed as an endosurgical therapy to treat achalasia. Achalasia is a condition where the esophagus lacks peristalsis and is accompanied by a failure of LES relaxation secondary to neuronal degeneration. Although there is no specific cure, many endoscopic and laparoscopic interventions including LHM, botox injections of the LES, PD, and POEM are designed to offer palliation. Dividing or relaxing the circular muscle fibers of the esophagus decreases the resting tone of the LES so that ingested material can pass into the stomach unimpeded. Several retrospective studies have shown POEM to be a very effective therapy in eliminating symptoms of dysphagia and chest pain in achalasia patients [3–5].

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_7

As a result, several surgeons have reported using versions of the POEM technique (extended or shortened myotomy) as a therapy to treat other esophageal motility disorders such as diffuse esophageal spasm (DES), nutcracker esophagus, or hypertensive lower esophageal spasm [4, 6, 7]. Given the lack of effective treatment alternatives for these patients, POEM appears to offer a reasonable strategy to effectively improve the symptoms in this cohort.

Preoperative Testing

Significant preoperative testing is recommended for any patient who is being considered for POEM. A thorough history and physical is necessary, where medical comorbidities, allergies, and prescription drug therapies need to be documented and evaluated, as this procedure should be done under general anesthesia. In addition, Eckardt scores, esophageal manometry, esophagogastroduodenoscopy (EGD), and a barium swallow should all be performed prior to the operating room. Eckardt scores are useful to determine how effective the procedure was in eliminating symptoms post-operatively. Scoring is based on grades of weight loss, retrosternal pain, regurgitation, and dysphagia. A post-operative score greater than 3 indicates treatment failure [8]. Manometry is useful to confirm the etiology of the esophageal motility disorder, whereas a preoperative EGD and barium swallow will help rule out any potential contraindications such as esophageal masses, diverticulae, Barrett's esophagus, esophageal varices, or large paraesophageal hernias that may prohibit a patient from undergoing POEM. We recommend that all patients consume a clear liquid diet for 48 h prior to the operation. This helps clear out the esophagus in case food is not completely evacuated due to the absence of peristalsis.

Technique

During the POEM procedure, patients are brought to an operating room, placed in the supine position and induced under general anesthesia. A high-definition endoscope is passed into the esophagus. The gastroesophageal (GE) junction is identified and the stomach and duodenum are inspected. Retroflexion is performed to inspect the GE junction prior to the start of the mucosotomy to confirm a tight junction is present. It is important to use carbon dioxide for insufflation, as the use of normal air is associated with a higher incidence of post-operative subcutaneous emphysema and tension pneumothorax. At this point an overtube is placed and an endoscopic mucosal resection (EMR) cap (angled cap) is placed on the end of the endoscope.

The site of the initial mucosotomy varies depending on whether or not spastic disease is present. If present, we typically make the mucosotomy just distal to the cricopharyngeus muscle. In patients with Chicago class I and II achalasia, the mucosotomy is measured 10 cm proximal to the GE junction. At this location a mixture of saline and methylene blue is injected into the submucosal space using either an endoscopic needle or a hybrid knife. Some endoscopic surgeons add epinephrine to this solution to minimize bleeding, but this is not routine. The site of the injection varies depending on the surgeon, however we advocate that the initial mucosotomy be done on the patient's right side at the 2–3 o'clock position, if the anterior surface of the esophagus is at 12 o'clock and the posterior esophagus is at 6 o'clock. This enables the myotomy to be carried down along the lesser curve of the stomach post-LES, which is technically easier and safer than doing it along the posterior stomach or near the Angle of His. Using the cut function of the energy device, a 2 cm vertical incision is made in the mucosa (Fig. 7.1). A vertical incision to get into the submucosal space makes it easier to close the mucosotomy at the end of the operation with endoscopic clips. If a horizontal mucosotomy is made, closure will likely be facilitated using an endosurgical suturing device. It is important to make sure the initial mucosotomy goes through the entire submucosa until the circular muscle is visualized. This guides the scope into the proper position for the submucosal dissection.

The scope is then inserted into the submucosal space and the space is dissected using a combination

Fig. 7.1 A 2 cm vertical mucosotomy is performed after the submucosal space is injected with saline and methylene blue. This is performed 10 cm proximal to the GE junction for Chicago class I and II achalasia and just distal to the cricopharyngeus for class III

Table 7.1 Typical ERBE generator settings used during poem

Initial incision:	EndoCut Q 3-1-1 (yellow pedal)
Tunneling:	Forced Coag E2 50W (blue pedal)
Myotomy:	EndoCut Q 3-1-1 (yellow pedal)
Bleeders:	Forced Coag E2 50W (blue pedal)
Visible vessels 2 mm+:	Forced Coag E2 50W (blue pedal)
High vascularity:	Spray Coag E2 50W (optional)
Coag graspers:	Soft Coag E5 80W (optional)

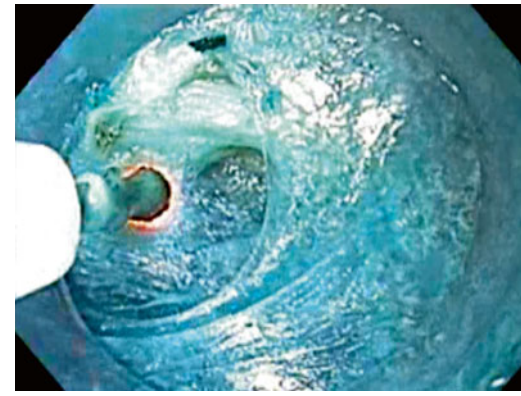

Fig. 7.2 The submucosa tunnel is injected with saline and methylene blue to more accurately identify and divide submucosal vessels

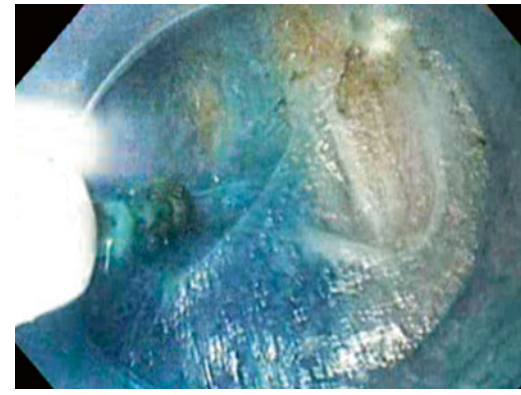

Fig. 7.3 The submucosal tunnel must extend approximately 3 cm distal to the GE junction (seen to the *right* of the figure) in order to provide adequate symptom relief

of cautery and cutting (Table 7.1). The endoscopic needle or hybrid knife should be routinely used to inject blue dye into the submucosal space. This helps create the submucosal tunnel through hydrodissection and displays blood vessels more clearly to allow for more accurate ligation (Fig. 7.2). If impedance is experienced at the GE junction or a stricture is encountered within the submucosal space, retracting the scope and making the submucosal space larger often facilitates easier dissection going forward (Fig. 7.3). It is important to continue the submucosal dissection at least 3 cm onto the stomach. The presence of palisading vessels provides a clue that one has reached the stomach.

The myotomy of the circular fibers of the esophagus begins 3 cm distal to the mucosotomy (Fig. 7.4). This is often performed by either using the cut or a combination cut-coagulation setting on the energy device. Using coagulation alone for this portion often causes excessive char, which may make visualization and staying anterior to the longitudinal fibers more difficult. An adequate myotomy onto the stomach can be confirmed by visualizing the presence of the pale appearing gastric mucosa upon intraluminal retroflexion of the endoscope. At least 3 cm of pale gastric mucosa should be visualized to ensure an adequate myotomy was performed (Fig. 7.5). Once this is confirmed, the mucosal defect is closed with sequential endoscopic clips (Fig. 7.6) or endoscopic suturing device (Fig. 7.7) depending on the direction of the ini-

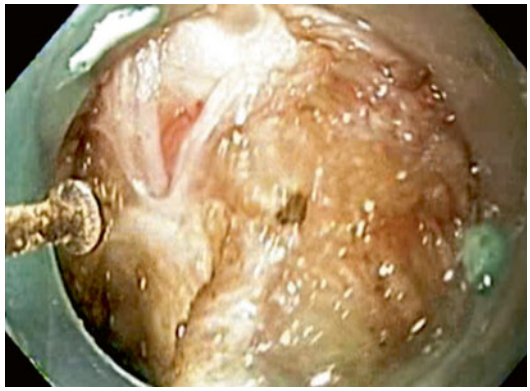

Fig. 7.4 Only the circular muscle fibers are cut during a peroral endoscopic myotomy, while the longitudinal muscle fibers of the esophagus are left intact. This provides a margin of safety, while treating the dysfunctting mechanics of the disease

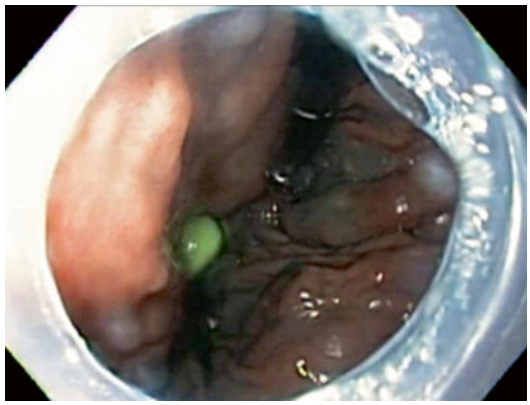

Fig. 7.5 At least 3 cm of pale gastric mucosa must be visualized on retroflexion once the myotomy is completed in order to ensure adequate symptom relief post-operatively

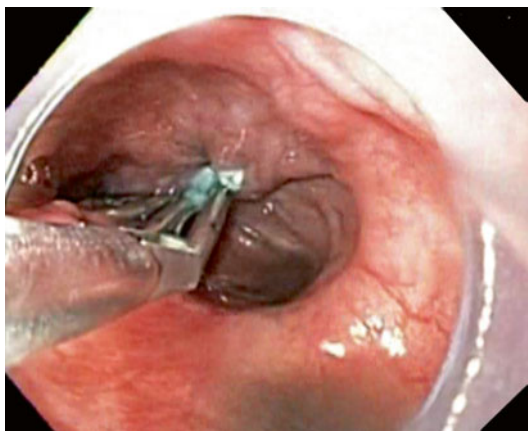

Fig. 7.6 Endoscopic clips are often used to close a vertical mucosotomy

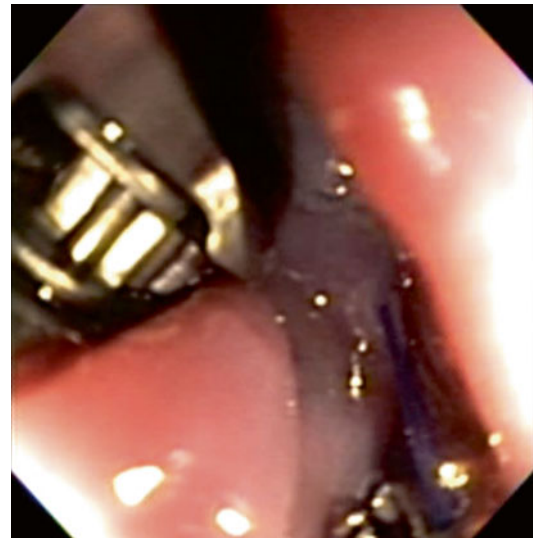

Fig. 7.7 An endoscopic suturing device is often used to close a horizontal muscosotomy

tial mucosotomy. The patient is then extubated and taken to a post-anesthesia care unit for post-operative monitoring.

Post-operative Care

Following the operation, we recommend admitting the patient for observation overnight. A water-soluble contrast swallow on post-operative day 1 is advised to ensure that no mucosal leak is present. Patients are maintained on a pureed diet following the procedure and told to continue it for 1 week once discharged from the hospital. The patient is then instructed to come back to the office for a routine post-operative visit 2–3 weeks following discharge. Since achalasia patients are four times more likely to develop esophageal cancer compared to the general public, an EGD at least every 5 years is advised in these patients.

Outcomes

Symptom relief in achalasia patients following POEM is excellent, as dysphagia and chest pain were resolved at rates of 98 % and 92 % respectively in the largest retrospective series to date [4]. In non-achalasia patients (DES, nutcracker esophagus,

Table 7.2 Portland esophagotomy classification

Portland I: full-thickness entry esophagotomy
Portland II: mediastinal exposure (longitudinal fiber split)
Portland III: inadvertent mucosotomy
Portland IV: full-thickness perforation

hypertensive LES) symptom relief was less impressive but sill greater than 70 % [4]. Several studies have shown that Eckardt scores are an average of 0–1 following POEM [9, 10]. The overall failure rate, defined as an Eckardt score greater than 3, is less than 2 %. One advantage of undergoing POEM is that in the rare case that it fails, other surgical procedures still remain viable options [11]. In addition, it has been shown that POEM is a feasible option for patients after a failed myotomy even in the presence of a fundoplication. Post-operative changes are not evident in these patients and the mean operating time is not affected by a previous myotomy [12].

Compared to LHM, which is currently viewed as the gold standard, POEM patients experience less pain, take fewer narcotics, and have a quicker return to activities of daily living (ADL) [13]. The average POEM patient is back to work within 3 days of the operation. Avoiding body wall trauma and extensive dissection of the esophageal hiatus are thought to be contributing factors to these findings. As a result, most patients report a significantly improved quality of life within 1 year following the operation. Results from studies using validated questionnaires evaluating quality of life following POEM are comparable to those done for LHM [14].

Overall, the morbidity surrounding this procedure is low [4, 5, 13, 15]. Although, intra-tunnel leaks, post-operative hemorrhage, and prolonged intubation due to persistent subcutaneous emphysema have all been reported, the overall morbidity rate is roughly 5 % in most studies. Mucosal injuries can occur in as high as 20 % of patients, but in the majority of cases are treated with endoscopic clips. The Portland Esophagotomy Criteria (Table 7.2) is a classification of intra-operative injuries caused by technical errors that may arise during the course of the procedure, but do not typically cause morbidity. It has been shown that POEM has a learning curve of around 20 cases and the rate of these non-morbid injuries decrease as surgeons become more familiar with the procedure [16].

The main criticism directed towards the use of POEM in the treatment of esophageal dysmotility is the incidence of post-operative gastroesophageal reflux disease (GERD). Unlike LHM, POEM is not followed by a fundoplication. As a result, roughly 1/3 of all POEM patients develop GERD according to 24 h pH studies [4, 10, 15]. Although only 50 % of these patients have reflux symptoms, most patients will require life-long proton pump inhibitor (PPI) therapy. According to current studies, reflux symptoms are well controlled in post-POEM patients with PPIs; however, the long-term impact of GERD development following POEM is unknown and will require further investigation.

Much of the data that has been collected on the outcomes of POEM has been retrospective. In addition, the follow-up is short and the long-term efficacy of the procedure is still unknown. Nonetheless, the initial data is promising and there appears to be a clear benefit for patients in terms of quality of life improvement, symptom resolution, decreased pain, and faster return to ADLs.

Conclusions

The excitement that surrounds POEM is due to the fact that it offers the efficacy of surgery with the cost and morbidity of purely an endoscopic procedure. Data supports POEM as a good alternative to surgical myotomy or pneumatic dilation as it is less morbid than surgery and more effective than pneumatic dilation or Botox treatments. Patient selection is crucial, however, as POEM appears to be a refluxogenic procedure for at least 1 in 3 patients. Overall, POEM is a safe and effective technique that can adequately treat achalasia and can be applied to a wide range of spastic esophageal motility disorders.

Conflict of Interest The authors have no conflict of interest.

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Heller Myotomy for Achalasia. From the Thoracoscopic to the Laparoscopic Approach

8

Marco E. Allaix, Mauricio Ramirez, and Marco G. Patti

Introduction

The treatment algorithm of patients with esophageal achalasia has radically changed during the last three decades after the development and the wide diffusion of minimally invasive surgical approaches. While in the "open" era, endoscopic pneumatic dilatation (PD) was the treatment option of choice and Heller myotomy (HM) was mostly performed in case of failure of PD, in the "minimally invasive" era HM has become the treatment modality of choice in most Centers [1].

The first minimally invasive HM was performed in 1991 through a left thoracoscopic approach, aiming to couple the benefits of HM and the advantages of a minimally invasive approach in the early postoperative course [2] (Fig. 8.1). However, the early results clearly showed some technical limitations of this approach, such as the occurrence of postoperative pathological gastroesophageal reflux in about 60 % of patients, since an antireflux procedure was not added to the HM.

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The ability of extending the myotomy easily onto the gastric wall and the ability of adding a partial fundoplication have made laparoscopic Heller myotomy (LHM) the procedure of choice in most Centers for the treatment of esophageal achalasia patients, with minimal perioperative morbidity and excellent long term functional outcomes [3]. Recently, the use of the robot [4–7] and the laparoscopic single-site (LESS) approach have been proposed aiming to further reduce the invasiveness and improve long term outcomes of LHM [8].

This chapter reviews the evolution of the surgical approach to achalasia patients over the last three decades, focusing on the technical aspects that have brought a progressive switch from open to laparoscopic Heller myotomy.

The Open Approach

A myotomy as surgical treatment of achalasia was first described by Heller in 1914 [9]. The original approach, consisting of two transabdominal extra-mucosal myotomies on both the anterior and the posterior esophageal wall, was then modified in 1923 by Zaaijer who performed only a myotomy on the anterior wall of the esophagus [10].

During the 1960s and 1970s, a short esophageal myotomy without an antireflux procedure was performed through an open approach, either

P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_8

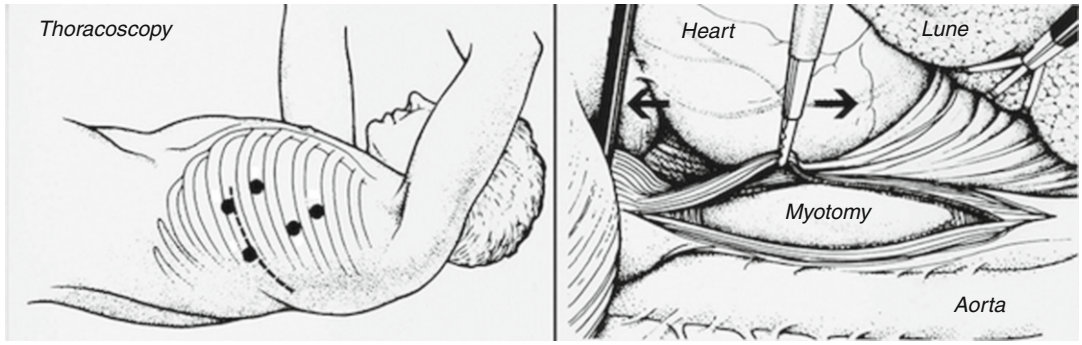

Fig. 8.1 Left thoracoscopy myotomy. (**a**) Position of trocars. (**b**) Myotomy

left transthoracic or transabdominal. The aim of a short myotomy was to treat dysphagia avoiding gastroesophageal reflux For instance, Ellis [11] reported in 1993 his 22-year personal experience with transthoracic short myotomy (only 5 mm onto the gastric wall) without an antireflux procedure in 179 achalasia patients. An overall improvement over a mean postoperative follow-up period of 9 years was reported in 89 % of patients, with no significant deterioration over time. Only nine (5 %) patients experienced poor results with marked gastroesophageal reflux symptoms, suggesting that a short transthoracic myotomy without a wrap was associated with relief of dysphagia in most cases and very low incidence of symptomatic gastroesophageal reflux. Others reported similar results [12, 13].

The open trans-abdominal approach without an antireflux procedure was mostly used in Europe and South America [14–16]. Excellent to good outcomes in terms of relief of dysphagia were reported in 80 to 95 % of patients, while the incidence of postoperative reflux symptoms ranged between 8.5 and 22 %. The trans-abdominal myotomy apparently resulted in a significantly higher incidence of postoperative gastroesophageal reflux than the transthoracic myotomy,. A longer myotomy onto the gastric wall, division of the phreno-esophageal ligament, and the more extensive mobilization of the esophagus were the suggested mechanisms to explain the higher incidence of postoperative gastroesophageal reflux. However, the results of the studies that assessed the occurrence of postoperative reflux were based on evaluation of symptoms only, thus underestimating the real incidence of reflux [17]. In fact, when an objective evaluation by 24-h pH monitoring was performed the incidence of postoperative reflux was significantly higher after a short myotomy. For instance, Streitz et al. assessed the gastroesophageal function by esophageal manometry and 24-h pH monitoring in 14 achalasia patients undergoing a short myotomy without an antireflux procedure [18]. They found that lower esophageal sphincter (LES) pressure decreased from a preoperative mean of 26.7 mmHg to a postoperative mean of 14.6 mmHg, and that the esophageal acid exposure was pathologic in four patients (28.6 %). By multivariate analysis, esophageal acid exposure correlated only with the value of residual LES pressure.

The addition of a partial anterior fundoplication to a long trans-abdominal myotomy with the goal of providing relief of dysphagia and minimizing the risk of postoperative pathologic gastroesophageal reflux was proposed by Dor in 1962 [19]. Since then the evidence supporting this strategy rapidly increased [20–26]. For instance, Csendes reported the long-term outcome in 100 achalasia patients treated by an anterior 6-cm myotomy (extending onto the gastric wall no more than 5–10 mm) associated with anterior fundoplication [22]. With a mean follow-up of 6.8 years in 92 of the 94 patients, occasional postoperative dysphagia was experienced by 8 % of patients only. In three patients, squamous esophageal carcinoma developed 5–9 years after surgery. Pathologic gastroesophageal reflux was present in 19 % of patients undergoing 24-h pH monitoring.

Bonavina et al. evaluated 193 achalasia patients who had undergone transabdominal Heller myotomy (8-cm long on the esophagus and 2-cm long on the stomach) and Dor fundoplication as primary treatment modality [23]. With a median follow-up period of 64.5 months (range, 12–144 months), good to excellent results were reported in about 94 % of patients, recurrent dysphagia occurred in 3.6 % of patients, and abnormal acid exposure at 24-h pH monitoring was found in only about 9 % of patients tested.

In conclusion, the evidence shows that both transthoracic and trans-abdominal myotomies are effective in the relief of dysphagia; however, a trans-abdominal myotomy with a partial anterior fundoplication is associated with significantly reduced postoperative pathologic gastroesophageal reflux rates.

From the Thoracoscopic to the Laparoscopic Heller Myotomy

In the early 1990s, minimally invasive surgical approaches were developed for the treatment several abdominal diseases including achalasia [27]. The first minimally invasive esophageal myotomy in the United States was performed with a left thoracoscopic approach in 1991 (Fig. 8.1). Pellegrini et al. published in 1992 the short-term outcomes in the first 17 achalasia patients after either thoracoscopic (n=15) or laparoscopic (n=2) myotomy [2]. The patient undergoing a thoracoscopic myotomy was placed in the right lateral decubitus position after insertion of a double lumen endotracheal tube to selectively intubate the right main stem bronchus. Two 5-mm trocars and two 10-mm trocars were used. Under endoscopic guidance, the myotomy was started on the esophageal wall at a point midway between the inferior pulmonary vein and the diaphragmatic hiatus and was extended distally for about 5 mm onto the gastric wall (reproducing the Ellis' procedure) until wide patency of the lumen at the level of the gastroesophageal junction was evident at endoscopy. Then, the edges of the muscular layers were separated by blunt dissection; a chest tube was placed at the end of the procedure.

A small intraoperative mucosal laceration was reported in two patients; in both cases, conversion to open surgery was needed to suture the defect. A soft diet was resumed on postoperative day 2 in all patients undergoing minimally invasive surgery, and they were all discharged on postoperative day 3. No postoperative morbidity or mortality was reported. Postoperative discomfort was only due to the chest tube that was removed after 24–48 h. The first three patients who were treated by thoracoscopic myotomy had no relief of dysphagia: the reason was a myotomy that was not carried far enough distally onto the gastric wall. All three patients underwent a second myotomy (one by open trans-abdominal approach and two by laparoscopy), with complete relief of dysphagia in two patients. At the end of follow-up, excellent to good results in terms of swallowing status were achieved in 82 % of patients. A postoperative 24-h pH monitoring was performed in four patients 1–13 months after surgery, showing pathologic acid exposure in 60 % of them.

Since an antireflux procedure was deemed not necessary when the myotomy was performed through the chest because there was no disruption of the antireflux barrier [28], the left thoracoscopic myotomy became quickly the recommended minimally invasive approach for the surgical treatment of achalasia patients. The laparoscopic approach was reserved for patients with a previous myotomy or for those who had already a left thoracotomy [2]. However, the evidence showing safety, feasibility and significantly better early and late outcomes after LHM than left thoracoscopic myotomy rapidly increased in the late 1990s [29–43]. LHM and partial fundoplication achieved reduced postoperative pain and discomfort, shorter hospital stay, better relief of dysphagia, and lower incidence of postoperative gastroesophageal reflux than thoracoscopic myotomy (Figs. 8.2 and 8.3). For instance, Patti et al. compared the outcomes in 60 achalasia patients treated by thoracoscopic myotomy (30 patients) or LHM plus anterior fundoplication (30 patients) [33]. Median hospital stay was shorter in the laparoscopic group than in the thoracoscopic group (42 h versus 84 h, respectively).

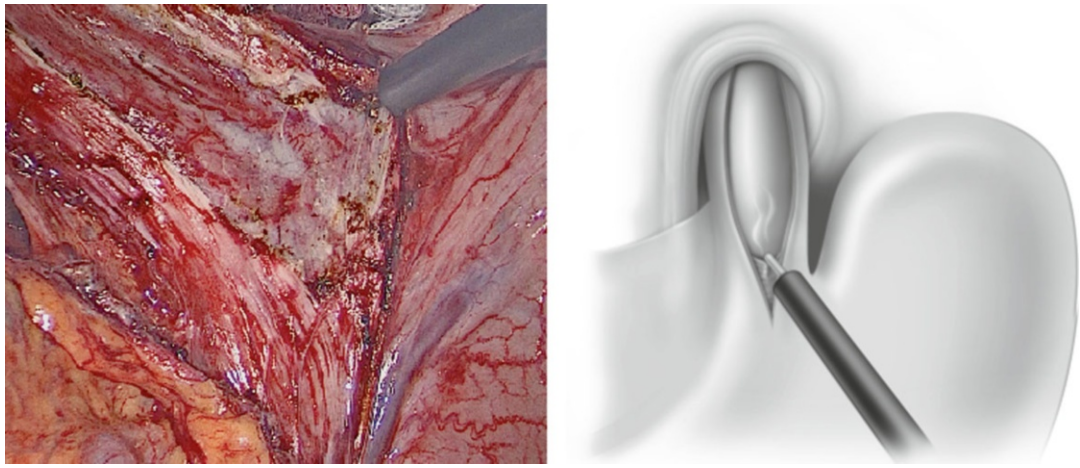

Fig. 8.2 Laparoscopic myotomy

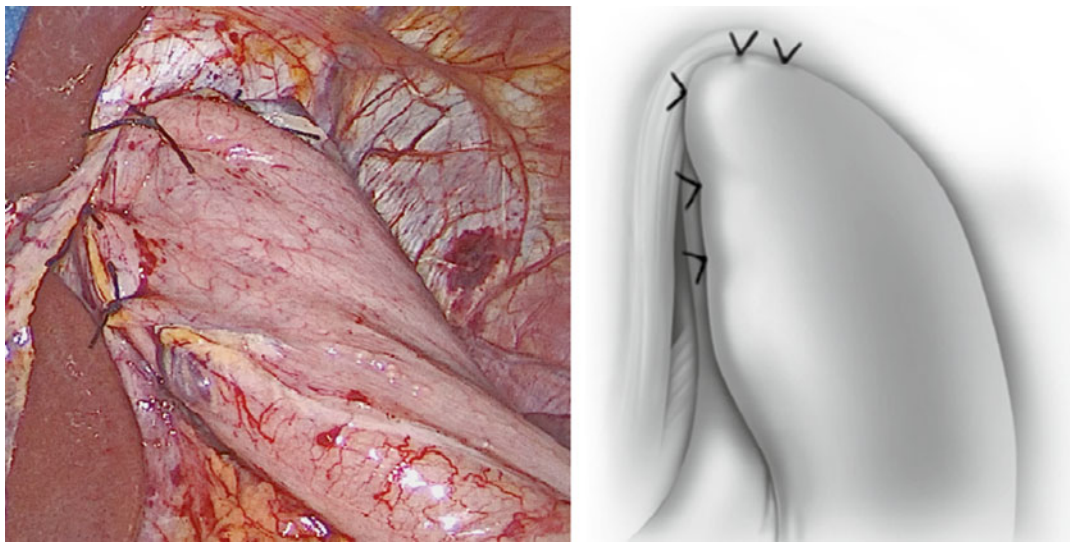

Fig. 8.3 Laparoscopic Dor fundoplication

Good to excellent results in terms of resolution of dysphagia were reported in 87 % of thoracoscopic myotomy group patients and 90 % of LHM group patients. A postoperative 24-h pH monitoring was obtained in ten patients in each group: abnormal reflux was found in 60 % of patients after thoracoscopic myotomy and in 10 % only of patients after LHM. Stewart et al. [42] retrospectively reviewed the intraoperative outcomes and postoperative symptoms in 24 achalasia patients treated by thoracoscopic myotomy and 63 patients treated by LHM and partial fundoplication. Mean operating room time was significantly shorter and there were fewer conversions to open surgery (2 % vs. 21 %) in the LHM group than the thoracoscopic group. No postoperative leaks were recorded. Mean postoperative length of stay was significantly shorter for patients undergoing LHM. Persistent dysphagia and heartburn were reported more frequently after thoracoscopic surgery. An incomplete myotomy on the gastric wall was the main cause of persistent dysphagia in patients undergoing thoracoscopic myotomy, while the addition of a

fundoplication by laparoscopy was key in preventing reflux [32, 44].

In the second half of the 1990s, several studies compared the results of laparoscopic and open trans-abdominal myotomy with Dor fundoplication [45–49]. For instance, Ancona et al. retrospectively analysed the short-term outcomes in 17 patients who had undergone LHM and 17 patients who had open myotomy [45]. Both groups of patients were similar in age, sex, symptom duration, maximum esophageal diameter, and length of follow-up. LHM took significantly longer than open myotomy. No mortality was observed, and morbidity rates did not differ between the two groups. Pain medications were less frequently requested by patients after LHM, who had a quicker resumption of gastrointestinal function, shorter hospital stay, and quicker return to daily activities. As a consequence total costs were lower after LHM. With a median follow-up of 6 months in both groups, one patient (5.8 %) in the laparoscopic group experienced recurrent dysphagia, and one (5.8 %) patient after open surgery was found to have pathologic acid exposure at 24-h pH monitoring.

Douard et al. [49] compared in a prospective and non-randomized study functional results after laparoscopic and open myotomy with Dor fundoplication: 52 were treated by laparoscopy, 30 by an open approach. Median follow-up was 51 months (range, 12–111). The evaluation included the assessment of presence and severity of dysphagia, chest pain, regurgitation and gastroesophageal reflux by using a clinical score at 3, 6, 12 months after surgery, then every year. Similar rates of excellent to satisfactory results were obtained in terms of relief of dysphagia: 92 % after LHM and 93 % after open myotomy. Median dysphagia score dropped at 3 months after surgery in both groups, with no significant changes over time. Typical reflux symptoms were experienced by 10 % of patients after LHM and 7 % of patients after open myotomy. The presence of pathological esophageal acid exposure was confirmed by 24-h pH monitoring in all symptomatic patients and in two asymptomatic patients.

In conclusion, the evidence shows that LHM achieves better early postoperative outcomes and similar long-term functional results when compared to the open myotomy, thus leading to a progressive switch in clinical practice from open to LHM. These benefits have (a) increased the number of achalasia patients referred for surgery rather than PD; (b) increased the number of patients referred for surgery without any previous endoscopic treatment; and (c) improved the surgical outcome of the procedure [1]. Transabdominal myotomy achieves better symptom control and lower incidence of postoperative gastroesophageal reflux than transthoracic myotomy. Therefore, LHM with partial fundoplication is the procedure of choice for the surgical treatment of achalasia patients [3].

New Trends in Heller Myotomy

More recently, new approaches, such as the LESS approach and the robotic approach have been developed aiming to further improve the surgical outcome in achalasia patients.

For instance, Barry et al. [8] reviewed the outcomes in 132 patients undergoing trans-umbilical LESS Heller myotomy and anterior fundoplication (66 patients) or conventional LHM and anterior fundoplication (66 patients) for achalasia. The operative time of the LESS procedure was significantly longer than conventional LHM; furthermore additional ports were used in 11 (16 %) LESS patients. No conversion to open surgery occurred in either group. Intraoperative and early postoperative morbidity rates were similar. Similar outcomes in symptom resolution were achieved in both groups (88 % of patients after LESS and 82 % of patients after conventional LHM).

These preliminary data are promising, however, large long follow-up studies are necessary to evaluate the real advantages of the LESS approach in terms of cosmesis, perioperative complications and functional outcomes.

Robotic myotomy is emerging as possible alternative to conventional LHM for the surgical treatment of achalasia patients. However, the current level of evidence supporting the use of robotic technology in this field is very low [4–6, 49]. For instance, Horgan et al. [4] conducted a multicenter retrospective study including 121 achalasia patients: 59 were

treated by a robotic myotomy and 62 patients underwent a conventional LHM.. The mean operative time was significantly shorter in the LHM group; however, there were no significant differences in operative time in the last 30 procedures. No esophageal perforations occurred during robotic myotomy, while a rate of 16 % was reported in the LHM group (16 % vs. 0 %). With a mean follow-up of 18 months for the robotic group and 22 months for the LHM group, similar dysphagia relief rates were observed: 92 % of patients after robotic surgery and 90 % of patients after LHM. No differences were reported in occurrence of postoperative gastroesophageal reflux.

Similar results were reported by Melvin et al. [5] in a multicenter prospective study including 104 achalasia patients treated by robotic myotomy. No esophageal intraoperative perforations were reported. Conversion rate to open surgery was 0.9 % (1 patient). Some 79 of 104 patients (76 %) underwent a symptom evaluation. Symptoms dramatically improved in all patients. With a mean follow-up period of 16 months, no patients underwent a reoperation. Huffmanm et al. [6] compared the results after 37 LHM and 24 robotic myotomies. The robotic group had a lower rate of esophageal perforations (0 % vs. 8 %) and higher postoperative quality-of-life indices than LHM group. Several technical variabilities, including the three-dimensional visualization, the lack of tremor and increased surgeon dexterity, have been proposed to explain the reduced risk of intraoperative esophageal perforation during robotic myotomy. However, data from larger studies on esophageal perforation after robotic or conventional laparoscopic myotomy are conflicting. A multicenter, retrospective analysis of a large administrative database including 2,116 laparoscopic myotomies and 149 robotic myotomies did not find any difference in intraoperative complications and postoperative course, but increased costs in the robotic group [7].

In conclusion, there is increasing interest in adopting the robotic technology for Heller myotomy; however, the current evidence does not support the use of the robot as the approach of choice in the management of achalasia.

Conflict of Interest The authors have no conflicts of interest to declare.

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Laparoscopic Heller Myotomy and Fundoplication. What Type?

9

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Esophageal achalasia is a primary esophageal motility disorder of unknown origin characterized by lack of esophageal peristalsis and inability of the lower esophageal sphincter (LES) to relax properly in response to swallowing. The goal of treatment is to relieve the functional obstruction caused by the LES, therefore allowing emptying of food into the stomach by gravity. However, the elimination of the LES may be followed by reflux of gastric contents into the aperistaltic esophagus, with slow clearance of the refluxate and the risk of developing esophagitis, strictures, Barrett's esophagus and even adenocarcinoma [1–4].

The following chapter reviews the results of surgery for achalasia, describing what is considered today the best procedure to achieve the goal of relieving dysphagia while avoiding development of reflux.

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Treatment of Esophageal Achalasia. The Open Era

During the 1970s and 1980s pneumatic balloon dilatation was considered the primary form of treatment for achalasia. During that period, very few myotomies were performed, mostly for patients whose dysphagia did not improve with balloon dilatation or whose esophagus was perforated during a balloon dilation [5]. In 1991 we performed the first thoracoscopic Heller myotomy [2]. We followed Ellis' technique and extended the myotomy for 5 mm only onto the gastric wall [2]. The rationale for this approach was to make the myotomy long enough to relieve dysphagia but short enough to avoid reflux and therefore the need for a fundoplication. In a review of his 22-year experience with 197 patients Ellis documented symptomatic reflux in only 9 (5 %) of them [2]. However, his analysis was based on symptom evaluation only (presence of heartburn) rather than objective evaluation of the reflux status by pH monitoring. Symptoms may underestimate the reflux as most patients who develop reflux after a Heller myotomy do not experience heartburn [6, 7]. As a matter of fact, when Ellis used pH monitoring to objectively assess gastroesophageal reflux after the myotomy, he found abnormal esophageal acid exposure in 29 % of patients [8].

To avoid or limit the development of gastroesophageal reflux, surgeons in Europe [9] and South America [10] traditionally used

P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_9

a transabdominal approach, performing a longer myotomy onto the gastric wall in combination with an anti-reflux procedure. For Bonavina and colleagues excellent or good results in 94 % of patients while the rate of postoperative reflux measured by pH monitoring was 8.6 % only [9].

Treatment of Esophageal Achalasia. The Minimally Invasive Surgery Era

Shimi and Cuschieri first reported in 1991 the performance of a Heller myotomy for esophageal achalasia by minimally invasive techniques [11]. In 1992 we described our initial experience with a thoracoscopic Heller myotomy [12] using the technique developed by Cuschieri [11], and performed a left thoracoscopic myotomy (with the guidance of intraoperative endoscopy) which extended for only 5 mm onto the gastric wall. The long-term follow-up in the first 30 patients who underwent a left thoracoscopic Heller myotomy confirmed the excellent outcome of the initial report: almost 90 % of patients had relief of dysphagia, the hospital stay was short, the postoperative discomfort was minimal, and the recovery was fast. However, some shortcomings of the thoracoscopic technique soon became apparent, particularly when compared to the laparoscopic approach [13]. We found in that a thoracoscopic myotomy was associated to reflux in 60 % of patients studied postoperatively by pH monitoring. We also encountered patients who already had abnormal reflux secondary to dilatation even though they still experienced dysphagia. Some of these patients had very low LES pressure [14].

These were probably the key reasons that made us switch to a laparoscopic myotomy and Dor fundoplication as suggested by Ancona and colleagues [15]. in the attempt to find a balance between relieving dysphagia and avoiding postoperative reflux. Others followed our example [16, 17].

Laparoscopic Heller Myotomy. Is a Fundoplication Necessary?

It is generally accepted that a fundoplication is necessary to prevent reflux after a laparoscopic Heller myotomy, by either performing a Dor fundoplication [18–24], a Toupet fundoplication [25–28], or a Nissen fundoplication [29–31].

This approach is based on some retrospective studies and two prospective randomized trials comparing laparoscopic myotomy alone versus myotomy and fundoplication. Kjellin and colleagues found abnormal reflux by pH monitoring in 8 of 14 (57 %) patients after laparoscopic myotomy without fundoplication [32]. Five of the 8 patients (62 %) were asymptomatic. Similarly, Burpee and colleagues documented reflux (by pH monitoring or endoscopy) in 18 of 30 patients (60 %) after laparoscopic Heller myotomy without fundoplication [33]. Thirty-nine per cent of patient with reflux were asymptomatic. Gupta and colleagues reported heartburn after laparoscopic myotomy in 80 % of their patients. They felt that it was not a problem as symptoms were well controlled with medications [34].

The observation of a very high incidence of reflux after laparoscopic myotomy alone has also been confirmed by two prospective and randomized trials. In 2003 Kalkenback and colleagues reported the results of a prospective randomized trial comparing myotomy alone versus myotomy and Nissen fundoplication [29]. Postoperative reflux was present in 25 % of patients who had a myotomy and fundoplication but in 100 % of patients who had a myotomy alone. Twenty-percent of the patients in the latter group developed Barrett's esophagus.

In 2004 Richards and colleagues reported the results of a prospective randomized trial comparing laparoscopic myotomy alone versus laparoscopic myotomy and Dor fundoplication [24]. Postoperative ambulatory pH monitoring showed reflux in 48 % of patients after myotomy alone but in only 9 % of patients when a Dor fundoplication was added to the myotomy. The incidence and the score of postoperative dysphagia were similar in the two groups.

Based on these data we feel that a fundoplication should be performed after a laparoscopic Heller myotomy. It is dangerous to claim that postoperative reflux does not matter and that nothing should be done to prevent it. Today we

are operating on many young patients [35] who may develop severe esophageal damage if exposed to years of reflux [1–4].

Which Fundoplication? Partial Versus Total Fundoplication

It has been shown that a laparoscopic total (360°) fundoplication is the procedure of choice in patients with gastroesophageal reflux disease. When compared to a partial fundoplication, a total fundoplication determines a better control of reflux without a higher incidence of postoperative dysphagia, even when esophageal peristalsis is weak [36]. In esophageal achalasia, however, there is no peristalsis. Therefore, a total fundoplication might determine too much of a resistance at the level of the gastroesophageal junction, impeding the emptying of food from the esophagus into the stomach by gravity, and eventually causing persistent or recurrent dysphagia. Albeit some groups still claim good results adding a total fundoplication after a myotomy [29–31], others have abandoned this approach and switched to a partial fundoplication. This decision was based on the results of long-term studies which showed that esophageal decompensation and recurrence of symptoms eventually occurs in most patients [37–41]. For instance, Duranceau and colleagues initially reported excellent results with a Heller myotomy and total fundoplication [39]. Ten years later, however, they noted that symptoms had recurred in 14 of 17 patients (82 %), five of whom required a second operation [40]. They felt that over time the total fundoplication determines a progressive increase in esophageal retention with poor emptying and recurrence of symptoms. They were able to correct this problem by switching to a partial fundoplication [41]. In 2008 Rebecchi and colleagues reported the results of a prospective and randomized trial comparing a Heller myotomy plus Nissen to a Heller myotomy plus Dor. At 10 year follow up the rate of recurrent dysphagia was 15 % after Nissen fundoplication, but only 2.8 % after Dor [42]

Today a laparoscopic Heller myotomy with partial fundoplication is considered the procedure of choice for esophageal achalasia, as it attains the best balance between relief of dysphagia and prevention of reflux [43].

Partial Fundoplication. Anterior Versus Posterior

Some groups feel that a posterior fundoplication is better choice as it keeps the edges of the myotomy separated and it is a more effective antireflux operation [25–28]. Others, however, feel that a Dor fundoplication is simpler to perform as it does not need posterior dissection, and it adds the advantage of covering the exposed mucosa [18–24]. A prospective, multicenter and randomized trial published in 2013 compared the results of a myotomy plus Dor with that a myotomy plus Toupet [44]. They found no difference of symptoms improvement and incidence of postoperative reflux.

Conclusions

The last decade has witnessed radical changes in the treatment of esophageal achalasia due to the adoption of minimally invasive techniques. The high success rate of laparoscopic Heller myotomy with partial fundoplication has brought a radical shift in practice, as surgery has become the preferred treatment modality of most gastroenterologists and other referring physicians.

Conflict of Interest The authors have no conflicts of interest to declare.

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Laparoscopic Heller Myotomy and Dor Fundoplication

10

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Esophageal achalasia is a primary esophageal motility disorder defined by lack of esophageal peristalsis and by a lower esophageal sphincter (LES) that fails to relax in response to swallowing. In about 50 % of patients the LES is hypertensive. These abnormalities lead to impaired emptying of food from the esophagus into the stomach with consequent food stasis.

Patients complain of dysphagia, regurgitation of undigested food, aspiration, heartburn, and chest pain [1]. In addition to symptomatic evaluation, the diagnostic work-up should include upper endoscopy, barium esophagogram, esophageal manometry and sometimes ambulatory 24-h pH monitoring [2].

Pneumatic dilatation (PD) and POEM are effective treatment modalities for esophageal achalasia [3, 4]. However, in most centers today a laparoscopic Heller myotomy with a partial fundoplication is considered the best treatment modality, relegating PD and POEM to the treatment of the few patients with post-operative recurrent dysphagia [5–15]. Surgical treatment is palliative, and it is based on a myotomy of the distal esophagus and proximal stomach with the goal of relieving the functional obstruction at the level of the gastroesophageal junction in order to improve esophageal emptying and relieve symptoms.

This chapter reviews the technical steps of a laparoscopic myotomy and a 180° anterior fundoplication (Dor fundoplication).

Positioning of the Patient

The patient is under general anesthesia with a single lumen endotracheal tube. The patient is placed over an inflated bean bag and the legs are extended on stirrups with the knees flexed only 20–30°. Pneumatic compression stockings are always used as prophylaxis against deep vein thrombosis. This is particularly important as the increased abdominal pressure secondary to the pneumoperitoneum and the steep Trendelenburg position decrease venous return. The surgeon stands between the patients legs (Fig. 10.1).

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_10

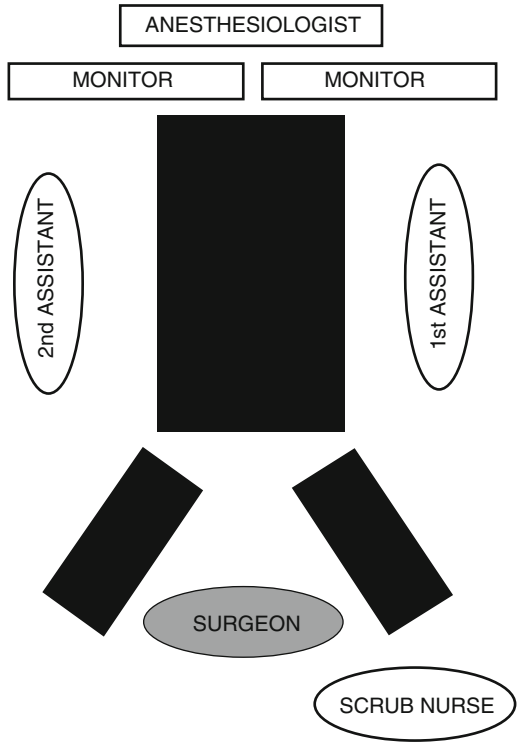

Fig. 10.1 Organization of the operating room for a laparoscopic Heller myotomy

Placement of the Trocars

Five trocars are used for the operation (Fig. 10.2).

Port A is placed in the midline 14 cm below the xiphoid process and is used for insertion of a 10 mm, 30° scope. Ports B and C are placed under the right and left costal margins and should form an axis of about 100–120°. They are used for dissecting and suturing.

Port D is inserted in the right mid-clavicular line at the level of port A, and it used for the liver retractor. Port E is placed in the left mid-clavicular line, and it used for insertion of a Babcock clamp and the instrument used to take down the short gastric vessels.

Troubleshooting A common mistake is to place the trocars too low. This makes the operation more challenging: for instance if port E is too low, it becomes difficult to take down the more proximal short gastric vessels and the Babcock clamp may not reach the gastroesophageal junction.

Division of the Gastrohepatic Ligament, Identification of the Right Crus of the Diaphragm and the Posterior Vagus Nerve

After the left lateral segment of the liver is lifted and the gastroesophageal junction is exposed, the gastrohepatic ligament id divided. The dissection begins above the caudate lobe of the liver and continues proximally until the right crus is identified. The crus is then separated from the esophagus by blunt dissection and the posterior vagus nerve is identified.

Troubleshooting An accessory left hepatic artery originating from the left gastric artery can be encountered. If it creates a problem with the exposure it can be divided.

The electrocautery should be used with caution next to the right pillar of the crus because the lateral spread of the current may injury the posterior vagus nerve, even without direct contact.

Division of the Peritoneum, Phrenoesophageal Membrane Above the Esophagus, Identification of the Left Crus and the Anterior Vagus Nerve

The peritoneum and the phrenoesophageal membrane above the esophagus are divided and the anterior vagus nerve is identified. The left pillar of the crus is separated from the esophagus. Dissection is limited to the anterior and lateral aspects of the esophagus. No posterior dissection is needed if a Dor is planned.

Troubleshooting Similar to the prior step, the electrocautery must be used with caution when in proximity of the anterior vagus nerve. A bipolar instrument is safer.

Division of the Short Gastric Vessels

Grasping instruments are placed through ports B and C to expose the short gastric vessels. A bipolar instrument is inserted through port E

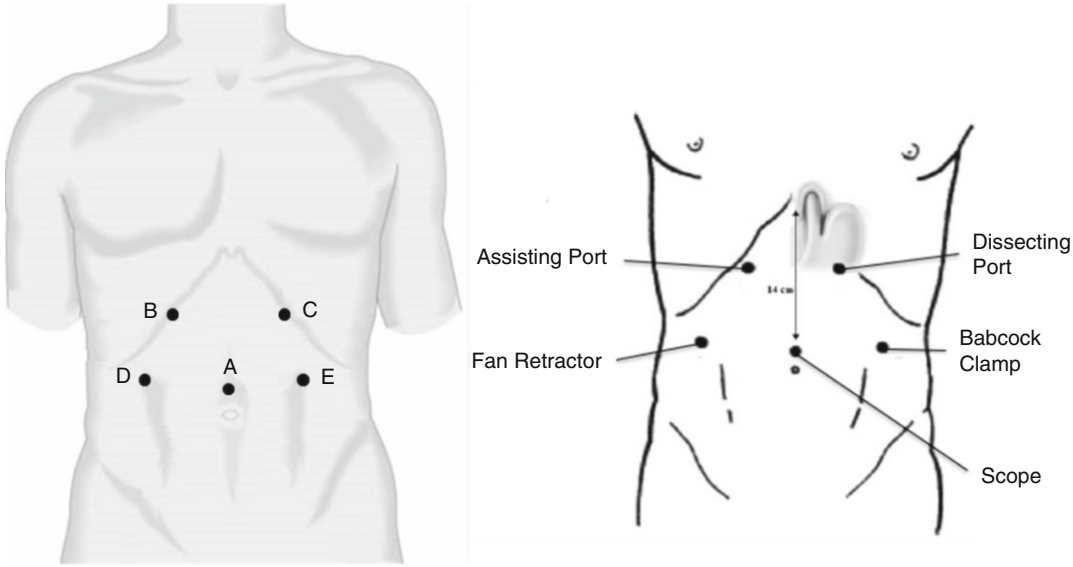

Fig. 10.2 Position of trocars for laparoscopic Heller myotomy

and the vessels are transected starting at a point midway along the greater curvature of the stomach.

Troubleshooting Bleeding from the gastric vessels or the spleen is usually caused by excessive traction or by transection of a vessel not completely sealed. Damage to the gastric wall can be caused by the grasping instruments of by the bipolar instrument.

Esophageal Myotomy

It is important to remove the fat pad in order to expose the gastroesophageal junction. A Babcock clamp is then inserted through port E to apply traction over the proximal stomach in order to expose the right side of the esophagus. The myotomy is then performed at the 11 o'clock position and it extends for about 6 cm on the esophagus and 2.5 cm below the gastroesophageal junction. It is helpful to mark with the electrocautery the surface of the esophagus along the line where the myotomy will be carried out. There are many instruments that can be used to perform the myotomy. We prefer an electrocautery with a 90° hook as it allows careful lifting and division of the circular fibers.

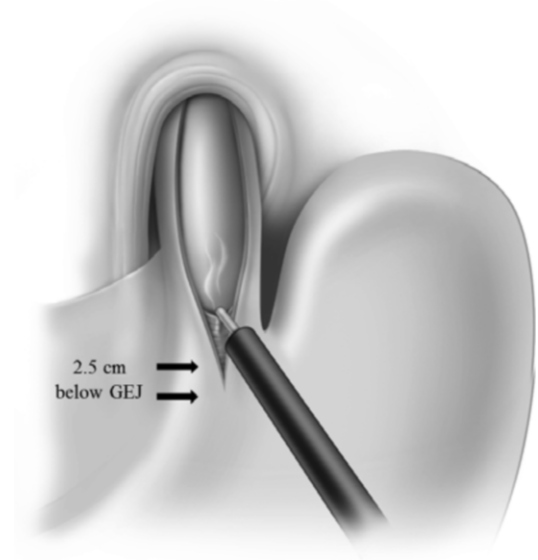

Fig. 10.3 Heller myotomy with 2.5 cm extension below the GEJ (gastroesophageal junction)

The myotomy is started about 3 cm above the gastroesophageal junction by reaching the proper submucosal plane. Subsequently it is extended proximally on the esophagus and distally onto the gastric wall (Fig. 10.3).

At the beginning of a surgeon's experience with a laparoscopic Heller myotomy, intraoperative endoscopy is very important as it allows the

visualization of the squamo-columnar junction so that the myotomy can be extended distally for about 2.5 cm from this point. However, once the surgeon has gained more experience with this procedure and has become more familiar with the anatomy, the endoscopy can be omitted.

Troubleshooting When removing the fat pad attention must be paid to anterior vagus nerve. In addition, if the anterior vagus nerve crosses the line of the myotomy it must be lifted away from the esophageal wall and the muscle layers must be cut under it

The myotomy should not be started too close to the gastroesophageal junction because at this level the layers are not well defined, particularly if multiple dilatations or injections of Botulinum toxin have been performed. It is easier to find the proper plane at this level and then to extend the myotomy proximally and distally. If bleeding occurs from the cut muscle fibers it is important not to use the cautery but to apply gentle pressure until the bleeding stops.

A perforation usually occurs at the level of the gastroesophageal junction, particularly if scar tissue with loss of the normal anatomic planes is present. Any perforation should be repaired using a fine absorbable suture material (4-0 or 5-0).

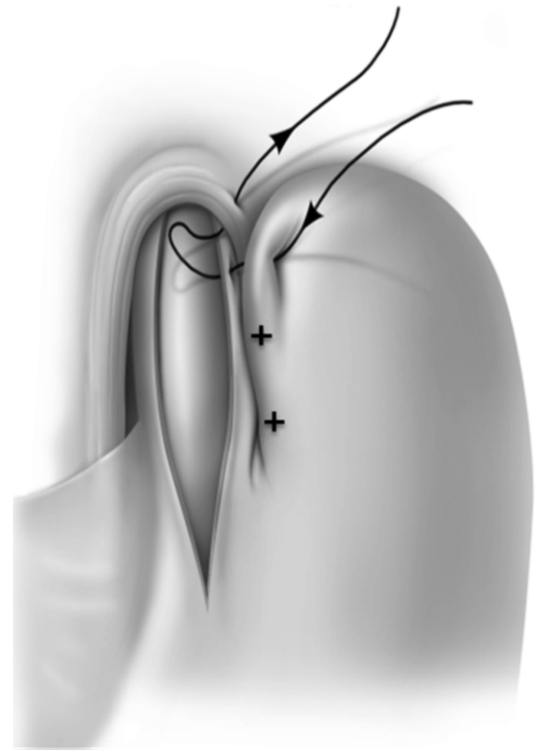

Fig. 10.4 Dor fundoplication, left row of sutures. Uppermost stitch

Dor Fundoplication

The Dor fundoplication (180° anterior) has two rows of sutures, one left and one right. The left row has three stitches. The uppermost stitch incorporates the fundus of the stomach, the esophageal wall and the left pillar of the crus (Fig. 10.4). The second and the third stiches incorporate the stomach and the esophageal wall (Fig. 10.5). The fundus of the stomach is then folded over the exposed mucosa so that the greater curvature is next to the right pillar of the crus. Two or three stitches are placed between the fundus and the right pillar and two additional stitches are then placed between the superior aspect of the fundoplication and the rim of the esophageal hiatus (Figs. 10.6 and 10.7). These stitches remove any tension from the right row of sutures. Overall, the Dor fundoplication covers almost all the myotomy (Fig. 10.8).

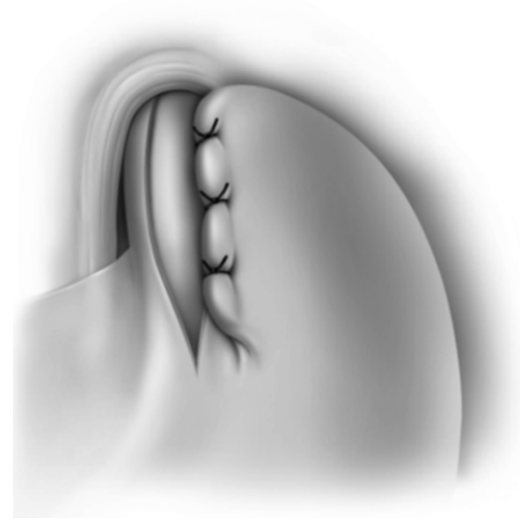

Fig. 10.5 Dor fundoplication, completed left row of sutures

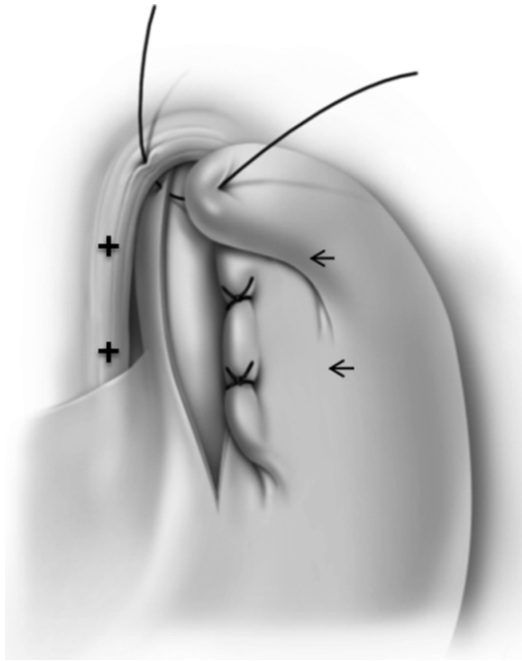

Fig. 10.6 Dor fundoplication, right row of sutures. Uppermost stitch

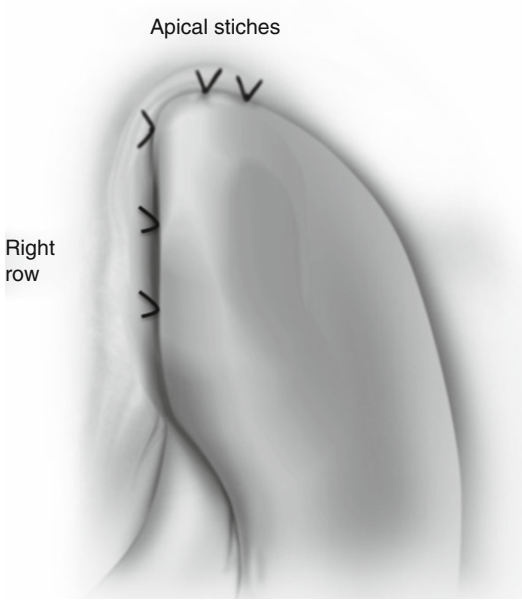

Fig. 10.7 Completed Dor fundoplication

Troubleshooting The fundoplication must be constructed without any tension. For this reason it is important to take down the short gastric vessels and to use the only the fundus of the stomach.

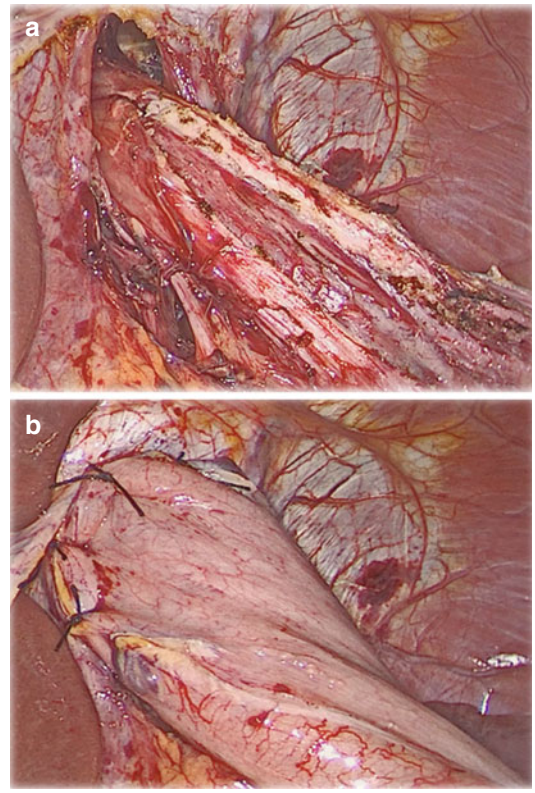

Fig. 10.8 Myotomy (**a**) and For fundoplication (**b**)

Postoperative Care

We do not routinely obtain an esophagogram before initiating feeding. On the morning of postoperative day # 1, patients have clear liquids for breakfast and then a soft mechanical diet for lunch. Most patients are discharged after 24 h and are able to resume their regular activities in 7–14 days.

Outcome

The results obtained with a laparoscopic Heller myotomy and a Dor fundoplication are usually excellent as symptoms are improved in more than 90 % of patients (3–10). Between 10 and

30 % of patients may develop reflux, albeit is asymptomatic in the majority of them. Heartburn is usually controlled with acid reducing medications. Patients should have an endoscopy every 2 or 3 years if asymptomatic or if dysphagia recurs.

Conflict of Interest The authors have no conflicts of interest to declare.

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Laparoscopic Heller Myotomy with Toupet Partial Posterior Fundoplication

11

Roger P. Tatum

Introduction

Invasive treatment for esophageal achalasia dates back to 1674 when Thomas Willis first described esophageal dilation for "cardiospasm" by means of a sponge-tipped whalebone [1, 2]. Heller's description of the anterior and posterior esophagogastric myotomy via a thoracotomy approach launched the era of achalasia as a surgical disease over 100 years ago [3]. Since that time, a large number of refinements in both the approach and procedure have been made, particularly with the advent of minimally invasive surgical techniques in the late 1980s and early 1990s. Though the thoracoscopic method was the first minimally invasive approach to be described, the laparoscopic anterior esophagogastric myotomy, allowing for a longer myotomy distal to the esophagogastric junction with even better results in relieving dysphagia [4] is currently the most commonly employed surgical approach to the patient with this disease. This is typically combined with an antireflux procedure, as the incidence of post-myotomy acid reflux (though often asymptomatic) in patients without an antireflux procedure is in excess of 50 %.

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Workup and Indications for Esophagogastric Myotomy

Since medical therapy is relatively ineffective in the treatment of achalasia, some form of invasive therapy is usually necessary. Endoscopic injection of botulinum toxin at the level of the LES has very limited efficacy, and further it is believed by many to make a subsequent surgical myotomy more difficult with a higher risk of esophageal perforation. Esophageal pneumatic balloon dilation is relatively effective, however is associated with an approximately 3 % risk of perforation, and has a higher likelihood of requiring subsequent therapy for recurrent symptoms than does surgical management. Therefore Heller myotomy is currently indicated as first-line therapy for the majority of patients with esophageal achalasia, provided that they are deemed fit enough to undergo a laparoscopic operation.

Most patients referred to the surgeon for treatment of achalasia have already undergone at least some of the necessary preoperative workup. These studies include upper endoscopy, upper GI radiography, and esophageal manometry. Further studies may be indicated depending on findings of the above-mentioned examinations, but are not routinely ordered in every patient.

The primary role of endoscopy in the workup of achalasia is to rule out any other cause of mechanical obstruction in the patient presenting with dysphagia, such as peptic stricture,

P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_11

esophageal cancer, or a benign esophageal tumor. Typically endoscopy will demonstrate a dilated esophageal lumen with retained food particles, and the LES will remain closed. Classically, the endoscope only enters the stomach by pushing through the esophagogastric junction with some resistance, giving rise to the term "clasp-knife sensation" that is often used by endoscopists to describe this finding in patients with achalasia.

Upper GI radiography is useful in further defining the anatomy of the esophagus, and may be able to better demonstrate findings that might suggest extrinsic compression on the distal esophagus as the true etiology of the patient's dysphagia symptoms. The demonstration of a "bird's beak" sharply tapered narrowing at the level of the esophagogastric junction is most commonly seen in achalasia and can help to confirm the diagnosis in conjunction with other studies. In addition, the degree of dilation and tortuosity (i.e., the presence or absence of "sigmoid esophagus") is assessed by radiography. This can be important in prognosis, as patients with severe dilation or sigmoid esophagus have been shown to have a higher incidence of symptom recurrence after myotomy [5, 6].

Esophageal manometry is diagnostic. Currently, high-resolution manometry (HRM) is commonly employed, and 3 distinct achalasia subtypes are recognized: type I (non-relaxing LES and complete absence of esophageal peristalsis or pressurization), type II (non-relaxing LES and at least 20 % of swallows resulting in pan-esophageal pressurization), and type III (non-relaxing LES without any true peristalsis at least 20 % of swallows resulting in simultaneous high-amplitude contractions, formerly recognized as "vigorous achalasia"). The subtypes may have some relevance to the surgeon in that some investigators have found that the outcomes of Heller myotomy in terms of symptom relief vary by subtype [7–9], which will be discussed later in the chapter.

While it is not customary to order ambulatory pH testing in patients with suspected achalasia, these studies are occasionally performed in cases in which the patient is initially suspected of having gastroesophageal reflux disease, since dysphagia is a common symptom presentation for that disorder. Numerically, achalasia patients will often have abnormal pH studies, however they typically exhibit a very characteristic "fermentation pattern" on pH monitoring wherein the pH in the distal esophagus will slowly drop below 4.0 and remain below this threshold for prolonged periods of time, because of the conversion of retained food to lactic acid by bacteria in the achalasia esophagus [10]. Thus, ambulatory pH monitoring can actually help to confirm the diagnosis in such situations.

Additional studies are occasionally warranted, particularly if the findings from the routine workup do not clearly indicate achalasia. Computed tomography can help to rule out causes of extrinsic compression of the distal esophagus, as can esophageal endoscopic ultrasound (EUS). EUS can be particularly useful in these situations, as a biopsy of such a lesion can often be obtained in order to achieve a more definitive diagnosis.

Technique of Esophagogastric Myotomy

Patient Preparation

In preparation for surgery, patients are kept NPO from midnight the night before the operation at a minimum. Depending on the degree of esophageal dilation and the practice of the surgeon, it may be helpful for the patient to actually be on a clear liquid diet for one or more days prior to the operation, to minimize the amount of retained food that will be present in the esophageal lumen at the time of surgery. This both reduces the risk of aspiration upon endotracheal intubation as well as facilitates the performance of intraoperative upper endoscopy if required.

Patient Positioning

As a minimally invasive foregut operation, the most practical patient positioning for laparoscopic Heller myotomy is identical to that most

commonly used for laparoscopic antireflux surgery, which is to have the patient supine with the legs spread apart, either by means of the low-lithotomy stirrup positioners or a split-leg table configuration in which the primary operating surgeon stands between the patient's legs and the assistant stands on the left side of the patient. Both arms may be left out, and it is often helpful to turn the axis of the table approximately 30° from the long axis of the room, with the left shoulder angled away from the anesthesia machine so that the monitor may be placed just above the left shoulder while leaving enough room for an upper endoscopy to be comfortably performed during the procedure. Since it will be necessary to place the patient in steep reverse-Trendelenberg position throughout the majority of the operation, the use of bilateral thigh straps mounted to the sides of the operating table, creating a "climbing harness" effect, is very helpful in preventing the patient from slipping during the case. Alternatively, one can use a bean-bag positioner, which can be molded into a kind of "saddle" below the perineum.

Trocar Placement

The first incision, big enough to accommodate an 11 mm laparoscopic trocar, is made just inferior to the left costal margin at the mid-clavicular line. After dissecting through the subcutaneous tissue, the fascia is grasped with two kocher clamps and elevated so that a veress needle may be inserted to insufflate the peritoneum to 15 mmHg pressure. The use of an optical trocar, in which entry through each layer of the abdominal wall and the peritoneum is visualized with the laparoscope, is particularly useful with this access technique and is quite safe. An 11 mm trocar is used at this site, which is necessary for laparoscopic suturing later in the procedure. While a Hassan "open" access technique may be used alternatively, this is considerably more difficult in this location because of the relative thickness of the abdominal wall here. Once the laparoscope has been introduced and an inspection of the peritoneal cavity has been made to ensure that there is no injury from the initial access, the next port is placed under laparoscopic guidance in the epigastrium just to the left of the midline between 2 and 6 cm above the level of the umbilicus, depending on the size of the patient. This may be either a 5 mm port, if a 5 mm laparoscope is used, or an 11 mm port if the 10 mm laparoscope is chosen; in either case a 30° laparoscope should be used. At this point, the laparoscope is moved to the epigastric port site and the remaining 3 ports, all 5 mm diameter, are placed in the left flank (for the assistant), right flank (for the liver retractor), and right subcostal (for the primary surgeon's left hand instrument) positions respectively. The left lateral segment is then retracted anteriorly with a flexible articulating 5 mm liver retracting device to expose the proximal stomach and region of the hiatus. Alternatively the Nathanson liver retractor may be used through a small stab incision just beneath the xiphoid without a trocar, in which case no right flank port is necessary. The liver retractor is secured with a table mounted self-retaining device (such as the "iron intern").

Dissection and Mobilization

Dissection is begun by dividing the hepatogastric omentum with either electrocautery or the ultrasonic coagulator, moving cephalad until the junction between the right crus of the hiatus and the phrenoesophageal membrane is reached. The hiatus is then opened anteriorly from right to left, exposing the distal esophagus and esophagogastric junction (EGJ) (Fig. 11.1). In addition, it is necessary to create a posterior window behind the esophagogastric junction but below the level of the hiatus, leaving the phrenoesophageal membrane intact posteriorly if possible. However, if there is a hiatus hernia as is sometimes observed, it may be necessary to fully dissect the hiatus and reduce the EGJ into the abdomen. A point along the greater curvature of the stomach approximately one-fourth to one-third of the way distal to the EGJ is chosen to begin dividing the short gastric vessels in order to mobilize the fundus for the creation of the Toupet partial posterior fundopli-

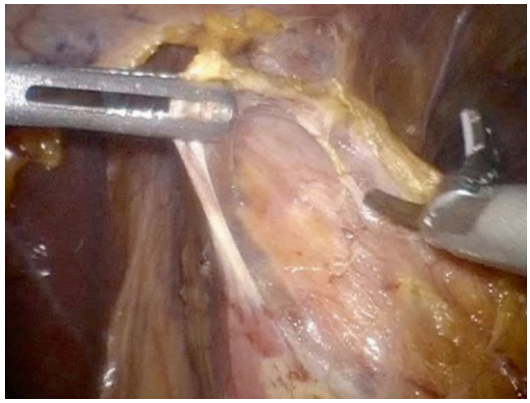

Fig. 11.1 Dissection along right crus

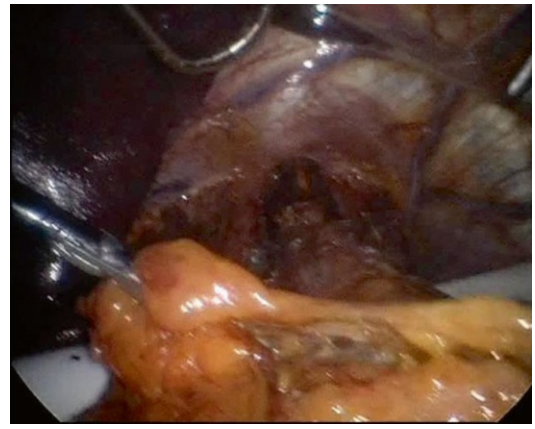

Fig. 11.2 Elevation of the epigastric fatpad

cation later in the case. The ultrasonic coagulator works very well for this purpose, and it is recommended to continue proximally along a line approximately 1 cm away from the gastric serosa. The short gastrics are divided all the way up to the level of the left crus. An alternative approach to this dissection is to begin with the division of the short gastrics, and then dissect the hiatus from left to right, which works equally well and is chosen based upon the preference of the surgeon.

At this point it is helpful to place a penrose drain around the esophagogastric junction, securing it loosely anteriorly with an endoloop suture. This enables retraction of the EGJ and distal esophagus, facilitating further dissection of the anterior esophagus above the hiatus and enabling a longer proximal myotomy. The hiatus is generally not closed even though it has typically been enlarged to some degree in the course of this dissection. However in the case of the patient with a hiatus hernia, the hiatus should be reapproximated with interrupted sutures posterior to the esophagus, taking care not to narrow the hiatus too much and ensuring that a grasper can easily be passed alongside the esophagus at a minimum once the sutures have been placed.

Performance of the Myotomy

The esophagogastric fatpad is elevated and carefully dissected off of the area of the esophagogastric junction, taking care to identify and preserve the anterior vagus nerve (Fig. 11.2). The ultrasonic coagulator is an ideal instrument for this purpose, as there are frequently small vessels in this area which can bleed and obscure the field. At this point some surgeons will prefer to have a lighted esophageal dilator placed transorally (which is ideally done by the anesthesiologist as long as they are experienced and comfortable with the procedure) which can serve as a sort of "platform" for the performance of the myotomy itself. A point on the anterior gastric cardia approximately 2–2.5 cm to the left of the lesser curvature and 3 cm distal to the esophagogastric junction is chosen to start the myotomy. This is typically begun by scoring the serosa with the electrocautery hook for a distance of at least 1 cm up towards the EGJ, and then carefully dividing the muscle fibers one layer at a time until the submucosa is reached (Fig. 11.3). The submucosa is identifiable as a smooth surface that has a texture distinctly different than the muscularis. The muscle fibers can be disrupted using elevation with the hook and employing cautery only very sparingly. Hooking large bundles of fibers at once should be avoided. Bleeding on the surface of the submucosa can usually be very easily controlled by the gentle application of pressure with a blunt grasper. Notably, this part of the myotomy is the most difficult, because of both the thickness of the muscle in this region and the organization of the "clasp and sling" fibers that make up the gastric component of the LES, which is organized

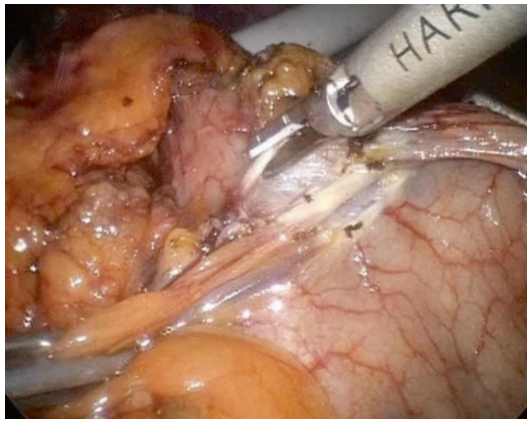

Fig. 11.3 The myotomy is begun 3 cm distal to the esophagogastric junction

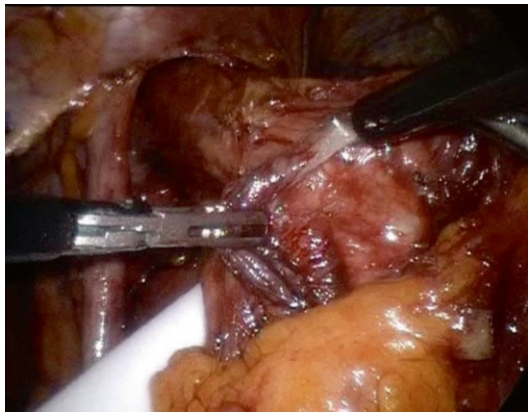

Fig. 11.4 The myotomy is continued using primarily blunt dissection with a hook cautery instrument

much differently than the more simple outer longitudinal and inner circular muscular layers of the esophageal body encountered in performing the proximal myotomy.

Once the initial area of the distal myotomy is established, blunt graspers are used to grasp either side of the muscularis on the myotomy edge with the assistant grasping the left side of the myotomy and the primary surgeon grasping the right, providing gentle traction which allows the myotomy to continue in a cephalad direction (Fig. 11.4). Alternatively, a babcock grasper can be used with jaws open to stretch the myotomy area laterally to achieve a similar effect. As the myotomy is carried underneath the epigastric fatpad and proximally past the EGJ, it becomes notably easier to bluntly divide the muscularis, particularly the longitudinal fibers, which become more distinct from the underlying circular fibers. Ultimately the myotomy should be continued proximally until the length above the EGJ is 6–8 cm with the esophagus not under tension. This can be measured directly by inserting a sterile measuring stick and holding it in place alongside the myotomy, or by introducing a pre-measured length of suture (Fig. 11.5).

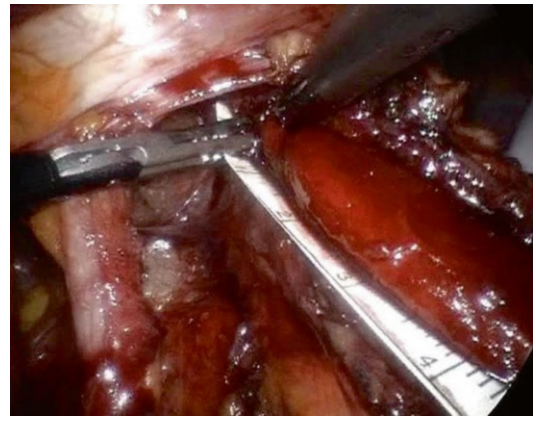

Fig. 11.5 Measuring the final length of the myotomy

Intraoperative Assessment of the Myotomy

At this point in the procedure, many surgeons will perform an upper endoscopy in order to evaluate the adequacy of the relief of the high-pressure zone of the LES. Observation that the area of the esophagogastric junction is widely patent and easily permits passage of the endoscope is a relatively easy method to determine the success of the procedure intraoperatively. In addition, this permits the visualization of any small areas of perforation that may have occurred during the myotomy, in the same way that the "leak test" is used after an anastomosis is performed in rectal surgery. The use of intraoperative esophageal manometry has been described, with the stated advantages being the ability to identify relatively small specific

points of remaining muscle fibers representing a residual high-pressure zone, as well as helping to guide length of the myotomy [11], however this is relatively cumbersome to perform.

Currently there is increasing interest in measuring the distensibility of the high-pressure zone during myotomy as a way to evaluate the success of the procedure intraoperatively. The functional luminal imaging probe (FLIP), using the principle of impedance planimetry to measure the cross-sectional area at several points along the myotomy in relation to pressure, generates a distensibility index expressed in mm^2/mmHg. Teitelbaum and colleagues have found that a distensibility index in the range of 4.5–8.5 mm^2/mmHg correlates with optimal symptom outcomes [12]. This technology is not widely available in clinical practice at the time of this writing, however, thus it remains to be seen whether or not the distensibility index will become a standard method for intraoperative assessment.

Creation of the Toupet Fundoplication

With the myotomy complete, the dilator, if used, can now be removed. To begin the Toupet fundoplication, the posterior fundus is passed through the retroesophageal window to the right side of the myotomy and its superior aspect can be fixed to the base of the right crus with a 2-0 silk or braided nylon to secure the fundus in this position. Next, a suture is placed between the superior aspect of the fundus on the right, the anterior right crus, and the right edge of the myotomy. This is followed by two additional sutures between the fundus and the right myotomy edge progressively more distally. These three sutures are repeated in an identical manner on the left side of the myotomy, adjoining the anteromedial aspect of the fundus to the cut muscularis edge (Fig. 11.6). The area is then inspected for bleeding, hemostasis is achieved as needed, the liver retractor is removed, and the port sites are all closed.

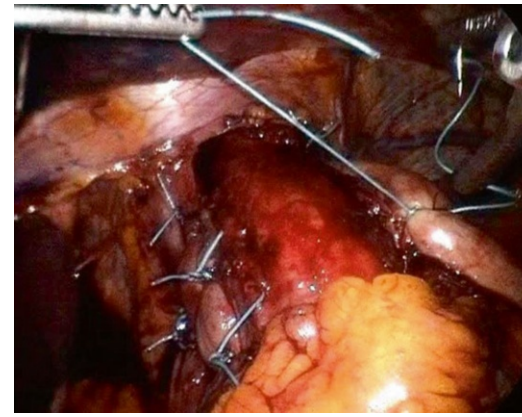

Fig. 11.6 Suturing the left aspect of the Toupet fundoplication

Postoperative Management

Immediately after transfer from the post-anesthesia recovery unit, patients may be started on a clear liquid diet, provided that there was no perforation of the esophagus during the myotomy. On postoperative day number one, a soft mechanical diet may be instituted. In the case of the patient in whom there was a perforation which was repaired intraoperatively, it is prudent to order a gastrografin esophagram on the first postoperative day to ensure that there is no leak; if none is seen, this is followed by barium, and if again there is no leak then the patient may begin a clear liquid diet with progression to the soft diet the following day. Initial pain management is best done with IV narcotics, and a patient-controlled analgesia technique works very well for this. Transition to oral narcotic pain medications, particularly those in elixir form, can usually be accomplished within 24 h or less, and most patients will be able to be discharged from the hospital on the first day after surgery. Generally, patients are maintained on the soft diet for 2–3 weeks after the operation, and if they are not experiencing any significant dysphagia at that time, they may fully liberalize their diet as tolerated.

Outcomes of Extended Esophagogastric Myotomy

Multiple studies have demonstrated that Heller myotomy is the most effective and durable treatment for esophageal achalasia when compared to other less invasive techniques such as botulinum toxin injection or esophageal balloon dilation [13–15]. Campos and colleagues have published the largest meta-analysis to date on this subject, which included a subset of 2507 patients undergoing laparoscopic Heller myotomy with an antireflux procedure who were followed for a mean of 35 months. The overall long-term success in relief of dysphagia in this group was 90 %, with only 9 % of those patients exhibiting evidence of gastroesophageal reflux after myotomy [15].

Using the specific technique of laparoscopic Heller myotomy with Toupet fundoplication described in this chapter, with particular emphasis on the extension of the myotomy to 3 cm onto the gastric cardia, Wright et al. reported excellent symptom relief in 63 patients followed for a mean of 45 months, with a need for re-intervention of any kind of only 5 %. This was significantly lower than a comparison group of patients undergoing a shorter distal myotomy (approximately 1.5 cm onto the gastric cardia) with Dor anterior fundoplasty, in whom the re-intervention rate was 17 % [4]. This data reinforces the importance of the distal aspect of the myotomy and the complete division of the "clasp and sling" fibers of the LES in producing the most durable symptom relief in patients with this disease.

As noted earlier in this chapter, some authors have found that the outcome of Heller myotomy with respect to symptom relief varies by the manometric subtype as observed with high-resolution manometry. Pandolfino and colleagues found that patients with type II achalasia, characterized by the presence of pan-esophageal pressurizations on HRM, respond better to either dilation or myotomy than do patients with type I (with no esophageal body contractions of any kind) or type III (spastic distal esophageal contractions) [7]. Better symptom outcome for type II patients after myotomy was also observed in two subsequent studies, both involving large numbers of patients [8, 9]. It is worth noting, however, that in both of these studies the surgical technique involves extension of the myotomy to no more than 2 cm onto the gastric cardia. In contrast, a 2014 study by Greene et al. in which a 3 cm myotomy onto the cardia as described in this chapter was used found that there were no significant differences in symptom outcome between the three subtypes [16]. Similar findings have been observed at the University of Washington (data not yet published).

In addition to the commonly described symptoms of dysphagia and regurgitation, it has also been noted that a large proportion of achalasia patients (up to 57 %) experience various respiratory symptoms, such as cough, shortness of breath, and wheezing, as well as in some cases having recurrent episodes of pneumonia [17, 18]. These complaints are improved in all patients undergoing Heller myotomy, and 82 % of patients are free of recurrent pneumonia at 5 years after the operation [18].

With respect to the particular choice of antireflux procedure in conjunction with Heller myotomy, this is typically a matter of surgeon preference, with particular reasons cited for one technique versus another. The rationale behind the use of the Toupet fundoplication is that it is thought to potentially help stent open the myotomy itself and avoid subsequent scarring of the myotomized muscle edges, as well as to create more bulk and fixation posterior to the esophagus in order to avoid hiatal herniation. To date there is only one randomized trial of one antireflux procedure versus another in Heller myotomy, published in 2012 by Rawlings et al. In this trial 60 patients with achalasia undergoing laparoscopic Heller myotomy were randomized to either Dor anterior fundoplasty or Toupet partial posterior fundoplication. On postoperative follow up with ambulatory 24-h pH testing, the authors found no statistically significant differences in DeMeester scores or the percentage of time with pH<4 between Dor or Toupet, and similar postoperative symptom scores for both groups [19].

Conclusion

For patients with achalasia, a complete workup including upper endoscopy, esophageal radiography, and esophageal manometry is essential to definitively confirm the diagnosis. Laparoscopic Heller myotomy with Toupet partial posterior fundoplication is an extremely effective treatment for symptoms of dysphagia and regurgitation, as well as the respiratory symptoms that frequently accompany this disease, and can be considered as first line of therapy in the majority of patients. In particular, it is important to ensure that the length of the myotomy onto the gastric cardia is at least 3 cm in order to achieve the highest patient satisfaction rates with the least likelihood of needing subsequent intervention for dysphagia.

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Achalasia and Epiphrenic Diverticulum

12

P. Marco Fisichella, Anahita Jalilvand, and Adrian Dobrowolsky

Introduction

Epiphrenic diverticulae are pulsion diverticula in which the mucosa and submucosa herniate through the muscular layers in the distal 10 cm of the esophagus [1]. Early treatment of epiphrenic diverticula included resection of the diverticulum with primary closure of the esophagus. However, Belsey and Effler suggested in the 60s that the diverticulum was due to an underlying esophageal motility disorder and proposed that a myotomy be performed together with the diverticulectomy [2, 3]. Today, the pathophysiologic link between the presence of an esophageal motility disorder and the epiphrenic diverticula has been well documented. In fact, numerous studies have shown that the vast majority of patients (75–100 %) with epiphrenic diverticula have achalasia or another esophageal motility disorder such as diffuse esophageal spasm or a nutcracker esophagus [4–7]. These findings have then suggested that such esophageal motor disorders may cause a contractile discoordination between the distal esophagus and the lower esophageal sphincter. Over time, this discoordination could lead to increased intraluminal pressure in the distal esophagus and the development of an out-pouching of its mucosal and submucosal layers. Failure to realize the pathophysiologic association between the presence of the diverticula and an underlying motility disorder of the esophagus and failure to include the treatment of the motility disorder into the management of epiphrenic diverticula sets up the stage for dire postoperative complications. By being constantly reminiscent of the pathophysiologic basis of the genesis of the diverticula, we therefore aim to describe the clinical presentation and proper methods of diagnosis, and to discuss indications for surgery, choice of surgical approach, and results of thoracoscopic and laparoscopic approaches.

Clinical Presentation

As many as 40 % of patients can be asymptomatic and their epiphrenic diverticula are found incidentally [8]. Symptomatic patients commonly complain of dysphagia, regurgitation of undigested food, chest pain, heartburn, nocturnal aspiration, aspiration pneumonia, and in severe cases, weight loss [8, 9]. Because the etiology of the diverticu-

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_12

lum is often the underlying motility disorder of the esophagus, most symptoms such as dysphagia, regurgitation, and chest pain may be due to the motility disorder rather than the diverticulum itself [9]. This might be the reason why the size of the diverticulum does not seem to correlate to the severity of symptoms experienced by the patient [9]. Similarly, regurgitation of undigested food, nocturnal aspiration, and aspiration pneumonia, which may be due to the motor discoordination of the esophageal motility disorder, might also be suggestive of a symptomatic diverticulum, but again, no correlation between the size of the diverticulum and the severity of these symptoms has been demonstrated. In addition, when the diverticulum becomes large enough, it may cause dysphagia with resultant weight loss by extrinsic compression of the distal esophagus.

While the vast majority of esophageal diverticulae are benign, malignant transformation from chronic inflammation – likely due to stasis and fermentation of food inside the diverticulum – rarely occurs and may be demonstrated by worsening regurgitation or odynophagia, hematemesis or hemoptysis [10]. Patients presenting with esophageal carcinoma from their diverticular disease present at late stages and therefore no surveillance program has been established in asymptomatic patients with unresected diverticula. Patients who develop cancer from an epiphrenic diverticulum are typically over 60 years of age, male, have large diverticula, and have endured an extended duration of symptoms [10]. The risk of carcinoma, however, is exceedingly rare. Herbella et al, have estimated that the incidence of cancer from epiphrenic diverticula is 0.6 %, with the majority of patients suffering from squamous cell carcinoma over adenocarcinoma [11].

Diagnostic Testing

The diagnostic workup includes barium esophagogram, upper endoscopy, and esophageal manometry [1].

Barium esophagogram is typically the first diagnostic test performed. Not only are the findings diagnostic, but also a contrast esophagogram can provide useful information for surgical planning, including the location of the diverticulum (left or right chest and distance from the diaphragmatic hiatus), diameter of its pouch, as well as the length and width of its neck [1]. A barium esophagogram can also show any abnormalities of the gastroesophageal junction, such as hiatal hernias or lesions suspicious for a malignant process. Furthermore, disordered contractions of the distal esophagus, such as a bird's beak from achalasia, a corkscrew esophagus from diffuse esophageal spasm, or pathologic tertiary contractions might also be seen on esophagograms, which can prove useful in addition to the information gathered from esophageal manometry.

Upper endoscopy is used to evaluate the presence of mucosal lesions within a large diverticulum and to search for any additional pathology in the upper gastrointestinal tract, such as esophageal and gastric ulcers, Barrett's esophagus, or esophagitis, which may overlap to the clinical presentation. The advantage of performing an upper endoscopy after the contrast study of the esophagus, when possible, is that the presence of the esophageal diverticulum detected on barium esophagogram may alert the provider performing the endoscopy and to avoid blindly intubating and perforating the diverticulum.

Esophageal manometry is usually performed to identify and confirm the presence of an underlying motility disorder. Some may argue, however, that manometry has only an academic role, as its results would not alter the patient's management, should one assume that almost, if not all, epiphrenic diverticula are caused by an underlying esophageal motility disorder [1]. Yet, some argue that the documentation of any existing esophageal dysmotility is fundamental to determining with certainty any underlying motility disorders. Although the identification of the esophageal dysmotility is very important and reassuring about the treatment plan proposed to the patient, normal manometry results should not be used to influence the surgical management [1]. In fact, in a few cases, due to the episodic nature of some motility disorders (or the inability of conventional manometry to detect subtle but

important motor disorders of the esophagus), normal manometry results do not necessarily exclude the presence of dysmotility.

Indications for Surgery

Most patients with epiphrenic diverticula are asymptomatic. When dysphagia and regurgitation are mild and infrequent and respiratory complications are absent, surgical treatment is generally not indicated [8]. Treatment of epiphrenic diverticula is usually reserved for symptomatic patients who complain of invalidating dysphagia and regurgitation, or for those who have had episodes of aspiration from large diverticula [8]. The size of the diverticulum is not an indication for surgery per se, although spontaneous rupture has been documented in very few patients with large diverticula [12]. Patient selection is paramount because surgical treatment of patients with epiphrenic diverticula carries a significant morbidity mainly due to leak from the staple line after the diverticulectomy. Zaninotto et al. compared the outcomes of 22 patients with epiphrenic diverticula (median follow-up of 53 months) with those of 19 patients who were managed non-operatively (median follow-up of 46 months) – only 3/19 patients received esophageal dilatations – and found that none of the patients died for reasons related to their diverticulum and that symptoms improved in all operated patients and, to a lesser extent, also in all non-operated patients [12]. However, four patients complained of new-onset heartburn and regurgitation with esophagitis and/or positive pH-monitoring and three patients had persistent dysphagia or regurgitation and were dissatisfied with the results of the operation. Zaninotto et al. concluded that surgery is an effective treatment but that a conservative management can be safely adopted in patients with minimal symptoms and small epiphrenic diverticula [12].

Choice of Surgical Approach

The management of epiphrenic diverticula requires addressing the underlying motility disorder with a cardiomyotomy accompanied by a partial fundoplication to prevent post-operative reflux, and addressing the diverticulum.

The treatment of an underlying motility disorder such as achalasia has been well codified [13]. The length of the cardiomyotomy and the choice of fundoplication have been extensively studied. The cardiomyotomy usually extends for 2–3 cm onto the gastric wall [14]. A fundoplication is always added to prevent postoperative reflux, because when this step is omitted, the incidence of reflux is 48 %, vs. 9.5 % when a Dor fundoplication is added to the myotomy [15]. As far as the type of partial fundoplication, a Dor or a Toupet fundoplication work equally well to relieve dysphagia and to provide control of postoperative reflux [16]. Conversely, a Nissen fundoplication is contraindicated [17]. In addition, the current recommendations from the Society of American Gastrointestinal and Endoscopic Surgeons advocate only a partial fundoplication – the specific type is left to the surgeon's preference – to prevent reflux [18].

If the treatment of the motility disorder underlying the epiphrenic diverticula has been well codified, the appropriate method to address the diverticulum itself is still unclear. Allaix et al. analyzed the outcomes of 13 patients with achalasia and epiphrenic diverticula who underwent laparoscopic myotomy and Dor fundoplication: 6 of which underwent also a diverticulectomy, whereas in 7 patients the diverticulum was left in place because it was too small (3 patients) or for technical reasons (4 patients) [19]. Allaix et al. found that all patients, even those who underwent a myotomy without diverticulectomy, had resolution of their symptoms. Allaix et al. then challenged the notion that all diverticula need to be excised, especially the small ones, and argued that the underlying motility disorder rather than the diverticulum, independent from its size, may be responsible for the symptoms experienced by the patients and that therefore it should be addressed regardless of the diverticulectomy [19].

Up until the 1990s, the transthoracic approach through a right thoracotomy (most diverticula arise from the right side of the esophagus) was the standard of care. This approach ensured optimal visualization and access to the distal esophagus and provided

the best exposure for the resection of the diverticulum and for oversewing the esophageal musculature over the staple line after the diverticulectomy, and allowed a contralateral distal esophageal cardiomyotomy. However, a right thoracotomy did not allow the addition of a partial fundoplication to control postoperative reflux after the cardiomyotomy.

With advances in minimally invasive operative techniques, laparoscopy has also become a reasonable alternative to open surgery, and it is now considered the approach of choice in most cases [4, 6, 7, 20–23]. The advantages of laparoscopic approach are related to avoiding a thoracotomy, which is a source of significant pain postoperatively as well as discomfort associated with the chest tube. A thoracoscopic approach can also prolong hospital stay and requires intubation with a double lumen endotracheal tube or bronchial block by the anesthesiologist, as it requires one-lung ventilation [20, 22]. Other advantages of the laparoscopic approach include an easier application of the endostapler to transect the diverticula – the endostapler needs in fact to be applied longitudinally, along the major axis of the esophagus – and greater ease in performing both the cardiomyotomy onto the stomach wall and a partial fundoplication. However, these advantages may be of limited application in patients with larger diverticula, a long distance between the neck of the diverticulum and the hiatus (usually about 10 cm), and the presence of dense adhesions between the diverticulum and the adjacent mediastinal structures, making the dissection, application of the stapler, and approximation of the muscle layers more difficult laparoscopically [1, 20, 22]. In these circumstances, video-assisted thoracoscopic surgery (VATS) may be more appropriately the approach of choice [21].

Results of Thoracoscopic and Laparoscopic Approaches

The most common complication from either surgical approach is leakage from the staple line after diverticulectomy, with resultant severe complications including sepsis, pneumonia, empyema, and abscess formation. Performing an appropriate myotomy is crucial to obtain resolution of symptoms when an esophageal motor disorder is identified and to eliminate the risk of a leak. When the diverticulectomy is performed without a myotomy, the staple line is subject to the same motor discoordination that caused the pulsion diverticula initially. To be effective, the esophageal myotomy should be made contralateral to the diverticulum and should extend 5–8 cm above the gastroesophageal junction and not less than 3 cm below the gastroesophageal junction, onto the anterior gastric wall. Vagal nerve injury or transection can also occur, particularly with aggressive mediastinal dissection.

Currently, there are no studies comparing the outcomes of laparoscopic and thoracoscopic approaches, and given the limited number of cases and the variety of surgical techniques and measured outcomes, it is difficult to make a quantitative conclusion about the superiority of one procedure over the other. The results of laparoscopic and thoracoscopic operations for epiphrenic diverticula are summarized in Tables 12.1 and 12.2 [24]. These data show that the incidence of complications is low; mortality rates range from 0 to 10 %, which are comparable to those of open approaches; and morbidity rates are similar between the two approaches, ranging from 0 to 33 %. Therefore, both laparoscopic and thoracoscopic treatment strategies have been shown to be very effective surgical modalities, each one having its own advantages and disadvantages and clear indications.

Table 12.1 Results of VATS for the treatment of esophageal diverticula

Authors (year)	N	Side	Procedures	Months of follow up (median)	Mortality, N	Complications, N (%)	Good outcome[a], %
Peracchia et al. (1994)	8	Right	Diverticulectomy = 3 (Converted to open surgery = 2) Diverticulectomy with preoperative pneumatic dilatation = 5	–	0	Overall = 0	83
van de Peet et al (2001)	5	Right	Diverticulectomy = 3 (Converted to laparoscopy = 1) Diverticulectomy with myotomy = 2	–	0	Overall = 1 (20 %) Leak with abscess/ sepsis = 1	–
Champion (2003)	3	Left	Diverticulectomy = 2 Myotomy = unknown Fundoplication = unknown	–	0	Overall –	–
Matthews et al. (2003)	1	Right	Diverticulectomy with myotomy = 1	16	0	Overall = 0	–
Fernando et al. (2005) [4]	9	Right	Diverticulectomy = 2 Diverticulectomy with myotomy = 4 Diverticulectomy, myotomy with fundoplication = 2 (Combined with laparoscopy) Other = 1	15	0	Overall – Leak = 2	–

[a]Good outcome = significant improvement or resolution of symptoms; N = Number of patients

Table 12.2 Results of laparoscopic treatment of esophageal diverticula

Authors (year)	N	Procedures	Months of follow up (mean/median)	Mortality, N (%)	Complications, N (%)	Good outcome[a], %
Klaus et al. (2003)	10	Diverticulectomy with myotomy = 6 Diverticulectomy = 4	26.4 (mean)	0	Overall = 2 (20 %) Empyema = 1 Leak = 1	–
Fraiji et al. (2003)	6	Diverticulectomy, myotomy with fundoplication = 6	9.3 (mean)	0	Overall = 2 (33 %) Empyema = 1 Ileus = 1	100
Del Genio et al. (2004)	13	Diverticulectomy, myotomy with fundoplication = 13	58 (mean)	1 (8 %)	Overall = 4 (30 %) Leak = 3 Myocardial infarction = 1	100
Tedesco et al. (2005) [7]	7	Diverticulectomy, myotomy with fundoplication = 7	60 (median)	0	Overall = 1 (14 %) Leak with paraesophageal hernia = 1	100
Fernando et al. (2005) [4]	10	Diverticulectomy, myotomy with fundoplication = 10	15 (median)	1 (10 %)	Overall – Leak = 2	–
Zaninotto et al. (2008)	17	Diverticulectomy, myotomy with fundoplication = 14 Diverticulectomy with fundoplication = 3	53 (median)	0	Overall –	–
Melman et al. (2009) [6]	13	Diverticulectomy, myotomy with fundoplication = 13	13.6 (mean)	0	Overall = 2 (15 %) Atelectasis = 1 Leak = 1	85
Rosati et al. (2011) [23]	20	Diverticulectomy, myotomy with fundoplication = 20	52 (median)	0	Overall = 1 (5 %) Leak = 1	100
Soares et al. (2011)	18	Diverticulectomy, myotomy with fundoplication = 16 Diverticulectomy with excision of leiomyoma = 1 Diverticulectomy, myotomy with fundoplication and Roux en Y Gastric bypass = 1	45 (median)	1 (5.6 %)	Overall = 5 (28 %) Bleeding = 1 Leak = 1 Pleural effusion = 2 Port site hernia = 1	86

[a]Good outcome = significant improvement or resolution of symptoms; N = Number of patients

Conclusions

Esophageal diverticulae are almost always due an esophageal motility disorder, such as achalasia. Treatment must aim to address such esophageal motility disorder in addition to a diverticulectomy in most cases. In general, surgical intervention is indicated for symptomatic patients depending on the size and location of the diverticulum, but not without seemingly high rates of morbidity, when the proper techniques are not utilized. The risk of carcinoma is exceedingly rare and it is usually discovered at late stages and no surveillance program has been established in asymptomatic patients with unresected diverticula.

Conflicts of Interest The authors have no conflicts of interest to declare.

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13 Thoracoscopic Treatment of Epiphrenic Diverticula Associated with Achalasia

Trevor Williams and Mark K. Ferguson

Introduction

Minimally invasive surgical treatment of epiphrenic diverticula is increasingly common. The laparoscopic route is favored as it affords a better view of the hiatus, easier application of an endostapler, and better access to the stomach for fundoplication. Thoracoscopic intervention may prove safer, however, in patients with larger diverticula, those located more distant from the gastroesophageal junction, or when associated inflammation or adhesions are expected.

Epiphrenic diverticula are related to esophageal motility disorders in virtually all patients, though detection may sometimes require 24 h ambulatory or high resolution manometry. Using these tests, achalasia and diffuse esophageal spasm appear to be the most common etiologies, and non-specific or segmental hypercontractility are reported in a minority of patients [1, 2] (Fig. 13.1). Whether routine manometric evaluation of epiphrenic diverticula is useful is unclear. The motility disturbances in the esophageal body may be intermittent in nature and have little influence on indications for or performance of a surgical procedure. However, if a specific motility disorder such as achalasia is suspected in conjunction with such a diverticulum, manometry is indicated to further define the type and extent of the disorder. In addition, if lower esophageal sphincter (LES) dysfunction (hypertension, failure of coordinated relaxation) is identified, this information helps identify patients who require that the esophageal myotomy required for treatment of the motility disorder associated with the diverticulum be extended onto the stomach to treat the LES disorder.

It is estimated that fewer than 10 % of patients develop symptoms or complications of their diverticula in the absence of additional motility abnormalities such as achalasia [3]. Patients with a diverticulum and an associated motility disorder that requires therapy should be offered surgery for management of both problems. Although dysphagia and regurgitation are the most common symptoms, patients should also be routinely asked about pain, weight loss and respiratory complaints [4]. The association of diverticulum size with symptoms is inconsistent and should not be used as a criterion for surgery [5]. The diameter of the neck of the diverticulum is related to the severity of symptoms in many patients. Those with a narrow-necked diverticulum experience more delayed regurgitation and risk of aspiration, whereas patients with a wide-necked diverticulum tend to empty their pouches readily and with less regurgitation.

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_13

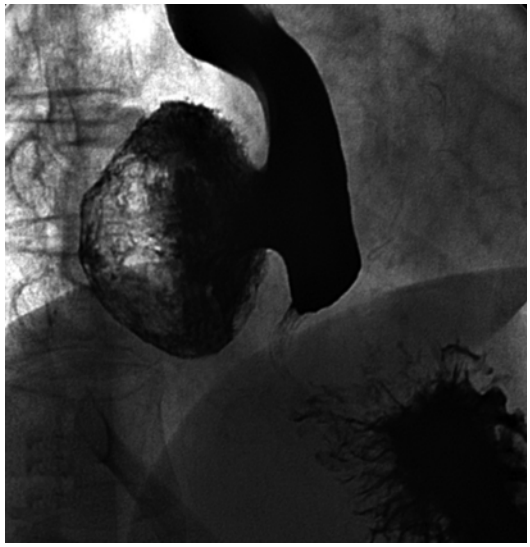

Fig. 13.1 Typical epiphrenic diverticulum in association with achalasia

A recent interesting study compared outcomes in patients with achalasia and epiphrenic diverticulum who underwent diverticulectomy to those who did not undergo diverticulectomy (small size or due to technical reasons – high sac or adhesions) with their laparoscopic myotomy and Dor fundoplication. Interestingly, the diverticula were larger in the group who did not undergo excision for technical reasons, the neck diameters were similar, and patients in both groups went from an average Eckardt score of 6.5 preoperatively to 0 postoperatively [6]. These findings suggest, at least in patients with achalasia, that treating the motor disorder may be all that is required and, subjecting these patients to the risk of leak associated with diverticulectomy may be unnecessary.

Dysplastic or neoplastic processes may affect the diverticulum in rare instances, and also may coincidentally occur in conjunction with a diverticulum resulting in spurious attribution of obstructive symptoms to the diverticulum. Thus, upper endoscopy should be part of the routine pre-operative work-up. Barium swallow and possibly computed tomography of the chest are the most important tests for preoperative planning. They define the size of the diverticulum, its radial location, the width of its neck, and the distance from the gastro-esophageal junction.

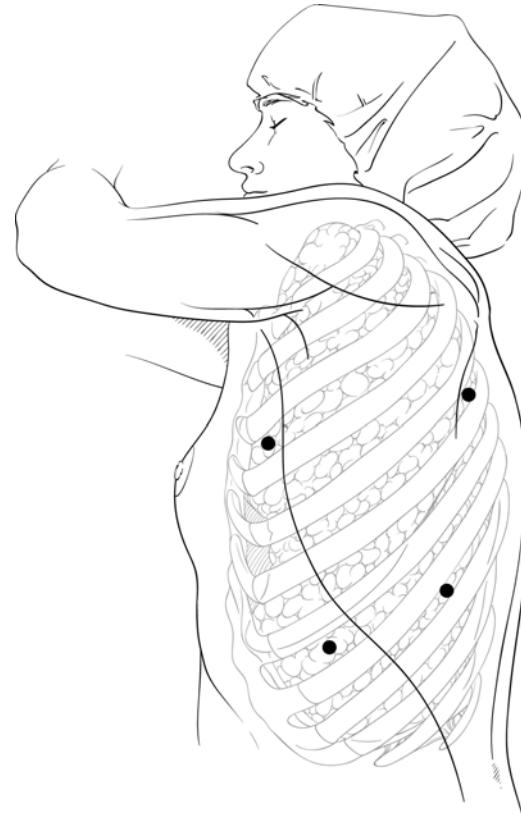

Fig. 13.2 Port placement for thoracoscopic diverticulectomy and esophagomyotomy

Operative Procedure

The patient is intubated with a double lumen endotracheal tube for single lung ventilation and positioned in the right lateral decubitus position with the left side up. After left lung isolation, four thoracoscopic ports are placed (Fig. 13.2). The camera port (5 mm) is placed in the seventh or eighth intercostal space in the center line of the chest. A 5 mm port is placed at the eighth or ninth intercostal space posteriorly for the surgeon's left hand. A 5 mm port is placed medial to the tip of the scapula for the surgeon's right hand, and a 5 mm port is placed in the fourth intercostal space anterior to the latissimus dorsi for retraction and counter-traction during the esophageal dissection. At least one of the ports will need upsizing for passage of sutures, an endo-stitch device, and a stapler. The decision regarding which port to upsize is made intraoperatively.

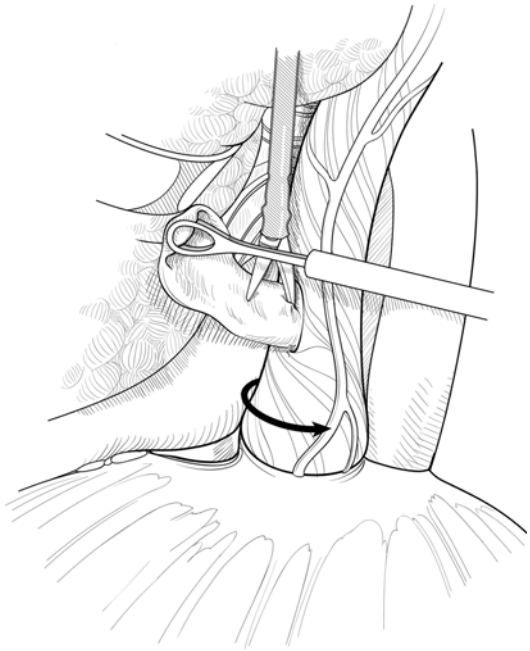

Fig. 13.3 The diverticulum is dissected of overlying soft tissues to the level of its neck

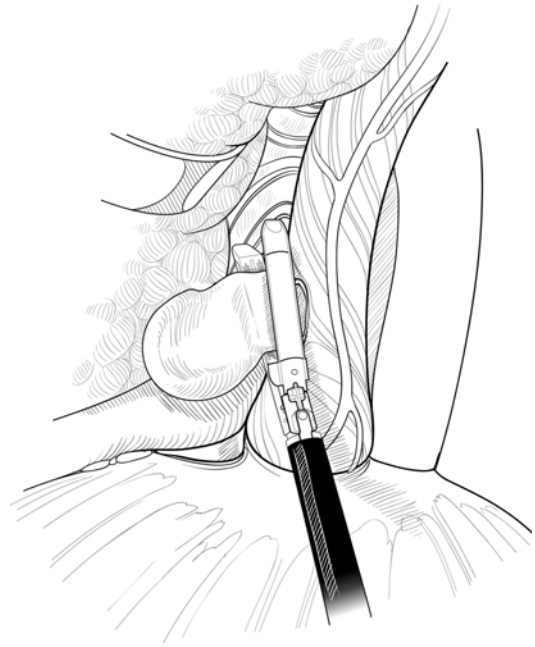

Fig. 13.4 A linear cutting stapler is fired across the neck of the diverticulum after placing a bougie down the esophagus to prevent narrowing the lumen

A 0 silk stitch is placed in the central tendon of the diaphragm and brought out of the anterior chest wall through a 3-mm skin nick at the level of the costophrenic sulcus using the endo-close device. This traction suture allows downward deflection of the diaphragm without the need for a retractor and gives good exposure of the distal esophagus.

The diverticulum most often presents to the patient's right. The pulmonary ligament is divided to the level of the inferior pulmonary vein. The mediastinal pleura is divided laterally along the esophagus from the hiatus to the aortic arch. The esophagus is dissected circumferentially from several centimeters proximal to the diverticulum to several centimeters distal to the diverticulum. A tape or Penrose drain is placed around the esophagus for use in retraction.

The diverticulum is freed from its mediastinal attachments and the esophagus is rotated 180° to enable visualization of its neck. The tip of the diverticulum is grasped and the overlying connective tissues are dissected free to clearly identify the neck of the diverticulum arising between the muscular fibers (Fig. 13.3). A 50 French bougie is guided down the esophagus and into the stomach while carefully retracting the diverticulum to aid with maintaining esophageal lumen diameter during the diverticulectomy.

An articulating endoscopic stapling device is placed parallel to the esophagus at the base of the diverticulum, through the port which provides the best angle of approach. There should be minimal traction on the diverticulum to avoid compromising the subsequent esophageal lumen. The stapler is fired (Fig. 13.4) and the diverticulum is removed. Esophagoscopy is performed to ensure that no mucosal leak is present. The esophagoscope is left in place. The esophageal muscle layers are closed over the stump with a running suture (Fig. 13.5).

The esophagus is rotated back to its normal orientation. At a point 180° from the diverticulectomy, an esophagomyotomy is performed from just above the level of the neck of the diverticulum distally (Fig. 13.6). The myotomy is extended to just below the LES; this limited extent obviates the need for a fundoplication. Esophagoscopy is performed again to ensure the absence of mucosal injury.

Alternatively, the myotomy can be extended onto the stomach to more completely ensure

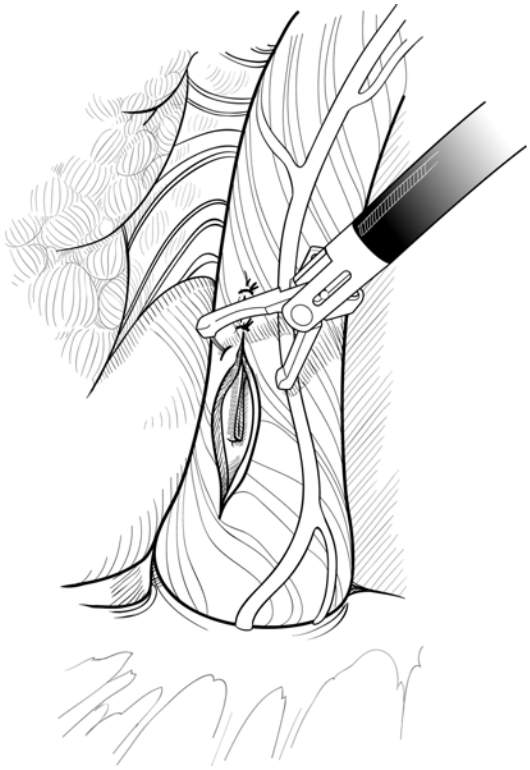

Fig. 13.5 Closure of muscle layers over diverticulum stump is performed in one or two layers

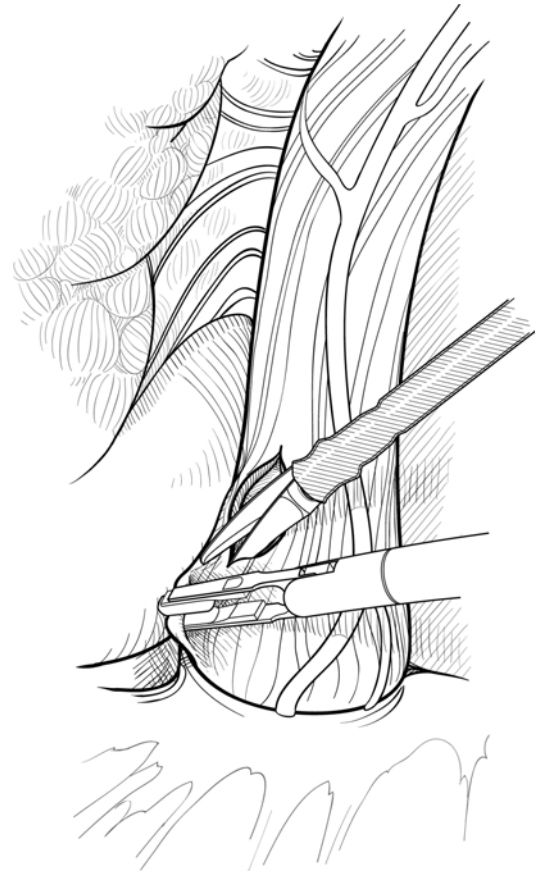

Fig. 13.6 An extended esophagomyotomy beginning above the diverticular neck and going through the lower esophageal sphincter onto the stomach

adequate treatment of achalasia. The phrenoesophageal membrane is divided and the hiatus is dissected free circumferentially to allow access to the cardia and fundus for fundoplication. The myotomy is carried down across the esophagogastric junction onto the stomach for 1–2 cm taking care to divide all circular muscle fibers of the esophagus. Esophagoscopy is performed again to ensure the absence of mucosal injury. A modified Belsey fundoplication is performed, omitting the middle of the 3 sutures in each layer. This procedure can be challenging, and requires that the esophagus and stomach be restored to their normal rotational position as the second row of sutures is placed and tied, anchoring the wrap to the underside of the diaphragm. The hiatus is typically of normal size, and the crural stitches that are typically placed for management of hiatal hernia are not necessary in this situation.

A chest drainage tube is placed. There is no need for a nasogastric tube. In the absence of suspected mucosal injury, the patient is started on clear liquids the same day as the operation and is discharged on a full liquid diet on the first or second postoperative day, with instructions to progress to soft solid foods during the ensuing week.

The main problem that can arise during this operation is injury to the esophageal or gastric mucosa. Esophagogastroscopy identifies almost all such leaks intraoperatively if performed carefully with appropriate insufflation. Such leaks are almost always associated with the neck of the diverticulum or the myotomy in the region of the esophagogastric junction. If such an injury is identified, it is sutured. The subsequent muscle closure over the diverticulum stump or the fundoplication wrap reinforces the closure. Patients who have a mucosal injury repaired are managed more conservatively postoperatively,

being kept with nothing by mouth at least until the first postoperative day. It is reasonable to obtain a contrast swallow study to ensure that no leak exists prior to beginning oral intake. The transition to solid foods should be slower than in the uncomplicated patient.

Results

Reports of outcomes of thoracoscopic diverticulectomy are limited in number. Reviews of all types of diverticulectomy and myotomy identify staple/suture line leak rates from 0 to 33 %, with an average of 12 %. Up to one third of series report no leaks, indicating to the importance of technique. Mortality rates range from 0 to 14 %, with an average of 4.7 % and more than half of series reporting no mortality. Recurrence of symptoms varies between 0 and 27 % while recurrence of diverticulum varies from 0 to 13 % [4, 7–10].

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The Surgical Management of Achalasia in the Morbid Obese Patient

14

P. Marco Fisichella, George Orthopoulos, Amy Holmstrom, and Marco G. Patti

Introduction

The relationship of esophageal diseases with obesity has gained considerable attention in the past few years. Epidemiologic studies have shown that obesity is frequently associated with esophageal motility disorders. For instance, Hong et al detected abnormal manometric findings in 54 % of morbidly obese patients with a mean BMI of 50.1 kg/m^2 [1]. Because the most common symptom of achalasia is dysphagia, which usually leads to some degree of weight loss, it may seem counterintuitive that patients with achalasia might be obese. However, current data show that achalasia may coexist in morbidly obese patients with a prevalence of 0.5–1 % [2, 3].

The surgical management of the morbidly obese patient with achalasia is complex, because it should aim to alleviate the dysphagia and to promote weight loss and resolve the co-morbid conditions. For these reasons, the most effective treatment of these patients is still controversial. The goal of our report is to describe our preferred and evidence-based approach to the patient with achalasia and morbid obesity using two clinical-case scenarios.

Clinical-Case Scenario 1

A 45-year-old morbidly obese female with a BMI of 45, hypertension, diabetes mellitus, asthma, and sleep apnea has been complaining for about 3 years of dysphagia, regurgitation, and postprandial cough. A barium esophagogram showed smooth distal esophageal narrowing; an upper endoscopy showed retained food in the esophagus and ruled out a peptic stricture or cancer; and an esophageal manometry showed type II achalasia according to the Chicago classification.

In this case, our approach of choice consists in performing a laparoscopic Heller myotomy in conjunction with a laparoscopic Roux-en-Y gastric bypass (LRYGB). In fact, the laparoscopic Heller myotomy provides excellent relief of dysphagia and regurgitation, whereas the LRYGB provides excellent control of reflux after the myotomy, weight loss, and resolution or improvement of

Submitted by invitation by Drs. Charles Yeo and Jeffrey Matthews.

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_14

comorbidities. We feel less inclined to performing a myotomy with a sleeve gastrectomy because the gastroesophageal reflux that ensues after both procedures might be even more prevalent and severe. We also feel less inclined to performing a myotomy with a duodenal switch because of the increased complexity and metabolic derangements of the duodenal switch.

Operative Planning

Regarding the critical part of the operation, we prefer to perform the myotomy first and then proceed with the gastric bypass performing a hand-sewn gastro-jejunal anastomosis, or a mechanical anastomosis using a linear stapler. The reason behind this choice is twofold: (1) performing the gastro-jejunal anastomosis with an EEA stapler after the myotomy exposes the patient to a perforation of the submucosa at the myotomy site by the anvil dragged through the mouth for the entire length of the esophagus; (2) especially when one anticipates a difficult myotomy (e.g., the patient had several pneumatic dilatations or Botulinum toxin injections), performing the myotomy first allows the surgeon to repair with 4-0 absorbable sutures any intraoperative perforation of the submucosa and protect the repair with an anterior fundoplication. In the event of a perforation the LRYGB is aborted, a possibility that needs to be discussed thoroughly with the patient at length. Below is the description of the technical details of the Heller myotomy and the preparation of gastric pouch of the LRYGB.

Heller Myotomy

The patient is placed in fully steep reverse Trendelenburg. The esophagus is then bluntly dissected away from the right crus while an Allis (or Babcock) clamp provides gentle downward traction of the gastroesophageal junction. The esophageal fat pad is excised to identify the gastroesophageal junction. The orogastric tube and the esophageal temperature probe are removed. The myotomy is performed at the 11 o'clock position, on the right aspect of the esophagus, between the anterior and posterior vagus nerves. The myotomy extends 6 cm cranially onto the esophagus and 2.5 cm caudally onto the anterior wall of the stomach as previously described [4]. Both vagi nerves are identified and preserved.

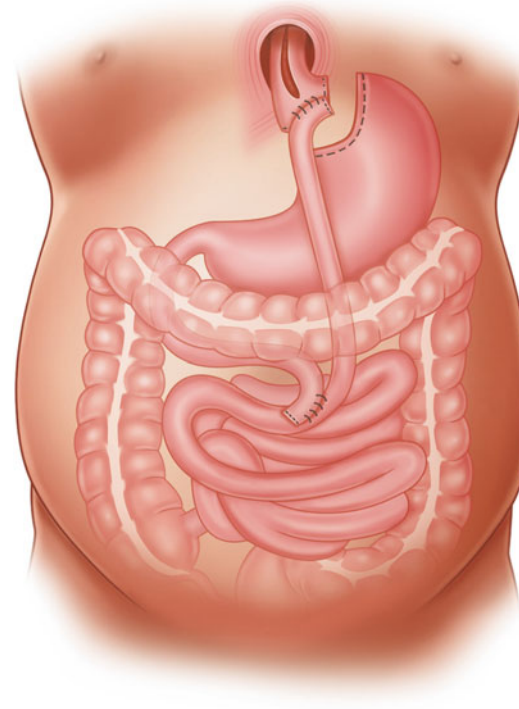

Fig. 14.1 Completed laparoscopic Heller myotomy and Roux-en-Y gastric bypass

Creation of the Gastric Pouch

Once the myotomy is completed, the hepatogastric ligament is incised and the neuro-vascular bundle of the stomach along the lesser curvature is transected with a stapler. The dissection of the posterior wall of the stomach is continued and a standard 30 cc pouch is created by firing one more load transversally and about two more loads longitudinally towards the angle of His. Once a standard LRYGB is performed, the patient is then placed supine and an air leak test is done using intraoperative endoscopy. Figure 14.1 shows the completed operation.

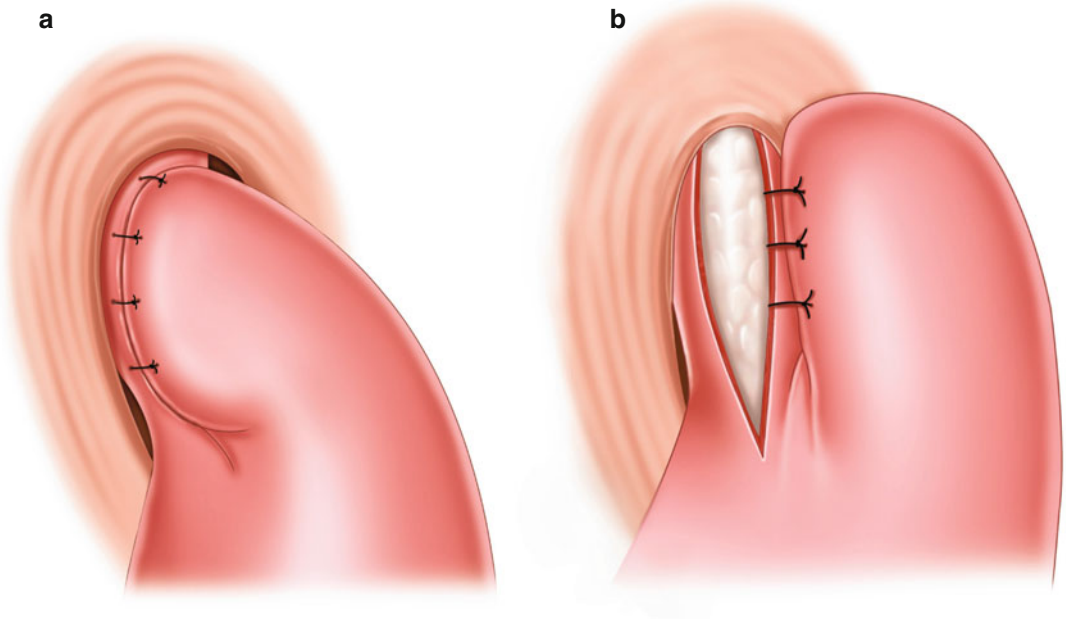

Fig. 14.2 Laparoscopic Heller myotomy (**a**) and Dor, partial anterior, fundoplication (**b**)

Clinical-Case Scenario 2

A 50-year-old morbidly obese man with a BMI of 51, hypertension, obstructive sleep apnea, and degenerative osteoarthritis had several episodes of aspiration pneumonia requiring hospitalization. He had been complaining for about one and a half year of progressive dysphagia, regurgitation, and coughing spells. An esophageal manometry showed type II achalasia according to the Chicago classification. He had been refusing surgery and had been treated with two pneumatic dilatations that resulted in mild and temporary resolution of dysphagia. Nevertheless, his dysphagia had worsened and now he is requesting surgical treatment for achalasia only. He is not interested in bariatric surgery.

In this case, our approach of choice consists in performing a laparoscopic Heller myotomy with a Dor fundoplication [4]. Figure 14.2 shows the completed operation.

The preoperative and postoperative management of patients with combined procedures is not any different from that of those who undergo only one procedure.

Discussion and Brief Review of the Literature

Achalasia and morbid obesity are two conditions that can be effectively treated surgically. However, the surgical treatment of achalasia may result in weight gain, which can be detrimental in patients with morbid obesity. On the other hand, the isolated treatment of morbid obesity does not treat the functional obstruction of the esophagus. Thus, surgical intervention should aim towards treating both diseases simultaneously and the approaches utilized should complement each other to achieve the desired outcome: relief of dysphagia and weight loss. Few reports in the literature have described three different techniques to achieve the goal of simultaneous treatment of achalasia and morbid obesity (Table 14.1).

The first approach consists in performing a laparoscopic Heller myotomy and a LRYGB [5, 6]. Kaufman et al. reported a case of a 25-year-old female who was diagnosed with achalasia and had a BMI of 58 kg/m^2. Achalasia was initially managed with pneumatic dilations, which resulted only in temporary relief of dysphagia.

Table 14.1 Literature on morbid obesity and achalasia

Type of study	Year published	Achalasia symptoms	Pre-op BMI (kg/m^2)	Achalasia procedure	Bariatric procedure
Kaufman et al. Case report	2005	Dysphagia, regurgitation	58	Laparoscopic esophagogastric myotomy	Laparoscopic Roux-en-Y gastric bypass
O'Rourke et al. Case report	2007	Dysphagia	52	Laparoscopic Heller myotomy	Laparoscopic Roux-en-Y gastric bypass
Almogy et al. Case series	2003	Regurgitation, nocturnal cough, recurrent aspiration	52	Laparoscopic Heller myotomy	Biliopancreatic diversion with duodenal switch
Herbella et al. Case report	2005	Dysphagia	43.2	Esophageal myotomy and partial fundoplication	Biliopancreatic diversion
Hagen et al. Case report	2010	Dysphagia	40	Robotic assisted Heller myotomy	Sleeve gastrectomy
Ramos et al. Case report	2009	Dysphagia, regurgitation	47	Laparoscopic anterior myotomy	Laparoscopic Roux-en-Y gastric bypass
Oh et al. Case report	2014	Dysphagia	49	Laparoscopic Heller myotomy	Laparoscopic sleeve gastrectomy followed by laparoscopic Roux-en-Y gastric bypass

After a simultaneous laparoscopic Heller myotomy and LRYGB, the patient had excellent relief of dysphagia, no heartburn, and a weight loss of 100-lbs. one year postoperatively [5]. Similarly, O'Rourke et al. described a case of a 60-year-old female with a BMI of 52 kg/m^2 and a 10-year history of progressively worsening dysphagia. After several ineffective endoscopic pneumatic dilations and botulinum toxin injections, the patient underwent a simultaneous laparoscopic Heller myotomy and LRYGB. This treatment resulted in complete relief of dysphagia and a loss of 23 kg (33 % of excess body weight) at 6 months follow-up [6]. The LRYGB is also a safe option for those morbidly obese patients in whom achalasia was not detected prior to their initial bariatric operation. Oh et al. reported a patient with BMI of 49 kg/m^2 who initially underwent laparoscopic sleeve gastrectomy and was subsequently diagnosed with achalasia. This patient underwent a laparoscopic Heller myotomy along with conversion of a sleeve into a LRYGB that resulted in complete resolution of dysphagia and a decrease of her BMI to 31.5 kg/m^2 at a 6-months follow-up [7]. Similarly, Ramos et al. presented a case of a patient with a BMI of 47 kg/m^2 who started experiencing regurgitation and dysphagia 4 years after undergoing LRYGB. Esophageal manometry diagnosed achalasia and a laparoscopic Heller myotomy resulted in resolution of symptoms [8].

The second surgical approach described in the literature consists in combining a duodenal switch with a laparoscopic Heller myotomy. Almogy et al. studied 638 patients who were screened with upper GI studies and eventually underwent weight reduction procedures. From the study group, three patients with BMI >40 kg/m^2 had achalasia. These patients were successfully treated with a laparoscopic Heller myotomy and a duodenal switch with a modified sleeve gastrectomy that preserved a small tongue of fundus to maintain the angle of His and to allow the creation of a partial fundoplication [2]. Herbella et al. reported a case of patient with BMI of 43.2 kg/m^2 with achalasia from Chagas' disease, which was treated with a laparoscopic Heller myotomy and partial fundoplication and 9 months later with a biliopancreatic diversion. However, even if this patient's BMI decreased to 36 kg/m^2, the resolution of dysphagia was not

satisfactory. The authors believed that the failure to improve dysphagia was not caused by the failure of the surgical procedure rather to alimentary compulsion from the Chagas' disease [9].

The third technique reported for the treatment of morbid obesity and achalasia consisted in performing a sleeve gastrectomy and a laparoscopic Heller myotomy. Hagen et al. reported a case of a 40 kg/m^2 who underwent a combined robotic-assisted Heller myotomy and sleeve gastrectomy. The procedure was uncomplicated and the patient had a complete resolution of dysphagia along with 11 lbs. loss 5 weeks after the procedure [10].

In cases like the one described in the first scenario, we added a LRYGB to the Heller myotomy, because this operation achieves a mean weight loss up to 70 % of excess body weight and resolves or improves obesity-related comorbidities, including hypertension, diabetes mellitus and gastroesophageal reflux (GERD) [11]. Because LRYGB creates a pouch devoid of acid-secreting parietal cells and because the Roux loop effectively protects against bile reflux, a LRYGB seems to be the ideal operation to couple with a Heller myotomy, given its ability to resolve any type of postoperative reflux more effectively than a partial fundoplication. Therefore, patients with morbid obesity and achalasia, who are willing to be treated for both conditions, can safely undergo a laparoscopic Heller myotomy and a LRYGB. Both procedures can be performed at the same time, minimizing the risk of a return to the operating room, and result in durable long-term outcomes. In addition, in the event the patient develops a peptic stricture, cancer, or if achalasia progresses to a very dilated and sigmoid esophagus, an esophagectomy is still technically feasible because, the remnant stomach that retains a preserved right gastroepiploic artery can be used as a conduit. On the other hand, a laparoscopic sleeve gastrectomy precludes the use of the stomach as a conduit, is less technically demanding, and has lower complication rates when compared to a LRYGB [11]. However, Dupree et al. suggested that a laparoscopic sleeve gastrectomy increases the risk of developing GERD [12]. Then, because gastroesophageal reflux might be significant when a myotomy is performed during a sleeve gastrectomy, this operation may not represent the best surgical option in these cases. We also feel less inclined to performing a Heller myotomy with a duodenal switch because of the increased complexity and severe malnutrition and vitamin deficiencies of the duodenal switch, even despite vitamin supplementation [14]. Similarly, a gastric banding in the setting of achalasia or other esophageal motility disorders is an absolute contraindication, as the band provides an outflow obstruction to an already compromised esophageal peristalsis.

Regarding cases like the one described in the second scenario, we have found that some of our morbidly obese patients with achalasia were not interested in undergoing a bariatric operation, as their main concern was to obtain relief of dysphagia. In these cases, or when dysphagia is so invalidating that the patient is not willing to wait for the necessary work-up prior to bariatric surgery, or when the patient does not qualify for a bariatric operation, the surgeon can perform a laparoscopic Heller myotomy with a partial fundoplication to prevent postoperative reflux. We have noticed that the myotomy is more difficult in obese patients because of the size of gastroesophageal fat pad, which could lead to injury the anterior vagus nerve. However, the patient will need to understand that the treatment of morbid obesity can be deferred to a later time but at an increased risk. Performing a LRYGB after a Heller myotomy is challenging because one should first take down the anterior fundoplication, or the adhesions between the myotomy with the left lobe of the liver (in case of a Toupet) with the risk of perforating the esophageal submucosa. Alternatively, one may choose to treat achalasia with a myotomy without a fundoplication, leaving the option open for a subsequent bariatric procedure. However, there is no guarantee that the patient may want to undergo a bariatric procedure in the future. In this case, the patient will have to bear with gastroesophageal reflux that has not been prevented by a fundoplication. Regardless, even this latter approach is technically challenging. In fact, the adhesions of the left lobe of the liver to the exposed esophageal submucosa may increase the risk of esophageal perforation. A potential alternative to treat

achalasia and obesity in a staged fashion is to perform a peroral endoscopic myotomy (POEM). This option may not preclude a future bariatric procedure. We believe that the clinician should have a thorough discussion of the risk, benefits, alternatives, and long-term outcomes of all procedures, as well as the operative planning, but in the end respect the ethical autonomy of the patient's decision-making.

Conclusions

In conclusion, achalasia and obesity can coexist, albeit infrequently. We favor a laparoscopic Heller myotomy with a LRYGB as the best comprehensive surgical management for the patient with achalasia and morbid obesity. In those patients who refuse bariatric a laparoscopic Heller myotomy with Dor fundoplication alone should be performed. A thorough discussion of the outcomes of the operative strategy and the respect of the ethical autonomy of the patient's decision-making should direct the proper surgical management.

Conflicts of Interest The authors have no conflicts of interest to declare.

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Treatment of Achalasia in Patients with Dilated Esophagus

15

Marco G. Patti, Mauricio Ramirez, and Fernando A.M. Herbella

Introduction

Achalasia is a neurodegenerative disorder of the esophagus characterized by lack of peristalsis of the esophageal body and a hypertensive lower esophageal sphincter which to relax appropriately in response to swallowing. These motility abnormalities lead to a very slow emptying of food from the esophagus into the stomach. As a consequence patients experience dysphagia, regurgitation, and chest discomfort [1]. In addition they can also experience heartburn due to stasis and fermentation of the food in the esophagus [2]. This stasis may lead to a progressive esophageal dilatation, although the degree of dilatation often does not correlate with the duration of symptoms or the clinical presentation (Fig. 15.1).

A dilated and sometimes sigmoid esophagus can be present at the time of the initial presentation, while others patients may develop it after failure of treatment. This has often been defined as "end-stage achalasia". This chapter will address the treatment of achalasia in the presence of a dilated esophagus.

Background

The treatment of end-stage achalasia is controversial, since some believe that an esophagectomy is always indicated [3–7], while others recommend that esophageal resection be consider a last resort [8–15].

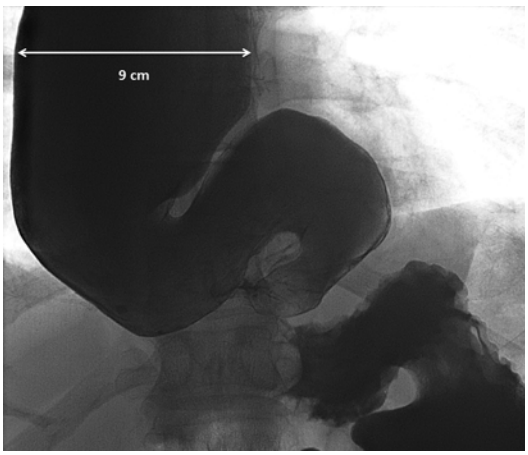

Fig. 15.1 Barium swallow. Dilated and sigmoid esophagus

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_15

Esophagectomy

Some surgeons recommend an esophagectomy as primary treatment for achalasia when the esophagus is dilated, on the assumption that a myotomy cannot improve esophageal emptying and relieve dysphagia. However, even in very experienced hands, this operation has a very high morbidity and mortality. Devaney and colleagues reported on 93 patients with achalasia who underwent esophagectomy [4]. Indications for the operation were a tortuous mega-esophagus in 64 % of patients, failure of a prior myotomy (63 %) or peptic stricture (7 %). The stomach was used as the esophageal substitute in 91 % of cases. The average blood loss was 672 ml, and the average hospital stay was 12.5 days. The morbidity was quite high, with many patients having an anastomotic leak (10 %), hoarseness (5 %), chylothorax (2 %), bleeding necessitating a thoracotomy (2 %), and a tracheal tear (1 %). In addition, 42 % of patients experienced severe regurgitation postoperatively, and 46 % developed an anastomotic stricture requiring dilatations. Two patients died. A 4.2 % mortality was also reported by Pinotti and colleagues among 122 patients operated on for Chagas disease [7].

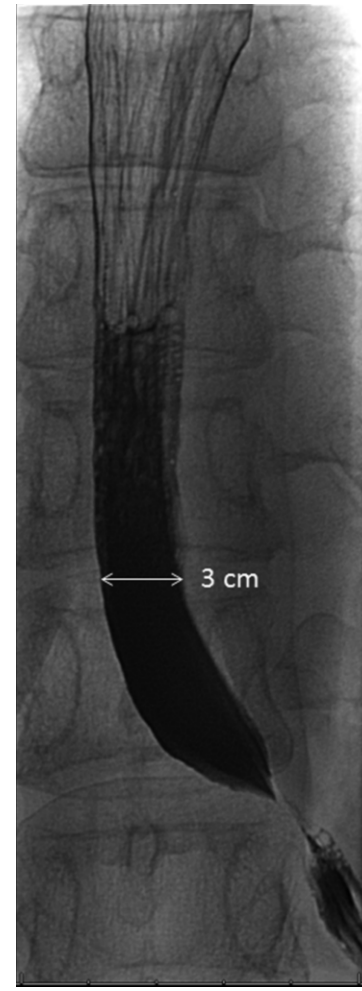

Fig. 15.2 Achalasia. Diameter <4 cm

Heller Myotomy

Others surgeons feel that a Heller myotomy should always be attempted regardless of the esophageal diameter. Sweet and colleagues evaluated the results of a laparoscopic Heller myotomy and Dor fundoplication in 113 patients with achalasia and various degrees of esophageal dilatation: group A 46 patients, diameter <4.0 cm (Fig. 15.2); group B 32 patients, diameter 4.0–6.0 cm (Fig. 15.3); group C 23 patients, diameter >6 cm and straight axis (Fig. 15.4); and group D 12 patients, diameter >6.0 cm and sigmoid shape esophagus (Fig. 15.5) [8]. The postoperative course was similar in the four groups. The degree of esophageal dilatation did not influence the outcome, as excellent or good results were obtained in 89 % of group A and 91 % of groups B, C, and D patients. None required esophagectomy to maintain clinically adequate swallowing [8].

Mineo and Pompeo performed a myotomy and an anterior fundoplication in 14 patients with achalasia and a dilated and sigmoid esophagus with excellent/good results in 10 patients and satisfactory results in 2. No patient required esophagectomy [9]. Similar results have been obtained by others in patients with idiopathic achalasia [10–12]. Pantanali and others, used this approach in 11 patients with Chagas disease and a massively dilated esophagus (diameter >10 cm) [13]. At a 31.5 month follow up, 5 patients (45 %) were asymptomatic, 4 patients (36 %) had mild and intermittent dysphagia, and two patients had no improvement. One of these patients eventually required an esophagectomy. Finally, Loviscek and colleagues evaluated a group of patients who had

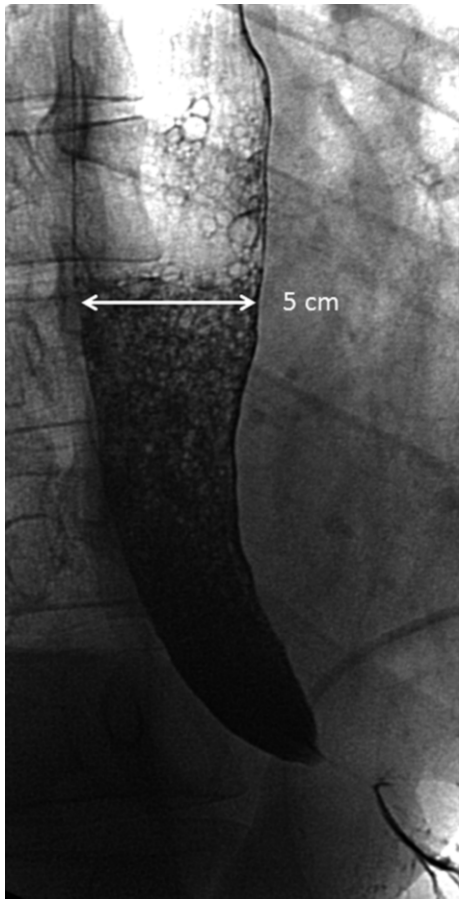

Fig. 15.3 Achalasia. Diameter 4–6 cm

recurrent dysphagia after Heller myotomy and were treated by a second myotomy [14]. At a median follow-up of 63 months 19 of 24 patients had good result, and only 4 required an esophagectomy. A second myotomy performed laparoscopically is particularly effective in patients with a prior failed left transthoracic or thoracoscopic myotomy as the abdominal cavity and the right side of the esophagus are usually free of adhesions [15].

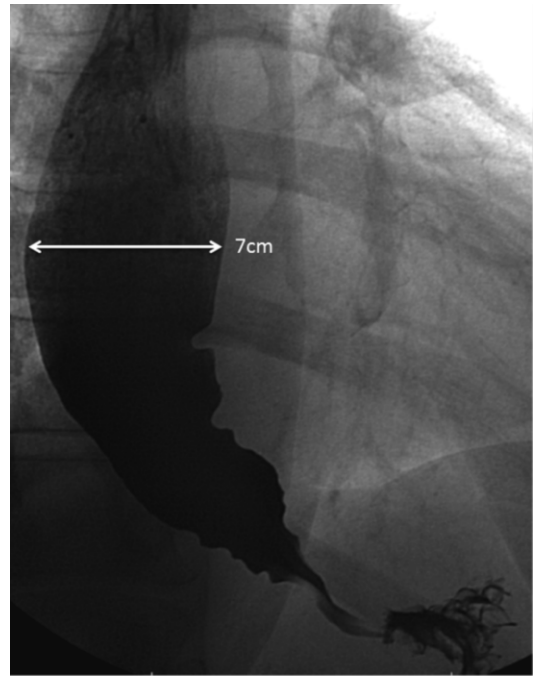

Fig. 15.4 Achalasia. Diameter >6 cm, straight axis

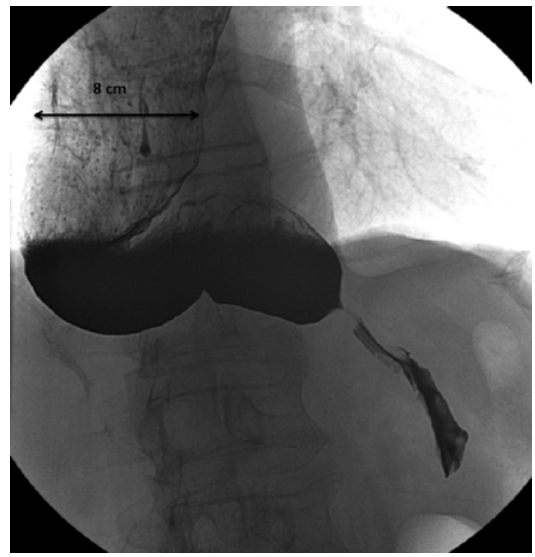

Fig. 15.5 Achalasia. Diameter >6 cm, sigmoid shape

Technical Aspects

Heller Myotomy

In Chap. 10 we have described the technical steps of the operation in patients with normal anatomy. When the esophagus is dilated and sigmoid some of the steps of the operation are quite different:

Mediastinal Dissection

When the operation is performed in the presence of normal anatomy, the dissection of the esophagus in the posterior mediastinum is minimal, and mostly limited to the lateral and anterior aspects. When the esophagus is dilated and sigmoid, the

goal is to perform a very extensive dissection circumferentially in order to eliminate the sigmoid shape and achieve a straight esophageal axis. This dissection is often carried quite high in the lower mediastinum and it also extends posteriorly. It is important to identify and preserve the posterior vagus nerve. Once the dissection is completed, it is often quite common to have at least a couple of inches of dilated esophagus below the diaphragm.

Closure of the Esophageal Hiatus

When the dissection is limited, this step is usually omitted. However, when extensive mediastinal dissection is performed, the hiatus is quite enlarged. We usually place interrupted silk sutures posterior to the esophagus avoiding any angulation. Sometimes one or two anterior stitches are necessary to further narrow the hiatus.

Partial Fundoplication

If the esophageal diameter is more than 6 cm or when the gastric fundus is small, it is better to avoid a fundoplication for the fear of creating outflow resistance at the level of the gastroesophageal junction. In these cases it is important to discuss with the patient preoperatively that more likely than not they will have abnormal gastroesophageal reflux postoperatively and they will need to take proton pump inhibitors.

If the patient has already had a laparoscopic myotomy with a partial fundoplication, it is important to consent the patient for a second myotomy explaining that if extensive damage to the mucosa occurs, an esophagectomy can be necessary. In these patients the first step is to take down the adhesions between the left lateral segment of the liver and the esophagus. Subsequently, the prior fundoplication is taken down and access to the mediastinum achieved. We do prefer to perform a second myotomy on the opposite side of the first myotomy as it is usually easier because of the absence of scar tissue (Fig. 15.6). Depending on the conditions of the fundus and the diameter of the esophagus a fundoplication can be added [14].

If the patient has recurrent dysphagia after either a left trans-thoracic or left thoracoscopic myotomy, the laparoscopic approach is relatively easy as the right side of the esophagus is free of adhesions. In these patients no dissection is performed between the esophagus and the left pillar of the crus [15].

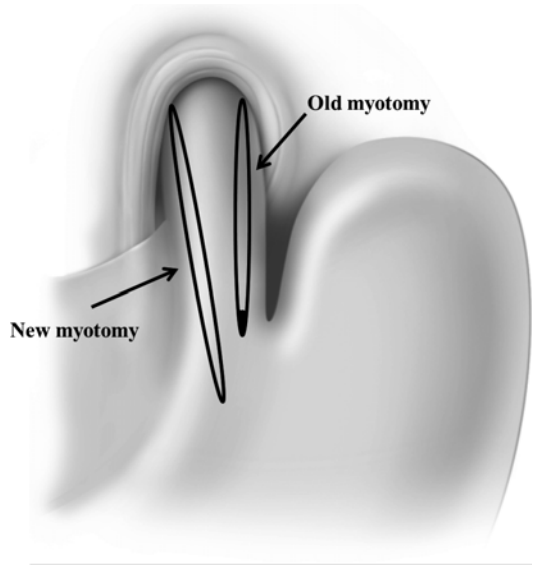

Fig. 15.6 Old and new myotomy

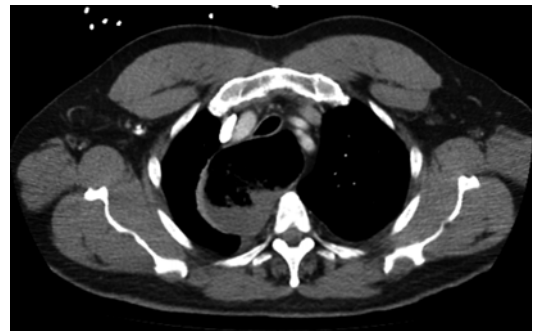

Fig. 15.7 CT scan. Dilated esophagus

Esophagectomy

An esophageal resection is quite complex as the enlarged esophagus occupies good part of the posterior mediastinum (Figs. 15.7 and 15.8). In addition the vessels feeding the esophagus are quite enlarged. Prior studies have shown a very high morbidity and mortality rate when a trans-hiatal esophagectomy is attempted [4, 7]. For these reasons we prefer to perform a "hybrid" transthoracic

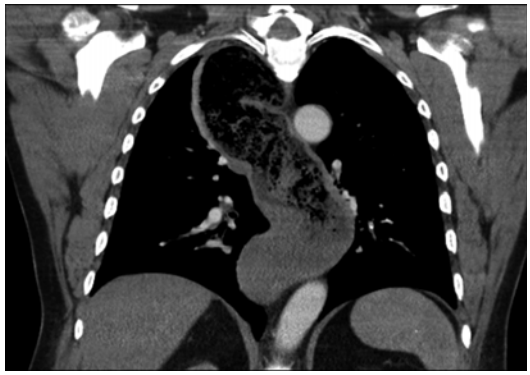

Fig. 15.8 CT scan. Dilated and sigmoid esophagus

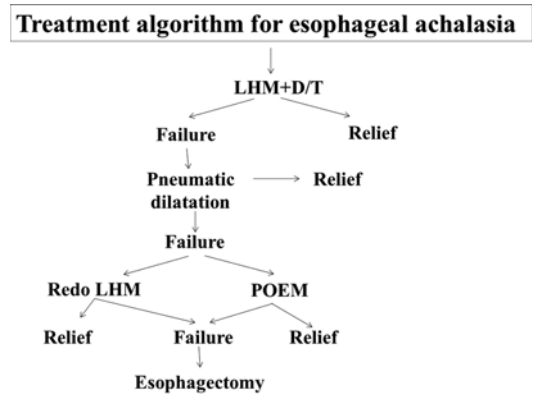

Fig. 15.9 Treatment algorithm for esophageal achalasia

esophagectomy, starting with the laparoscopic preparation of the stomach, followed by a right thoracotomy [16]. Contrary to other surgeons who use preferentially the colon as esophageal substitute [3], we routinely use the stomach when available. During the thoracotomy the dissection is performed under direct vision and the vessels feeding the esophagus are individually ligated. The esophago-gastric anastomosis is performed above the azygous vein at the apex of the chest. Our technique of choice is a semi-mechanical anastomosis, with the posterior aspect accomplished with a linear stapler and the anterior aspect hand sewn in two layers (inner layer running 3-0 absorbable material and outer layer interrupted 3-0 silk) [16]. However, if the esophageal wall is very thick while the fundus of the stomach has normal thickness, it is safer to perform a hand sewn anastomosis in two layers, inner layer running absorbable material and outer layer interrupted silk.

Conclusions

Figure 15.9 describes the treatment algorithm for achalasia at the University of Chicago. Our initial treatment is a laparoscopic Heller myotomy with a partial fundoplication, either a Dor or a Toupet. If the patient experiences recurrent dysphagia he/she is treated with pneumatic dilatations. In case of failure, a second myotomy is performed, either laparoscopically or endoscopically (POEM). It is only when a patient fails all these interventions that an esophagectomy is considered.

Conflict of Interest The authors have no conflicts of interest to declare.

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16 Evaluation and Treatment of Patients with Recurrent Dysphagia After Heller Myotomy

Marco G. Patti and Marco E. Allaix

Introduction

The introduction of minimally invasive surgery during the last two decades has led to a slow shift in the treatment algorithm of esophageal achalasia secondary to, and today a laparoscopic Heller myotomy (LHM) with partial fundoplication is considered the initial treatment modality of choice in most Centers [1–14].

The technique of the minimally invasive approach to achalasia patients has evolved over the last 20 years. Our initial experience with a myotomy performed through a left thoracoscopic approach was first reported in 1992 [15]. Using the guidance provided by intraoperative upper endoscopy, a short myotomy extending for only 5 mm onto the gastric wall, without an antireflux procedure was performed. It became soon clear that the thoracoscopic approach had several advantages when compared to the classic approach by a left thoracotomy, including a shorter hospital stay, reduced postoperative discomfort, and a faster recovery [15]. Long-term follow-up showed that relief of dysphagia was achieved in almost 90 % of patients, but unfortunately abnormal reflux was documented in 60 % of patients [1]. The laparoscopic approach was then chosen as it provided a better exposure of the gastroesophageal junction (GEJ), the ability to easily extend the myotomy for 1–1.5 cm onto the gastric wall, and the performance of a partial fundoplication [1]. Over time, the length of the myotomy onto the gastric wall was increased, as studies showed that better relief of dysphagia was obtained with a longer myotomy [3, 6]. For instance, Oelschlager et al. compared the outcomes of a conventional myotomy (which extended 1.5 cm onto the gastric wall) to those obtained with an "extended" myotomy (which extended 3 cm below the GEJ) [3] showing long-term relief of dysphagia in 83 and 97 % of patients respectively [6]. Today, our standard technique for patients with achalasia includes an extended myotomy of this sort. As the first branch of the left gastric artery is used as a landmark to gauge the extent of the myotomy onto the gastric wall, we feel that in most cases intraoperative upper endoscopy is not necessary to assess the distal extension of the myotomy in relationship to the GEJ.

Overall, about 90 % of patients undergoing LHM have a major improvement in esophageal emptying and symptom relief [4, 6, 7, 10]. Some patients however experience recurrent dysphagia over time [16]. This chapter will focus on the technical elements that are important for a successful

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_16

and long-lasting operation, and our approach to the diagnosis and treatment of patients with recurrent dysphagia after a LHM.

Recurrent Dysphagia

These are patients who experience substantial relief of symptoms for months or years after the initial LHM and then eventually experience again progressive dysphagia [16]. It is not always easy to elucidate the specific cause of recurrent dysphagia. These are the most common causes:

1. *Scarring of the distal edge of the myotomy*. The most common cause in patients who experience recurrent symptoms after a long symptom free interval is the scarring at the distal edge of the myotomy [2, 17, 18]. While no predictive factors have been identified, we believe that a longer myotomy and a wider separation of the edges of the myotomy at the time of initial LHM should decrease the occurrence of this problem [3, 6].
2. *Wrong fundoplication*. In 2004, Richards et al. reported the outcomes of a prospective randomized trial comparing LHM alone and LHM with Dor fundoplication [5]. While similar improvement of dysphagia was reported in the two groups, abnormal reflux was found at post-operative pH monitoring in 48 % of patients after LHM alone and in only 9 % of patients when a Dor was added, suggesting that the addition of a Dor fundoplication prevented reflux in most patients without impairing esophageal emptying [5]. The use of a total fundoplication has been proposed as a more effective antireflux procedure [19]. This approach however is associated with poor long-term results [20, 21]. For instance, Rebecchi et al. compared 71 patients who underwent a LHM and Dor fundoplication to 67 patients who had a LHM and a Nissen fundoplication [21]. With a mean follow-up of 125 months, the incidence of pathologic reflux was similar in the two groups but dysphagia was present in 2.8 and 15 % of patients respectively, suggesting that a 360° fundoplication causes too much resistance at the level of the GEJ, thus impairing esophageal emptying. To date a partial fundoplication is the recommended antireflux procedure in addition to a LHM as it takes into consideration the lack of esophageal peristalsis [9, 11, 12]. There is evidence suggesting that the anterior (Dor) posterior (Toupet) fundoplication are equally effective in preventing reflux [14].
3. *Gastroesophageal reflux disease*. Pathologic reflux is present postoperatively in 50–60 % of patients when a LHM alone is performed, and in 20–40 % when a partial fundoplication is added. Abnormal reflux is considered a common cause of recurrent dysphagia. For instance, Csendes et al. documented a progressive clinical deterioration of the initially good results after a Heller myotomy mainly due to an increase in pathologic reflux and the development of short or long-segment Barrett's esophagus [16]. Unfortunately most patients who develop pathologic reflux are asymptomatic [1]. Therefore, an ambulatory 24-h pH monitoring after the operation is recommended to rule out the presence of reflux, particularly in young patients [22]. If abnormal reflux is demonstrated, acid-reducing medications should be prescribed, and closer endoscopic follow-up obtained.
4. *Effect of previous treatment.* This may occur due to the presence of scar tissue at the level of the GEJ secondary to prior endoscopic treatments [7, 17, 23–25]. Both pneumatic dilatation and intra-sphincteric injection of Botulinum toxin can cause scarring at the level of the GEJ, fibrosis and loss of the normal anatomic planes. In these cases the myotomy performed after endoscopic treatment is more challenging, is associated with higher risk of mucosal perforation, and the outcomes are worse. For instance, Smith et al. compared 154 patients who had undergone endoscopic therapy before surgery to 55 patients who were referred directly to surgery [25]. A higher failure rate of the myotomy was found in the endoscopically treated group (19.5 % versus 10.1 %).
5. *Esophageal cancer.* In achalasia patients the risk of developing squamous cell carcinoma is

increased. In addition, Barrett's esophagus and adenocarcinoma can develop in the presence of pathologic reflux after the myotomy, causing recurrent dysphagia [26]. Even though there are no specific recommendations about endoscopic follow-up of achalasia patients, an upper endoscopy should be routinely performed every 3–5 years.

Diagnostic Evaluation

When patients complain of persistent or recurrent dysphagia, a thorough work-up is critical to identify the cause and site of obstruction in order to formulate a tailored treatment plan.

The first step should always include the revision of the entire history. It is very useful to review when available the diagnostic tests performed before the initial operation as sometimes a wrong diagnosis of achalasia is made. It is also very important to review the report of the original operation. Often there are clues that explain the recurrent dysphagia, such as the description of scar tissue at the level of the GEJ due to prior treatment, failure of identifying the anatomic planes, a short myotomy, or something related to the fundoplication, including a wrong configuration of the wrap.

The symptomatic evaluation is the next step to determine which symptoms are present, and to compare them to the symptoms present before the first operation.

A barium swallow is probably the most useful diagnostic test to evaluate the cause of recurrent dysphagia. It assesses the emptying of the barium from the esophagus into the stomach and shows the diameter and shape (straight versus sigmoid) of the esophagus. Loviscek et al. recently reported a series of patients with recurrent dysphagia after Heller myotomy who underwent redo surgery. They correlated the preoperative radiologic findings on barium swallow to the postoperative symptom improvement. All patients with a straight esophagus (normal or dilated caliber) experienced improvement of dysphagia postoperatively, whereas poorer results were obtained in patients with a sigmoidesophagus [27].

An upper endoscopy should be obtained in every patient. It shows if there is mucosal damage secondary to reflux, or Candida esophagitis due to slow emptying, and rules out the presence of cancer. When pseudo-achalasia secondary to the presence of a sub-mucosal tumor or a tumor outside the esophagus is suspected, endoscopic ultrasound and computed tomography can help establish the diagnosis [28].

Esophageal manometry is the key test to confirm the diagnosis of achalasia and to measure the pressure and length of the lower esophageal sphincter. When compared to the preoperative test, the postoperative manometry can show if the extension of the myotomy onto the gastric wall has been appropriate, or if a residual high-pressure zone is still present.

Ambulatory 24-h pH monitoring should also be obtained. The analysis of the pH tracing besides the reflux score is critical to distinguish between real reflux and false reflux due to stasis and fermentation of esophageal contents [29].

Treatment

Figure 16.1 summarizes our treatment algorithm for patients with recurrent dysphagia after Heller myotomy.

Pneumatic Balloon Dilatation

The initial treatment of these patients should always include a pneumatic balloon dilatation in these patients. Contrary to common belief, the risk of esophageal perforation is very low since the stomach if a Dor fundoplication was performed or the left lateral segment of the liver if a Toupet was added to the myotomy cover the myotomy, or by. Zaninotto et al. reported recurrent dysphagia in 9 of 113 patients (8 %) after LHM and Dor fundoplication [17]. Seven of the nine patients were effectively treated by balloon dilatation (median two dilatations, range 1–4), while a second operation was necessary in two. Similar outcomes were described by Sweet et al. who reported on the effectiveness of dilatation for the treatment of both persistent and recurrent dysphagia [7].

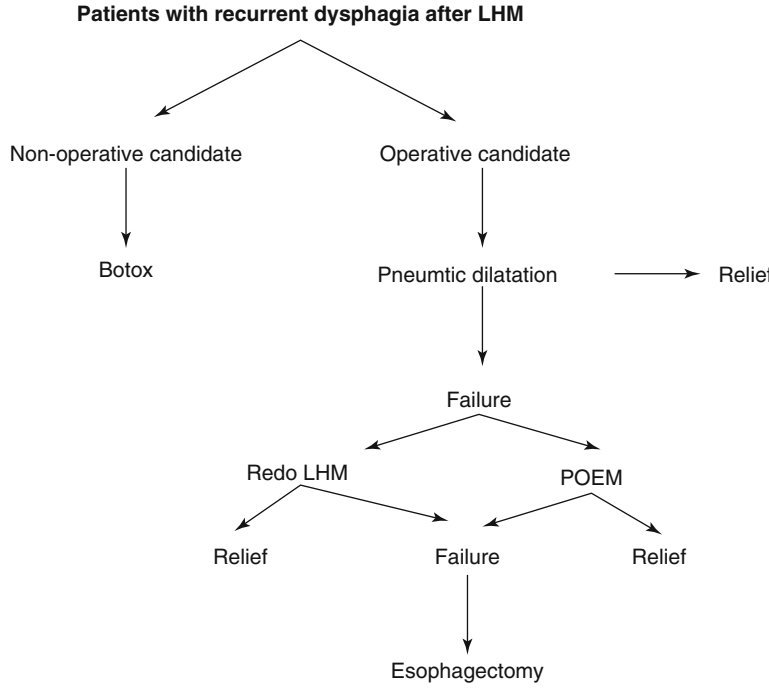

Fig. 16.1 Treatment algorithm of recurrent dysphagia after Heller myotomy. *LHM* laparoscopic Heller myotomy, *POEM* peroral endoscopic myotomy

Revisional Surgery

If dysphagia is not relieved by dilatations, a re-operation must be considered. When discussing with the patient the risks and benefits, it is important to stress that even though the laparoscopic approach is feasible in most cases, a laparotomy might be needed. In addition, patients must be aware that in case of severe damage to the mucosa during the course of the operation, an esophagectomy may be necessary.

The first step of the operation consists in separating the liver from the stomach and the esophagus. The fundoplication must be then taken down and the fundus brought to the left in order to expose the esophageal wall. Adequate and complete exposure of the esophageal wall, including a thorough dissection of the previous myotomy is the next step. Once this has been accomplished, it is easier to perform a new myotomy rather than trying to extend the prior myotomy. The new myotomy is performed on the opposite side on an unscarred part of the esophageal wall (Fig. 16.2). The myotomy should be extended for about 3 cm below the GEJ, and intra-operative endoscopy should be performed to evaluate for inadvertent esophageal or gastric mucosal injury. After the myotomy is completed, consideration should be given whether or not to add a fundoplication. Certainly, if a mucosal injury has occurred, a Dor fundoplication may decrease the risk of a leak and prevent reflux in most patients. Otherwise it is important to make it sure that a fundoplication

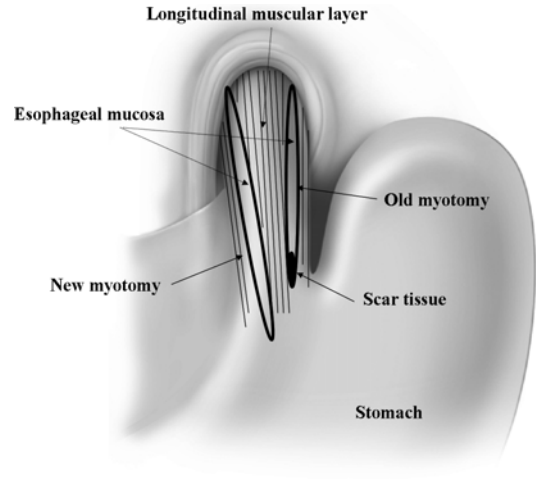

Fig. 16.2 New myotomy performed on the opposite side of the esophagus

will not cause any added resistance at the level of the GEJ. In cases when the esophagus is dilated, or when part of the fundus of the stomach has been damaged during the dissection, is better to avoid performing a fundoplication. If the patient develops abnormal reflux, it can be treated with proton pump inhibitors. Loviscek et al. recently showed excellent results using this approach [27]. They analyzed the outcome in 43 achalasia patients who had re-do Heller myotomy for recurrent dysphagia between 1994 and 2011. The only take down of the previous fundoplication was performed in 3 patients, while a redo myotomy extending for 3 cm onto the gastric wall was also performed in the remaining 40 patients. A fundoplication was recreated in only about one quarter of these patients. All patients were followed for at least 1 year after the operation. At a median follow-up of 63 months in 24 patients, improvement of dysphagia, with median overall satisfaction rating of 7 (range 3–10) was reported in 19 patients (79 %). An esophagectomy was necessary in four patients for persistent dysphagia. Other authors have reported similar results [30–32].

Sometimes patients present with recurrent dysphagia after a Heller myotomy performed through either a left thoracotomy or a left thoracoscopic approach. Because there are no adhesions in the abdomen and the right side of the esophagus is free of scar tissue created by the first operation, a LHM can be safely performed on the right side of the esophagus with excellent outcomes [33]. Depending on the esophageal size, a partial fundoplication can be added to the myotomy.

Esophagectomy

Esophagectomy should be avoided whenever possible as it is associated with a mortality rate ranging between 2 and 4 % and high morbidity even in expert hands and high volume Centers [34, 35]. For instance, Devaney et al. reported a 10 % rate of anastomotic leak, 5 % rate of hoarseness, and 2 % rate of bleeding and chylothorax requiring thoracotomy among 93 patients who had an esophagectomy for achalasia [35]. In addition, dysphagia secondary to an anastomotic stricture requiring dilatation occurred in 46 % of patients, regurgitation was complaint by 42 % of patients, and dumping syndrome was demonstrated in 39 % of patients. The average hospital stay was 12.5 days. Despite these shortcomings, esophagectomy is sometimes the only option in patients with end-stage achalasia, dilated and sigmoid shaped esophagus who have already had a failed Heller myotomy and sometimes a re-do Heller myotomy. When performing an esophagectomy, we prefer to use the stomach as an esophageal substitute. Because the esophagus is frequently dilated and fed by large blood vessels, the dissection of the thoracic esophagus is safer under direct vision, either thoracoscopically or by a right thoracotomy. The esophago-gastric anastomosis can be placed either in the neck or at the apex of the right chest.

Alternative Treatment Modalities

A peroral endoscopic myotomy (POEM) is a new treatment modality proposed in achalasia patients, with short term relief of dysphagia in most patients [36, 37]. Because LHM is performed on the anterior wall of the esophagus, POEM could be used instead of a redo Heller myotomy in patients with persistent or recurrent dysphagia by performing a myotomy on the posterior wall of the esophagus [38, 39]. For instance, Onimaru et al. reported excellent short-term results in ten patients undergoing POEM for recurrent dysphagia after Heller myotomy [38]. At 3 months after POEM, the lower esophageal sphincter pressure decreased from 22.1 ± 6.6 to 10.9 ± 4.5 mmHg and the Eckardt score decreased from 6.5 ± 1.3 to 1.1 ± 1.3. Long term follow-up will be needed to confirm the validity of these short term results.

Conclusions

A LHM with partial fundoplication is today the recommended treatment modality for achalasia patients. The technical steps have been clearly established, and failure to follow them is the main cause of persistent or recurrent dysphagia.

Even though the success rate of LHM is very high, recurrence of symptoms eventually occurs in some patients, with the need for further treatment, particularly if the first operation was done at an early age. When this occurs, a thorough work-up is important for the identification of the cause and to plan a tailored treatment. The best outcomes are obtained in high volume Centers where radiologists, gastroenterologists and surgeons with experience in the diagnosis and treatment of this disease work as a team.

Conflict of Interest The authors have no conflicts of interest to declare.

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Esophageal Resection for End-Stage Achalasia

17

Yalini Vigneswaran, Marco G. Patti, Mauricio Ramirez, and Wickii T. Vigneswaran

Introduction

Primary treatment modalities for esophageal achalasia include pneumatic dilatation, per oral endoscopic myotomy (POEM), and laparoscopic Heller myotomy. The same options are available when patients experience post-treatment recurrent dysphagia. However, when these interventions are unsuccessful, and the esophagus becomes dilated and sigmoid in shape, the only remaining option is to perform an esophagectomy.

Historically about 5 % of all patients with achalasia will eventually require an esophagectomy [1–3]. This procedure is associated with a high morbidity, and a mortality rate as high as 5 %, even in the hands of experienced surgeons at high volume centers [4, 5].

In this chapter we will discuss patient selection, surgical approaches, conduit selection, reconstruction options and the expected outcomes after esophageal resection for achalasia.

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Indications

The classic and most common indication for esophagectomy for achalasia is end-stage disease in patients with a megaesophagus who have failed multiple prior therapeutic interventions.

Megaesophagus is defined as an esophagus with a diameter greater than 6 cm, as seen in Fig. 17.1. Sometimes the esophagus is not only dilated but it assumes a sigmoid configuration (Fig. 17.2). In these patients, not only dysphagia and regurgitation are very common, but often they experience pulmonary complications due to aspiration and have a 30–40-fold increased risk for developing cancer as compared to the general population [6, 7]. While some surgeons such as Orringer recommend esophagectomy as the initial treatment on the assumption that a myotomy will not improve esophageal emptying, most experts advocated esophagomyotomy as initial treatment prior to esophagectomy [8–11]. In addition, although some reports show that 20 % patients fail a second myotomy [12, 13], long-term results demonstrate that over two thirds of these patients salvage their esophagus [14]. POEM can also prove successful in previously failed myotomy, expanding the therapeutic options in these patients [15, 16].

P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_17

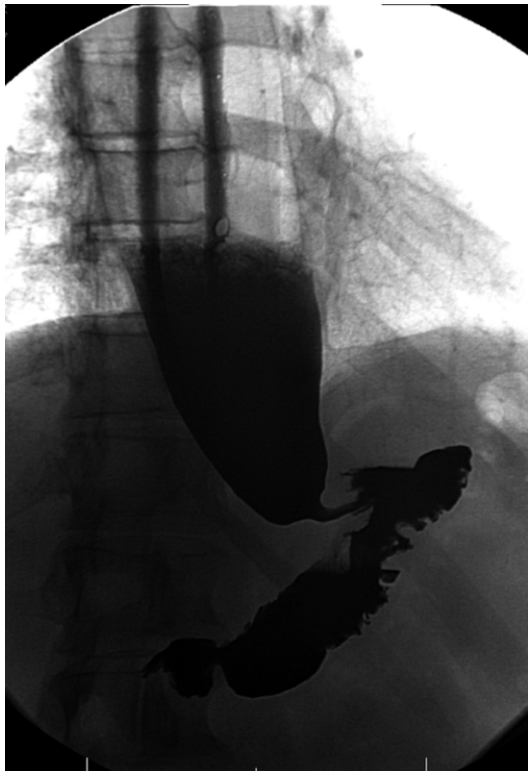

Fig. 17.1 Dilated esophagus

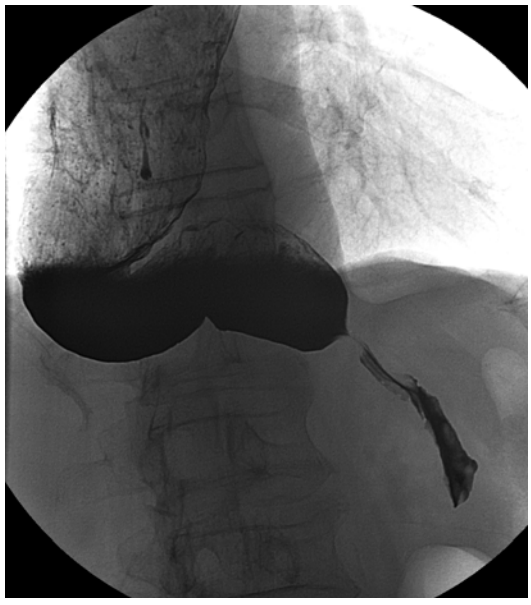

Fig. 17.2 Dilated and sigmoid esophagus

Operative Technique

Esophagectomy for achalasia requires resection of the non-functioning part of the esophagus and reconstruction to the functioning striated muscle portion. Before the operation it is important to optimize the patient's nutritional status, treating any pre-existing pulmonary complications. After the preoperative workup has deemed the patient to be an appropriate candidate to undergo resection, the operative decisions of conduit type and surgical approach should be explored with the patient's specific characteristics in mind.

Gastric, Colonic and Jejunal Conduit

The choice of conduit for esophageal reconstruction in benign disease requires consideration of patient specific characteristics and concerns for reflux esophagitis. Factors that contribute to this decision include previous operations on the stomach or colon, other diseases of the gastrointestinal tract, and reliable blood supply to these organs. A gastric conduit allows for a less complex operation with only one anastomosis, whereas colonic or jejunal interposition requires a much more complex operation. The debate still continues as to which reconstruction results in better physiologic gastrointestinal functioning, but in recent reports many prefer to use the stomach as a conduit if this is available. Effective medications to treat reflux disease undoubtedly had a role influencing this practice [11, 17, 18]. Colonic interposition outcomes have demonstrated possibly lower risks of chronic reflux, anastomotic stricture and dumping syndrome.

Gastric Conduit

The gastric conduit constructed as a 5–6 cm wide gastric tube has an abundant and reliable blood supply from the preserved right gastric and right gastroepiploic arteries. Depending on the chosen surgical approach, the gastric conduit is brought up to the proximal esophagus, and the anastomosis is completed either in the upper chest or neck. The orthotopic position, through the posterior mediastinum, has been the preferred approach for

esophageal replacement with good to excellent results at long term follow up [17, 19, 20]. However the use of the stomach can be challenging if the patient has had a previous fundoplication, as taking down the wrap can compromise part of the stomach. This becomes of particular importance if the intention is to perform a cervical anastomosis.

Colonic Conduit

Colonic replacement was popular for replacement of the esophagus for benign disease before the 1990s. The theoretical advantages of colonic interposition include protecting the proximal esophagus from chronic reflux and a reduced incidence of postoperative anastomotic stricture, regurgitation and dumping syndrome. However currently most surgeons reserve the use of the colon if the gastric conduit blood supply is compromised. For colonic interposition, a preoperative colonoscopy is performed to exclude any pathology such as extensive diverticulosis, polyposis or malignancy. Often an arteriogram is performed to help establish the vascular anatomy, aiding in the selection of the colonic segment for interposition. The distal transverse and the left colon are often preferred. It is based on the ascending branch of the left colic artery, and it is placed in an iso-peristaltic fashion (Fig. 17.3). Depending on the surgical approach, the esophago-colic anastomosis is performed either in the neck [18] or in the chest [21]. The colo-gastric anastomosis is usually performed on the anterior wall of the stomach. With the colon used as a conduit, it is important to avoid redundant colon in the chest, which seems to be a more significant problem with long-segment interposition [22].

Jejunal Conduit

Jejunal interposition is rarely used for replacing the esophagus. Even though this technique is associated with good long term results for achalasia patients [23], it should be used only when the stomach and the colon are not suitable as a conduit for replacement.

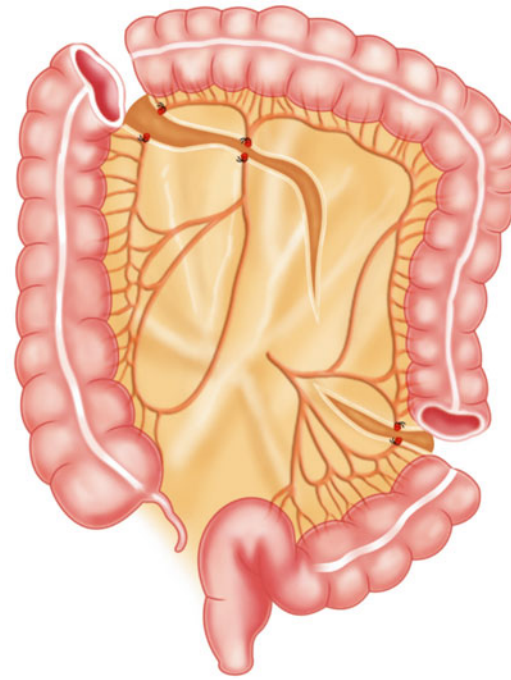

Fig. 17.3 Colon interposition based on the ascending branch of the left colic artery

Surgical Approach

Each of the surgical approaches has its own risks and benefits. The choice of the surgical approach should take into account the patient specific characteristics, conduit choice and surgeon's personal preferences. The options include [1] an abdominal and transthoracic approach with either right thoracotomy and laparotomy or thoracoscopy and laparoscopy; [2] a left thoracotomy or thoraco-abdominal approach; and [3] a transhiatal approach with a laparotomy or laparoscopy and left neck incision. Due to the challenges specific to the achalasic patient as described above, some surgeons recommend a transthoracic approach to deal with the hypertrophied arterial supply, mediastinal scaring, and adhesions. In fact Miller et al. demonstrated a significantly higher blood loss and intraoperative complications for patients undergoing trans-hiatal esophagectomy as compared to a trans-thoracic approach [17].

Table 17.1 Reported outcomes after esophagectomy for end-stage achalasia

Reference	Size	Approach	Conduit	Mortality Morbidity	Follow up	Outcome
Devaney et al. [19]	93	Transhiatal (87) Transthoracic (6) (conversion)	Gastric (91) Colonic (2)	Mortality 2 % Morbidity 30 % Leak 10 %	3.2 years	95 % Asymptomatic
Miller et al. [17]	37	Transhiatal (9) Transthoracic 28)	Gastric (31) Colonic (6)	Mortality 5.4 % Morbidity 32.4 % Leak 5.4 %	6.3 years	91.4 % Excellent/ good
Banbury et al. [20]	32	Transhiatal (21) Transthoracic (11)	Gastric (32)	Mortality 0 % Leak 13 %	3.5 years	87 % Felt better
Orringer and Stirling [11]	26	Transhiatal (24) Transthoracic (2) (conversion)	Gastric (26)	Mortality 0 % Morbidity 19 % Leak 4 %	2.5 years	96 % Normal diet
Peters et al. [18]	19	Transthoracic with cervical anastomosis (19)	Colonic (19)	Morality 0 % Morbidity 21 %	Not reported	93 % Felt cured
Hsu et al. [21]	9	Left thoracoabdominal (9)	Colonic (9)	Mortality 0 %	6 years	75 % Good
Glatz and Richardson [29]	8	Transthoracic (8)	Gastric (8)	Mortality 0 %	6 years	100 % Well
Schuchert et al. [30]	6	Laparoscopic transhiatal (6)	Gastric (6)	Mortality 0 % Morbidity 50 % Leak 16.7 %	Not reported	Not reported

These outcomes were also reflected in the 93 patient series by Devaney et al. with a 6.5 % conversion rate from trans-hiatal to right thoracotomy [19]. However many groups have reported comparable long-term outcomes regardless of which of these type of approaches was used (Table 17.1) [19, 24].

Mobilization of the Esophagus

All approaches require proper exposure and careful dissection of the esophagus due to the changes secondary to the disease. First, due to the size of the megaesophagus, mediastinal organs are often displaced and the esophagus deviates into the right chest. This makes entry into the pleural cavity more common during esophageal mobilization, requiring tube thoracotomy if occurs. Mobilization of the distal esophagus and stomach can be complicated if a fundoplication had been previously performed. The wrap must be carefully undone with preservation of the stomach if a gastric conduit is planned. Mobilization of the proximal esophagus can also be challenging in these patients since the dilation of the esophagus will often extend all the way to the cervical esophagus at the thoracic inlet difficult, and extra attention must be given to the recurrent laryngeal nerves during the cervical dissection. In the thoracic esophagus, the hypertrophied esophagus muscle leads to a hyper-vascular esophagus with

hypertrophied thoracic aortic branches. This factor exposes to the risk of bleeding and that it is why many surgeons prefer a trans-thoracic approach, which allows careful ligation of these vessels. Lastly, a large challenge in these patients is the adhesions secondary to previous interventions on the esophagus. A prior esophagomyotomy is often associated to adhesions between the esophagus and surrounding structures such as the aorta or lung. Thus dissection must be performed under direct vision and care taken to dissect the esophagus from these structures. This dissection may lead to entry into the esophageal lumen and spillage into the mediastinum, which should be treated with suture closure and copious irrigation of the mediastinum.

Vagal-Sparing Esophagectomy

Esophageal resection can be simply performed en bloc, but since achalasia is a benign disease not requiring lymphadenectomy, a vagal-sparing esophagectomy can be considered. This procedure can be performed with the use of a vein stripper passed either through a gastrostomy in anterior cardia or the divided stomach up the esophagus to the divided proximal esophagus. The vein stripper, attached to the proximal esophagus is then used to pull the invaginated esophagus back through the stomach thus stripping the esophagus while leaving its mediastinal structures such as the vagal nerves. Vagal-sparing esophagectomy for patients with benign or pre-malignant disease not requiring lymphadenectomy, is associated with reduced post-vagotomy symptoms, less weight loss and fewer perioperative complications [25]. However these outcomes are reported for patients with otherwise normal esophageal function and minimal prior esophageal interventions. End-stage achalasia patients have a number of prior interventions and for the most part a non-functional esophagus, thus patients may already have disruption of the vagus nerve and if not the subsequent identification and preservation of the nerve during esophagectomy may not always be possible.

Trans-Thoracic Esophagectomy

For trans-thoracic esophagectomy the esophagus is mobilized from both the abdomen and the right chest. The abdominal portion can be done either through a laparotomy or with laparoscopy. Mobilization of the distal esophagus begins with division of the gastrohepatic ligament after retraction of the left lobe of the liver. If a fundoplication is present and a gastric conduit is planned, this should be first undone carefully to preserve the stomach. Mobilization of the stomach is accomplished with dissection along the greater curvature and ligation of the short gastric vessels. The posterior attachments to the pancreas are then divided, as well as the left gastric vessels at the base, and gastrocolic ligament. Once the stomach is mobilized and the gastric tube is formed (if gastric conduit chosen) the abdomen incision is closed. This approach requires the use of a double lumen endotracheal tube and single-lung ventilation with the patient in left lateral decubitus during the thoracic portion of the case. Once the right thoracic cavity is entered via thoracotomy or thorocoscopy, the inferior pulmonary ligament is divided and right lung is retracted. The esophagus is mobilized from the diaphragm to the thoracic outlet. The overlying pleura is divided avoiding the thoracic duct, and the esophagus is carefully dissected from the aorta, the trachea, and the pericardium anteriorly. When the esophagus is mobilized, the proximal esophagus is transected above the azygos vein.

Trans-Hiatal Esophagectomy

For trans-hiatal esophagectomy, mobilization of the esophagus occurs from the abdomen through a laparotomy or laparoscopy. The steps to mobilize the stomach are similar to those described above. With the stomach completely mobilized the cervical esophagus is approached with an incision over the left sternocleidomastoid through the strap muscles. Blunt dissection to the prevertebral fascia must be performed with caution to avoid injury to the recurrent laryngeal nerve.

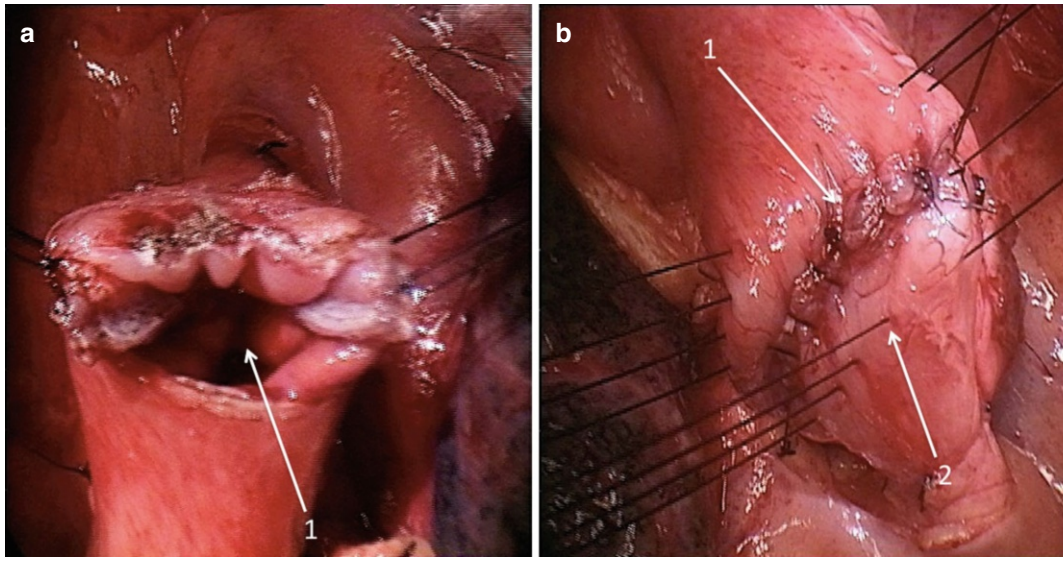

Fig. 17.4 Hybrid anastomosis. (**a**) Stapled anastomosis (*1*-linear stapler) between the posterior wall of the esophagus and the anterior wall of the stomach; (**b**) Closure in two layers (*1*, absorbable running suture; and *2*, interrupted silk) of the anterior opening

The esophagus is encircled with a Penrose drain. The mediastinal dissection can now proceed from the abdomen. The distal esophagus is retracted caudally and attachments to distal esophagus are divided under direct vision. This is continued cephalad while mobilizing the distal esophagus to the level of the carina. The posterior plane is then further developed with blunt dissection along the pre-vertebral fascia. The anterior plane is developed through both the hiatus and the cervical incision with care to avoid injury to the azygos vein. With the esophagus mobilized, the proximal esophagus is transected. If at any point the dissection becomes too difficult or unsafe with limited exposure in the thoracic cavity, the surgeon must be ready to perform a thoracotomy or thoracoscopy.

Anastomotic Technique

Construction of the proximal esophageal anastomosis can be particularly challenging due to the changes from the disease. The esophagus can be quite thick and dilated compared to the conduit. Generally the size mismatch of the dilated esophagus is not as much of a problem with a colonic conduit, however construction of the gastric tube requires special consideration of the dilated proximal esophagus.

Several options for the anastomosis is available based on both the conduit/esophagus characteristics and surgeon preference. These options include a single layer hand sewn, double layer hand sewn, mechanical with a circular stapled or a hybrid approach with using a linear stapler for the posterior wall and hand swing the anterior wall (Fig. 17.4a, b). The use of the circular stapler can be used with success when the esophagus wall is not extremely hypertrophied. Larger diameter circular staplers are generally necessary for a dilated esophagus, however when the wall is thick, the circular stapler may not be appropriate due to the limited standard staple heights. Conversely the construction of an anastomosis using a hybrid linear stapler/hand sewn anastomosis can be successfully used in these patients as the linear stapler has multiple staple height options. However the technique is generally aimed at creating a large anastomosis and a dilated esophagus may impose some limitation, since the use of a linear stapler will create an even larger anastomosis. Hand sewn anastomosis remains a good option; absorbable sutures are

generally used for the inner layer closure with either absorbable or non-absorbable for the outer layer if a two layer anastomosis is chosen.

Short Segment Esophagectomy

Sometimes a partial or short segment esophagectomy has been used for treatment of the end-stage achalasia patient because the pathology of the disease is associated only with the gastroesophageal junction and the distal esophagus. Hsu et al. demonstrated in a series of nine patients that a partial esophagectomy with a short colon interposition can be successfully performed through a left thoracoabdominal incision [21]. The outcomes of this series are described in Table 17.1. This has been previously explored by Picchio et al. [23] but with the use of a jejunal interposition for patients with peptic stricture secondary to myotomy demonstrating good symptomatic outcome in 85 % of patients at average 11 year follow up.

Outcomes

Several groups have shared their own experiences with esophageal resection for end-stage disease with good postoperative outcomes. These single center experiences demonstrated that 75–100 % of patients observed improved symptoms at long-term follow up (Table 17.1). Patients reported improved dysphagia and eating normal consistency food without postprandial regurgitation. Although these series included different surgical approaches and different conduit types, patients appeared to have good outcomes regardless.

Perioperative Complications

The mortality rate after esophagectomy for achalasia has been reported as high as 5 %, with a morbidity rate ranging from 19 to 50 %. The major complications specific to esophagectomy include anastomotic leak, with rates ranging from 4 to 17 % depending on the series as seen in Table 17.1. Devaney et al. reported other major complications related to trans-hiatal esophagectomy such as recurrent laryngeal nerve injury (2 %), chylothorax (2 %) and mediastinal bleeding (2 %) requiring reoperation. Additionally due to a high rate of preexisting pulmonary dysfunction, these patients are at higher risk for pneumonia and pulmonary compromise at reported rates of 14.5–21 % [20, 26]. The average length of stay in the largest single institution study was 12.5 days [19].

The incidence of perioperative complications for these achalasia patients are similar to patients undergoing resection for cancer A recent study on a large database, the Nationwide Inpatient Sample, examined the outcomes for achalasia patients (n = 963) as compared to cancer patients (n = 18,003) after esophagectomy [27]. In this study patients with achalasia following esophagectomy had a median length of 12 days and mortality of 2.85 %. The highest postoperative complications reported were pulmonary compromise (30.88 %), pneumonia (18.11 %) and urinary tract infection (8.26 %). Through a multivariate analysis they found age and comorbidities were predictive of mortality and in particular patients with renal disease were at the greatest risk (odds ratio 8.81). In the study, the outcomes for achalasia patients were found to be comparable to outcomes of patients undergoing esophagectomy for cancer. The group concluded that the functional and anatomical changes associated with achalasia did not result in significantly different outcomes as compared to those of cancer patients.

Long-Term Effects

Because esophageal achalasia is a benign disease with relatively long life expectancy, patients may suffer from unusual complications and long-term effects related to reflux, stasis and malabsorption. These complications depend on the conduit used for esophageal replacement. Dumping syndrome characterized by postprandial diarrhea and cramping appears to be related to disruption of the vagal

nerves. Although many have explored the possibility of vagal-sparing esophagectomy, many of these patients with achalasia already have generalized parasympathetic dystrophy and/or prior vagus nerve dysfunction. Patients experiencing these symptoms can be treated with antidiarrheal agents such as diphenoxylate or somatostatin in more severe cases. Devaney et al. reported that 39 % patients experienced mild dumping symptoms which were self-limited and controlled with dietary modifications or medications, while 4 % of patients had severe refractory dumping syndrome that required somatostatin. In addition, they reported that 46 % of patients required dilation for anastomotic stricture [19]. Other case reports describe rare complications such as tracheal or bronchial to conduit fistula, and conduit to pericardial fistula [28].

Conclusions

Esophagectomy for end-stage achalasia is a safe and effective procedure for the carefully selected patient but is not without a relevant mortality and morbidity. End-stage achalasia is a challenging disease to treat, but despite the rare occurrence of this disease, the reported literature supports reserving esophagectomy as a last resort with reported success of other interventions first. Many different approaches and reconstruction options are available to the surgeon when treating a patient that requires esophagectomy. These options should be considered with the specific patient in mind. However when performed in high volume specialized centers, patients appear to have good outcome regardless of the type of approach. Further long term studies are required to better understand and treat the long term effects expected after esophageal resection and reconstruction in these patients. The observed long-term effects such as dumping, regurgitation and stricture must be discussed with the patient preoperatively. However esophageal resection for the appropriate patient does successfully palliate symptoms and improve quality of life in this challenging group of patients.

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Achalasia and Eating Disorders

18

Deborah Lynn Reas

Introduction

Eating disorders and achalasia share clinical features involving food, eating, and weight. The significant overlap in clinical presentation corresponds to a diagnostic dilemma. A systematic literature review found 36 cases in which achalasia had been mistakenly diagnosed as an eating disorder [1]. Some cases had undergone lengthy or repeated admissions to psychiatric or eating disorder inpatient units [2, 3] with the discovery of achalasia only after attempts to pass a nasogastric feeding tube failed due to difficult placement [4, 5]. In this chapter, the feeding and eating disorders in the Diagnostic and Statistical Manual (DSM-5) [6] are briefly summarized, followed by a discussion of clinical issues relevant to the differential diagnosis between eating disorders and achalasia.

It is generally estimated that up to 50 % of achalasia cases are initially misdiagnosed [7, 8]. Patients may receive various alternative diagnoses including gastroesophageal reflux disease (GERD), peptic stricture, allergies, or as discussed in detail here, eating disorders [9]. Several authors have argued that treatment delay is due to misinterpretation or misattribution of clinical findings, rather than an atypical presentation of the disease [10, 11]. An overreliance on upper endoscopy, which yields results appearing normal in the early stages of achalasia, has also been implicated in the poor rate of early detection of achalasia [8, 12].

Swallowing difficulties are sometimes misinterpreted to be psychological in origin [3, 13] and patients, especially of younger age, may themselves have difficulties recognizing or describing symptoms [14–16] that are often vague or transient in the initial stages [17]. The misattribution of symptoms such as rapid weight loss to an eating disorder is a particular concern for young women, who constitute the most at-risk demographic for anorexia nervosa and bulimia nervosa. Prevailing stereotypes of eating disorders as manipulative or secretive may also perpetuate the rate of misdiagnosis.

Eating disorders are serious psychiatric illnesses characterized by disturbed eating behaviors leading to significantly impaired physical health or psychosocial functioning, sometimes associated with life-threatening morbidity and mortality [18]. The main diagnostic categories distinguished in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* [6] are anorexia nervosa (AN), bulimia nervosa (BN), and recently added binge eating disorder (BED). Other feeding and eating disorders

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_18

include pica, rumination disorder, and avoidant/restrictive food intake disorder (ARFID). Although eating disorders typically develop in adolescence or young adulthood, with a highly skewed sex distribution for AN and BN [19], these conditions are known to affect both males and females across the lifespan [20, 21]. In the next section, a brief description of the main feeding and eating disorders is provided, with expanded discussion related to the diagnosis of avoidant/restrictive food intake disorder within the context of a medical condition.

Anorexia nervosa (AN) is characterized by (1) restriction of energy intake leading to a significantly low weight, intense fear of gaining weight or persistent behavior that interferes with weight gain, and (2) disturbance in body image, undue influence of body weight or shape on self-evaluation, or a persistent lack of recognition of the seriousness of current low body weight [6]. Anorexia nervosa is further classified into two subtypes: AN-restricting type or AN-binge-eating/purging type, depending on the presence or absence of binge eating (subjective or objective) and purging behavior (i.e., self-induced vomiting, laxative use, etc.). Bulimia nervosa (BN) is characterized by recurrent episodes of binge eating (objectively large amount of food eaten in a discrete period of time accompanied by a sense of loss of control) and inappropriate weight compensatory behavior, such as self-induced vomiting, laxative use, fasting, or excessive exercise [6]. Self-evaluation is unduly influenced by body shape and weight. In contrast to AN, however, individuals with bulimia nervosa are typically of normal weight or overweight (BMI $\geq$18.5–30). Reas and colleagues (2014) found that anorexia nervosa and bulimia nervosa were the most likely eating disorders to be confused with achalasia.

Binge eating disorder (BED) is a recently included formal psychiatric diagnosis in the DSM-5, and it is characterized by recurrent binge eating in the absence of inappropriate weight compensatory behaviors. Although body image dissatisfaction may be present, there is no diagnostic requirement for a drive for thinness or undue influence of weight or shape on self-esteem. Binge eating disorder has a far less skewed gender distribution, with a higher age at treatment presentation (mid-40s), and it is reliably associated with overweight or obesity in treatment-seeking samples [22]. Of the major eating disorder diagnoses, binge eating disorder is arguably the least challenging differential diagnosis for achalasia, given the functional limitations in swallowing which limit the regular consumption of objectively large amounts of food, and the absence of vomiting.

Other Feeding and Eating Disorders included in the DSM-5 include pica, rumination disorder, and avoidant/restrictive food intake disorder (ARFID). Pica is the persistent eating of nonnutritive, nonfood substances inappropriate to developmental level and not consistent with a culturally supported or socially normative practice. If occurring within the context of other mental disorders (e.g., autism, intellectual development disorder), a separate diagnosis of pica is only warranted if the eating disturbance is severe enough to warrant additional clinical attention. Rumination disorder is the repeated regurgitation of food, without apparent nausea, involuntary retching, or disgust. Regurgitated food may be re-chewed, re-swallowed, or spit out. Diagnostic criteria specify that a diagnosis of rumination disorder is not applied if regurgitation behavior is better explained by gastrointestinal or other medical conditions [6]. As such, rumination disorder might be considered as a rule-out diagnosis, but it would not be applied concurrently if achalasia is diagnosed.

Avoidant/restrictive food intake disorder (AFRID) is characterized by restriction or avoidance of food intake resulting in a persistent failure to meet appropriate nutritional and/or energy needs as evidenced by one (or more) of the following: significant weight loss, nutritional deficiency, dependence of enteral feeding or nutritional supplements, and marked impairment on psychosocial functioning [6, 23]. This diagnosis has replaced the DSM-IV diagnosis of feeding disorder of infancy or early childhood [24]. Clinical presentations are diverse, but include a pattern of severely restricted eating due to a history of pain related to gastrointestinal illness, insult or injury [25]. In avoidant/restrictive food intake disorder,

and contrary to the hallmark diagnostic feature of AN and BN, there is no undue influence of body weight or shape on self-evaluation.

Importantly, ARFID is often associated with coexisting medical comorbidity or other mental disorders and it can be concurrently diagnosed. In accordance with DSM-5 guidelines, a concurrent diagnosis of ARFID in the context of a medical condition *may* be warranted if (1) all diagnostic criteria for both the medical condition and ARFID are fulfilled, and the eating disturbance (2) exceeds that directly accounted for and routinely associated with the medical condition, (3) persists following successful treatment or resolution of the medical condition, and (4) is considered a primary focus for intervention requiring specific clinical attention. Thus, the application of this diagnosis can be quite challenging in gastroenterological samples [26] and requires a sufficient level of knowledge regarding the symptoms and functional impairment associated with the medical condition, as well as expected prognosis, course, and outcome. The following section presents a detailed overview of shared and distinguishing features of achalasia and eating disorders.

Regarding overlap in clinical presentation, weight loss and vomiting and/or regurgitation are the most prominent shared features. Further complicating the diagnostic pictures, individuals with achalasia may self-induce vomiting to relieve pain and discomfort [13, 27], which closely mimics purgative behaviors in bulimia nervosa or anorexia nervosa-binge/purge subtype. Pain related to worsening dysphagia and aperistalsis in undetected or untreated achalasia may suffice to drastically alter eating patterns, leading to an increasingly restricted dietary intake. A variety of other aberrant eating behaviors typically associated with eating disorders are seen in achalasia, including ritualistic or rule-governed eating, eating in secret, and chewing and spitting [1]. Avoidance of types or textures of food proven difficult to eat may be perceived by others as "picky" or "selective eating" and affected individuals may avoid social situations involving food due to eating-related pain or discomfort, or embarrassment about symptoms.

As is similarly observed in eating disorders, functional impairment owing to eating difficulties or malnutrition can affect multiple life domains (academic, athletic, occupational) [14]. Lastly, psychiatric comorbidity typical of eating disorders, such as depression or anxiety, is observed among individuals with achalasia, owing to the distressing nature of the illness itself, or related to misdiagnosis or inadequate treatment [28, 29]. Thus, above and beyond symptoms and signs, eating disorders and achalasia share a similar pattern of functional impairment, as well similar types of psychiatric comorbidity.

Despite this overlap in clinical features, several principles and distinguishing characteristics of achalasia are useful to assist the differential diagnosis between achalasia and anorexia nervosa, bulimia nervosa, or their subthreshold presentations. First, as argued previously, low weight alone is insufficient conclude the presence of an eating disorder, even among at-risk populations such as younger females [30]. Additionally, body shape dissatisfaction in general is neither diagnostic nor specific to an eating disorder, as some degree of body shape or weight dissatisfaction is nearly universal across women of all ages [31]. To conclude a diagnosis of an eating disorder, careful and comprehensive assessment of the core psychopathology of eating disorders, i.e., undue influence of shape and weight on self-esteem, intense fear of gaining weight, or drive for thinness is warranted.

Second, it is important to note that malnutrition or undernutrition resulting from severe achalasia can have profound and seemingly 'eating-disordered'-like effects of behavior [32], including obsessive-compulsive tendencies, food preoccupation, hiding or hoarding food, as well as physiological effects such as poor concentration or distractibility, social withdrawal and depression. These effects are secondary to malnutrition and are expected to resolve following weight gain or nutritional restoration. Third, other seemingly 'eating disordered' behaviors observed in achalasia such as eating slowly, eating in secret, cutting food into small pieces, or chewing and spitting out food should be

conceptualized as negatively-conditioned behaviors attributable to the extreme pain and discomfort involved in swallowing. Fourth, the goal or purpose of self-induced vomiting in achalasia is pain relief, or sometimes to reduce discomfort to promote sleep. In contrast, self-induced vomiting in eating disorders is considered an inappropriate weight compensatory behavior.

Clinicians might suspect achalasia rather than ED if regurgitation or vomiting worsens at night or while lying down, is persistent across settings, occurs following the intake of both liquids and solids, or occurs spontaneously in front of others [5]. In contrast, purging behavior in BN is characteristically private or furtive, and is not readily disclosed. Achalasia might also be suspected if the regurgitated material is bubbly, or non-acidic in taste, consistent with regurgitation of undigested food [33]. Other distinguishing features unique to achalasia but distinct from eating disorders include: persistent cough or history of asthma or pneumonia, chest pain, wheezing or eyes tearing up during meals, atypical stereotyped behaviors during eating [34], such as arching the neck and shoulders, standing or sitting up straight during meals removal of necklaces, scarves, or neckties during meals, and visible relief upon the passage of food into the stomach with a resumption of eating.

In closing, two special diagnostic issues regarding comorbidity are emphasized in this chapter. First, in their review of the literature, Reas and colleagues (2014) identified five reports describing concurrent diagnostic comorbidity between achalasia and BN. For example, two cases described the gradual development of involuntary and frequent vomiting within the context of self-induced vomiting. One involved a 52-year old woman with an established 30-year history of bulimia nervosa [35] and one involved a 34-year old woman with an 18-month history of self-induced vomiting [36]. Repeated referrals by the GP for manometric testing for the 52-year old patient [35] had been denied due to a history of BN and attribution of swallowing difficulties to the ED, a delay leading to worsening of symptoms.

Achalasia was eventually confirmed in these cases with manometric testing and treated with pneumatic dilation, yet the resolution of dysphagia and subsequent weight gain intensified the patients' weight and shape concerns, triggering a relapse of eating disorder behaviors. Symptoms of achalasia can be obscured by coexisting bulimic behavior, complicating detection [15], and clinicians should be aware that new pathology may arise in the context of chronic symptoms or known illness.

Second, clinicians treating patients with achalasia should be aware that a concurrent diagnosis of DSM-5 avoidant/restrictive food intake disorder might be considered if negatively-conditioned restrictive eating and food avoidance behaviors persist 1) following successful medical treatment of achalasia and 2) are uniquely associated with or directly responsible for significant impairment in psychosocial functioning or physical health (i.e., malnutrition, poor growth, weight loss). In this case, specific clinical attention to eating difficulties might be warranted to maintain adequate nutrition or improve well-being or social functioning. For example, foods which used to get 'stuck' prior to treatment, but pass easily into the stomach following treatment, might be slowly and gradually incorporated into diet to maintain adequate nutrition. If a persistent pattern of food avoidance interferes with psychosocial functioning (e.g., academic or occupational impairment, social eating, relationship problems), specific clinical attention to these issues might be warranted to improve overall well-being and quality of life.

To summarize, as with other gastroenterological populations, patients with achalasia may fall into a pattern of severely restricted eating with associated functional impairment which persists even following medical treatment due to a history of eating-related pain or discomfort. Very little is known about the long-term eating behavior and quality of life among individuals living with achalasia, and this represents an important direction for future research.

Conclusion

In the field of eating disorders, numerous clinically significant presentations of feeding or eating disturbances are known to exist that are

associated with or primarily explained by a medical condition. Although other rare or uncommon diseases (e.g., Kleine-Levin syndrome) have received specific mention in the DSM-5 as an important differential diagnosis to consider [6], achalasia has received far less attention than other gastrointestinal illnesses in the field of eating disorders [37]. Several case reports in the literature have documented the erroneous misdiagnosis of achalasia as an eating disorder. Increased awareness and greater attention to issues surrounding the differential diagnosis between eating disorders and achalasia will hopefully speed recognition and reduce diagnostic delay for both conditions.

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Pediatric Achalasia

19

Farhana Shariff and Monica Langer

Introduction

Achalasia is a rare entity in the pediatric population. It is estimated to affect between 0.11 and 0.18/100,000 children annually [1, 2]. It can occur as young as 7 weeks of age, but children under 15 years of age account for less than 5 % of all achalasia cases [3–6]. As in adults, pediatric achalasia is most commonly idiopathic and isolated; however, it occurs infrequently in the setting of genetic and familial conditions. Symptoms of vomiting, progressive dysphagia, and weight loss are a result of failure of relaxation of the lower esophageal sphincter (LES), impaired peristalsis, and increased LES resting pressures [7, 8]. Diagnosis and treatment are similar to adults, with no curative treatment available, but a number of different options for symptom palliation.

For the majority of children with achalasia the pathophysiology is the same as adults, with some histologic studies suggesting an autoimmune component [9], but children may also develop this in the setting of genetic conditions. Familial achalasia is extremely rare, with case reports of parent and child with achalasia and multiple siblings from consanguineous relationships affected suggesting an autosomal recessive inheritance [10–13]. Genetic analysis of one set of siblings demonstrated a mutation in nitric oxide synthase, requiring sildenafil treatment after failure to improve with cardiomyotomy [11]. Achalasia may also occur in the setting of multiple syndromes including Allgrove's syndrome, Sjogren's syndrome, Rozychi's syndrome, and Down's syndrome [14–16]. Since Allgrove's first description of patients with achalasia, alacrima, and adrenal insufficiency in 1978, there have been multiple reports of patients with Triple A syndrome [16]. Also known as Allgrove syndrome or 4A syndrome (including autonomic disturbance), children may present first with achalasia, necessitating careful clinical evaluation for signs of hyperpigmentation and abnormal lacrimation that may allow treatment before life-threatening complications of adrenal insufficiency develop [10, 17, 18]. There is no consensus as to the optimal therapy for patients with Triple A syndrome, but multiple reports show improvement with esophageal cardiomyotomy with or without partial fundoplication [10, 19]. Heller's myotomy has also been successful for the rare children who develop achalasia in the setting of Down's syndrome [3, 14]. One recent series of three pediatric achalasia patients suggests a possible association

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P.M. Fisichella et al. (eds.), *Achalasia: Diagnosis and Treatment*,
DOI 10.1007/978-3-319-13569-4_19

with autism, highlighting the need for evaluation of autistic children suffering from eating disorders or esophageal symptoms with barium swallow and manometry [20].

The rarity of achalasia and presence of symptoms that mimic common pediatric diagnoses may lead to misdiagnosis in children with this disease. Achalasia symptoms often mimic those of gastroesophageal reflux disease (GERD) in younger children who present with failure to thrive, feeding difficulties, and recurrent pneumonia [5, 21]. This atypical presentation can lead to a delay in diagnosis anywhere from a few months to more than 5 years [5]. Confounding the picture, GERD has also been reported in some series to accompany or precede achalasia, leading to recommendations to consider high-resolution manometry (HRM) in those children who do not respond to initial reflux treatment [22]. Given the relative frequency of GERD compared to achalasia, up to 50 % of children are treated with prokinetic or antacid medications prior to receiving a definitive diagnosis of this condition [5, 7]. A study of Brazilian children revealed that many patients are misdiagnosed with asthma, with 46 % of those eventually diagnosed with achalasia receiving ineffective asthma therapy for chronic cough that resolved with esophageal myotomy or pneumatic dilation [5]. In three children thought to have refractory asthma, the diagnosis was only suspected once tracheal obstruction was identified on pulmonary function testing, leading to further work-up with diagnosis and successful treatment of their achalasia [23–25]. Achalasia can also be confused with eosinophilic esophagitis, with one study reporting elevated intraepithelial eosinophils in 34 % of patients, and 8 % meeting criteria for eosinophilic esophagitis [26]. Common symptoms have also contributed to multiple reports of adolescents and children diagnosed and treated for eating disorders, (both anorexia nervosa and bulimia) who were eventually diagnosed and successfully treated for esophageal achalasia [5, 27, 28]. These highlight the need to fully evaluate children with dysphagia, even if symptoms suggest a psychiatric etiology.

Importantly, esophageal dysmotility and distension have been misdiagnosed as achalasia in multiple adolescents who were eventually diagnosed with an H-type trachea-esophageal fistula [29–31]. H-type fistulas can cause chronic overdistension of the esophagus and affect peristalsis, leading to the diagnosis of achalasia, but not necessarily requiring any other treatment once the fistula is closed [31].

Diagnostic Workup

Diagnosis of achalasia in children is made by a combination of careful history and symptom review, barium swallow study and if necessary, esophageal manometric studies. Upper endoscopy should also be considered to exclude other potential causes of dysphagia.

Barium Swallow Study

Barium studies typically demonstrate proximal esophageal dilatation, with a “bird’s beak” narrowing distally at the level of the contracted lower esophageal sphincter [5]. This can be especially apparent in type 1 achalasia cases or where there has been a significant delay in diagnosis, and is diagnostic in approximately 2/3 of pediatric cases [32]. Barium swallow may not be diagnostic in types 2 and 3 achalasia (using the Chicago Classification); therefore further testing with high resolution manometry may be needed to make the diagnosis [33].

Esophageal Manometry

Esophageal manometry, the gold standard for diagnosis, classically demonstrates increased LES resting pressures, impaired esophageal peristalsis, and abnormal relaxation of the LES with swallowing [5, 34, 35]. Interestingly, however, up to 31 % of pediatric patients with achalasia may demonstrate variable LES resting pressures, which fluctuate from between normal and abnormally elevated. In addition, normal relaxation of the LES can be seen in response to wet swallows in some pediatric patients [35]. This is contrary to traditional perceptions that achalasia is consistently associated

with insufficient or absent LES relaxation [36]. As a consequence, absence of these features does not definitively rule out a diagnosis of achalasia. Although LES function parameters do not seem to vary with the patient's age at diagnosis, those with longer symptom duration may demonstrate more consistently abnormal LES behaviour [35]. Prior to high resolution manometry (HRM) availability in children, manometry was infrequently used due to poor tolerance and large catheter size, often requiring sedation and limiting interpretation [37]. HRM now allows unsedated studies in the majority of infants and children and experts demonstrate moderate reliability using the Chicago Classification in diagnosing children with achalasia [37, 38].

Endoscopy

Upper endoscopy is a useful adjunct and should be used to rule out other potential etiologies of dysphagia and feeding intolerance. These include eosinophilic esophagitis, malignancy, candidal infection, mechanical strictures or rings, and sequelae of advanced GERD [5, 35]. In many institutions, endoscopy with esophageal biopsy is included routinely in the workup of achalasia [32].

Other Diagnostic Modalities

There are case reports of other imaging modalities including gastroesophageal radionuclide studies [39, 40] and ultrasonography [41] for both diagnosis and treatment monitoring in children with achalasia, and may be useful adjuncts when specific considerations limit the use of other diagnostic modalities.

Therapy and Outcomes

In the pediatric population, there are currently no definitive guidelines for treating achalasia. The general principles of treatment are similar to those utilized in adults, although responses to specific interventions differ somewhat.

Medical/Pharmacologic

While not considered definitive therapy for achalasia in children, certain pharmacologic agents may be considered for symptom relief either as a bridge to further treatment, or in patients who have strong medical contraindications to balloon dilation or esophagomyotomy. Calcium channel blockers such as nifedipine have been used in adults, but there is minimal study around their use in children. One series of four adolescent patients treated with nifedipine demonstrated significant symptom improvement and increased LES relaxation [42], while other sources suggest that side effects of these drugs are poorly tolerated in this population with increasing doses and they are not recommended as first line treatment [43].

Endoscopic Botox Injection

Botulinum toxin inhibits acetylcholine release by binding presynaptic cholinergic nerve terminals, resulting in smooth muscle relaxation. When injected endoscopically into the LES, Botox has demonstrated efficacy in relieving symptoms of achalasia in both the adult and pediatric populations [44–46]. The procedure is fairly easy to perform, with very few complications [46]. In the pediatric population, an initial response rate of approximately 80 % has been shown with a mean duration effect of 4–6 months [44, 46]. Unfortunately, only a small proportion of pediatric patients respond to a single injection without need for any further medical or surgical intervention [46], suggesting that while botulinum injection is an effective intervention for symptom relief, dilation or myotomy should still be considered for definitive treatment.

Endoscopic Balloon Dilation

Balloon dilatation (BD) with resultant disruption of the LES has been well established as an effective intervention for achalasia in adults. Several retrospective case series report on the use of this intervention in children with long-term symptom

relief in 65–80 % of patients followed for 2–8 years [47–50]. Possible complications include gastroesophageal reflux, prolonged retrosternal or epigastric pain and perforation. The risk of perforation in adult literature is less than 5 % in most series [36, 51] and one series of 50 pediatric procedures demonstrated similar results, with a perforation rate of 6 % [52]. While successful balloon dilations have been done for achalasia patients as young as 7 weeks, many authors recommend avoiding balloon dilation in younger children (under 5–9 years) due to technical limitations and perceived increased risk of complications [48, 53, 54]. A recent systematic review comparing balloon dilation to Heller myotomy concluded that there is insufficient evidence to recommend an optimal treatment algorithm, but that both adult and pediatric studies suggest poorer outcomes from balloon dilation in younger patients [6].

Despite the need for repeat intervention, balloon dilation has been demonstrated to be a cost effective, relatively low risk procedure for achalasia treatment [32, 34]. If this treatment modality is chosen, those who fail to improve with more than one dilation over the course of a year should be considered for surgical myotomy [7].

Surgical Myotomy

Cardiomyotomy, first described by Heller, involves division of the LES, from the esophageal wall, with extension interiorly over the first 2 cm of the gastric cardia [43]. Although originally performed through a laparotomy, open myotomy has largely been replaced by the Laparoscopic Heller Myotomy (LHM) with an antireflux procedure. As with many other laparoscopic procedures, a minimally invasive approach offers numerous benefits including improved cosmesis, decreased post operative pain, shorter hospital stay, and faster return to activity [55, 56]. At present, surgery is considered the most definitive treatment for achalasia [32, 57] with longer symptom resolution than balloon dilation in multiple pediatric studies [7, 34, 53, 54]. Potential complications include immediate or delayed perforations of the esophageal mucosa, recurrent dysphagia, GERD, and incomplete myotomy necessitating balloon dilation, or repeat surgical intervention [32, 57]. To limit complications, some centers performing pediatric laparoscopic Heller myotomy also advocate for use of intraoperative manometry or endoscopy to avoid incomplete myotomy and possibly aid intraoperative identification of perforation [58, 59].

The need for antireflux procedure in combination with myotomy is somewhat controversial. Although a single series of patients treated with LHM alone did not demonstrate significant reflux post-operatively [60], the majority of pediatric studies suggest LHM with fundoplication is superior to LHM alone for prevention of post-operative GERD [8, 32]. While the type of antireflux procedure has not been examined in depth in the pediatric population, randomized studies in adults have demonstrated significantly more post-operative dysphagia in achalasia patients who received a Nissen fundoplication when compared to those receiving a Dor [57]. At present, most pediatric studies have utilized the Dor fundoplication [7, 8, 32, 61].

Per Oral Endoscopic Myotomy (POEM)

Although the Heller myotomy is still considered the surgical treatment of choice for children with Achalasia, more evidence is gathering to support the use of POEM in this population. The technique of POEM has been described previously [62, 63] and consists of a longitudinal myotomy of the circular esophageal musculature once a submucosal tunnel using carbon dioxide insufflation and coagulation has been created. A recent retrospective study of eighteen pediatric patients with achalasia examined outcomes of LHM with Dor fundoplication compared with the POEM technique, and demonstrated comparable symptom improvement in both groups, with similar times to feeding and discharge from hospital [62].

Current concerns surrounding the use of POEM include the inability to perform an antireflux procedure, potential increased risk of iatrogenic

GERD [64]. Technical factors related to patient weight/size in addition to the learning curve of the endoscopist also deserve more attention and consideration as utilization of this procedure increases [62]. While more investigation into long-term outcomes in larger numbers is certainly needed, early results suggest POEM may be a promising option for the treatment of pediatric achalasia in coming years.

In summary, achalasia is rare in pediatrics and the majority of diagnostic and therapeutic considerations are similar to adults. Special considerations in children include identification of achalasia in the setting of genetic syndromes and difficulties making the diagnosis due to symptoms that mimic more common childhood illnesses. Special diagnostic and treatment concerns also relate to the size of younger patients affecting manometry and endoscopic procedures, and the need for longer-term efficacy of symptom palliation in a child with his or her life ahead of them. Further studies are needed to determine the ideal treatment option and develop a cure for children and adults with this disease.

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DOI 10.1007/978-3-319-13569-4