Achalasia: From Bench to Peroral Endoscopic Myotomy

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Key Words

Achalasia · Dysphagia · Enteric neurons · Manometry · Laparoscopic Heller myotomy · Endoscopic pneumatic dilation · Peroral endoscopic myotomy

Abstract

Achalasia is a primary esophageal motility disorder with an estimated annual incidence of 1 per 100,000 persons. It is characterized by the absence of esophageal peristalsis and failure of the lower esophageal sphincter (LES) to relax upon swallowing, resulting in progressively severe dysphagia for solids and liquids, regurgitation, aspiration, chest pain and weight loss. Achalasia results from a loss of enteric neurons, most likely due to an autoimmune reaction in patients with a particular immunogenetic background. To date, 3 manometric subtypes have been identified based on high resolution manometry. To what extent these subtypes also indicate differences in underlying pathophysiological mechanisms is however unclear. As achalasia cannot be cured, treatment is confined to disruption of the LES to improve bolus passage and thereby relieving symptoms. The 2 most commonly used treatment modalities available for this purpose include pneumatic dilation and laparoscopic Heller myotomy. Both treatments have been shown repeatedly to be successful; however, success rates decline in time, most likely due to progression of the disease. A recent European randomized trial provides objective data indicating that both treatments are equally effective. In view of these data and the low incidence of the disease, the choice between these

2 treatments should be based on the expertise and experience available. Recently, excellent short-term success rates have been reported with a new endoscopic technique, that is, peroral endoscopic myotomy. However, longer follow-up data are absolutely needed before accepting this technique as a new treatment option for achalasia in clinical practice.

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Introduction

Achalasia is a rare motility disorder of the esophagus with a mean incidence ranging between 0.3 and 1.63 per 100,000 year in adults [1]. It presents with symptoms of dysphagia, regurgitation of undigested food, respiratory symptoms (nocturnal cough, recurrent aspiration and pneumonia), chest pain and weight loss [2, 3]. Since its first description in 1674 by Sir Thomas Willis [4], 'spasm' or failure to relax of the lower esophageal sphincter (LES) has been identified as the cause of achalasia, resulting in impaired flow of ingested food into the stomach and subsequent stasis of food and secretions in the esophagus. With the introduction of manometry, it is now well established that the coordination of contractions in the esophagus is also compromised resulting in absence of peristalsis. These motor abnormalities are due to loss of myenteric neurons that coordinate esophageal peristalsis and LES relaxation [5].

The most common form of achalasia is idiopathic achalasia and is mostly observed as sporadic cases. Other conditions leading to loss of neurons, such as pseudo-

achalasia or Chagas disease (infection with *Trypanosoma cruzi*), may give rise to a similar clinical picture. This review will, however, focus on the current insights and recent developments in the management of idiopathic achalasia.

Pathophysiology

Histological studies have abundantly shown that myenteric neurons are decreased or even completely absent in esophageal resection specimens obtained from patients with achalasia [6, 7]. These neurons are essential for the coordination of peristalsis and the relaxation of the LES. Loss of these neurons indeed results in failure of isolated muscle strips of the esophagus and LES upon nerve stimulation and explains the absence of peristalsis and swallow-induced relaxation on manometry in patients with achalasia [5]. The current thinking is that a viral infection, in particular herpes simplex virus 1 (HSV-1), triggers an autoimmune reaction to esophageal neurons, leading to a chronic ganglionitis and disappearance of the enteric neurons [8]. The fact that HSV-1 is a neurotropic virus with a predilection for squamous epithelium might explain why the esophagus and LES are almost exclusively affected. The aberrant immune reaction against myenteric ganglia is supported by detailed examination of resection specimens showing infiltration of cytotoxic T lymphocytes within myenteric ganglia [9]. These T cells possess a monoclonal T cell receptor repertoire and are activated when co-cultured with HSV-1 antigens [10]. In addition to a cell-mediated immune response, anti-neural antibodies may contribute and are especially detected in patients with a specific HLA genotype, namely those carrying the DQA1*0103 and DQB1*0603 alleles [11]. In line, we recently showed that common variants in the HLA-DQ region indeed confer susceptibility to idiopathic achalasia, confirming that immune-mediated processes indeed are involved in the pathophysiology of achalasia [12, 13].

With the introduction of high resolution manometry, 3 (and perhaps even 4) different subtypes of achalasia have been identified based on the pressure patterns recorded in the esophageal body: type I is characterized by impaired LES relaxation (elevated IRP of >15 mm Hg), 100% failed peristalsis and absence of esophageal pressurization; in type II there is pressurization of the esophagus; while in type III premature spastic contractions are recorded in $\geq 20\%$ of the swallows [14]. To what extent these different manometric patterns are associated with

different underlying mechanism remains unclear. Goldblum et al. [6] reported that 3 out of 3 specimens taken from patients with 'vigorous' achalasia had myenteric inflammation, but a normal number of ganglion cells (20–22 ganglion cells per section). The remaining 8 patients with 'classical' achalasia had low to no ganglion cells. This led those investigators to propose that 'vigorous' achalasia may be the earliest phase of achalasia with preservation of the motor response of the esophageal body, thereafter progressing to more typical achalasia. However, there are several arguments against that hypothesis, the most obvious being that one of these 'vigorous' achalasia patients had symptoms for 15 years without obvious progression prior to treatment. Similarly, when subtyped according to the Chicago Classification, type III (spastic) patients enrolled in the recent European Achalasia Trial, all had persistent esophageal spasm at follow-up [15]. Hence, although prospective studies would be required to definitively address this question, neither the available published data nor the bulk of clinical experience suggests progression from type III to type I or II achalasia.

If not representative of an early stage in disease progression, type III achalasia patients likely represent a distinct entity characterized by a less 'aggressive' immune response impacting on neuronal function, but not causing apoptosis [16]. Supportive of that hypothesis, incubation of resected human gastric fundus tissue with serum of achalasia patients induced downregulation of NO synthase expression and increased cholinergic sensitivity, without affecting neuron number [17]. Circulating cytokines such as IL-8 may mediate this response suggesting that local cytokine release could induce an imbalance between inhibitory and excitatory postganglionic neuronal function, thereby explaining the preserved neuron number but reduced inhibition and enhanced excitation observed in type III patients. In contrast to type III, types I and II achalasia likely both result from a cytotoxic immune attack leading to progressive myenteric plexus neuronal apoptosis without selectivity among subsets of myenteric plexus neurons. Rather, variability among patients is reflective of the rapidity with which this occurs. Demonstrative of this variability, Goldblum et al. [6] reported that patients with no myenteric plexus infiltrate had a shorter duration of symptoms and more severe loss of nerve fibers compared to patients with myenteric infiltrate; they even observed complete aganglionosis in some patients who were symptomatic for less than a year. These findings suggest that the type of immune response and the intensity of the cytotoxic T cell attack are the most relevant determinants of the clinical presentation of the disease. Of interest, clinical

Fig. 1. Schematic representation of the pathophysiological model underlying the different manometric subtypes of achalasia. Adapted from Kahrilas and Boeckstaens [16].

practice and some reports show that peristalsis returns to some extent after treatment in patients with type II [18]. In the small intestine, chronic obstruction inhibits motility most likely by loss of interstitial cells of Cajal [19], a phenomenon that is reversible given that neurons are still present. One might speculate that return of peristalsis in these type II achalasics indicates that some neurons are still present, and regain normal function following removal of the obstruction. With time, these neurons will further disappear, thereby giving rise to type I achalasia.

Based on the above, one could forward the hypothesis that depending on immunogenetic background, prior exposure to HSV-1 and the associated immune response, patients may alternatively present with chronic inflammation in the absence of neuronal loss (Chicago Classifi-

cation type III) or a predominantly cytotoxic immune response with progressive loss of enteric neurons (Chicago Classification types I and II). The time course of progression that may ultimately lead to aganglionosis and fibrosis in these patients depends on the intensity of the initial and sustained immune response, and localization of the inflammatory response may determine the specific manometric abnormalities (fig. 1).

Treatment

Accepting that the loss of neurons (type I and II) or imbalance in nitrergic and cholinergic innervation (type III) is immune-mediated, the ideal treatment should aim

Fig. 2. a Long-term success rates of pneumodilation (solid lines: single series of pneumodilation, dotted lines: repeated pneumodilation) [22, 26, 47]. **b** Long-term success rates of laparoscopic Heller myotomy [32–34].

to stop this process. This will only be effective if a substantial number of neurons is still present, and thus may only apply for type III and some patients with type II achalasia. In case of total loss of neurons, as in type I, neuronal or stem cell transplantation would be the ideal therapeutic approach. Unfortunately, no studies using immunosuppressants have been performed, and stem cell transplantation still requires further optimization and validation. So anno 2015, treatment is mainly restricted to reduction of the resistance at the level of the LES by ‘destruction’ of the LES.

Although botulinum toxin results in a short lasting improvement of dysphagia, its use is currently restricted to patients with significant comorbidity and a high risk to undergo either an endoscopic/surgical procedure. In some cases, it can be used to bridge the time until surgery, although botulinum toxin injection jeopardizes the dissection during laparoscopic Heller myotomy.

Thus, the 2 main treatment option routinely used today are endoscopic pneumodilation and laparoscopic Heller myotomy. Both treatments will be discussed and compared, however for a more detailed review of the available literature, the reader is referred to some other excellent reviews [1, 3, 20].

Pneumodilation

Dilation of the LES as treatment of achalasia was first described by Sir Thomas Willis in 1674 using a whale bone [4]. To date, inflatable non-compliant air-filled balloons of variable diameter (30–40 mm) are used to dilate

the LES. Under fluoroscopic or endoscopic guidance, the balloon is positioned across the LES and gradually inflated until the waist, caused by the non-relaxing LES, is flattened. Subsequent dilations are spaced over 2–4 weeks intervals based on symptom relief correlated with repeat LES pressure measurements [21, 22] or improvement in esophageal emptying [23, 24].

The success rate of pneumodilation varies enormously in literature, mainly as there is a large variety in dilation protocol used, study design, duration of follow-up and size of dilation balloons used. With respect to the latter, good to excellent symptom relief is for example achieved in 74, 86 or 90% (average follow-up of 37 months) of patients if treated with a 30, 35 or 40 mm balloon, respectively [25]. On average, one-third of patients will have recurrent symptoms and are often considered as failures. However, these patients respond excellent to re-dilation with success rates of up to 97%, even after 8 years of follow-up [26] (fig. 2a). Hence, in several large centers of expertise, re-dilation ‘on demand’ is accepted as a routine and effective treatment of achalasia. Another factor significantly affecting outcome is the duration of follow-up, especially as success rates for both pneumodilation and laparoscopic Heller myotomy decline in time. Although success rates at 1-year follow-up may be higher than 90%, a gradual decline to 44 and 57% after 6 years is observed for both graded pneumodilation and laparoscopic Heller myotomy [24]. So, all these considerations should be taken into account when success rates of different treatment options are discussed.

Esophageal perforation is the most serious complication with an overall rate of 2.0% (range 0–16%) in experienced hands of which 50% required surgery [27]. In a recent series of 16 transmural perforations, however, all cases were managed conservatively [28]. Small perforations and painful deep tears can be treated with antibiotics and total parental nutrition for days to weeks [28]. However, surgical repair through a thoracotomy is best for large, symptomatic perforations with extensive soilage of the mediastinum. Most perforations occur during the initial dilation, with difficulty in keeping the balloon in position as a potential risk factor [29]. Although other predictors for perforation have not been identified, the recent European Achalasia Trial reported more perforations, primarily in older subjects, when the first pneumodilation was performed with a 35 mm compared to a 30 mm balloon [30]. Complications of severe GERD are rare after pneumodilation, but 15–35% of patients have heartburn improving with proton pump inhibitors [25].

Laparoscopic Heller Myotomy

Since the introduction of minimal invasive surgery, the enthusiasm to perform a laparoscopic myotomy according to Heller combined with an antireflux procedure has significantly increased, especially as excellent short-term success rates approaching 100% have been reported. Laparoscopic Heller myotomy combined with partial fundoplication is a remarkably safe operation with the reported mortality of 0.1% [31]. The most common complication is perforation of the esophageal or gastric mucosa during the myotomy, which is usually recognized during the procedure and repaired immediately without any consequences. Clinical success rates are very high, that is, on average 89% (ranging from 76 to 100%) at a median follow-up of 35 months (range 8–38) [31]. It should be emphasized though that success rates drop (depending on the definition used) to 65–85% at 5-year follow-up, probably as a result of progression of the disease [32–34] (fig. 2b). Although no difference in outcome was noted between achalasia type I and II patients, type III patients seem nonetheless to respond better to Heller myotomy than to pneumodilation [15], probably because the former entails a more extensive and more proximal disruption of the esophageal muscle than the latter [35]. The influence of prior endoscopic treatment on the outcome of LM is controversial; some studies [33, 36, 37] indicated that multiple endoscopic treatments could hamper the results of surgery whereas Portale et al. [38] reported that only patients previously treated with both botulinum tox-

in injection and pneumodilation had a less favorable outcome. However, to what extent these patients are less responsive to any treatment remains unclear.

Pneumodilation vs. Laparoscopic Heller Myotomy

Objective comparison between 2 different treatment options requires large randomized comparative studies, especially as the data presented in meta-analyses are often misleading. Studies with different definitions of success are pooled, while often these definitions of success are rather subjective. Moreover, data obtained with only single dilations are used [31, 39], while it is well established that the success rate of pneumodilation is significantly increased with graded dilation. Moreover, data are misinterpreted or even incorrectly cited. In a recent meta-analysis, 17 patients were identified as lost to follow-up or discontinued the study in the pneumodilation arm of the European Achalasia Trial [39], while the original publication reveals only 10 [30]. So as long as no or different objective measures are used to score efficacy allowing objective comparison, and data are misinterpreted or incorrectly used, the conclusions presented in meta-analyses should be interpreted with care.

The single scientifically solid approach to compare different treatments is via large randomized trials. To date, the European Achalasia Trial is the only large randomized study comparing pneumodilation and laparoscopic Heller myotomy as the treatment of achalasia [30]. In this study, 201 newly diagnosed patients were randomly assigned to pneumodilation or laparoscopic Heller myotomy combined with a Dor anti-reflux procedure. The primary outcome parameter was success rate defined as an Eckardt score ≤ 3 (sum of dysphagia, regurgitation, chest pain and weight loss scores, each scored on a scale from 0 to 3). After a follow-up of 2 years, the success rates were comparable, that is, 92% for pneumodilation and 87% for laparoscopic myotomy. Similarly, no differences in secondary outcome measures, that is, barium emptying, LES pressure and quality of life, were observed. Subsequent analysis learned that irrespective of treatment arm, type II patients (96%) responded best to treatment, followed by type I (81%) while only 66% of type III patients were treated successfully [15]. When the manometric subtype was taken into consideration, treatment success of pneumodilation was significantly higher in type II achalasia compared to laparoscopic Heller myotomy. In type III patients the success rate after laparoscopic Heller myotomy was higher than after PD (86 vs. 40%); however, due to the small patient number, statistical significance was not reached. For type I achalasia, laparoscopic Heller my-

otomy and PD had similar success rates (81 vs. 85%, $p = 0.84$).

The pneumodilation protocol used in the European Achalasia Trial has been criticized and forwarded as potential bias explaining the lack of superiority of laparoscopic Heller myotomy. Retreatment of patients with recurrent symptoms was indeed only allowed in the pneumodilation and not in the laparoscopic Heller myotomy group. This decision has been based on the fact that repeated dilation is internationally accepted and most importantly widely reflects daily clinical practice [26, 40]. Moreover, it should be emphasized that the number of pneumatic dilations was limited to a maximum of 3 series of dilations, while the third and final series was allowed only if it occurred more than 2 years after the second series of dilations. Although one might argue that this protocol could favor pneumodilation especially with regard to short-term results, we recently analyzed the 5-year follow-up data, showing similar results and thus arguing against this reasoning. There was no significant difference in success rate between the 2 treatments with 84 and 82% success after 5 years for laparoscopic Heller myotomy and pneumodilation, respectively. It should be emphasized though that after a median follow-up of more than 6 years, 25% of patients treated with pneumodilation required retreatment, a figure comparable to previous studies [26]. Of these patients, only 5 were treated with a third and final dilation, indicating that patients responding to pneumodilation can be efficiently managed with repeated pneumodilation.

Another point of critique is the high perforation rate (4%). Comparison with perforation rates reported in the literature however shows that this number is at the lower end of the spectrum [31]. Although esophageal perforation is indeed a serious complication, patients were managed conservatively or surgically with an excellent outcome [28, 30]. Nevertheless, patients have to be informed properly and most importantly, the procedure should only be performed by experienced endoscopists. Also a lack of surgical experience (high mucosal perforation rate) and short extension of the myotomy toward the stomach (at least 1–1.5 cm) have been mentioned as shortcomings of the European trial. Again, the mucosal perforation rate is comparable to other series [31], while no difference in outcome is noted if the myotomy is extended to 2.5–3.0 cm [41].

Taken together, the European Achalasia Trial shows that after 5 years of follow-up, no difference in the success rate of laparoscopic Heller myotomy and pneumodilation could be detected, at least if limited re-dilation is allowed in the pneumodilation group. Hence, either treat-

ment can be proposed as initial treatment for achalasia, but patients have to be informed that pneumodilation requires retreatment in 25% of cases. Moreover, and perhaps most importantly, the choice between laparoscopic Heller myotomy and pneumodilation should be based on the expertise available in the respective center.

Peroral Endoscopic Myotomy

Peroral endoscopic myotomy (POEM) is a new elegant technique in which the endoscope is advanced in a submucosal tunnel toward the LES and a myotomy is performed. For technical details, the reader is referred to the original paper of Inoue et al. [42]. Since the first report on POEM, the discussion on the optimal treatment of achalasia received a new impulse. Although this technique is definitely elegant and technically impressive, most data published so far only report on small patient numbers with a very short follow-up, that is, up to 12 months [43]. Success rates vary between 89 and 100%, but, similar to pneumodilation and laparoscopic Heller myotomy, these figures seem to decline with longer follow-up. Werner et al. [44] indeed report a reduction of success rate to 79% after a follow-up of 2 years. More optimistic data are reported by Inoue et al. [45] with a success rate of 88.5% after 3 years of follow-up. The main problem with this new technique is however the increased risk for gastroesophageal reflux. Up to 65% of patients have esophagitis 2 months after the procedure [45], including esophagitis grade C and D. Werner et al. [44] even reports 2 new cases of Barrett's esophagus in this short (2 years) period, and 1 patient with a peptic stricture. Another concern is that the technique requires high endoscopic skills, as evidenced by the long learning curve of up to 40 procedures [46], questioning how this quota will be achieved knowing that achalasia is such a rare disease. It is therefore of concern to observe the great enthusiasm and eagerness of many endoscopists to learn this new technique, even though the efficacy and long-term complications such as GERD and fibrosis are still to be awaited. So, clearly, more attention should be given to these aspects before introducing POEM into routine clinical care and before considering it as a valuable alternative for PD or LHM. Randomized trials comparing POEM with pneumodilation or laparoscopic Heller myotomy are ongoing, hopefully guiding the clinician to choose the most optimal treatment option.

Disclosure Statement

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