Achalasia

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Achalasia is a rare motor disorder of the oesophagus, characterised by the absence of peristalsis and impaired swallow-induced relaxation. These motor abnormalities result in stasis of ingested food in the oesophagus, leading to clinical symptoms, such as dysphagia, regurgitation of food, retrosternal pain and weight loss. Although it is well demonstrated that loss of myenteric oesophageal neurons is the underlying problem, it still remains unclear why these neurons are preferentially attacked and destroyed by the immune system. This limited insight into pathophysiology explains the fact that treatment is limited to interventions aimed at reducing the pressure of the lower oesophageal sphincter. The most successful therapies are clearly pneumatic dilatation and Heller myotomy with short-term success rates of 70–90%, declining to 50–65% after more than 15 years. The challenge for the coming years will undoubtedly be to get more insight into the underlying disease mechanisms and to develop a treatment to restore function.

Key words: achalasia; Heller myotomy; pneumatic dilatation; botulinum toxin.

Dysphagia for both solids and liquids, regurgitation of undigested food, respiratory complications (nocturnal cough and aspiration), chest pain and weight loss are the main symptoms of achalasia, a rare motor disorder of the oesophagus and lower oesophageal sphincter (LOS). Since the first description of achalasia by Sir Thomas Willis in 1674, several theories on the aetiology and pathophysiology have been reported. To date, it is widely accepted that loss of peristalsis and absence of swallow-induced relaxation of the LOS are the main functional abnormalities caused by loss of the inhibitory innervation. Nevertheless, the exact mechanism causing this loss of inhibitory neurons is far from elucidated and treatment is still limited to mechanical or surgical disruption of the LOS. In this review, the current knowledge on achalasia and its treatment will be summarised.

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THE LOWER OESOPHAGEAL SPHINCTER AND SWALLOW-INDUCED RELAXATION

The junction between the oesophagus and the stomach is a specialised region, composed of the LOS and its adjacent anatomic structures, the gastric sling and the crural diaphragm. Together these structures aim to prevent reflux of gastric contents across the oesophagogastric junction (OGJ) into the oesophagus. However, with each swallow, the LOS has to relax to allow passage of ingested food into the stomach. Swallow-induced relaxation is part of primary peristalsis, a complex reflex generated by the swallowing program generator in the swallowing centre in the brain stem. It involves the activation of sensory afferents in the pharyngeal area (superior laryngeal nerve, glossopharyngeal nerves) connected to the neurons of the swallowing centre. These neurons also receive input from other areas of the central nervous system, particularly from the cerebral cortex and regional afferents from the pharyngo-oesophageal tube. Although the brain stem neurons that constitute the swallowing centre are not well understood, they are most likely located in the nucleus of the solitary tract and the adjoining reticular formation. Stimulation of the superior laryngeal nerve at high frequencies elicits a full swallowing response whereas lower frequency stimulation results in isolated small LOS relaxation. In addition to swallowing, the LOS relaxes also as part of secondary peristalsis. The pathways and brain centres involved are described in more detail elsewhere.

The motor innervation to the LOS is provided by the vagus nerve, either increasing or decreasing LOS tone by stimulation of excitatory or inhibitory motor neurons, respectively, in the myenteric plexus of the LOS. The excitatory myenteric neurons in the LOS are cholinergic in nature and act to stimulate muscarinic receptors on the smooth muscle. Inhibitory motor neurons to the LOS are abundant and receive powerful cholinergic nicotinic inputs from the vagal efferents. The inhibitory myenteric neurons innervating the LOS are nitric in nature. Both in vitro and in vivo studies in many different species have shown that LOS relaxation to electrical field stimulation, vagal nerve stimulation or swallowing are blocked by inhibitors of nitric oxide (NO) synthase or the NO/cGMP pathway. However, other neurotransmitters including ATP, vasoactive intestinal peptide (VIP) and carbon monoxide may also be involved. For example, in the opossum, electrical field stimulation induces a biphasic relaxation with a rapid initial and a slower sustained relaxation. The first phase is clearly nitric, however, the second one is mediated by an as yet unidentified neurotransmitter. Although VIP has been suggested as inhibitory neurotransmitter in the LOS, VIP antagonists or VIP antiserum did not antagonise the second phase of the relaxation, suggesting that other mediators are released. Not only in animals, but also in humans evidence has been reported illustrating the importance of NO in the LOS.

LOSS OF INHIBITORY INNERVATION IN ACHALASIA

As described above, the LOS pressure decreases upon swallowing in order to allow passage of the ingested food to the stomach. In patients with achalasia, however, manometry typically shows an incomplete relaxation of the LOS upon deglutition. In addition, oesophageal peristalsis is absent and resting tone of the LOS will often be elevated. The loss of the nitric neurons results in the absence of relaxation of the LOS in response to various stimuli both in vitro and in vivo. Muscle strips taken from
the LOS of patients with achalasia fail to relax in response to electrical field stimulation.\textsuperscript{21,22} In addition, infusion of cholecystokinin, known to relax the LOS in healthy volunteers, contracts the LOS in patients with achalasia\textsuperscript{23} and LOS relaxation to oesophageal distension is reduced.\textsuperscript{24} Finally, gastric distension fails to induce transient lower oesophageal sphincter relaxations in achalasics,\textsuperscript{25} further illustrating the absence of inhibitory innervation to the LOS.

Although achalasia is the best characterised oesophageal motor disorder, its pathogenesis is still not fully elucidated.\textsuperscript{26} Histological examination reveals a significant decrease in the number of myenteric neurons, especially inhibitory NO releasing neurons in the distal oesophagus and at the level of the LOS.\textsuperscript{27} Why exactly these neurons disappear at this level and not elsewhere in the gastrointestinal tract remains unclear. Detailed examination of resection specimens shows infiltration of myenteric ganglia with CD3/CD8 positive lymphocytes expressing activation markers.\textsuperscript{28,29} In addition, IgM antibodies and evidence of complement activation were shown within myenteric ganglia.\textsuperscript{30} Finally, antibodies against myenteric neurons were repeatedly shown in serum of achalasia patients,\textsuperscript{31,32} especially in patients with a specific HLA genotype, namely those carrying the DQA1*0103 and DQB1*0603 alleles.\textsuperscript{33} These findings all point towards an auto-immune origin of the myenteric ganglionitis. Other investigators, however, have also demonstrated antineuronal antibodies in serum from GORD patients, suggesting that the antineuronal antibodies are generated in response to tissue damage and thus rather represent an epiphenomenon and not a causative factor.\textsuperscript{32} Recently, Bruley des Varannes and co-workers\textsuperscript{34} suggested that a neurotoxic factor present in serum may be involved. Indeed, whereas only 12\% of the sera studied were found to contain antineuronal antibodies, incubation of gastric tissue with serum from achalasics altered the chemical coding of myenteric neurons with a significant decrease in NOS positive neurons and an increase in cholinergic neurons. Interestingly, an increase in IL-8 levels in the sera of achalasia patients compared to controls was detected suggesting that circulating cytokines, i.e. IL-8 may be involved. Although these findings are all very interesting, it still remains obscure why only neurons in the oesophagus and LOS are destroyed. Furthermore, the exact stimulus initiating this immune response or the antigen targeted remain, however, to be identified. The fact that mainly the oesophagus and LOS are affected has led to the hypothesis that neurotropic viruses, especially viruses with a predilection for squamous epithelium,\textsuperscript{35} may be involved. Data from studies focussing on the presence of viral antibodies in the serum of patients or viral DNA in oesophageal tissue showed rather conflicting results.\textsuperscript{30,36–38} On the other hand, mononuclear cells isolated from the LOS from achalasia patients showed a higher proliferative index and released more interferon gamma in response to HSV-1, suggesting a causal role for a subpopulation of cytotoxic lymphocytes activated by HSV-1 antigens or antigens on neurons similar to HSV-1.

**Epidemiology and Diagnosis**

Achalasia is a rare disorder with an estimated prevalence of 0.5–1 per 100 000 per year without a clear age predilection.\textsuperscript{20} In children, it is part of the Triple A syndrome, characterised by achalasia, alacrima and adrenocorticotropic hormone resistant adrenal insufficiency, and has been suggested to be part of Alport’s syndrome in some patients. Recent observations also suggest that achalasia is more frequent in Down’s syndrome,\textsuperscript{39} and may even be related to previous trauma.\textsuperscript{40} In a retrospective study, Shah et al\textsuperscript{40} observed that significantly more patients with achalasia had a history
of antecedent trauma. All cases of non-operative trauma occurred in motor vehicle accidents. Cases of operative trauma included mainly coronary artery bypass surgery, bariatric surgery and fundoplication. The authors suggest that the increased risk to develop achalasia most likely results from neuropathic dysfunction due to vagus nerve damage. Besides the predominantly idiopathic achalasia, Chagasic achalasia may lead to a similar clinical picture. This infectious disease is endemic in South-America as a consequence of an infection with the parasite *Trypanosoma cruzi*.

Pseudoachalasia is a clinical syndrome similar to achalasia. Approximately 2–4% of patients suspected of achalasia suffer from pseudoachalasia. In general, patients with pseudoachalasia are older and have a shorter history of dysphagia and weight loss. The most common cause of pseudoachalasia is a malignancy infiltrating the gastro-oesophageal junction. In most cases a gastric adenocarcinoma is damaging the myenteric plexus, but bronchogenic carcinoma, lymphoma and pancreatic carcinoma as cause of pseudoachalasia have been described. Only a few cases with benign reversible causes of pseudoachalasia such as a leiomyoma have been reported. Because achalasia and pseudoachalasia can have a similar clinical presentation, pseudoachalasia can be easily misdiagnosed.

The most frequently occurring symptoms of achalasia are dysphagia for both solids and liquids, regurgitation of undigested food, respiratory complications (nocturnal cough and aspiration), chest pain and weight loss. The first diagnostic step is to rule out anatomical lesions using endoscopy or radiology. In early stages both endoscopy and radiology may be completely normal. In advanced cases, endoscopy may reveal a dilated oesophagus with retained food and some increased resistance at the gastro-oesophageal junction. Radiological examination may show a typical 'bird-beak' image at the junction, with a dilated oesophageal body, sometimes with an air-fluid level and absence of an intragastric air bubble. Endoscopy is diagnostic in about one third and radiology in about two thirds of the patients; diagnostic certainty is provided by manometry in over 90% of cases. Manometry typically shows an aperistaltic oesophageal body, sometimes with elevated intra-oesophageal pressure due to stasis of food and saliva, and incomplete relaxation of the lower oesophageal sphincter upon deglutition (Figure 1). In addition, resting tone of the lower oesophageal sphincter will often be elevated. Deglutition may trigger simultaneous pressure waves of low amplitude and similar morphology in all channels in the oesophageal body, which are so-called common cavity waves. When pressure waves have a high amplitude and different morphology, indicating active contraction of the oesophageal body, it is called vigorous achalasia.

*Figure 1.* Schematic representation of a manometric tracing from a control subject and a patient with achalasia.
Although the above-mentioned symptoms may seem rather obvious and diagnostic
evaluation has certainly improved, there is still a considerable delay between the onset
of symptoms and the diagnosis. According to Eckardt et al., patients on average
report symptoms of dysphagia during approximately 5 years before the diagnosis is
finally made. Interestingly, the frequent delay in the diagnosis is not due to an atypical
clinical presentation of the disease, but rather to misinterpretation of typical findings
by the physician consulted. Therefore, clinicians should be more alert for this diagnosis
in patients presenting with dysphagia. Especially differentiation between pseudoachalasia
and idiopathic achalasia is clinically of crucial importance and requires meticulous
endoscopic inspection, endoscopic ultrasound examination or CT scanning to exclude
an infiltrating malignancy. Certainly in case of rapidly progressing dysphagia, significant
weight loss and older age, this diagnosis should be suspected.

TREATMENT

The treatment of achalasia is aimed at improving bolus transport across the LOS
by reducing the pressure at the LOS. At present, treatment options in achalasia are
pharmacotherapy, pneumatic dilatation, surgery or injection of botulinum toxin. For
a detailed overview, the reader is referred to excellent reviews on this matter.  

Pharmacological therapy

Reduction in the LOS pressure can be achieved by smooth muscle relaxants. Nitrates,
acting by release of NO or NO related molecules, and calcium channel blockers, acting
by reducing intracellular calcium, can indeed reduce LOS pressure in patients with
achalasia. When these agents are taken 30–60 min before the meal, oesophageal emp-
tying could theoretically improve. The results published, however, are rather scarce
and show only variable results with initial improvement ranging between 50% and
90%. The effect, however, is transient due to tolerance and is accompanied by
side effects such as hypotension, headache and peripheral oedema. Although the effect
of isosorbide dinitrate is faster in onset and is more intense than that of nifedipine, the
side effects are more pronounced. Especially as the clinical benefit of this approach is
rather limited, there is hardly any place for these drugs in the clinical management of
achalasia. The same holds good for sildenafil, a phosphodiesterase inhibitor that
reduces the breakdown of cyclic GMP, the second messenger mediating NO induced
relaxation.

Endoscopic injection of botulinum neurotoxin

Botulinum neurotoxin (BoTx), produced by Clostridium botulinum, exists in several
isoforms, from A to G, of which A and B are currently used in clinical practice. Initially, BoTx was introduced to treat spastic disorders of striated musculature. How-
ever, in the last few decades, it became clear that the toxin can also be used to reduce
smooth muscle tone in the gastrointestinal tract, and as such BoTx was studied in
1994 as possible treatment of achalasia.

The toxin consists of two heavy chains and one light chain. The latter degrades
intracellular proteins involved in the exocytosis of vesicles containing the neurotrans-
mmitter acetylcholine. The mechanism of action thus consists of a temporary blockade
of release of acetylcholine from excitatory motor neurons at the level of the LOS. In
addition, BoTx injection results in a limited degeneration of the nerve endings, an effect which is, however, short lasting as nerve endings will regenerate after a few months. BoTx A is commercially available as Botox® or Dysport® (3–5 times less potent). These products are provided as a lyophilised powder and should be stored below –5 °C. Botox® is most commonly used and is available in vials of 100 IU per vial (IU = mouse LD 50). A total dose of 80–100 IU Botox (or 250 IU Dysport) is endoscopically injected in the LOS using a sclerotherapy needle and is divided into four gifts, one in each quadrant. Increasing the dose to 200 IU does not improve success rate, whereas prolongation of the therapeutic success has been reported by injection of 100 IU twice, 1 month apart.58 Several techniques, including intramuscular injection under endosonographic guidance, have been explored to improve the clinical response. No differences in clinical response were observed, suggesting that the toxin most likely spreads by diffusion into the surrounding tissue.

Injection of botulinum toxin significantly reduces LOS pressure, improves oesophageal emptying and leads to clinical improvement. Unfortunately, these effects are only short lasting and decline in time; success rates drop from 80–90% after 1 month, to 60–70% after 6 months and to only 53–54% after 1 year.53–55 By consequence, treatment has to be repeated, on average every 6–12 months, although one study reports significant improvement with a relapse rate of only 19% after 1 year when 100 IU of BoTx are injected twice 1 month apart. Predictors of good clinical response are age (>50) and vigorous achalasia. Based on these data, treatment of achalasia with BoTx should be preferentially reserved for patients with significant co-morbidity excluding conventional treatment with surgical myotomy or pneumatic dilatation, or for patients on a waiting list for surgery.

Endoscopic pneumatic dilatation

Pneumatic dilatation aims at disruption of the LOS by forceful dilatation using an air-filled balloon. To date, the most commonly used balloon is the Rigiflex balloon (Microvasive®), which is available in three sizes (30, 35 and 40 mm diameter). Briefly, the balloon is introduced over an endoscopically introduced guide wire and positioned across the LOS. After confirmation of the correct position, either by fluoroscopy or endoscopy, the balloon is inflated. Although this technique has been introduced many years ago and is currently widely accepted, there is no real consensus on the distension protocol. Some investigators only perform one dilatation,59 others use a graded dilatation protocol starting with 30 mm followed by 35 or even 40 mm balloon dilatation in subsequent sessions.48,60,61 Similarly, the duration of dilatation and the intraballoon pressure applied vary tremendously. Nevertheless, graded dilatation with a Rigiflex balloon is more effective than a single dilatation. For example, 3 year success rates for a single 30 mm balloon dilatation, two dilatations with a 30 mm followed by a 35 mm balloon or three dilatations (30, 35 and 40 mm balloon) are 37, 76 and 88%, respectively.62 The need for further dilatation is determined by the persistence of complaints assessed approximately 4 weeks after treatment. In contrast, Eckardt et al, using a different type of dilatation balloon (Browne–McHardy dilator, 40 mm diameter), did not find a significant improvement of repeated dilatation in patients not responding to a single treatment session,59 and therefore suggest to refer these patients to the surgeon.

Irrespective of the protocol used, a large proportion of patients will relapse, mainly during the first year after treatment.60,61 Risk factors for relapse are mainly young age (<40 years), male sex, single dilatation with a 30 mm balloon, and a post-treatment
LOS pressure above 10 mmHg\(^{59,61}\) (Table 1). In case of relapse, patients can be retreated with pneumatic dilatation; however, it remains a matter of debate how often patients can be re-dilated before the patient should be referred to the surgeon. Recently, Zerbib et al\(^{48}\) presented data indicating that those patients responding to the first treatment can be managed with repeated dilatation on a long-term basis with excellent results (\(>90\%\) remission). In the Academic Medical Centre of Amsterdam, patients were also treated with unlimited re-dilatation\(^{60}\) until the recent introduction of laparoscopic Heller myotomy. To date, however, with the introduction of laparoscopic Heller myotomy, patients relapsing after 4–5 dilatations, especially young patients, are now referred to the surgeon.

Whether or not a patient should be offered pneumatic dilatation undoubtedly depends on the expected success rate. On average, the overall clinical response varies between 70% and 90% during the first 5 years or so.\(^{63}\) As mentioned above, age is an important determinant of clinical success. Eckardt et al\(^{59}\) demonstrate a 5-year remission rate of 16% for patients younger than 40 years, compared to 58% for those older than 40 years. Similarly, Farhoomand et al\(^{62}\) report that 88% of patients that relapse within 3 months after dilatation with a 30 mm balloon are younger than 45 years. Therefore, younger male patients most likely should be offered an alternative treatment, i.e. laparoscopic Heller myotomy, although age related data for this treatment are presently lacking.

Another important issue to consider is the fact that most data on clinical outcome involve relatively short periods of follow-up, on average 1–2 years. Therefore, we decided to retrospectively analyse the success rate in a cohort of patients with long-standing achalasia.\(^{60}\) We selected 81 patients who were treated more than 5 years ago, with a mean follow-up of 12 years. Patients had been treated with graded pneumatic dilatation and re-dilated unlimited with recurrence of symptoms. One series of graded dilatation was sufficient in only 13%, the rest of the patients needed re-treatment, on average after 2.3 years. In other words, one third of patients were retreated within 2 years. Interestingly, the overall therapeutic success was only 50%, with a clear time-related decline in success rate. Patients treated 5–9 years ago had an excellent to good response in 60% of cases, declining to 50% in patients treated 10–14 years ago and to 40% in the group treated \(>15\) years ago.\(^{60}\) Similarly, Karamanolis et al\(^{64}\) reported a success rate of 51% in 35 patients treated with repeated pneumatic dilatation for more than 15 years. In contrast, Zerbib et al\(^{48}\) recently reported that those patients responding to pneumatic dilatation can be managed successfully with 97% and 93% probability of being in remission after repeated treatment at 5 and 10 years, respectively.

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<th>Table 1. Pneumatic dilatation: predictors of therapeutic failure.</th>
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<td><strong>Related to patient</strong></td>
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<td>- Younger age (&lt;40–45 years)</td>
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<td>- Male sex</td>
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<td>- Wide oesophagus</td>
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<tr>
<td><strong>Related to procedure</strong></td>
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<tr>
<td>- Single dilatation</td>
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<td>- Small size balloon (30 mm)</td>
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<td>- LES pressure &gt; 10 mmHg post-treatment</td>
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<td>- Poor oesophageal emptying post-treatment</td>
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In contrast to endoscopic injection of BoTx, pneumatic dilatation can be accompanied by serious complications; in particular, oesophageal perforation. The risk of perforation varies between 1% and 3%, and depends on the experience of the endoscopist, the presence of high distal oesophageal contraction amplitudes, and is greatest on the initial dilatation.\(^{65,66}\) In case of perforation, early diagnosis is essential. Extreme pain when the patient drinks some water is very much indicative of a perforation and urges radiological confirmation. When the perforation is diagnosed immediately, this complication can be managed conservatively with nothing by mouth and antibiotics. Another early complication involves aspiration of intra-oesophageal contents, although good preparation of the patient (2–3 days on a fluid diet) can greatly reduce this risk. The most important late complication is gastro-oesophageal reflux occurring in 10–20%.\(^{63}\)

**Surgery**

Reduction of LOS pressure and improvement of transport across the oesophagogastric junction can also be obtained by surgical cleavage of the LOS. Before the introduction of minimal invasive surgery, an abdominal or a thoracic incision was performed to perform this procedure. Although success rates were reported to be high (80–90%),\(^ {63}\) surgery was accompanied by a high postoperative morbidity, making this treatment modality less attractive. Recently, Csendes et al\(^ {67}\) reported on the very late results of myotomy in a cohort of 67 patients. These patients were studied in a prospective manner and subdivided into three subgroups according to the duration of follow-up. Similar to pneumatic dilatation, the success rate decreased significantly from 93% to 65% when patients were treated more than 20 years before. Mainly reflux was the underlying cause of failure.

Since the first reports on laparoscopic Heller myotomy in 1991,\(^ {68}\) this approach, mostly combined with an anti-reflux procedure, is becoming increasingly popular, especially as morbidity is low, hospitalisation is short and short-term results are comparable to conventional Heller myotomy.\(^ {69}\) Short-term follow-up studies indeed report success rates of 90–94%.\(^ {70–73}\) In their first 100 consecutive patients, Zaninotto et al\(^ {74}\) report a median operative duration of 150 min, with a conversion rate to conventional surgery in 6%. Dysphagia or chest pain persisted in 7% of patients. Seven of these eight failures were treated with multiple pneumatic dilatations, successful in six. Importantly, patients who failed on pneumatic dilatation or BoTx treatment can be successfully treated by laparoscopic myotomy. It should be emphasised though that BoTx injection significantly hampers the dissection of the submucosal plane in half of the cases, leading to mucosal laceration in 13%.\(^ {75}\) Although these mucosal lacerations are repaired laparoscopically and patients recover without sequelae, these data clearly indicate that previous BoTx injection is preferably avoided. Recently, Portale et al\(^ {76}\) evaluated the effect of previous endoscopic treatment (BoTx or pneumatic dilatation) on the long-term outcome of laparoscopic Heller–Dor myotomy. Of 248 patients, 19 were previously treated with pneumatic dilatations and 26 had BoTx injections. Success rate after 5 years was 94% in patients who underwent pneumatic dilatation, but only 75% in those who were initially treated with BoTx. Thus, BoTx injection not only makes surgery technically more difficult, but more importantly, it also seems to negatively affect long-term results.

Although short-term results of laparoscopic Heller myotomy are excellent, it remains to be awaited whether the long-term results are as favourable. Recently, Costantini et al\(^ {77}\) reported 6-year follow-up data of 71 consecutive patients. During
this follow-up period, 13 patients had recurrence of symptoms, half of them during the first year. The most frequent cause of failure was incomplete myotomy; in particular, at the gastric side. All patients were successfully treated with complementary pneumatic dilatation. Overall, 82% of the patients were satisfied with the treatment and were able to eat normally. Gastro-oesophageal reflux, i.e. abnormal pHmetry or on PPI treatment, was present in 12.7%.

**Surgery or pneumatic dilatation?**

Ideally, the choice between two treatment options should be based on prospective randomised comparative studies. Unfortunately, these data are very scarce. Only Csendes et al\(^{78,79}\) performed a randomised prospective study involving 81 patients comparing open Heller myotomy with pneumatic dilatation. After a median follow-up of approximately 5 years, 65% of patients treated with pneumatic dilatation reported good control of symptoms compared to 95% of patients who underwent surgery. It should be emphasised though that the dilatation protocol used in this study has been criticised, possibly explaining the difference in outcome. Nevertheless, large reviews comparing the outcome of surgical and endoscopic treatment indeed suggest that patients treated surgically have a lower risk of subsequent intervention and have a better symptom control.\(^{63,80}\) The criteria used to define success vary, however, enormously making comparison rather impossible. Studies performed in one centre using a single scoring system indeed failed to show a difference in outcome, both for short- and long-term follow-up.\(^{61,81}\)

Before the introduction of laparoscopic surgery, most centres preferred pneumatic dilatation as treatment of choice. This choice was mainly based on the fact that open Heller myotomy is accompanied by a significant postoperative morbidity and requires several days of hospitalisation. Recently, however, the situation has changed enormously in favour of surgery as most procedures are performed via the laparoscopic approach. So far, only one small randomised study has prospectively compared laparoscopic Heller myotomy (\(n = 14\)) with pneumatic dilatation (\(n = 16\)), showing no difference in success rate.\(^{68}\) Clearly, a larger study with acceptable statistical power is required to evaluate which of these techniques is superior to the other, or to determine which therapy should be reserved for a certain subgroup of patients. To this end, a large European prospective randomised study is ongoing aiming to include 200 patients.

**Future therapies**

Unfortunately, none of the therapies described in the previous paragraphs corrects the underlying abnormality. Assuming that the enteric neurons innervating the oesophagus and the LOS disappear due to an auto-immune mechanism, one possible alternative therapeutic approach would be to consider immune modulatory drugs. However, at the time of diagnosis the number of neurons has already decreased to a critical level leading to significant dysfunction and symptoms. In fact, although this approach may theoretically prevent further disappearance of neurons, it will always come too late and will fail to restore function. Recent studies in mice suggest that transplantation of neuronal stem cells may be a new therapeutic option. Indeed, neuronal stem cells injected in the pylorus survived and even expressed NO synthase.\(^{82}\) The advantage of such a technique would be that not only sphincter function will be restored, but perhaps even peristalsis. Clearly, a lot of research remains to be done further exploring this approach.
INCREASED RISK OF OESOPHAGEAL CARCINOMA?

In the Amsterdam cohort of patients, \(^\text{60}\) 32 of the 249 patients had deceased, \(6\) (19\%) of them died of oesophageal carcinoma. Three had a squamous cell carcinoma, two had an adenocarcinoma while the cause of cancer was unknown in the remaining patients. Similar data were reported previously \(^\text{83}\) confirming that achalasia is a risk factor for oesophageal carcinoma. Earlier reports have indeed indicated that the incidence of oesophageal carcinoma in achalasia patients is up to 33 times higher \(^\text{83–85}\) compared to the general population. Both squamous cell carcinoma and adenocarcinoma \(^\text{23}\) are associated with achalasia. Squamous cell carcinoma is thought to develop as a consequence of chronic inflammation of the squamous epithelium caused by retention and stasis of food and secretions. \(^\text{83,84,86}\) In contrast, adenocarcinoma is thought to develop in Barrett’s oesophagus due to excessive gastro-oesophageal reflux following complete abolishment of LOS pressure. \(^\text{87,88}\) In our study, the time interval between the first treatment for achalasia and death was 10 years. Other studies have reported an interval of 5–17 years \(^\text{67}\) or 17–28 years \(^\text{89}\) between the diagnosis and treatment of achalasia and carcinoma. Oesophageal cancer is often detected at a late stage in achalasia patients resulting in a poor prognosis, \(^\text{83,84,86}\) especially as patients present rather late to the physician for a number of reasons. \(^\text{84}\) Most patients are used to have some residual degree of dysphagia even after treatment unmasking the increase in dysphagia caused by a carcinoma. Furthermore, these patients become adapted to changes in swallow patterns and seek medical care at a much later stage. Finally, as the oesophagus is often dilated, a malignant lesion must reach a substantial size before causing additional dysphagia or other symptoms, such as necrosis or bleeding. Whether the increased risk and the poor prognosis of oesophagus carcinoma in achalasia patients justify a need for screening remains a matter of debate.

SUMMARY

Although achalasia is a well defined and intensely studied disorder, the insight into the underlying pathogenesis is still very limited. Moreover, although the ultimate goal of treatment should be restoration of oesophageal peristalsis and LOS relaxation, gastroenterologists and surgeons continue to destroy the LOS. Heller myotomy and pneumatic dilatation are successful in 70–90\% of patients in the first years, but the success rate slowly declines with time. Which of these treatments is the therapy of choice for achalasia to particular subgroups of patients remains to be investigated. Clearly, more research is required to develop therapies that restore function in order to treat patients more efficiently.

<table>
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<tr>
<td>Achalasia is a rare motor disorder with an incidence of 1 per 100,000 per year.</td>
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<td>Manometry is the most sensitive technique to diagnose achalasia.</td>
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<td>Fast onset of dysphagia, extreme weight loss and older age should alert the clinician to exclude pseudoachalasia using CT scan or endoscopic ultrasound.</td>
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<td>Endoscopic injection of BoTx is a safe technique but its effect is only short lasting (6 months).</td>
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Pneumatic dilatation has a success rate of approximately 70%, further declining with time.

Laparoscopic Heller myotomy is becoming increasingly popular as treatment of achalasia.

**Research agenda**

- The triggers leading to destruction of the oesophageal and LOS neurons and antigens targeted by the immune system remain to be identified.
- A large randomised prospective trial comparing laparoscopic myotomy and pneumatic dilatation is warranted.
- Long-term outcome of laparoscopic surgery needs to be established.
- Animal studies should continue to explore the potential of stem cell transplantation to restore oesophageal and LOS function.
- Detailed studies are required to determine whether the risk of oesophageal cancer is increased in patients with achalasia, and screening is required.

**REFERENCES**


