PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Presentation, Diagnosis, and Management of Achalasia

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The literal definition of achalasia is "failure of a ring muscle to relax." Despite this general definition, the term has been adopted to specifically describe esophageal achalasia, an entity also sometimes named cardiospasm or esophageal aperistalsis. Achalasia is characterized by impaired lower esophageal sphincter (LES) relaxation and aperistalsis in the distal esophagus. However, it is important to note that aperistalsis, also termed absent peristalsis, means that there is no progressively sequenced esophageal contraction; it does not imply the complete absence of intraluminal pressure. Consequently, absent peristalsis does not exclude the occurrence of spastic contractions or panesophageal pressurization. In fact, understanding these patterns of pressurization is the key to understanding the current classification scheme for achalasia and management of this disease.[1]

Pathophysiology

Achalasia is associated with functional loss of myenteric plexus ganglion cells in the distal esophagus and LES.[2] Although the ultimate initiating factor for the neuronal degeneration is uncertain, it is an autoimmune process that is likely triggered by an indolent viral infection (herpes, measles) in conjunction with a genetically susceptible host.[3] The inflammatory reaction is associated with a T-cell lymphocyte infiltrate that leads to a slow destruction of ganglion cells. The distribution and end result of this plexitis are variable and may be modified by the host response or the etiologic stimulus. Data to support a genetic basis come from studies in twins and siblings as well as its association with genetic diseases such as Allgrove syndrome, Down's syndrome, and Parkinson disease.[4–6] Alternatively, achalasia can be one of several manifestations of the widespread myenteric plexus destruction found in Chagas disease, a late consequence of infection with the parasite *Trypanosoma cruzi*.[7]

The consequences of the myenteric plexus inflammation leading to achalasia are degeneration and dysfunction of inhibitory postganglionic neurons in the distal esophagus, including the LES. These neurons use nitric oxide and vasoactive intestinal peptide as neurotransmitters, and their dysfunction results in an imbalance between excitatory and inhibitory control of the sphincter and adjacent esophagus. Unopposed cholinergic stimulation can result in impairment of LES relaxation, hypercontractility of the distal esophagus including the LES, and rapidly propagated contractions in the distal esophagus. However, there is variable expression of these abnormalities among individuals, with specific features dominating in some and not manifest in others; only impaired deglutitive LES relaxation is universally required as a defining feature of achalasia.

Many of the contractile abnormalities observed in achalasia can be explained by the imbalance between the excitatory and inhibitory innervation of the distal esophagus. Key functions of the inhibitory ganglionic neurons are to facilitate LES relaxation and to sequence the peristaltic contraction in the distal esophagus.[8] Without them, the sphincter cannot negate its myogenic tone and may actually contract after swallows because of stimulation by unopposed cholinergic neurons. This is even the case during transient LES relaxations, elegantly demonstrating the selective physiological defect in achalasia. Achalasia can still trigger transient LES relaxations in response to gastric distention and still exhibit the ensuing complex motor pattern of crural diaphragm inhibition, esophageal shortening, and an esophageal after-contraction, but the LES paroxysmally contracts rather than relaxes.[9]

Adjacent to the LES, the distal esophagus has no myogenic tone and is flaccid in the absence of neuronal stimulation. However, inhibitory ganglionic cells are normally dominant in this area, delaying the swallow-initiated peristaltic contraction such that it occurs only after several seconds of LES relaxation. In the absence of that inhibitory innervation, a pattern of premature contraction occurs, not allowing sufficient time for esophageal emptying and trapping the bolus in the distal esophagus. On X-ray, the trapped bolus sometimes assumes a "corkscrew" or "rosary bead" configuration, consistent with the textbook description of distal esophageal spasm. One proposed model of disease progression in achalasia is that the neuronal degeneration at the ganglionic level then progresses to involve the cholinergic neurons, eventually leading to the classic pattern of absent peristalsis. However, it is also proposed that the subsequent loss of contractility may result from progressive esophageal dilatation that occurs as a consequence of chronic functional obstruction. That model of disease progression hypothesizes that panesophageal pressurization represents an early stage of achalasia when the primary abnormality of outflow obstruction is associated with preserved esophageal short-

Abbreviations used in this paper: **EGJ, esophagogastric junction; EPT, esophageal pressure topography; HRM, high-resolution manometry; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; POEM, per oral endoscopic myotomy.**

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ening, upper esophageal sphincter contraction, and some circular muscle contraction.[10,11] Absent peristalsis would then represent a later stage of the disease that is attributable to more widespread neuronal degeneration or long-term obstruction. By either pathway, if left untreated, achalasia can progress to severe esophageal dilatation, an undesirable and unnecessary outcome potentially associated with severe morbidity.

Clinical Presentation

Achalasia occurs with an annual incidence of 1 in 100,000 and prevalence of 10 in 100,000.[12] There is no racial or gender preference, and although the onset of symptoms can occur at any age, they most commonly manifest between the ages of 25 and 60 years. The primary presenting symptom is dysphagia for both solids and liquids that is constant rather than intermittent. Patients learn to adapt to the condition and often describe themselves as "slow eaters." Ironically, weight loss is unusual until the end-stage of the disease. Dysphagia in achalasia differs from that attributable to mechanical causes, because it is often accompanied by regurgitation of undigested food and saliva minutes or even hours after the meal. The regurgitation can occur at night, and patients sometimes compensate by elevating their head or even sitting upright to sleep. Regurgitation in achalasia can be distinguished from reflux-related regurgitation by its bland taste, which is devoid of gastric acid or bile. However, patients sometimes also experience chest pain or heartburn, making this distinction difficult.[13] This observation has led to the recommendation that an esophageal manometry study be obtained in the evaluation of refractory reflux to rule out achalasia before contemplating antireflux surgery or accepting a diagnosis of functional heartburn.[14] It is also important to note that the etiology of chest pain in achalasia is less clear than is that of dysphagia or regurgitation, and its response to therapy is usually less satisfactory.

Diagnosis

The diagnosis of achalasia is contingent on demonstrating impaired LES relaxation and absent peristalsis in the absence of partial esophageal obstruction near the LES by a stricture, tumor, vascular structure, implanted device (eg, LAP-BAND, Allergan, Inc., Irvine CA), or infiltrating process.[14] Thus, the minimal requisite evaluation should include manometry to document the motor findings and appropriate imaging studies to rule out obstruction. There are many nuances to both evaluations to keep in mind. Straightforward cases are straightforward, but the increasing sophistication of diagnostic methods has led to increasing recognition of variations in the physiological manifestations of achalasia and of alternative disease processes that can mimic the disease.

With regard to esophageal manometry, a major technological evolution has occurred during the last decade wherein conventional water perfused or strain gauge systems with a polygraph and line tracing output have been replaced by high-resolution manometry (HRM) systems outputting pressure data in esophageal pressure topography (EPT). Nowhere has this evolution had more impact than in the diagnosis of achalasia. Diagnostic criteria have been tightened,[1] and relevant physiological subtypes have been identified.[10] Particularly instrumental in establishing uniform diagnostic criteria for achalasia was the development of a new metric devised for EPT to quantify esophagogastric junction (EGJ) relaxation, the integrated relaxation pressure (IRP). Measurement of the IRP uses an electronic sleeve sensor initially described by Clouse and Staino[15] and conceptually similar to a Dent sleeve that compensates for potential LES movement by tracking the sphincter within a specified zone. This avoids the artifact of pseudorelaxation (apparent sphincter relaxation caused by elevation of the sphincter above the sensor, displacing it into the stomach), which was a fatal flaw in the assessment of LES relaxation with nonsleeve conventional systems. The IRP is calculated from the electronic sleeve as the mean of 4 seconds of maximal EGJ relaxation after the pharyngeal contraction. The time scored can be continuous or noncontinuous, as when it is interrupted by a crural diaphragm contraction. The IRP provides a robust and accurate assessment of deglutitive EGJ relaxation and optimally discriminates defects of sphincter relaxation characteristic of achalasia.[16]

Before the introduction of HRM and EPT, there were no data substantiating the prognostic value of conventional manometric measures in achalasia, although there were qualitative descriptions of variants such as vigorous achalasia, achalasia with preserved peristalsis, and cases with complete or partial LES relaxation.[17,18] There were no established conventions for making these measurements. However, with the adoption of HRM with EPT, 3 distinct subtypes of achalasia were quantitatively defined by using novel EPT metrics (Figure 1).[10] Furthermore, there are now 5 publications supporting the prognostic value of these achalasia subtypes that consistently observe that (1) type II patients have the best prognosis with myotomy or pneumatic dilation, (2) the treatment response of type I patients is less robust (and reduced further as the degree of esophageal dilatation increases), and (3) type III patients have a worse prognosis, likely because the associated spasm is less likely to respond to therapies directed at the LES.[10,19–22] In addition, patients with impaired EGJ relaxation but some preserved peristalsis (Figure 2) are now recognized as a distinct entity that can be a variant phenotype of achalasia. However, EGJ outflow obstruction can also be a manifestation of other disease entities including eosinophilic esophagitis, LES hypertrophy, strictures, paraesophageal hernia, and pseudoachalasia that is due to tumor infiltration. Consequently, this finding always mandates carefully imaging (often with biopsies) the EGJ. Table 1 contrasts the defining manometric measures of achalasia in conventional and EPT terms.[1,23] Highlighted in Table 1 is the finding that threshold values for abnormal deglutitive EGJ relaxation by using the IRP are altered by the pressurization pattern in the esophageal body such that a value above 10 mm Hg is abnormal in type I patients and that panesophageal pressurization is diagnostic of type II achalasia, independent of the IRP value.[24]

The other requisite evaluation to establish a diagnosis of achalasia is of imaging studies to rule out obstruction in the region of the EGJ. In most instances, endoscopy will suffice. Endoscopy may also be helpful in determining the degree of esophageal dilatation, whether there is significant esophageal retention of food and fluid, and whether there is coexistent stasis or fungal esophagitis. A barium esophagogram may suffice in this capacity in instances that there are equivocal manometric findings or when manometry is not feasible because of severe dilatation and an inability to intubate the stomach with