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Gastroesophageal Sphincter Pressure and Histological Changes in Distal Esophagus in Patients with Achalasia of the Esophagus

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A prospective study was performed in 17 patients with achalasia of the esophagus determining the manometric characteristics of the gastroesophageal sphincter, correlating it with hisotological analysis by biopsies taken during surgery at the distal narrowed segment of the esophagus, at the location of the sphincter. The histological findings were compared to 10 control cases. Presence or absence of ganglion cells at the Auerbach's plexuses and appearance of smooth muscle fibers were evaluated. Only one case (6%) had Chagas' disease. The mean sphincter pressure was 41 mm Hg, with incomplete relaxation in all patients. Histological analysis showed a complete disappearance of ganglion cells in 94% of the cases and a decrease in the number of neurons with marked chronic inflammatory cells in one case (6%). In all control cases, the ganglion cells were normal. Smooth muscle fibers were normal on light microscopy. No relationship was found between resting gastroesophageal sphincter pressure, length and relaxation, and histological findings at the distal esophagus. These findings suggest that the denervation in the majority of cases is located in the Auerbach plexus, with complete absence of ganglion cells and, therefore, absence of postganglionic nerve fibers.

Achalasia of the esophagus is a motor disorder characterized by a significant alteration or delay of esophageal emptying, due to the presence of a hypertensive gastroesophageal sphincter with impairment or incomplete relaxation of the sphincter during swallowing and abnormal esophageal peristalsis (1–4). The genesis of this motor defect is not fully understood, but it has been postulated that it is due to an alteration in the controlling innervation of the lower esophageal sphincter and the tubular esophagus. The majority of the authors agree that there are fewer ganglion cells in the Auerbach plexus and that, in some cases, the ganglion cells are surrounded by chronic inflammatory cells (5–12). Pharmacologic studies have revealed a supersensitivity to cholinergic- (13, 14) and gastrin-stimulated responses (15). This has been explained on the basis of Cannon's law of sensitization by denervation (16). Therefore our hypothesis was that there might be a correlation between the magnitude of reduction or absence of ganglion cells and the values of sphincter pressure in these patients. The purpose of the present prospective study was to evaluate the pressure of the resting gastroesophageal sphincter and its manometric characteristics,

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correlated with histological findings in Auerbach's plexus by biopsies taken during surgery, compared to control subjects.

MATERIALS AND METHODS

Patients Studied. Seventeen consecutive cases, 11 males and 6 females with a mean age of 44 years (range 15–72) were included in this prospective study. None of them had other gastrointestinal disease. In all cases, Chagas' serological examination was performed, with negative results in 16 (94%) and a positive result in one case (6%). This patient had also cardiac involvement with Chagas' disease. In order to compare the histological findings in normal subjects, 10 autopsy cases were studied 2–3 hr after death, removing the distal esophagus in order to take the same type of biopsy as in the achalasia cases.

Diagnosis of Achalasia. All patients had intermittent dysphagia with a mean duration of 4.5 years. In all cases an upper gastrointestinal radiological examination revealed the typical findings of achalasia. In all, upper endoscopy was performed in order to exclude any other esophageal or gastric lesion.

Manometric Examination. The details of the manometric test have been published previously (2, 3). Basically, a three-lumen polyvinyl catheter (Arndorfer) with lateral orifices was employed, connected to a pneumohydraulic pump (Arndorfer) and perfused constantly with water at a rate of 0.5 ml/min. In all cases rapid and slow pull-throughs were performed several times (at least four) in each patient. Gastroesophageal sphincter length, location, and pressure and relaxation during swallowing were evaluated. End-expiratory fundic pressure was considered as a zero reference. All pressures were expressed in mm Hg. The sensors were connected to Statham transducers and manometric tracings were read in a Gilson eight-channel polygraph. The resting sphincter pressure was taken as the mean of all sphincter measurements in each case. Esophageal peristalsis and intraesophageal resting pressure were also determined.

Operative Technique and Biopsy Procedure. All cases were operated by the same surgical team, by the abdominal route. The details of the surgical procedure have been described elsewhere (3). After an esophagomyotomy of 5–6 cm was performed on the abdominal esophagus, a 15-mm-long and 3- to 4-mm-wide segment of esophageal muscle was taken from the right border of the muscular incision, always at the same level, which corresponded to the narrow distal segment of the gastroesophageal sphincter. The biopsy immediately was fixed in formalin and sent for pathological studies. The same technique was employed in the 10 autopsy control cases.

Pathological Examination. All biopsies were examined blindly by the same person (G.S.) under light microscopy. Three main staining techniques were employed: hematoxylin–eosin, argent after thrichromic staining. The presence, decrease, or absence of ganglion cells at the Auerbach plexus was noted, while the appearance of inflammatory cells and the appearance of muscle cells at the lower esophagus were also evaluated.

RESULTS

Manometric Studies. The mean resting gastroesophageal sphincter pressure was 41.2 ± 2.3 mm Hg in patients which achalasia (range 16–75 mm Hg). Our normal values fall between 10 and 25 mm Hg. The location of the sphincter was a mean distance of 44 cm from the incisor teeth. The mean length was 3.1 ± 0.4 cm. An incomplete relaxation was observed in all cases, that is, after swallowing, sphincter relaxation never reached the level of the fundic pressure. The mean relaxation of the sphincter was 55% of normal relaxation. In all 17 patients, resting intraesophageal pressure and aperistalsis in the thoracic esophagus was demonstrated together with low simultaneous waves.

Histological Analysis. In the 10 normal cases studied at autopsy, Auerbach's plexus was normal and no inflammatory cells were found (Figure 1). In the 17 cases with achalasia, all biopsies were taken at the same level involving both longitudinal and circular muscle fibers of the distal esophagus, in the narrowest segment. Both Auerbach's plexus and smooth muscle fibers were analyzed. In 16 patients (94%), a complete absence of ganglion cells was observed in the Auerbach's plexus (Figure 2). One patient (6%) had degenerative lesions and a decrease in the number of neurons, together with a marked lymphoreticular infiltration in the nervous plexuses (Figure 3). In none of the biopsies were any significant alterations of the muscle cells observed.

Relationship Between Manometric and Histological Findings. No relationship was observed between the reduction or absence of ganglion cells and the resting gastroesophageal sphincter pressure (Table 1). Patients were divided into cases with sphincter pressures above and below 25 mm Hg, which is the upper limit of our normal values, but again no relationship was found. In the only patient with Chagas' disease, the resting gastroesophageal sphincter pressure was 35 mm Hg and a complete absence of ganglion cells was noted. No relationship was found between the magnitude of sphincter relaxation, sphincter length, or intraesophageal resting pressure and the histological findings. No relationship was found between the duration of dysphagia and the manometric characteristics of the lower esophageal sphincter or the histological findings.

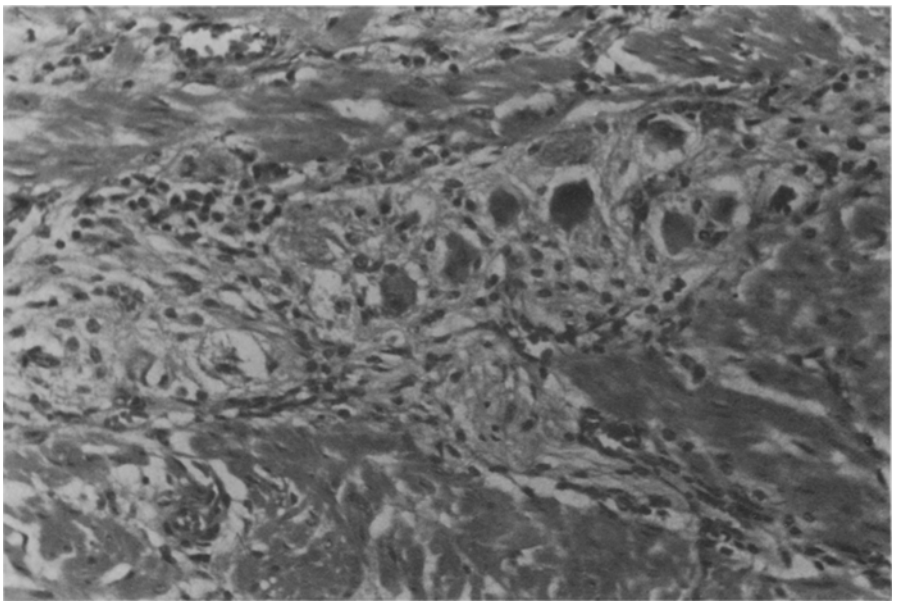

Fig 1. Normal Auerbach plexus in control cases.

DISCUSSION

The results of the present study suggest, first, that there is a complete absence of ganglion cells at the site of the gastroesophageal sphincter in 94% of the patients with achalasia and, second, that there is no relationship between the magnitude of denervation of the lower esophagus and the resting hypertensive gastroesophageal sphincter pressure in these patients.

The etiology of achalasia is unknown. Chagas' disease was responsible for this pathological alteration in only one patient (6%), similar to other reports, since Chagas' disease is prevalent in Brazilian achalasia (17). The pathological changes that occur in achalasia are seen mainly in the nervous

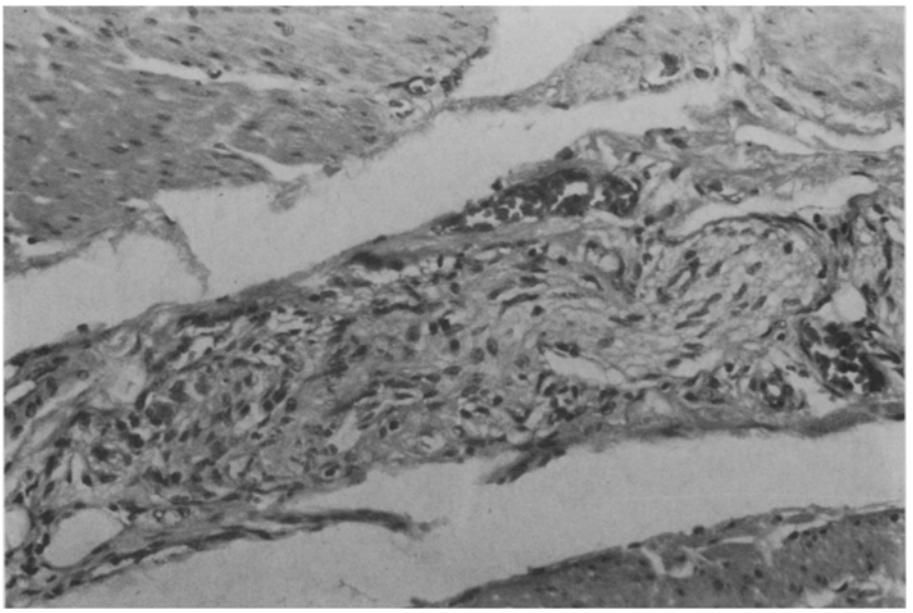

Fig 2. Absence of ganglion cells in Auerbach plexus in achalasia patients.

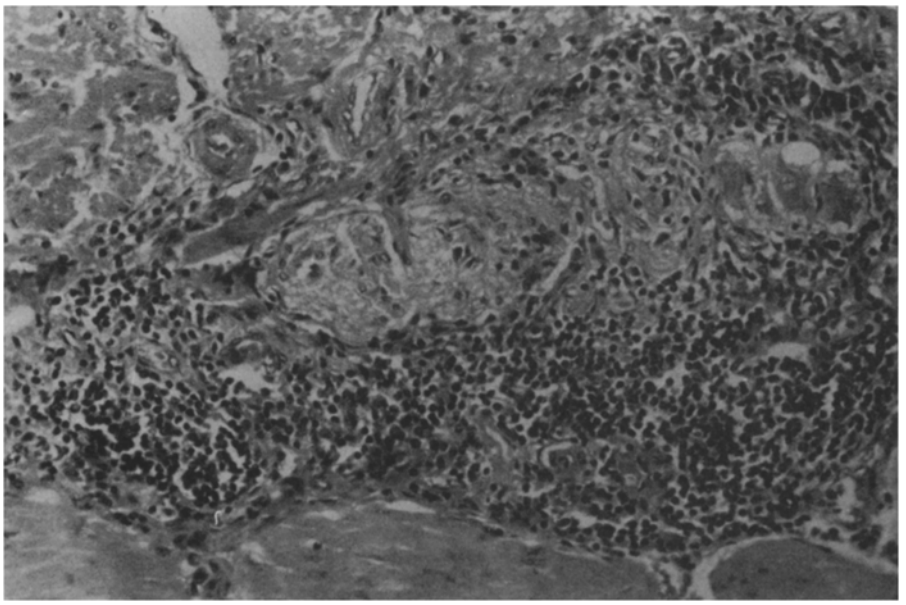

Fig 3. Auerbach plexus in a patient with a decrease of ganglion cells and marked inflammatory infiltration.

structures of the esophagus both in the intrinsic (Auerbach plexus) and extrinsic innervation (vagus nerves) (8). One of the mot controversial changes is that related to Auerbach's plexus. Most observers agree that achalasia is associated with fewer ganglion cells or a complete absence of them in the esophageal body. These ganglion cells may be surrounded by chronic inflammatory cells. However, in the area of the lower esophageal sphincter, the number of ganglion cells at the Auerbach plexuses has been reported as normal (11), reduced in number (8), or most frequently, absent (5–9).

In the present study, biopsies taken in a large number of patients showed disappearance of ganglion cells in more than 90% of the cases, with inflammatory cells present in only one patient, who showed a decrease in these neurons, in contrast to 10 control patients, in whom the nervous plexuses were normal. The classical findings of Casella et al (8) showed only a 50% decrease of ganglion cells at this level but no complete absence in any patient. Some observers have attributed the decrease of the ganglion cells to a mechanical separation of the neurons by the esophageal dilatation. This could be correct in some patients when the thoracic esophagus is examined, where the greatest dilatation is observed. However, our biopsies were taken in the narrowest segment of the esophagus without muscle thickening or edema. Our histological findings are similar to those reported by Misiewicz et al (7) and Smith (9), who found usually an absence of ganglion cells with mild chronic inflammatory infiltration. There is evidence that pathological changes also involve the extrinsic innervation of the esophagus (8), producing a wallerian type of degeneration of the axons of the vagus nerves and the plexus. However, this aspect could not be evaluated in the present study. The esophageal smooth muscle cells at the site of the lower esophageal sphincter showed no change on light microscopy in the present study, as has been reported previously (8, 19). Only some minor changes on electron

TABLE 1. RELATIONSHIP BETWEEN SPHINCTER PRESSURE AND HISTOLOGICAL ANALYSIS

Gastroesophageal sphincter pressure (mm Hg)		*Histological analysis*	
Above 25	12 cases	Absence of ganglion cells	11 cases
		Decrease of ganglion cells	1 case
Below 25	5 cases	Absence of ganglion cells	5 cases

microscopy can be detected, such as detachment of the myofilaments from the surface membrane (19).

The gastroesophageal sphincter in achalasia is hypertensive with partial or incomplete relaxation (1, 4). This has been attributed to Cannon's law of denervation (16). Also, the sphincter is highly sensitive to exogenous stimulants such as gastrin or cholinergic drugs (13, 15). We thought that there could be a relationship between the magnitude of the denervation and the values of the gastroesophageal sphincter pressure in these achalasic patients. The hypothesis was that the decrease or complete absence of ganglion cells could be correlated with the highest sphincter pressure values. Our study is the first prospective evaluation of both parameters in achalasia. However, this hypothesis was not confirmed in the present study, and no correlation was found between the manometric characteristics of the lower esophageal sphincter and the histological analysis. It is probable that other factors such as local regulatory peptides (VIP or others) could be responsible for sphincter pressure changes in the absence of innervation. We cannot account for the findings of Cohen et al (20), who reported by pharmacological analysis that the site of denervation in achalasia is preganglionic, based on the fact that the response to edrophonium chloride is preserved, postulating that postganglionic innervation is normal. The neurons in the Auerbach plexuses are completely absent in the majority of cases, and no postganglionic nerves can be found (8). Therefore there must be another explanation for these findings. In summary, our findings have confirmed that at the distal narrow segment of the esophagus in patients with achalasia, at the level of the gastroesophageal sphincter, a complete absence of ganglion cells was observed in almost 95% of the cases, and there was no relationship between the magnitude of this decrease or absence of neurons and the resting gastroesophageal hypertensive sphincter pressure.

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