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DISEASES OF THE ESOPHAGUS

Original article

Progression of diffuse esophageal spasm to achalasia: incidence and predictive factors

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SUMMARY. **The progression of certain primary esophageal motor disorders to achalasia has been documented; however, the true incidence of this decay is still elusive. This study aims to evaluate: (i) the incidence of the progression of diffuse esophageal spasm to achalasia, and (ii) predictive factors to this progression. Thirty-five patients (mean age 53 years, 80% females) with a manometric picture of diffuse esophageal spasm were followed for at least 1 year. Patients with gastroesophageal reflux disease confirmed by pH monitoring or systemic diseases that may affect esophageal motility were excluded. Esophageal manometry was repeated in all patients. Five (14%) of the patients progressed to achalasia at a mean follow-up of 2.1 (range 1–4) years. Demographic characteristics were not predictive of transition to achalasia, while dysphagia ($P = 0.005$) as the main symptom and the wave amplitude of simultaneous waves less than 50 mmHg ($P = 0.003$) were statistically significant. In conclusion, the transition of diffuse esophageal spasm to achalasia is not frequent at a 2-year follow-up. Dysphagia and simultaneous waves with low amplitude are predictive factors for this degeneration.**

KEY WORDS: **achalasia, diffuse esophageal spasm, disease progression, manometry.**

INTRODUCTION

The transition of certain primary esophageal motor disorders into achalasia is unquestionably a possible event. The change of nutcracker esophagus to achalasia[1,2] and especially diffuse esophageal spasm (DES) to achalasia[3–12] have been documented. Most studies, however, are case reports, and the true incidence of these manometric changes is still elusive.

The outcomes for the treatment of DES, either medical or surgical, is more unpredictable compared with achalasia. Furthermore, achalasia, but not DES, is a premalignant disease. Thus, the identification of patients at risk for progression into achalasia would lead to a quicker and proper therapy and follow-up.

This study aims to evaluate: (i) the incidence of the progression of DES to achalasia, and (ii) predictive factors to this progression.

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METHODS

Seventy-three patients had manometric findings of DES out of 2353 manometries performed between 2000 and 2007. These patients were recalled for a repeated manometry. Individuals were excluded from analysis in case of age >70 years ($n = 13$) because of the chance of a presbyesophagus,[13] gastroesophageal reflux disease ($n = 12$) diagnosed by endoscopy or pH monitoring, systemic diseases that may affect esophageal motility, such as diabetes or Chagas' disease ($n = 2$), or refusal to participate ($n = 11$). Thus, 35 patients (mean age 53 years, 80% females) were available to follow-up.

Symptoms

Symptoms were assessed at the time of the first endoscopy and esophageal manometry and were present in the following prevalence: chest pain (48.6%), dysphagia (42.9%), heartburn (48.8%), regurgitation (40.0%), epigastric pain (22.9%), and cough (2.9%). The mean length of symptoms was 2.21 ± 3.03 (range 3–17 months) years.

Upper digestive endoscopy

All patients underwent an upper digestive endoscopy at the time of the first manometry. Seven (20.0%) patients had a hiatal hernia, and three (8.6%) had erosive esophagitis.

Esophageal manometry

Esophageal manometry was repeated in all patients at least 1 year after the initial test. Medications that interfere with esophageal motility were discontinued 2 days before the study. The patients were studied after fasting for 6 hours, using an eight-lumen manometry catheter, continuously perfused by a pneumohydraulic capillary infusion system connected to a polygraph. Position, pressure, and length of the lower esophageal sphincter (LES) were measured using the station pull-through technique. Esophageal body function was assessed by giving 10 wet swallows of 5-mL water boluses at 30-second intervals. Amplitude and propagation of the peristaltic waves (simultaneous vs. propagating) were assessed. The data were analyzed by a commercially available software program. All tests were performed by the same examiner.

DES was defined by the presence of intermittent peristalsis with more than 20% of simultaneous contractions (velocity > 8 cm/second) with amplitude higher than 30 mmHg[13–15] (Fig. 1). Achalasia was defined by the absence of peristalsis (Fig. 2) and failure of LES relaxation (residual pressure > 8 mmHg).[16,17]

The data found in the first manometry were: LES mean basal pressure was 21.7 ± 6.2 (range 10.1–33.8) mmHg. Relaxation was normal in all patients (mean residual pressure 3.2 ± 3.4 mmHg; range 0.2–7.3). Mean esophageal body amplitude was 108.3 ± 55.3 (range 55.0–317.5) mmHg, and the mean amplitude of the simultaneous waves was 70.7 ± 38.2 (range 35.6–202.5) mmHg. Simultaneous waves were present in a mean of 44.9 ± 13.4 (30–80) % of wet swallows.

pH monitoring

All patients underwent an esophageal pH monitoring at the time of the first esophageal manometry. Acid-suppressing medications (proton pump inhibitors and H2 blocking agents) were discontinued 7 days before the study. Prokinetic agents were discontinued 3 days before the study. During the study, the patients consumed an unrestricted diet. Ambulatory pH monitoring was performed by placing a pH probe 5 cm above the upper border of the manometric determined LES.

Abnormal gastroesophageal reflux was considered if DeMeester score >14.74.[18] Tracings were manually reviewed for the presence of pseudoreflux because of food fermentation defined by a gradual decrease in pH sustained for a long period of time with gradual return to non-acid state. All patients had a normal (physiologic) gastroesophageal reflux.

Therapy

All patients underwent clinical treatment with calcium-channel blockers. Botulin toxin injection was not used in this study.

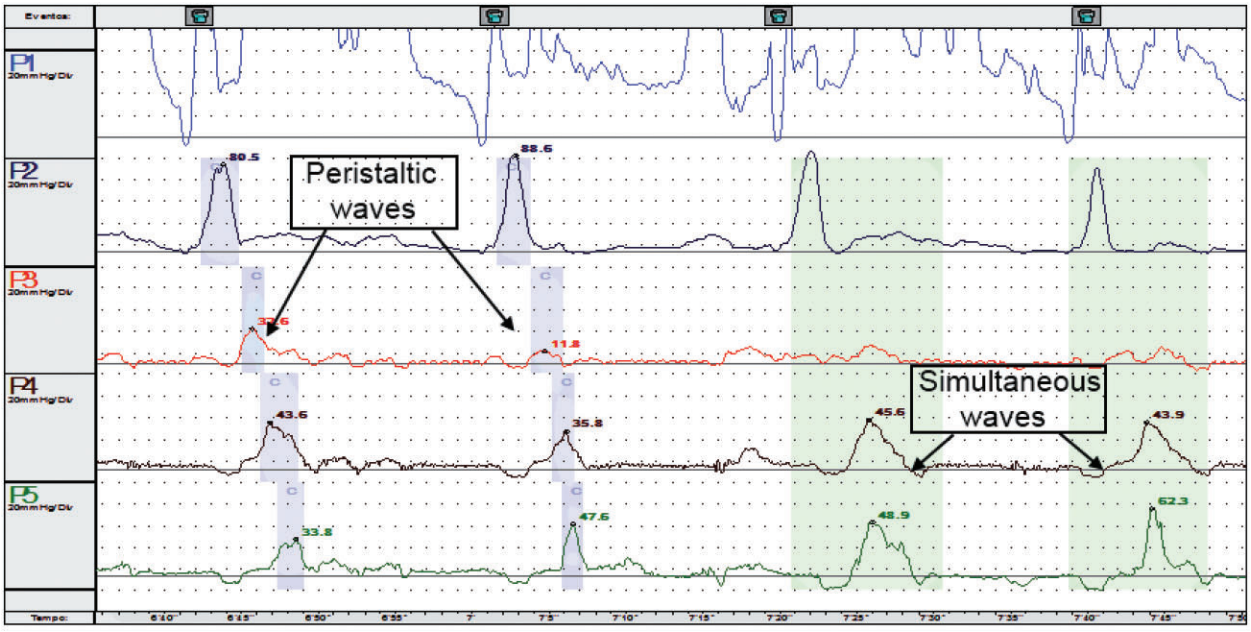

Fig. 1 First manometry – esophageal body – tracing with diffuse esophageal spasm.

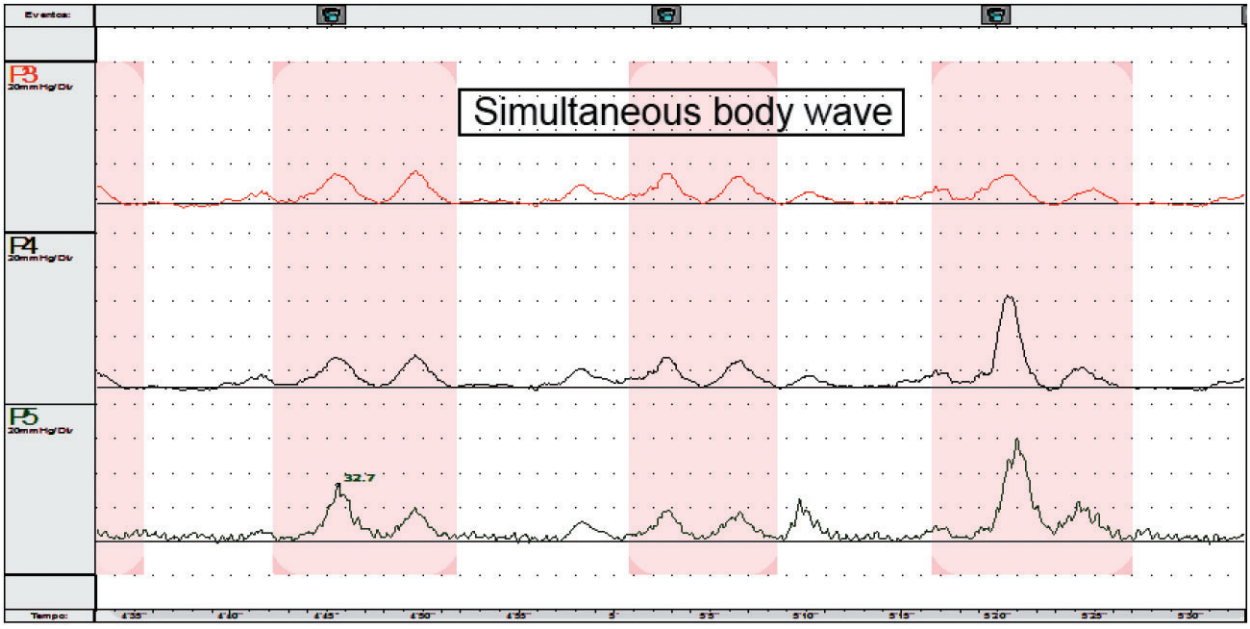

Fig. 2 Second manometry – esophageal body – tracing with achalasia.

Ethics

The study was approved by the Federal University of São Paulo institutional review board. Informed consent was obtained from all individuals.

Statistics

Wilcoxon test, Mann–Whitney test, logistic regression, and the equality of two proportions test were used when appropriate. Variables are presented as mean ± standard deviation (range). A $P < 0.05$ was considered significant.

RESULTS

The 35 patients repeated the manometry at a mean time of 2.1 ± 0.8 (range 1–4) years. Five (14%) of the patients progressed to achalasia. Vigorous achalasia was found in one patient (amplitude 60.6 mmHg). Mean time for progression was 2.1 ± 1.0 (range 1–3) years. Four (11.4%) patients had a normal manometry, and 26 (74.3%) kept the diagnosis of DES.

Table 1 compares the demographics and symptoms according to the progression to achalasia or not.

Table 2 summarizes manometric data for both groups at the time of the first manometry. Demographic characteristics were not predictive of transition to achalasia, while dysphagia ($P = 0.005$) as the main symptom and amplitude simultaneous waves less than 50 mmHg ($P = 0.003$) were statistically significant. Heartburn was protective against degeneration ($P = 0.019$).

The amplitude of simultaneous waves was significantly lower in patients with dysphagia (56.0 ± 36.6 mmHg vs. 82.0 ± 38.2 mmHg, $P = 0.013$).

At the multivariate analysis, only the amplitude of simultaneous waves remained as an independent predictor for achalasia (Table 3).

Table 1 Group comparison – demographic data and symptoms

		Gender	Symptoms						
Patients	Age	Females	Dysphagia	Heartburn	Chest pain	Epigastric pain	Regurgitation	Cough	Otorhinolaryngologic
No progression ($n = 30$)	53.27 ± 14.09	80% (24)	33% (10)	57% (17)	50% (15)	23% (7)	43% (13)	13% (4)	3% (1)
Progression ($n = 5$)	55.20 ± 7.16	80% (4)	100% (5)	0% (0)	40% (2)	20% (1)	20% (1)	0% (0)	0% (0)
P-value	0.850	–	0.005	0.019	0.679	0.869	0.324	0.386	0.679

–, *P*-value wasn't considered.

Table 2 Group comparison – manometric findings (first manometry)

	Esophageal body			Low esophageal sphincter	
Patients	Simultaneous waves (%)	Amplitude simultaneous waves (mmHg)	Amplitude of peristaltic waves (mmHg)	Pressure (mmHg)	Relaxation (residual pressure) (mmHg)
No progression ($n = 30$)	43.7% ± 13.7	75.01 ± 39.57	99.73 ± 39.84	13.33 ± 3.85	3.18
Progression ($n = 5$)	52% ± 10.4	44.76 ± 6.14	159.94 ± 102.98	17.04 ± 7.36	3.32
P-value	0.116	0.003	0.109	0.315	0.903

DISCUSSION

The treatment of DES, either medical or surgical, is associated to disappointing outcomes. Approximately 75% of medically treated patients with DES will persist with symptoms.[15,19–21] Surgical outcomes are better in selected patients but still far from excellent.[22] On the other side, the treatment of achalasia is well established and linked to better outcomes.[23] Probably, the identification of the patients with DES prone to the progression to achalasia would allow a quick proper treatment for these patients. We recommend, based on our results, the repetition of the esophageal manometry 2 years after the initial diagnosis, especially on those patients with risk factors.

Some studies have reported the progression of the DES for achalasia, but most of these are case reports. Khatami *et al*.[5] conducted the first prospective cohort study with 12 patients. They found progression of the DES for achalasia in only one patient (8%) with a time of symptoms of 10.6 years. Other studies with a small number of patients documented degeneration starting from 1 to 4 years of DES diagnosis.[4–11] Interestingly, gastroesophageal reflux disease was not excluded in these studies.

Low esophageal body amplitude has been previously reported as a predictive for the progression of DES to achalasia[5] in accordance to our results. We also found dysphagia as a predictive factor for the degeneration, a symptom very common in achalasia patients. Di Marino[24] and Tutuian *et al*.[25] reported that low-amplitude contractions and impaired bolus transit are more frequent in patients presenting with dysphagia than with chest pain suggesting a certain covariation between dysphagia and low-amplitude contractions. Following these data, our results also showed that the amplitude of waves is the only independent factor for the progression at the multivariate analysis. Interestingly, however, heartburn was a protective symptom. Symptoms cannot differentiate DES as a primary motor disorder from a disease secondary to gastroesophageal reflux;[21] however, a careful analysis of our data show that if patients with hiatal hernia, esophagitis, or heartburn are excluded from the analysis (with the assumption that they represent pH monitoring false negatives), the index rate of degeneration increases to 4 out of 13 patients or 30%. The repetition of the pH monitoring at the time of the second manometry was not consented by most patients.

Because of the rarity of the disease, the number of patients is small; however, our study represents the series with the higher number of patients studied. The minimum interval was established at 12 months because this is the minimum time frame previously reported in the literature. The time of follow-up seems to be an important point in the study of the progression of DES to achalasia. Other authors showed a period for progression ranging from 1 year with cases reported of progression after 8 years. Thus, our time of follow-up may be considered short.

High-resolution manometry is a promising new technology for the diagnosis of esophageal motility disorders. It is still unclear if this method can identify more precisely the details that indicate that patients with DES may progresses into achalasia, as some simultaneous contractions observed on conventional manometry might correspond to panesophageal pressurization rather than simultaneous contractions.[26]

Table 3 Multivariate analysis

Variable	Odds ratio	*P*
Age	0.2122	0.9996
Gender	0.0000	0.9998
Dysphagia	0.0000	0.9997
Lower esophageal sphincter basal pressure	0.0104	0.9994
% simultaneous waves	0.2006	0.9999
Amplitude simultaneous waves	733.0593	0.002*
Overall amplitude waves	0.1567	0.9999

*Statistically significant.

CONCLUSIONS

The transition of DES to achalasia is not frequent. However, patients with risk factors (dysphagia and distal simultaneous waves with low amplitude) must be studied with a repeated manometry after 2 years of diagnosis. Gastroesophageal reflux disease must be excluded in patients with DES.

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