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Does Diffuse Esophageal Spasm Progress to Achalasia? A Prospective Cohort Study

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Diffuse esophageal spasm (DES) and achalasia share both clinical and manometric characteristics. Some reports support the notion of progression of DES to achalasia. However, there are currently no prospective data in support of this theory. To assess prospectively the rate of manometric progression of DES to achalasia. Manometry tracings of DES patients diagnosed between 1992 and 2003 were independently reviewed blindly and agreed on by two esophageal experts. Patients with DES who agreed to undergo repeat esophageal manometry constituted the study cohort. Follow-up manometry tracings were evaluated blindly and independently by the same two interpreters to determine the rate of manometric progression to achalasia. Predictors of manometric progression were assessed. A total of 32 patients were diagnosed with DES between 1992–2003. Twelve patients (9M/3F; median age 62 years) agreed to participate and underwent second manometry (mean $\pm$ SD follow-up of 4.8 ± 3.4 years). Achalasia was diagnosed on follow-up manometry in one patient (8%), seven (58%) patients continued to have DES, three (25%) had normal motility, and one (8%) had nutcracker esophagus. There were no predictors of progression to achalasia based on the initial manometry parameters. A subgroup of DES patients with initial low esophageal body amplitude developed increase in esophageal simultaneous contractions on follow-up similar to the patient who evolved to achalasia. Following were the results. 1) Progression from DES to achalasia is uncommon. 2) DES patients with low esophageal body amplitude may develop increased simultaneous contractions over time. 3) DES remains an elusive diagnosis clinically and manometrically.

KEY WORDS: diffuse esophageal spasm; achalasia; progression.

Diffuse Esophageal Spasm (DES) first described by Osgood in 1989 (1) is an esophageal motor disorder characterized by frequent, intermittent simultaneous esophageal contractions accompanied by dysphagia and chest pain. It is a rare disease with an incidence of 0.2/100,000 per year occurring commonly in patients older than 50 years of age (2, 3). Patients often present with dysphagia to solids and liquids sometimes exacerbated by very cold or hot foods (3). Barium swallow suggests beaded and corkscrew appearance first described by Moersh and Camp in 1934 (4). The etiology of DES is still unknown. It is characterized manometrically by the presence of 20% or more swallow-induced repetitive contractions of the simultaneous onset, often high amplitude and long duration in the distal esophageal body with intermittent normal peristalsis (Table 1) (5–10).

Clinical and manometric patterns of DES may overlap with achalasia (5, 6). In achalasia, there is complete loss of peristalsis with normal or high lower esophageal sphincter pressure with incomplete swallow induced relaxation. Clinically, patients with achalasia also have dysphagia to solids and liquids and may have chest pain. Are these two motility disorders separate entities, or do they simply represent a spectrum of the same disease? A few case reports support the notion of progression of DES to achalasia

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TABLE 1. CRITERIA FOR DIAGNOSING ESOPHAGEAL MOTILITY ABNORMALITIES (ADAPTED FROM REFERENCES (5, 6))

Diagnosis	*Manometric findings*
Achalasia	• Absent distal peristalsis • Elevated LES pressure (>45 mmHg) • Incomplete LES relaxation
Diffuse esophageal spasm	• ≥20% Simultaneous contractions • Repetitive contractions (>3 peaks) • Prolonged duration contractions • Incomplete LES relaxation
Nutcracker esophagus	• Increased amplitude (>180 mm Hg) • Increased peristaltic duration

(11–15). However, there is no prospective follow-up study of patients with DES to determine potential progression to achalasia over time. Thus, our aim was to conduct a prospective cohort study in patients with DES to determine the rate of manometric progression to achalasia and to assess potential predictors of such a progression.

MATERIALS AND METHODS

The study was approved by Institutional Board Review (IRB) and conducted at the Center for Swallowing and Esophageal Disorders in the Department of Gastroenterology at the Cleveland Clinic Foundation (CCF). Informed consent was obtained from all identified participants prior to study enrollment.

Patients Selection and Study Protocol. We identified all patients previously diagnosed with DES between 1992 and 2003 from the CCF manometry database. The diagnosis of DES was based on published criteria (5, 6) and included repetitive simultaneous, non-peristaltic normal amplitude contractions involving ≥20% of swallows in the distal esophagus (Table 1). Male and female subjects ages 18 and older were potential candidates. Patients with esophageal motility disorders other than DES, unwillingness to participate and those with prior esophageal surgery were excluded. Two experts in the Center for Swallowing and Esophageal Disorders then independently and blindly reviewed manometry tracings of all patients. The diagnosis of DES was confirmed only when both reviewers agreed.

All DES patients identified were then asked to participate in the study and undergo a repeat esophageal manometry. The follow-up manometry tracings were also evaluated blindly and independently by the same two esophageal experts. Upon arrival and prior to repeat manometry patients completed a questionnaire assessing *current* symptoms of dysphagia, chest pain, heartburn and regurgitation (0 = none, 1 = once/month or less, 2 = once/week up to 3–4/week, 3 = two to four times/week, 5 = once per day, 6 = several times a day). Patients' current symptoms were compared to their prior presenting symptoms collected from archival database. Patients also completed a previously validated Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire (16) containing 25 questions (maximum score of 7 points each) assessing five dimensions: emotional distress, sleep disturbance, food/drink problems, physical/social functioning and vitality.

Manometry. Patients undergoing manometry were seated comfortably and asked to gently sniff a sprayed decongestant (1% Neosynephrine) and anesthetic solution (4% Xylocaine) through a single nare. Esophageal manometry was performed in the supine position. After fasting overnight, the test was performed using a low compliance, pneumohydraulic, water infusion system (Arndorfer Medical Specialties, Milwaukee, Wisconsin) and an eight-lumen manometry catheter (Arndorfer Medical Specialties). The catheter had four proximal recording ports located at 5-cm intervals along its length and another four ports radially oriented (90 degrees) near the tip. The recording sites were interfaced to an eight-channel polygraph (Synectics Medical AB, Stockholm, Sweden). LES pressure was measured by the station pull-through technique and recorded as the mean of four measurements at mid-respiration determined by computer analysis after swallows. Completeness of LES relaxation (normal >85%) was assessed as the percent decrease from mean resting LES pressure to gastric baseline after wet swallows. The catheter was then anchored with the most distal tip located 3 cm above the upper border of LES and 10–12 swallows of 5 ml water were given at 30 s intervals. The following were the normative values in our laboratory (17): LES pressure (10–45 mmHg), esophageal body amplitude (30–180 mmHg), contraction duration (1.5–7 s), UES pressure (50–150 mmHg).

Data Analysis. Data were described with summary statistics including median (25, 75%) for patient demographics and manometry parameters. Wilcoxon rank sum tests were used to compare continuous variables, while Chi-square and Fisher's exact tests were used to compare categorical variables. Visual trends in manometric changes were explored and are presented by scatter plots. Predictors of manometric progression were assessed by comparing manometric and demographic factors.

RESULTS

Review of manometry reports identified 32 patients diagnosed with DES between 1992–2003. Twenty patients did not participate due to death ($n = 6$), inaccessibility ($n = 6$) or refusal ($n = 8$). Twelve patients agreed to participate and underwent second manometry constituting our study cohort. Table 2 lists the comparison of continuous and categorical variables between the study cohort ($n = 12$) and the DES patients not included in the study ($n = 20$). There were no differences between the two groups with respect to age, presenting symptoms or manometric finding (Table 2), suggesting that the study cohort was representative of the total DES population seen in our institution. The study cohort had a significantly ($p < .01$) more males (Table 2).

Predominant symptoms in the study cohort on follow-up included dysphagia (83%) (median score 2.3), chest pain (50%) (median score 1.9), heartburn (8%) (median score 0.9), and regurgitation (33%) (median score 1.1). Although, the overall distribution of presenting symptoms had not changed, the intensity of symptoms were significantly ($p < 0.01$) less on follow-up (median score 1.6) than with the initial evaluation (median score 4.6). Mean (±SE) QOLRAD was 6.1 (±0.3) (from a 7 point possible score) suggesting minimal effect. Additionally, the five inclusive dimensions of QOLRAD were minimally

TABLE 2. DEMOGRAPHIC AND MANOMETRY DATA AMONG DES POPULATION NOT IN THE STUDY AND THE STUDY COHORT

Variables	*Population cohort*		P *value*
	Not in study (N = *20*)	*Study Cohort* (N = *12*)	
Median age (25%, 75%)	63.3 (50.1, 72.2)	62.1 (50.2, 71.0)	0.71
Gender (% Male)	25%	75%	<0.01
Symptoms (%)			
Dysphagia	85%	83%	0.99
Regurgitation	35%	33%	0.99
Chest pain	45%	50%	0.99
Heartburn	5%	8%	0.99
Manometry data median (25%, 75%)			
LES pressure	34.5 (22.0, 48.5)	33.2 (19.0, 39)	0.85
Esophageal body amplitude	104.0 (68.5, 149.5)	109.8 (82.5, 135)	0.80
% Incomplete relaxation	37%	36%	0.99

affected: emotional distress (6.1 ± 0.3), sleep disturbance (6.2 ± 0.2), food and drink problems (6.3 ± 0.2), physical and social function (6.1 ± 0.3) and vitality (6.0 ± 0.2).

EGD had been performed previously in 5/12 (42%) patients: one patient had a small hiatal hernia and one patient was diagnosed with LA grade A esophagitis who also had esophageal dysmotility on barium swallow. A 24 h pH monitoring was abnormal in 1/3 (33%) other patients. Thus, GERD was diagnosed in 2/12 (16%) patients. These two patients symptoms responded moderately to treatment with PPIs. The remaining patients had previously been treated with calcium-channel blockers or esophageal dilation with Maloney dilators and continued to be symptomatic.

Follow-up (mean $\pm$ SD) for the study cohort was 4.8 ± 3.4 years (Figure 1). Achalasia was diagnosed on follow-up manometry in one patient (8%), whereas seven (58%) patients continued to have DES, three (25%) had normal motility, and one (8%) had nutcracker esophagus. The patient with the diagnosis of achalasia (age 72 years) had the longest follow-up of 10.6 years (Figure 1). The initial and follow-up manometric characteristics of the patient who progressed to achalasia were: LES pressure—35 and 46 mmHg, esophageal body amplitude—68 and 81 mmHg, and percentage simultaneous contractions—65 and 100%, respectively (Figure 2). The predominant presenting symptom of dysphagia and chest pain had worsened over time requiring botox injection once diagnosis of achalasia was made on the basis of this study. Due to other co-morbid health conditions he was not a candidate for more aggressive therapy. His dysphagia improved by 70% post-botox injection, but he continued to have mild chest pain post-prandially.

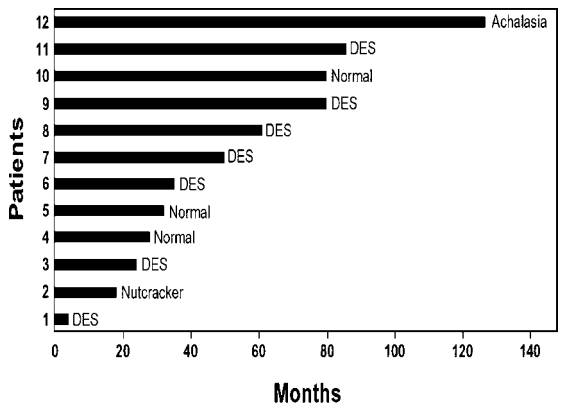

Fig 1. Manometry diagnoses on follow up.

Table 3 shows initial and follows-up manometry parameters for the study cohort. There was no significant difference between pre- and follow-up mean LES pressure, mean body amplitude and percentage simultaneous esophageal body contractions. There appeared to be no predictors of progression to achalasia on the basis of the initial manometry parameters of percentage simultaneous contractions, esophageal body amplitude, LES pressure, peristaltic velocity or degree of LES relaxation.

Two groups of DES patients were identified on the basis of the worsening in the degree of esophageal simultaneous contractions. The initial mean esophageal body amplitude in the three patients with increasing simultaneous contractions were significantly ($p = 0.04$) lower (84 mmHg) than the four patients with no follow up change in percentage simultaneous contractions (131 mmHg). In fact, the initial esophageal body amplitude of these three patients were similar to the patient who over time progressed to achalasia. There was no difference ($p = 0.6$) in mean length of follow-up between these two DES groups (5.0 vs. 4.1 years, respectively).

DISCUSSION

To our knowledge, this is the first prospective cohort study of DES patients to assess manometric change over

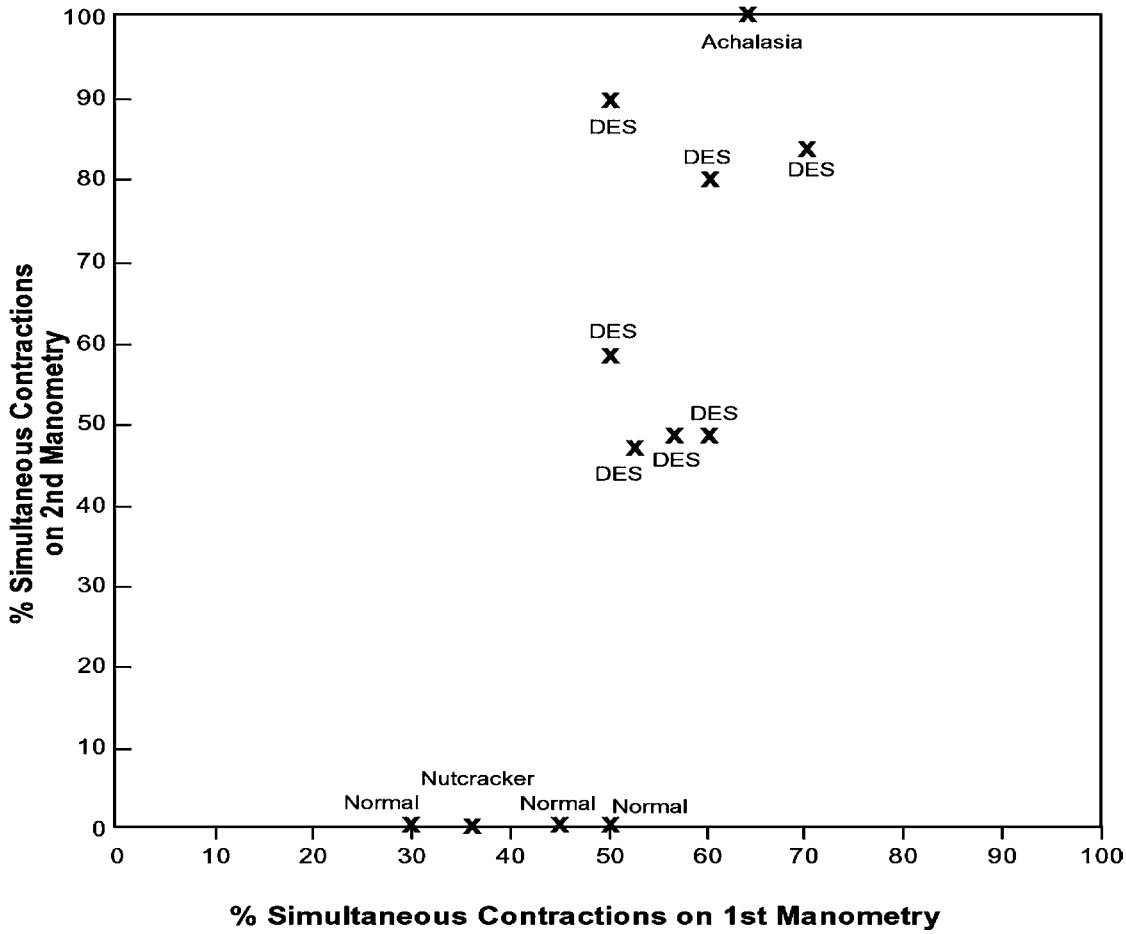

Fig 2. Percentage simultaneous contractions in the first and second manometries as a function of final diagnoses in study cohort. None of the motility parameters predicted progression of DES to any other diagnoses including achalasia.

time. We found that in 12 patients with DES only 1 developed achalasia 10.6 years after the original test. Majority of patients continued to have manometric characteristics of DES. Surprisingly, one patient had nutcracker esophagus and three patients no longer had any manometric abnormalities on follow-up which was highlighted by the reduced symptom scores over time. We also found that there were no manometric or demographic predictors of progression to achalasia. However, two groups of DES patients were identified suggesting that progression may be a function of esophageal body amplitude; however, small patient sample size limits the confidence for this finding.

Several reports have suggested that esophageal motor disorders constitute a spectrum and that some patients may progress from one motor disorder to another (11–14, 18–21). Kramer *et al.* (13) were among the first to report transition of diffuse esophageal spasm to achalasia in a 70-year-old male over 8 years. This progression was accompanied by changes in barium swallow from "corkscrew" esophagus to dilated esophagus with "bird's beaking." Similarly, Millan *et al*. (11) reported manometric progression from

TABLE 3. INITIAL AND FOLLOW-UP MANOMETRY PARAMETERS IN THE STUDY COHORT

Manometry parameters mean (25%, 75%)	*Initial*	*Follow-up**
LES pressure (mmHg)	31.0 (17.9, 42.9)	33.2 (19.0, 39.0)
Esophageal body amplitude	113.5 (79.0, 155.0)	109.8 (82.5, 135.0)
Simultaneous contraction (%)	60 (40, 80)	50 (50, 60)

*No significant difference between the initial and follow-up manometry parameters.

DES to achalasia in a 19-year-old male in 1 year follow-up. More recently, Giniatsos *et al*. (12) reported progression of DES to achalasia in a 41-year-old female who was initially treated with thoracoscopic esophagomyotomy for DES but required a subsequent Heller's myotomy once she had progressed to achalasia. Progression from other motility disorders to achalasia have also been reported (18–21).

However, such data are based on case reports with no prospective long-term follow-up. Case reports often generate interest; however, they have many shortcomings. First, case reports are often published because of the rare occurrence of the phenomenon being reported and do not provide data on the rate or incidence of the disease. Also, the above case reports on the progression of DES to achalasia ignore the inter- and intra-observer variability of manometric interpretation. The progression could represent a prior mis-diagnosis due to interpreter error or it could represent presentation of a disease variant. In a prospective-blinded randomized assessment of intra-interpreter variability we recently showed that the kappa score for diagnosis of DES was only 0.16, suggesting poor observer agreement (22). Thus, studies without adequate measures to control for this observation suffer from over-interpretation. In our study, the initial diagnosis of DES and the subsequent diagnoses had to be agreed on by two interpreters independently in a blinded manner to reduce diagnosis and report bias.

We found that the progression from DES to achalasia does occur but not commonly. Our data suggest that DES is more likely to remain unchanged over time. More interesting observation was that in many of our subjects esophageal motility disturbances were normalized, suggesting that the manometric diagnosis of DES may not be static. Manometric abnormalities noted in a 30-min examination may not be representative of true esophageal motility pattern. Additionally, we found that the progression to achalasia or normality was not dependent on the degree of initial manometric simultaneous esophageal contractions, esophageal body amplitude or LES pressure (Table 3; Figure 2). Although, one may expect degree of simultaneous contractions or degree of LES relaxation on initial manometry to play a role in predicting future worsening of esophageal function and possible progression to achalasia, our data did not find this to be the case.

However, on the basis of the initial and follow-up manometries, we noted two groups of DES patients. One which patients have minimal if any change in the degree of percentage simultaneous contractions over time (Group B) and others in which patients have substantially increased simultaneous contractions, but insufficient for achalasia diagnosis (Group A). Importantly, similar to the patient who progressed to achalasia, the three group A DES patients had the weakest initial esophageal body amplitude. Whether or not these three patients may later progress to achalasia was beyond the scope of this study. However, we intend to follow our current cohort of patients for longer periods to assess this possibility.

Although the etiology of DES is unknown, some classify DES into reflux associated, caused by acid exposure, and idiopathic (23–26). Recent evaluation by 24-h pH monitoring has questioned such a distinction finding no significant difference in mean esophageal acid exposure between the two groups (27). Only 16% of our patients had GERD diagnosed by pH monitoring, endoscopy or barium swallow. Additionally, the predominant symptoms in our patients were dysphagia and chest pain. Heartburn was less prevalent with low severity score. Additionally, our patients' QOL was minimally affected by reflux or dyspepsia symptoms highlighted by near normal QOLRAD scores. Thus, GERD did not appear to play a significant role in our cohort.

One shortcoming of our study, which could have impacted the rate of progression from DES to achalasia, was the variable length of follow-up (Figure 1). It is possible that more of the DES patients may progress to achalasia if followed longer. However, equal length of follow-up is often difficult to achieve in a rare disorder such as DES. An additional limitation of our study is that we were able to study only 12 of the 32 DES patients identified over the study period. This limitation was not avoidable since the majority of patients previously diagnosed with DES were either deceased, inaccessible, or refused to have repeat manometry. However, in order to ensure lack of population bias, we compared the study cohort to the DES patients who did not have repeat manometry showing that other than gender difference our study cohort was representative of the overall DES population diagnosed in our institution (Table 2).

In conclusion, DES patients may progress to achalasia but not as commonly as suggested by earlier case reports. Most DES patients continue to have manometric characteristics of DES over time; however, dysmotility may normalize in a substantial minority. The fact that changes in manometric pattern is seen in 42% with DES raising doubt about the specific nature of such a diagnosis. Clinically and manometrically DES remains an elusive entity. Although, our study did not identify predictors of manometric changes, future studies need to focus on the rate of progression in those with low amplitude esophageal contractions. Longer follow-up may help assess more accurately the true rate of manometric progression from DES to achalasia.

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