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Clinical and Manometric Characteristics of Patients with Achalasia: One Disease with Three Presentations or Three Diseases with One Presentation?

Teodora Surdea-Blaga[1], Liliana David[1], Andrei Pop[1], Marcel Tantau[2], Dan L. Dumitrascu[1]

1) 2nd Medical Department, Emergency County Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca;
2) 3rd Medical Department, Octavian Fodor Institute of Gastroenterology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Address for correspondence:
Teodora Surdea-Blaga
2nd Medical Department, Emergency County Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca
Teodora.Surdea@umfcluj.ro; dora_blaga@yahoo.com

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ABSTRACT

Background & Aims: The three manometric patterns of achalasia are considered by some authors as different stages in the evolution of the same disorder. The aims of our study were to characterize patients with achalasia, in order to find key differences supporting the idea of progression from one type to the other, and to assess the clinical evolution in time.

Methods: From 280 high resolution esophageal manometry recordings we selected unique patients with achalasia. A standardized questionnaire used prior to each manometry recorded their symptoms. Manometric parameters (resting lower esophageal sphincter (LES) pressure, 4s-integrated relaxation pressure (IRP), length of the esophagus, etc.) were recorded. Patients were contacted to establish the clinical evolution.

Results: We identified 108 new achalasia cases (mean age 48.2±16.2 years, 52.8% type I, 42.6% type II), 52 (48.1%) women. Dysphagia (98.1%), cough (64.8%), belching (60.2%) and reflux symptoms (53.7%) were frequently reported. Patients with type I achalasia reported more often that dysphagia worsened, compared to type II patients ($\chi 2=7.3$, $p=0.007$). Age, duration of dysphagia, body mass index ($p=0.067$) and esophageal length were similar in type I and type II achalasia. Resting LES pressure (64.7±22.6 mmHg vs. 54.3±21.6 mmHg, $p=0.019$) and 4s-IRP (45.3±17.6 mmHg vs. 38.4±15.5 mmHg, $p=0.036$) were higher in type II compared to type I achalasia. Overweight patients had a lower LES resting pressure and 4s-IRP compared to lean subjects. After a mean follow-up of 36.8±13.4 months, 49 (45.3%) patients responded to our follow-up, and 77.5% had an Eckardt score ≤ 3.

Conclusions: Type I achalasia was the most common in our group. Type I patients had lower BMI but similar duration of dysphagia and mean age compared to type II. Type III is seldom and present in older patients. These findings suggest low probability of progression from type III and II to type I achalasia. Patients with type II achalasia had higher resting LES pressure and 4s-IRP than type I achalasia patients.

Key words: achalasia – dysphagia – high resolution esophageal manometry – endoscopic treatment – balloon dilation – POEM

Abbreviations: 4s-IRP: 4 seconds integrated relaxation pressure; BMI: body mass index; CCB: calcium channel blocker; DCI: distal contractile integral; EGJ: esophago-gastric junction; HREM-PT: high-resolution esophageal manometry with pressure topography; IQ: inter quartile; LES: lower esophageal sphincter; MRS: multiple rapid swallows; POEM: per oral endoscopic myotomy; PPI: proton pump inhibitor.

INTRODUCTION

The etiology of achalasia, characterized by an impaired relaxation of the lower esophageal sphincter (LES) and absence of peristalsis in the esophageal body, is poorly understood [1]. High-resolution esophageal manometry with pressure topography (HREM-PT) identifies three distinct manometric patterns of achalasia [2]. Recent reports suggested that the three manometric patterns are different stages in the evolution of the same disorder, with type III achalasia being the early stage, suggested by a shorter duration of symptoms, a higher incidence of chest pain and less dilated esophagus on the esophagogram. Type II achalasia is the intermediate stage, while type I would be the final stage characterized by a sigmoid shaped esophagus on barium swallow, and a longer history of symptoms [3].

Histologic specimens from achalasia patients showed a greater degree of ganglion cell loss in type I compared to

type II achalasia [4]. After multiple rapid swallows (MRS), patients with type III achalasia responded with a profound esophago-gastric junction (EGJ) relaxation and vigorous contraction of the smooth muscle esophagus, an aspect close to normal. Patients with type I and II achalasia had less LES relaxation and no esophageal body contraction in response to MRS, suggesting that the inhibitory neuron network had been severely disrupted in type I and II achalasia, but almost preserved in type III achalasia [5]. After surgical or endoscopic treatment, some patients with type II achalasia have a type I pattern, and patients with type III have type I or type II pattern [3]. Therefore, there are some clinical, radiological and histological data that support the idea that achalasia might change its manometric appearance in time, and that achalasia heterogeneity is a continuum, the persistence of LES obstruction leading to different patterns in time.

The aim of our study was to evaluate the clinical and manometric findings of patients with achalasia, in order to identify key differences between the three types of achalasia that could suggest a progression from one type to the other. The secondary objective was the clinical evolution in time.

METHODS

We retrospectively analyzed all the recordings of HREM-PT performed in our motility department from November 2014, until July 2019, and we selected unique patients with a manometric aspect of achalasia, based on Chicago classification v3.0 [2]. Our patients were from different parts of Transylvania, and endoscopy was performed before manometry in all cases by the referring physician.

We excluded the patients previously treated for achalasia (using endoscopic procedures or surgical cardio-myotomy), with major surgery involving upper gastrointestinal tract (procedures for gastroesophageal reflux disease or gastric resection), or with biopsy proven eosinophilic esophagitis.

High-resolution esophageal manometries with pressure topography were performed using the ISOLAB manometry system (Standard Instruments GmbH, Germany) and Unisensor® solid state probe. The probe has 36 circumferential sensors, spaced at 1 cm. Patients were instructed to stop prokinetic drugs, calcium channel blockers (CCBs) and nitrates, the day prior to manometry. The probe was placed trans-nasally, with at least 3 sensors in the stomach. Ten wet swallows (5 ml of water) spaced at 30 seconds were performed, with the patient in supine position and the thorax angulated at 30°.

The diagnosis of achalasia was based on the latest classification of esophageal motility disorders, Chicago v3.0 and included the absence of relaxation of the LES and one of the following: 1) absence of peristaltic waves in 100% of swallows, in type I achalasia; 2) pan-esophageal pressurization in ≥20% of swallows, in type II achalasia, and 3) abnormal peristaltic waves, with ≥20% spastic waves in type III achalasia. Based on previous studies, the upper normal limit of 4s-integrated relaxation pressure (4s-IRP) when using Unisensor® probes was set at 28 mmHg. Patients with aperistalsis but normal 4s-IRP, were classified as achalasia if pan-esophageal pressurization was present [2]. For patients with aperistalsis, normal 4s-IRP and no pan-esophageal pressurization, the final diagnosis was based on endoscopic changes (dilated esophagus, with liquid or solid residue, and a functional stenosis of the EGJ) or typical radiologic findings (dilated esophagus, bird beak sign and stasis of barium in the esophagus). Only tracings with at least 8 correct swallows were included.

Collected manometric parameters were: resting LES pressure (automatically measured before each swallow, the software providing median values), 4s-IRP, length of the esophagus (measured between the lower border of upper esophageal sphincter, and the upper border of LES), EGJ length (measured between the upper border of LES and the lower border of LES / crural diaphragm, if hiatus hernia was present), proportion of swallows with pan-esophageal pressurization, and LES relaxation.

A standardized questionnaire was used prior to each manometry to record demographic data, symptoms, previous manometric, endoscopic, radiological findings, current medical treatments, history of surgery. Time of onset was noted for dysphagia, thoracic pain and reflux symptoms. Details about dysphagia were collected: more severe to solids, to liquids or if the patient perceived that dysphagia worsened in time. Other symptoms (i.e. belching, nausea, bloating, globus, satiety, epigastric fullness, pain, burning or discomfort) were also recorded.

The follow-up questionnaire included: the type of treatment (endoscopic balloon dilations, per oral endoscopic myotomy (POEM), Heller cardio-myotomy, botulin toxin injections, medication, none), global assessment of symptoms (improvement / persistence / aggravation) as perceived by the patient, current symptoms, their relation with food, weight loss/gain, diet pattern if any (vegetarian, eating less and often, avoided foods, etc.), frequency of symptoms included in the Eckardt score (never, occasionally, daily, every meal) and drug use. An Eckardt score (range 0 to 12, higher scores indicating more severe symptoms) ≤3 points was considered as a good response to treatment [6, 7]. The follow-up period was the time between the first manometry and March 2020, the patients being contacted by telephone or mail.

Statistical analysis was performed using MedCalc. Descriptive statistics were used to characterize the study group. Continuous parametric data were presented as mean±SD, non-parametric continuous data were reported as median (interquartile (IQ) range 25-75%). Categorical data were presented as frequencies. The independent two-sample Student's t-test was used for continuous parametric variables, and two-tailed p was reported. The Man-Whitney test was used for non-parametric data. Categorical variables were compared using n x n tables and the Chi-square test. A p value less than 0.05 was considered significant.

The study protocol was approved by the Committee of Ethics of the University of Medicine and Pharmacy, Cluj-Napoca, Romania (No. 105/9 March 2020).

RESULTS

From 280 HREM-PT recordings, we identified 108 untreated achalasia cases (Fig. 1). In this cohort, 52 (48.1%) patients were women. The mean age was 48.2±16.2 years (range

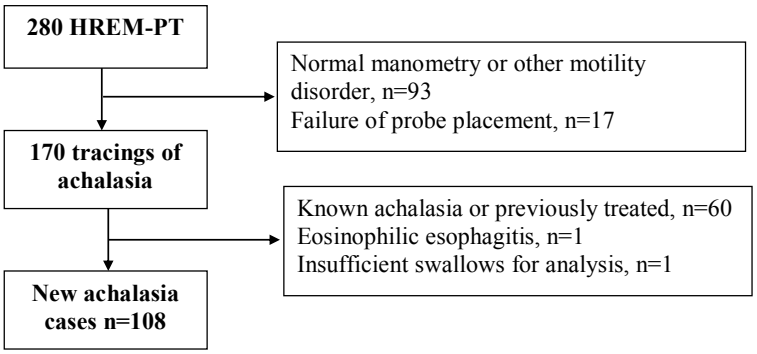

Fig. 1. Selection of untreated achalasia patients from a total of 280 high resolution esophageal manometry with pressure topography (HREM-PT) tracings.

14-83 years), with 41.6% of patients between 30–50 years old, 39.8% of patients >50 years old and 12.9% of patients >65 years. Fifty-seven patients (52.8%) had type I achalasia, 46 (42.6%) patients had type II, and 5 (4.6%) patients had type III. Twenty-two patients (20.3%) had a normal 4s-IRP (< 28 mmHg), and among them 14 patients (58.3 %) had type I achalasia, and none had type III achalasia.

The most frequently reported symptoms were dysphagia (98.1%), cough (64.8%) and belching (60.2%) (Fig. 2). Half of the patients (53.7%) had reflux symptoms (heartburn, regurgitation or both). Dysphagia worsened in time in 61.1% of patients. A chi-square test of independence was performed to examine the relation between the achalasia type and the sensation of progression. The relation between these variables was significant, $\chi^2(1,N=103)=7.3$, p=0.007. Significantly more patients with type I achalasia reported progressive dysphagia compared to patients with type II achalasia. Half of the patients (55.6%) had dysphagia both for solids and liquids, 20.4% of patients reported dysphagia especially to liquids, and 19.4 % of patients responded that it was more severe to solids.

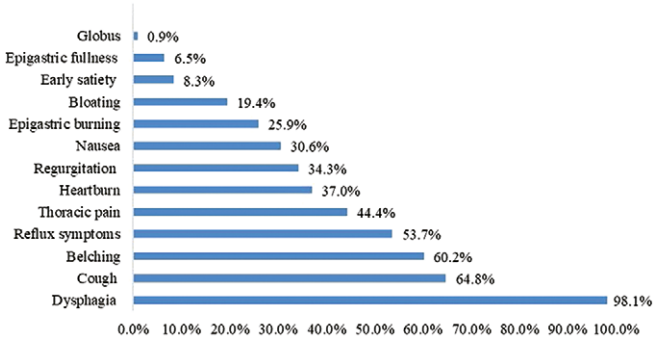

Fig. 2. Frequency of upper gastrointestinal symptoms in all achalasia cases (n= 108)

Because only 5 patients had type III achalasia (median age 65 years old, range 42-79 years), the following results and comparisons refer only to patients with type I and type II achalasia (n=103) (Table I). Thirty patients had a body mass index (BMI) ≥ 25 kg/m^2, while 9 patients were underweight (BMI < 18 Kg/m^2). The patients with type II achalasia had a higher BMI compared with type I achalasia, but the difference did not reach a statistical significance (Table I).

Table I. Demographic and clinical data in type I and type II achalasia cases

Achalasia	Type I n = 57	Type II n = 46	p
Demographic information			
Females, n (%)	26 (45.6)	25 (54.3)	0.38
Age, years, mean ± SD	45.6 ± 15.8	49.8 ± 15.9	0.18
BMI (kg/m^2), mean ± SD	22.9 ± 4.5	24.8 ± 6.1	0.07
Lean subjects (BMI < 25 kg/m^2), n (%)	42 (73.6)	29 (65.9)	0.39
Duration of dysphagia (months)	15, IQ: 12-36	12, IQ: 6-36	0.7
Symptoms %			
Dysphagia	98.2	97.8	0.88
Progressive dysphagia	71.9	45.7	0.01
Thoracic pain	49.1	41.3	0.43
Reflux symptoms	50.9	54.3	0.73
Heartburn	42.1	26.1	0.09
Regurgitation	28.1	43.5	0.10
Epigastric pain or burning	29.8	21.7	0.35
Cough	68.4	63.0	0.57
Belching	59.6	60.9	0.90
Nausea	29.8	32.6	0.76
Early satiety	8.7	10.9	0.72
Epigastric fullness	3.5	10.8	0.14
Bloating	12.3	26.1	0.07
Globus	1.7	0	0.88

Esophageal length was similar in type I and type II achalasia (24.6±2.5 cm vs. 23.9±2.7 cm, p=0.15). Patients with type II achalasia had significantly higher LES resting pressure (64.7±22.6 mmHg vs. 54.3±21.6 mmHg, p=0.019) and 4s-IRP (45.3±17.6 mmHg vs. 38.4±15.5 mmHg, p= 0.036) compared with patients with type I achalasia. Lower esophageal sphincter relaxation was similar in type I and type II achalasia.

Patients with type II achalasia and pressurization in ≥ 50% of swallows (n=26, 56.5%) had higher LES values (median 68.1mmHg, IQ range: 54.1-80.3mmHg vs. 57.5mmHg, IQ range: 40.1-71.7mmHg, p=0.037), and higher 4s-IRP values (50.2mmHg, IQ range: 41.5-57 mmHg vs. 39mmHg, IQ range: 26.6-51.4mmHg, p= 0.038), compared to patients with pressurization in < 50% of swallows.

Overweight patients (BMI ≥25 kg/m², n=30) had lower LES resting pressure when compared to patients with normal or low BMI (< 25kg/m², n=71) (51.9±22.3 mmHg vs. 62.6±22.2 mmHg, p=0.014). 4s-IRP was significantly lower in overweight patients, compared to lean patients (34.2±15.0mmHg vs. 45.1±16.5 mmHg, p=0.02). Esophageal length tended to be smaller in overweight compared with lean patients (23.6±2.7 kg/m² vs. 24.7±2.6kg/m², p=0.057). Subgroup analysis based on BMI is summarized in Table II.

Table II. Comparison of manometric characteristics in lean versus overweight patients with type I and type II achalasia

	BMI < 25 kg/m²	BMI ≥ 25 kg/m²	p**
Type I achalasia, LES resting pressure	57.6 ± 21.6	45.4 ± 19.6	0.06
Type II achalasia, LES resting pressure	69.8 ± 21.3	58.9, IQ range: 45.3-66.2	0.11
p*	0.021	0.22	
Type I achalasia, 4s-IRP	41.2 ± 15.6	30.7 ± 12.5	0.024
Type II achalasia, 4s-IRP	50.7 ± 16.3	37.5 ± 16.8	0.016
p*	0.016	0.223	
Type I achalasia, esophageal length, cm	25.0 ± 2.6	23.9 ± 2.4	0.187
Type II achalasia, esophageal length, cm	24.3 ± 2.7	23.3 ± 3.0	0.229
p*	0.34	0.50	
Esophago-gastric junction length, cm	2.5 (IQ 2-3)	3 (IQ 2-3)	0.047

BMI: body mass index; p*: comparison between type I and type II achalasia patients; p**: comparisons between overweight and lean patients; LES: lower esophageal sphincter; IRP: integrated relaxation pressure.

From 108 patients with achalasia, 49 (45.3%) responded to our follow-up questionnaire (23 with type I achalasia, 23 with type II and 3 with type III). All the patients were treated in the same week the manometry was performed, except one case, treated after one year. The treatment in each achalasia subgroup is presented in Table III. One patient (type III achalasia) refused treatment to avoid gaining weight; another patient (type II achalasia) felt better using a CCB, and another patient (type III achalasia) claimed she had some symptoms when manometry was performed, but afterwards she had no symptoms.

At follow-up, 45 (91.8%) patients considered that their global symptoms improved after treatment. The mean Eckardt score was 2.4±1.5 (from 0 to 7). Eight patients (16.3%) had no weight gain, and the remaining gained between 1 and 34 kg (median: 10 kg, IQ range 4.6-13 kg), in the period between treatment and follow-up. After a median follow-up of 3 years, 38 respondents (77.5%) had an Eckardt score ≤ 3 points, therefore maintained a good response, and were equally distributed between dilation and POEM subgroups. Seven out of 11 patients with Eckardt score ≥4 points, considered that their global symptoms improved after treatment. Three (6.1%) patients (one with dilation, one with POEM, one with no treatment) considered that their symptoms persisted (Eckardt score from 5 to 7 points).

Regarding the symptoms at follow-up, dysphagia and cough frequency decreased significantly, thoracic pain persisted

Table III. Treatment procedures in 49 achalasia respondents to the follow-up questionnaire

Achalasia	Type I (n=23)	Type II (n=23)	Type III (n=3)	Total
Treatment				
Dilation	9	8	1	18
1 session	4	6	-	10
2 sessions	3	1	-	4
3 sessions	1	1	1	3
Doesn't remember the number of sessions	1	-	-	1
Follow-up (months, mean)	27.7	40.0	20	
POEM	13	13	-	26
Follow-up (months)	38.2	41.2	-	
Dilation followed by POEM	-	1	-	1
POEM followed by dilation	1	-	-	1
No interventional treatment	-	1	2	3
Follow-up (months)	-	34	31.0	

POEM: peroral endoscopic myotomy.

(equally distributed between POEM and dilation) and reflux symptoms increased in frequency, but without reaching statistical significance (Fig. 3). Twenty-three respondents had persistent reflux, 9 developed reflux after treatment, in 10 cases reflux symptoms disappeared and 7 never had reflux symptoms. Reflux symptoms were equally distributed between the dilation (n=14, 73.6%) and POEM (n=17, 62.9%) groups.

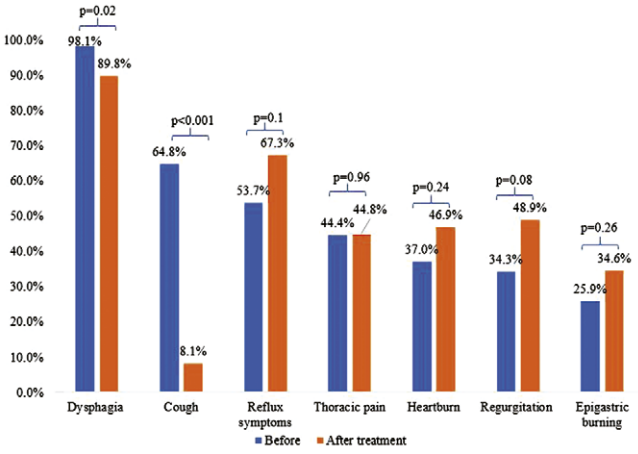

Fig. 3. Frequency of upper gastrointestinal symptoms in respondents (n=49) after a mean follow-up period of 3 years, compared to the frequency of symptoms observed before treatment in the entire group of achalasia patients (n=108).

One third of patients with reflux symptoms reported that reflux was related to certain fruits or vegetables, too much food or the body position (lying on their back or leaning forward). The profile of dysphagia changed after treatment, with the majority of patients reporting dysphagia when eating solid or dry foods, 4.5% had dysphagia especially to liquids and 11.3% had mixed dysphagia. Four patients were unable to identify a context for dysphagia (Fig. 4).

Thirty (61.2%) respondents had no medication. One patient was on proton pump inhibitors (PPIs) twice a day,

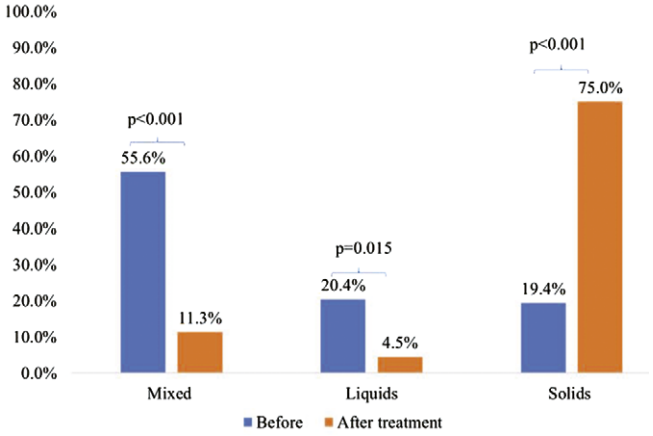

Fig. 4. Perceived dysphagia, before (n=106) and at post-treatment follow-up (n=44). Mixed - dysphagia both to liquids and solids, liquids – dysphagia observed especially when eating liquid foods, solids – dysphagia observed while eating solid or dried foods.

while the others used drugs on demand (2-3 times a month): alginate (n=8), PPIs (n=5), prokinetics (n=3), CCBs (n=1), antacids (n=1), and antalgics (n=1). Regarding dietary habits, 34 (69.3%) patients had no particular diet, 5 (10.2%) patients drank water (200-500ml/meal) during meals to prevent dysphagia, 5 (10.2%) patients chewed carefully, ate more meals a day in small amounts, 3 patients avoided certain foods (fruits, tea, chocolate, fried foods), and one used alternative remedies.

Twenty-two patients were re-evaluated using HREM-PT after treatment (18 underwent POEM, 4 had endoscopic dilation). Fourteen patients had type I achalasia, two of which had endoscopic dilation. The remaining had type II achalasia. Patients were evaluated after variable periods, between 4 and 24 weeks after the procedure, with a median of 6 weeks (IQ: 6-11). Symptoms improved in 16 patients, and dysphagia persisted in 6 patients: rarely in 3 cases, without other symptoms, while 3 patients had dysphagia, reflux symptoms and thoracic pain. After endoscopic treatment, LES resting pressure, 4s-IRP and esophageal length significantly diminished, and there was a tendency towards an increase in the EGJ length (Table IV).

In patients with type II achalasia, pan-esophageal pressurization completely disappeared, except one case (one patient exhibited 1 swallow followed by pan-esophageal pressurization), after treatment. Therefore, patients with type II achalasia assessed after treatment displayed a type I manometric pattern, including the patient with a rise in pressures. Four patients (18.1%) had 4s-IRP >28mmHg after treatment (3 had type I and 1 patient had type II achalasia): 2 patients had dilations, 1 had POEM and the other POEM followed by dilations (with manometry after the last dilation). In 5 (22.7%) cases (all underwent POEM, 4 had type I and 1 had type II achalasia) we observed in 3 to 7 swallows, the appearance of a high pressure zone (4-5 cm in length), located 10-12 cm above LES, but inefficient (distal contractile integral (DCI) <150mmHg*cm*s). At an individual level, after endoscopic procedures, LES resting pressure rose in 2 patients, while IRP increased in one case (Fig. 5).

Table IV. Manometric characteristics, before and after endoscopic treatment

Achalasia	Before treatment	After treatment	p
LES resting pressure, mmHg	61.6 ± 17.5	33.3 ± 10.4	<0.001
4s-IRP, mmHg	44.1 ± 13.1	22.5 (IQ:18.7-25.0)	<0.001
Esophageal length, cm	24.5 ± 2.7	23.1 ± 2.7	0.001
Esophago-gastric junction length, cm	2.75 (IQ:2-3)	3 (IQ:2.6-3)	0.07

LES: lower esophageal sphincter; 4s-IRP: 4s integrated relaxation pressure.

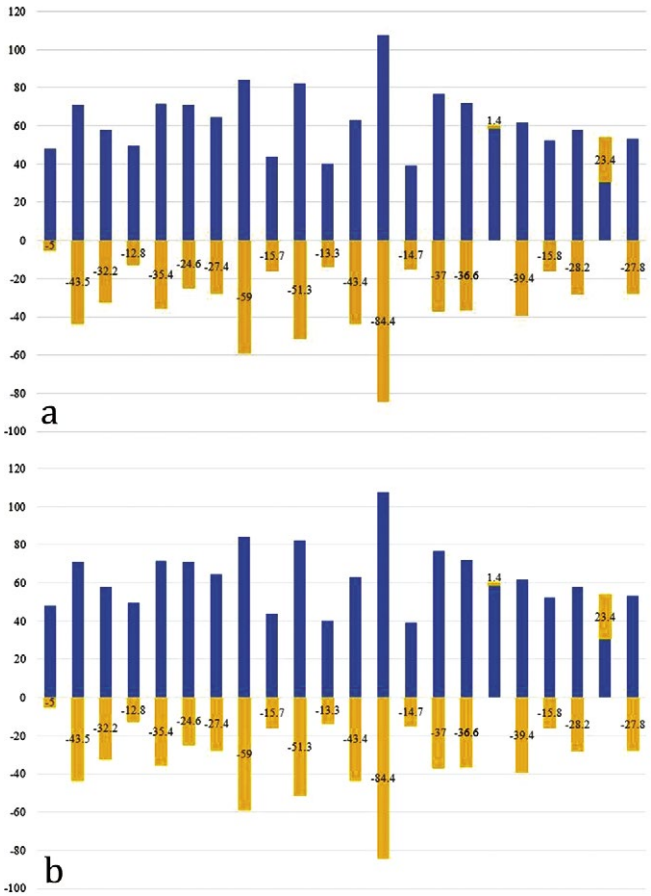

Fig. 5. a) Lower esophageal sphincter pressure (mmHg) before treatment (blue) and variation (mmHg) after endoscopic treatment, at a short-term follow-up, in 22 achalasia cases; b) 4s-integrated relaxation pressure (mmHg) before (blue) and its variation (mmHg) after endoscopic treatment, at short-term follow-up, in 22 achalasia cases.

DISCUSSION

This study provides a clinical and manometric characterization of a group of patients with achalasia. In addition, we report data regarding the clinical outcome after a median follow-up of 3 years. Most of our patients had type I or type II achalasia, type III achalasia being rarely observed, as reported also by other studies [6].

There are some positive arguments toward a progression from type II to type I achalasia. First, a significantly higher number of patients with type I achalasia reported that

dysphagia worsened in time, suggesting a longer disease course in type I cases. Second, patients with type I achalasia had a lower BMI compared to type II achalasia patients, another argument in favor of a long-lasting disease, with nutritional consequences secondary to persistent dysphagia in type I pattern. Unfortunately, the data regarding the weight loss in our study are missing. Another study reported that weight loss was more likely in type II achalasia, and that patients with constant weight, had a longer duration of symptoms and a lower LES residual pressure [8]. In another study, BMI was lower in type I achalasia (n=14) compared to type II achalasia (n=36), but the difference was not significant, possibly due to sampling influence [9]. Third, both LES resting pressure and 4s-IRP were higher in type II compared to type I achalasia. Another study also reported lower 4s-IRP values in type I achalasia compared to type II achalasia, but possibly due to the sampling influence, the difference was not significant [9]. The study of Lee et al. [6], found a higher basal LES pressure in type II, compared to type I achalasia, and a similar 4s-IRP. Another study reported less ganglion cells per nerve bundle in type I compared to type II achalasia. However, there was no difference in EGJ relaxation pressure and mean resting EGJ pressure when comparing aganglionosis specimens with achalasia specimens with at least one ganglion cell per nerve bundle [4]. Why the tone of the LES would change in time remains to be elucidated. We can hypothesize that the dilated esophagus containing food and liquid, partially opens the LES, leading to lower measured LES resting pressure and 4s-IRP.

Some of our results do not support the hypothesis of a progression. First, patients with type I achalasia were younger, but not significantly, compared with patients with type II achalasia. The mean age of patients with type III achalasia was 65 years, making less probable this subtype as the first one in the progression mentioned above. The duration of dysphagia was similar in type I compared to type II achalasia. However, some patients ignored the symptoms for years, did not consult, especially if dysphagia was rare in occurrence. Therefore, in a lot of cases, the date of the first symptom was only vaguely recalled.

We also reported the influence of BMI on manometry parameters. Overweight patients had LES resting pressure lower than lean subjects, similar to previous reports [10]. Also, in overweight patients 4s-IRP was lower than in lean subjects, and EGJ was longer. The difference in pressures could partly be determined by the upward displacement of the LES in overweight patients (suggested by the longer EGJ), resulting in a decrease in LES pressure because the role of crural diaphragm diminishes. Few studies reported data regarding BMI and LES function using HREM-PT. In subjects without major esophageal motility disorders, Tanaka et al. [11] reported that BMI was negatively associated with 4s-IRP.

No symptoms' association differentiates between type I and type II achalasia. Dysphagia, cough, thoracic pain and reflux symptoms were observed with the same frequency in both subtypes and were the most frequent symptoms. Similar findings were reported by Lee et al. [6]. Reflux symptoms were reported by half of our patients. In other studies, more than 80% of patients with achalasia had regurgitations [12]. Almost 2 out of 3 patients in our group experienced cough, especially during the night. Other studies also reported a high prevalence of respiratory symptoms (51%) in achalasia patients [13] and even parenchymal lung changes and restrictive airway disease [14].

Both POEM and endoscopic dilation significantly reduced LES resting pressure and 4s-IRP in short term follow-up and improved symptoms in most patients. After a median follow-up of 3 years, a good response (Eckardt score ≤ 3) was observed in 77.5% of cases, while more than 90% of patients considered that their condition improved after treatment. Cough was very common before treatment in our cohort; after treatment less than 10% of patients had a persistent cough. Improvement of respiratory symptoms was also reported after Heller myotomy [13]. The presumed mechanisms of cough in achalasia are related with food retention in the dilated esophagus, leading to regurgitation of content towards upper airways and compression of trachea, triggering cough reflexogenic zones [13, 14]. After treatment, resting LES pressure and 4s-IRP diminished, allowing a better esophageal emptying, less esophago-pharyngeal reflux and the disappearance of mass effect on the trachea.

Gastroesophageal reflux after POEM represents a major concern [7, 15]. In our study, reflux symptoms increased in frequency after treatment, with more than 60% of patients who responded to our follow-up questionnaire having at least 1 reflux symptom. In some cases, reflux symptoms disappeared after treatment; probably the reflux was eso-esophageal, secondary to stasis of foods in the esophagus. Only half of our patients with reflux at follow-up used anti-reflux drugs (alginates, PPIs, prokinetics or antacids) "on demand" (2-3 times a month), suggesting that reflux was not bothersome in most cases. A large European trial reported that 6 months after POEM, 39.3% of patients used daily PPIs, and 7.5% used PPIs occasionally [7]. In our study, reflux symptoms were present in similar proportions after endoscopic dilation or POEM. Clinical trials reported that reflux esophagitis is far more common after POEM (41%) than after endoscopic dilation (7%), after 2 years follow-up [16]. A similar prevalence (44%) of reflux esophagitis 2 years after POEM was reported in another trial [7].

It is worth mentioning that despite the reduction of intra-esophageal pressure after reducing LES resting pressure, thoracic pain persisted. Patients with type II achalasia, did not report thoracic pain more often compared with patients with type I. Patients with type II achalasia, high LES resting pressure and high 4s-IRP had significantly more swallows followed by pan-esophageal pressurization, but thoracic pain was not seen more frequently in this subgroup. Therefore, pan-esophageal pressurization is less likely the cause of pain in achalasia. Persistence of chest pain after endoscopic treatment was reported by other researchers [17]. In other esophageal motility disorders, such as jackhammer esophagus, diffuse esophageal spasm or EGJ outflow obstruction, POEM improved chest pain in more than 80% of patients [18]. Most patients with type III achalasia and chest pain, also reported improvement of chest pain after POEM [19].

Previous studies reported that after treatment the manometric aspect can change [3]. In our opinion a change from type II to type I pattern is the result of a successful

treatment, and our results confirm this aspect. As mentioned above, high LES resting pressure and 4s-IRP, was accompanied by a higher proportion of swallows with pan-esophageal pressurization. By reducing the LES pressures, pan-esophageal pressurization disappears, and the manometric aspect changes to type I achalasia. Some studies reported a partial recovery of peristalsis after POEM in half of the patients [20]. Others reported higher rates (>50%) of patients with intact, weak, or frequently failed peristalsis after myotomy (either surgical or endoscopic) [21]. In our group, from 22 patients (18 assessed 6 weeks after POEM) only 5 presented some increased pressure distal to the transition zone and above the site where myotomy started. This aspect suggests that in the case of recovery of peristalsis, this would appear mainly above the myotomy zone. However, the waves were classified as "failed peristalsis" based on Chicago classification, because the DCI (using the 20-mmHg isobaric contour) was very low. We cannot explain why our numbers are so low, less than 30%, compared to previous studies. The main differences were that our patients were evaluated after a shorter period (median - 6 weeks) compared to the study of Roman et al. [21] (median - 10 weeks) and that endoscopic myotomy was predominant in our group, compared to surgical myotomy in Roman's group. According to Roman et al. [21], the procedure used or the dilation of the esophagus prior to treatment did not influence the recovery of peristalsis, but only 5 patients had POEM in their study.

This study has some limitations: first, it was a retrospective analysis, and data about weight loss and Eckardt score at baseline was available in a limited number of patients, and therefore were not presented; second, the number of type III achalasia patients was very small and we did not analyze manometric parameters for this subgroup; other studies also reported the rarity of type III achalasia; third, less than half of the patients responded to our questionnaire, and even less returned to our department for manometry after treatment.

CONCLUSIONS

Type I achalasia was the most common in our group. Type I patients had lower BMI but similar duration of dysphagia and mean age compared to type II. Type III is seldom and present in older patients. These findings suggest a low probability of progression from type III and II to type I achalasia. Patients with type II achalasia had higher resting LES pressure and 4s-IRP than patients with type I achalasia. Panesophageal pressurization disappears after endoscopic therapy. BMI influences both LES resting pressure and 4s-IRP, being lower in obese subjects. After a median follow-up of 3 years, 77.5% of patients maintained a good therapeutic response.

Conflicts of interest: None to declare.

Authors' contributions T.S.B. conceived and designed the study, analyzed the data, drafted the manuscript. A.P. and L.D. contributed to the acquisition, analysis and interpretation of data. M.T. and D.L.D. analyzed the data and critically revised the manuscript for important intellectual content. All authors revised the manuscript and accepted the final version to be published.

REFERENCES

1. Pandolfino JE, Gawron AJ. Achalasia: a systematic review. JAMA 2015;313:1841-1852. doi:10.1001/jama.2015.2996
2. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160-174. doi:10.1111/nmo.12477
3. Salvador R, Voltarel G, Savarino E, et al. The natural history of achalasia: Evidence of a continuum-"The evolutive pattern theory". Dig Liver Dis 2018;50:342-347. doi:10.1016/j.dld.2017.11.012
4. Sodikoff JB, Lo AA, Shetuni BB, Kahrilas PJ, Yang GY, Pandolfino JE. Histopathologic patterns among achalasia subtypes. Neurogastroenterol Motil 2016;28:139-145. doi:10.1111/nmo.12711
5. Kushnir V, Sayuk GS, Gyawali CP. Multiple rapid swallow responses segregate achalasia subtypes on high-resolution manometry. Neurogastroenterol Motil 2012;24:1069-e561. doi:10.1111/j.1365-2982.2012.01971.x
6. Lee JY, Kim N, Kim SE, et al. Clinical characteristics and treatment outcomes of 3 subtypes of achalasia according to the Chicago classification in a tertiary institute in Korea. J Neurogastroenterol Motil 2013;19:485-494. doi:10.5056/jnm.2013.19.4.485
7. Werner YB, Hakanson B, Martinek J, et al. Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia. N Engl J Med 2019;381:2219-2229. doi:10.1056/NEJMoa1905380
8. Patel DA, Naik R, Slaughter JC, Higginbotham T, Silver H, Vaezi MF. Weight loss in achalasia is determined by its phenotype. Dis Esophagus 2018;31:doy046. doi:10.1093/dote/doy046
9. Lin Z, Carlson DA, Dykstra K, et al. High-resolution impedance manometry measurement of bolus flow time in achalasia and its correlation with dysphagia. Neurogastroenterol Motil 2015;27:1232-1238. doi:10.1111/nmo.12613
10. Küper MA, Kramer KM, Kirschniak A, et al. Dysfunction of the lower esophageal sphincter and dysmotility of the tubular esophagus in morbidly obese patients. Obes Surg 2009;19:1143-1149. doi:10.1007/s11695-009-9881-z
11. Tanaka Y, Ihara E, Nakamura K, et al. Clinical characteristics associated with esophageal motility function. J Gastroenterol Hepatol 2016;31:1133-1140. doi:10.1111/jgh.13262
12. Niebisch S, Hadzijusufovic E, Mehdorn M, et al. Achalasia-an unnecessary long way to diagnosis. Dis Esophagus 2017;30:1-6. doi:10.1093/dote/dow004
13. Sinan H, Tatum RP, Soares RV, Martin AV, Pellegrini CA, Oelschlager BK. Prevalence of respiratory symptoms in patients with achalasia. Dis Esophagus 2011;24:224-228. doi:10.1111/j.1442-2050.2010.01126.x
14. Parshad R, Devana SK, Panchanatheeswaran K, et al. Clinical, radiological and functional assessment of pulmonary status in patients with achalasia cardia before and after treatment. Eur J Cardiothorac Surg 2012;42:e90-e95. doi:10.1093/ejcts/ezs421
15. Nabi Z, Ramchandani M, Kotla R, et al. Gastroesophageal reflux disease after peroral endoscopic myotomy is unpredictable, but responsive to proton pump inhibitor therapy: a large, single-center study. Endoscopy 2020;52:643-651. doi:10.1055/a-1133-4354
16. Ponds FA, Fockens P, Lei A, et al. Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia: A Randomized Clinical Trial. JAMA 2019;322:134-144. doi:10.1001/jama.2019.8859
17. Tang Y, Xie C, Wang M, Jiang L, Shi R, Lin L. Association of High-Resolution Manometry Metrics with the Symptoms of Achalasia and

the Symptomatic Outcomes of Peroral Esophageal Myotomy. PLoS One 2015;10:e0139385. doi:10.1371/journal.pone.0139385

18. Khashab MA, Familiari P, Draganov PV, et al. Peroral endoscopic myotomy is effective and safe in non-achalasia esophageal motility disorders: an international multicenter study. Endosc Int Open 2018;6:E1031-E1036. doi:10.1055/a-0625-6288
19. Khashab MA, Messallam AA, Onimaru M, et al. International multicenter experience with peroral endoscopic myotomy for the treatment of spastic esophageal disorders refractory to medical therapy (with video). Gastrointest Endosc 2015;81:1170-1177. doi:10.1016/j.gie.2014.10.011
20. Teitelbaum EN, Soper NJ, Santos BF, et al. Symptomatic and physiologic outcomes one year after peroral esophageal myotomy (POEM) for treatment of achalasia. Surg Endosc 2014;28:3359-3365. doi:10.1007/s00464-014-3628-1
21. Roman S, Kahrilas PJ, Mion F, et al. Partial recovery of peristalsis after myotomy for achalasia: more the rule than the exception. JAMA Surg 2013;148:157-164. doi:10.1001/2013.jamasurg.38