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ORIGINAL ARTICLE—ALIMENTARY TRACT

Achalasia symptom response after Heller myotomy segregated by high-resolution manometry subtypes

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Abstract
Background Achalasia is classified into three HRM subtypes that predict outcomes from diverse management strategies. We assessed if symptomatic response varied when a single management strategy—Heller myotomy (HM)—is employed.
Methods Treatment-naive subjects with achalasia referred for HM were followed in this observational cohort study. Chicago criteria designated achalasia subtypes (subtype I: no esophageal pressurization; subtype II: panesophageal pressurization in ≥20 % swallows; subtype III: premature contractions in ≥20 % swallows). Symptom questionnaires assessed symptom burden before and after HM on five-point Likert scales (0 = no symptoms, 4 = severe symptoms) and on 10-cm visual analog scales (global symptom severity, GSS); satisfaction with HM was recorded similarly. Data were analyzed to determine predictors of GSS change across subtypes.
Results Sixty achalasia subjects (56.1 ± 2.4 years, 55 % female) fulfilled inclusion criteria, 15 % with subtype I, 58 % with subtype II, and 27 % with subtype III achalasia. Baseline symptoms included dysphagia (solids: 85 %, liquids: 73 %), regurgitation (84 %), and chest pain (35 %); mean GSS was 7.1 ± 0.3. Upon follow-up 2.1 ± 0.2 years after HM, GSS declined to 1.9 ± 0.4 ($p < 0.001$), with surgical satisfaction score of 8.7 ± 0.3 out of 10; these were similar across achalasia subtypes. On univariate analysis, female gender, Eckardt score, severity of transit symptoms, and maximal IRP predicted linear GSS improvement; female gender ($p = 0.003$) and dysphagia for liquids ($p = 0.043$) remained predictive on multivariate analysis.
Conclusions When a uniform surgical approach is utilized, symptomatic outcome and satisfaction with therapy are similar across achalasia subtypes. Female gender and severity of dysphagia for solids may predict better HM outcome.

Keywords Achalasia · High-resolution manometry · Heller myotomy

Introduction

Achalasia, the most investigated esophageal motor disorder, is characterized by impaired relaxation of the lower esophageal sphincter (LES) and loss of coordinated esophageal body peristalsis on motor testing [1]. With esophageal high-resolution manometry (HRM), achalasia spectrum disorders have been categorized into clinically relevant subtypes based on esophageal body motor patterns [2–4]. In particular, type II (panesophageal compartmentalization of intrabolus pressure ≥30 mmHg in ≥20 % test swallows) is associated with a significantly better treatment response compared to type I or III, while type III (preserved but premature esophageal body peristalsis in ≥20 % test swallows) is associated with worse outcomes and can be the most challenging to manage [5]. Common management approaches associated with a durable response include pneumatic dilation (PD), Heller myotomy (HM), and peroral endoscopic myotomy (POEM), while botulinum toxin injection into the LES can provide temporary benefit [1].

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Recent studies suggest a better response to HM compared to other therapies in subtype III, while both PD and HM can provide good benefit in other subtypes [6]. PD and HM have been designated equivalent, with institutional expertise determining a final choice between these two modalities [1, 7]. These and other reports suggest that HM may represent the common thread providing symptomatic benefit regardless of subtype [8].

In this study, we aimed to evaluate how symptomatic response to achalasia varied by subtype if a single approach, i.e., HM, was utilized in a cohort of prospectively followed patients. A secondary aim was to determine demographic, clinical, and motor predictors of treatment outcome.

Methods

Subjects

Subjects were identified from a prospectively maintained database of clinical HRM studies at Washington University in St. Louis, Missouri, USA. All subjects >18 years of age with achalasia identified on HRM over a 5-year period underwent laparoscopic HM with partial Dor fundoplication by the Washington University minimally invasive surgical group were eligible for inclusion. Exclusion criteria included previous foregut surgery or pneumatic dilation, structural mechanical obstruction on upper endoscopy, technically imperfect studies with the LES not traversed, an inability to subtype achalasia due to incomplete swallow sequences, and surgery performed at other institutions. Subjects completed symptom assessments in questionnaire format when they presented for esophageal HRM, and were contacted for follow-up symptom assessment after surgery, at which time satisfaction with surgical management was also assessed; patients who could not be contacted were not considered for this study. This protocol was approved by the Human Research Protection Office (Institutional Review Board) at Washington University in St. Louis.

Esophageal HRM

Subjects underwent HRM following an overnight fast, and medications that can affect esophageal motor function were discontinued for 5–7 days prior to the HRM study whenever possible. Studies were performed with a solid-state, 36-channel catheter system with high-fidelity circumferential sensors at 1-cm intervals (Given Imaging, Los Angeles, CA, USA). After calibration, the catheter was passed through an anesthetized nasal canal by experienced nurses well versed in performing esophageal HRM. A 20-s swallow-free or "landmark" period was obtained during quiet rest to assess basal LES pressures. Next, a standard HRM protocol was performed with ten routine swallows of 5 ml of ambient temperature water spaced 20–30 s apart, with the patient in a supine position and slightly tilted to the left, with the head elevated to 15° to facilitate swallowing. Analysis of Clouse plots was performed using dedicated computerized HRM acquisition, display and analysis systems (ManoView, Given Imaging, Los Angeles, CA, USA).

For a diagnosis of achalasia, impaired LES relaxation defined by 4-s LES integrated relaxation pressure (IRP) >15 mmHg was required, along with documentation of absence of an alternate mechanism for symptoms. Achalasia was subtyped according to the Chicago classification [9]: (1) subtype I with absence of esophageal pressurization; (2) subtype II with ≥2 test swallows associated with pan-esophageal pressurization >30 mmHg; (3) subtype III with ≥2 premature contractions with or without compartmentalized pressurization between the contraction front and the LES.

Esophageal HRM studies were evaluated by an investigator (FM) not involved in clinical care of the patients. In addition to parameters required for achalasia subtyping, maximal IRP, as well as mean and maximal distal contractile integral (DCI) when available (in subtype III), were also extracted from the HRM studies.

Symptom assessment

Symptom questionnaires evaluating specific achalasia symptoms (dysphagia for solids, dysphagia for liquids, regurgitation, chest pain) as well as global symptom severity (GSS) were completed at the time of HRM testing. Patients rated symptom frequency and severity on five-point Likert scales generated a priori for esophageal testing at our institution and used in previous reports; these have been validated for assessment of esophageal symptoms [10–13]. On these scales, patients rate symptom frequency from 0 (no symptoms) to 4 (multiple daily episodes) and symptom severity from 0 (no symptoms) to 4 (very severe symptoms). A symptom intensity score is then calculated as the product of the frequency and severity for each symptom, for a total score from 0 to 16. GSS was assessed using a ten-point visual analog scale. Both of these symptom-assessment tools have been extensively used by our group to assess initial and follow-up esophageal symptoms, both within the realm of achalasia spectrum disorders [14–16], and reflux disease [10, 13, 17]. These parameters were reassessed prospectively upon follow-up, and changes in individual symptoms as well as global symptoms (using GSS) were recorded. Eckardt scores were determined, which takes into consideration dysphagia,

chest pain, and weight loss [18]. Additionally, satisfaction with HM was evaluated at follow-up on a similar ten-point scale, from 0 (extremely dissatisfied) to 10 (extremely satisfied).

Statistical analysis

Data are reported as mean ± standard error of mean (SEM), unless otherwise stated. Categorical and grouped data were compared using the Chi-square test, one-way ANOVA, or two-tailed Student's *t* test, as appropriate. Univariate and multivariate regression analyses were performed to identify predictors of treatment outcome. Statistical analysis was performed with SPSS 22.0 (IBM, Armonk, NY, USA).

Results

Sixty subjects (mean age 56.1 ± 2.4 years, 55.0 % female) fulfilled the study criteria and were successfully contacted for follow-up symptom assessment. There were no age or gender differences between the achalasia subtypes (Table 1). Among the cardinal achalasia symptoms (dysphagia, regurgitation, and chest pain), dysphagia for liquids was proportionately higher in subtypes II and III compared to subtype I ($p = 0.04$), but proportions of other symptoms were similar across groups. Symptom scores for transit and perceptive symptoms, GSS, and Eckardt scores were also similar at baseline across subtypes. Subjects with achalasia subtype III trended towards a higher mean IRP ($p = 0.065$) and had a significantly higher maximal IRP compared to the other subtypes ($p = 0.029$). Pre-HM symptom scores for transit symptoms (dysphagia, both solid and liquid, and regurgitation) were significantly higher than that for perceptive symptoms overall, and did not differ by achalasia subtype.

As required by the study protocol, all subjects underwent HM with partial fundoplication. After a mean of 2.1 ± 0.2 years of follow-up after HM, there was marked symptom improvement, with a 75.0 % overall decline in GSS (pre HM: 7.1 ± 0.3, post HM 1.9 ± 0.4, $p < 0.001$, Fig. 1). Numerically, subtype I had the highest residual GSS score (3.1 ± 1.3) compared to the other two subtypes (subtype II: 1.6 ± 0.4, subtype III: 1.6 ± 0.8). All of the cardinal achalasia symptoms improved with HM (Fig. 2). Satisfaction with HM was rated as 8.7 ± 0.3 on a ten-point scale, and was similar across achalasia subtypes ($p = 0.95$, Fig. 1).

Univariate analyses evaluating potential predictors of linear GSS improvement with HM were performed to evaluate demographic parameters, symptom intensity, and Eckardt scores, achalasia subtype, and IRP on HRM. On univariate analyses, female gender, Eckardt score, dysphagia to solids, dysphagia to liquids, regurgitation, and maximal IRP significantly predicted GSS improvement ($p \leq 0.050$ for all), while mean IRP strongly trended towards doing so ($p = 0.059$, Table 2). However, age, chest pain, and achalasia subtypes did not predict GSS improvement ($p \geq 0.15$ for all). Multivariate analysis was conducted to include age, gender, severity of dysphagia for liquids, achalasia subtype, and mean IRP, and only female gender and more severe dysphagia for liquids significantly predicted better GSS improvement ($p = 0.003$, 0.043, respectively), whereas achalasia subtype did not (Table 2).

Table 1 Baseline demographic and clinical characteristics

	All subjects ($n = 60$)	Subtype I ($n = 9$)	Subtype II ($n = 35$)	Subtype III ($n = 16$)	*p* values*
Age (years)	56.1 ± 2.4	55.0 ± 6.5	53.0 ± 3.3	63.3 ± 3.8	0.189
Female gender	33 (55 %)	6 (67 %)	19 (54 %)	8 (50 %)	0.718
Presenting symptoms					
Dysphagia (solids)	91.1 %	85.7 %	97.1 %	80.0 %	0.135
Dysphagia (liquids)	78.6 %	42.9 %	85.3 %	80.0 %	0.044
Regurgitation	85.7 %	85.7 %	85.3 %	86.7 %	0.992
Chest pain	37.5 %	57.1 %	35.3 %	33.3 %	0.513
Symptom scores					
Transit symptoms	9.4 ± 0.7	10.3 ± 1.2	9.7 ± 0.8	8.2 ± 1.7	0.951
Perceptive symptoms	2.4 ± 0.5	3.6 ± 1.6	2.0 ± 0.5	3.0 ± 1.5	0.541
GSS	7.1 ± 0.3	8.0 ± 0.7	7.0 ± 0.4	7.0 ± 0.7	0.594
Eckardt score	4.4 ± 0.3	4.3 ± 1.0	4.7 ± 0.4	3.8 ± 0.7	0.500
Motor characteristics					
Mean IRP	29.7 ± 1.3	23.4 ± 2.7	29.8 ± 1.5	33.1 ± 3.1	0.065
Highest IRP	40.9 ± 2.4	29.3 ± 2.8	40.1 ± 2.5	49.0 ± 6.1	0.029

Discussion

In this observational cohort study, we report that when a uniform surgical approach is utilized for achalasia, global and individual symptoms improve significantly following HM over a mean follow-up of over 2 years. Further, this improvement is not predicted by achalasia subtype, but instead by the severity of transit symptoms. On multivariate analysis, female gender and greater severity of preoperative dysphagia predicted superior post-surgical outcomes in our study cohort.

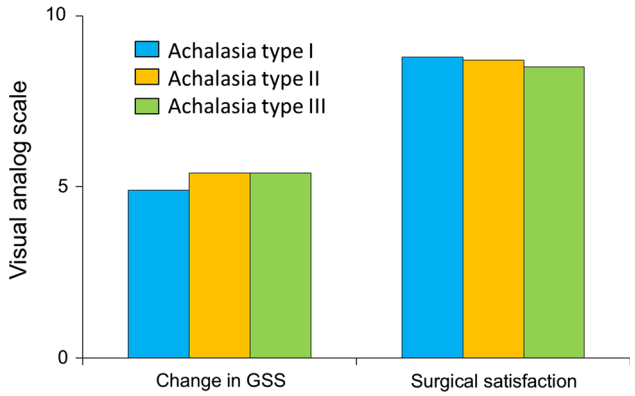

Fig. 1 Response to Heller myotomy. Change in global symptom severity (GSS) on a 10-cm visual analog scale was similar across the three achalasia subtypes following Heller myotomy (p = ns). Similarly, all three subtypes had high satisfaction from surgery on a 10-cm visual analog scale

Esophageal innervation, particularly inhibitory innervation, is compromised to varying degrees in the achalasia subtypes. The most profound motor abnormality in achalasia consists of esophageal outflow obstruction, which drives symptoms of dysphagia, esophageal retention of ingested food, and regurgitation [1]. The fact that esophageal body peristalsis is either absent (type I and II) or premature (type III) further complicates esophageal emptying, in that residual pressure within the poorly relaxing LES cannot be overcome by hydrostatic pressure in the esophageal lumen, complemented to varying degrees by contractile activity in particularly type III achalasia. When adequately performed, HM significantly lowers residual LES pressure, thus allowing esophageal body hydrostatic pressure to overcome any remaining residual LES pressure and thereby improve transit across the LES. We took care to only include patients who were treatment-naive, so that only the effects of HM were assessed, without contamination from possible partial benefit from other prior therapies. Our findings are consistent with those reported by Greene et al. [8] who also observed symptomatic improvement with HM regardless of achalasia subtype.

Multiple reports suggest that symptomatic responses vary depending on achalasia subtype [5, 19]. In type I achalasia, where the esophageal body is dilated and potentially tortuous, esophageal emptying may remain suboptimal despite adequate resolution of esophageal outflow obstruction. Our findings support these concepts, as type I achalasia had the highest residual symptoms in our cohort. Partial return of esophageal body peristalsis has been

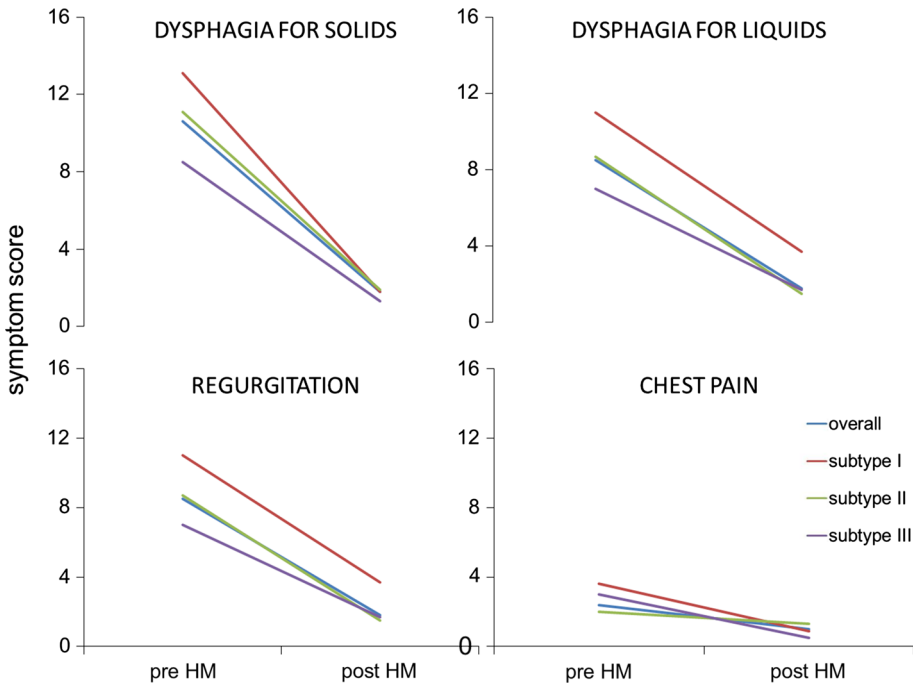

Fig. 2 Individual symptom improvement after Heller myotomy. Dysphagia (solids, liquids) and regurgitation improved significantly after Heller myotomy, both collectively ($p < 0.001$ for each comparison) and individually within each achalasia subtype ($p \leq 0.03$ for each comparison). While numerical improvement was seen with chest pain, differences did not reach statistical significance ($p \geq 0.1$)

Table 2 Univariate and multivariate analysis for predictors of linear GSS change

Predictors of GSS change	Univariate	Multivariate
Demographic		
Age	$p = 0.395$	$p = 0.869$
Female gender	$B = 2.678$, $p = 0.003$	$B = 2.549$, $p = 0.003$
Symptom intensity		
Dysphagia to solids	$B = 0.158$, $p = 0.029$	–
Dysphagia to liquids	$B = 0.152$, $p = 0.024$	$B = 0.130$, $p = 0.043$
Regurgitation	$B = 0.146$, $p = 0.036$	–
Chest pain	$p = 0.149$	–
Eckardt score	$B = 0.409$, $p = 0.040$	–
Achalasia subtype	$p = 0.916$	$p = 0.502$
I	$p = 0.782$	–
II	$p = 0.878$	–
III	$p = 0.708$	–
HRM		
Mean IRP	$B = 0.084$, $p = 0.059$	$p = 0.114$
Maximal IRP	$B = 0.049$, $p = 0.050$	–

demonstrated in type II achalasia, which may aid esophageal emptying following HM [20]. Additionally, the esophageal body is not dilated, and has tensile strength and retained longitudinal muscle contraction, allowing development of hydrostatic pressure that can overcome residual resistance at the esophagogastric junction [21]. These factors ensure a good symptomatic response in type II achalasia regardless of the mode of LES disruption. Our study findings are consistent with this evidence, and demonstrate a good response in type II achalasia.

With type III achalasia, in addition to esophageal outflow obstruction, there is premature and non-peristaltic esophageal body contraction, which has the potential to grip the bolus in the esophageal body despite resolution of resistance at the LES [5, 22]. Additionally, perceptive symptoms (i.e., chest pain) have been demonstrated to be more profound in some reports, which can contribute to residual symptoms [22]. Reports in the literature suggest suboptimal symptomatic response in type III achalasia treated with a mixed approach including pneumatic dilation, HM and botulinum toxin injection [5, 19]. However, on further subgroup analysis, there is evidence to suggest that the best responses in type III achalasia can be achieved with HM rather than pneumatic dilation [6]. Our results do not disprove speculation that pathophysiologic processes underlying types I and II may be different from that in type III [14, 16, 23], but we concur with Greene et al. [8] that type III achalasia patients respond symptomatically to HM at a rate not different from that seen with types I and II. Unless all the esophageal body sequences are premature and non-peristaltic, any retained esophageal body peristaltic response in type III achalasia will benefit esophageal emptying after HM. We used Chicago Classification 2.0 criteria for characterization of achalasia subtypes, but Chicago Classification 3.0 criteria are similar [9, 24]. In particular, diagnostic criteria for type III are lenient enough that up to 80 % of esophageal body sequences could be peristaltic (i.e., not premature) albeit spastic or exaggerated, with criteria requiring only 20 % of esophageal body sequences to be premature to make a diagnosis of type III achalasia. This leniency may contribute to the adequacy of HM in type III achalasia. Further, recommendations for an extended HM were generally made to our surgical colleagues for type III achalasia. While not systematically measured during surgery, the prematurely contracting esophageal body segment was potentially included in the myotomy—this may be one of the reasons why HM provides better benefit than PD in type III achalasia.

We report that patients with the most profound dysphagia (and consequently those with the highest IRP) do best with LES disruption, regardless of achalasia subtype. We speculate that abnormal transit across the gastroesophageal junction is the prime determinant of symptom benefit from disruption of the LES, since both profound dysphagia and high IRP are markers of abnormal esophageal emptying. In reporting good symptom response in their mixed-subtype achalasia cohort, Greene et al. [8] describe a dysphagia-predominant symptom presentation, and consistently abnormal esophageal emptying on timed upright barium swallow. Therefore, if clinical patient selection targets patients with the most profound abnormalities in esophageal emptying, HM can result in significant improvement.

Our study has a few limitations, the most prominent of which is the retrospective identification of our patient

cohort, despite the fact that symptom assessment was performed prospectively. Only patients who were deemed good candidates for surgery or were accepting of a surgical approach were included in this study. Further, only patients who could be contacted for follow-up and consented to symptom questionnaires were included. Both of these could have introduced selection bias in symptom reporting and outcomes. Further, overall patient numbers and proportions of patients in each subgroup were small, which could have underpowered subgroups and may have introduced a type II error in our findings. The follow-up period of 2 years is relatively short considering the natural history of achalasia, but patient attrition is a major factor in follow-up studies, as those with a good outcome are not interested in further follow-up, while those with a suboptimal outcome continue to return for follow-up, and this can influence outcome metrics. We also did not use objective measures such as repeat HRM or timed upright barium swallow to assess esophageal emptying post-operatively, which would have enhanced our evaluation of HM outcome, and may have demonstrated a dichotomy between symptomatic outcome and objective metrics. HM was performed by four different surgeons, which could have impacted symptom outcome from inter-operator and intra-operator differences in surgical technique, and this was not addressed in our study methodology. Nevertheless, the salient finding in this study is that a uniform surgical approach can provide an acceptable level of symptom resolution in achalasia regardless of subtype, despite potential biases from inter- and intra-operator variations in operation technique. This may be relevant to centers where advanced interventional techniques such as pneumatic dilation and POEM are not easily available, where at the very least, a surgical approach to management can be offered. However, caution may need to be exercised regarding generalizability of our findings, since this experience comes from a tertiary care institution where surgeons specializing in minimally invasive esophageal surgery performed all the procedures, where a standardized surgical approach is followed. Of note, our study was not designed to address the medical treatment of achalasia or histopathology.

In summary, we demonstrate that both global and individual symptoms significantly improve with a uniform surgical approach in achalasia; the degree of improvement is predicted by pre-surgical severity of transit symptoms and degree of IRP abnormality. In contrast, we report that achalasia subtypes did not predict symptom improvement with HM. Further larger and longer-term prospective studies are needed to evaluate management outcome as it relates to the subtypes of achalasia.

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Conflict of interest The authors declare that they have no conflict of interest.

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