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RETROSPECTIVE STUDY

Upper esophageal sphincter abnormalities are strongly predictive of treatment response in patients with achalasia

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Abstract

AIM: To investigate the relationship between upper esophageal sphincter abnormalities achalasia treatment

METHODS: We performed a retrospective study of 41 consecutive patients referred for high resolution esophageal manometry with a final manometric diagnosis of achalasia. Patients were sub-divided by presence or absence of Upper esophageal sphincter (UES) abnormality, and clinical and manometric profiles were compared. Correlation between UES abnormality and sub-type (*i.e.*, hypertensive, hypotensive or impaired relaxation) and a number of variables, including qualitative treatment response, achalasia sub-type, co-morbid medical illness, psychiatric illness, surgical history, dominant presenting symptom, treatment type, age and gender were also evaluated.

RESULTS: Among all 41 patients, 24 (58.54%) had a UES abnormality present. There were no significant differences between the groups in terms of age, gender or any other clinical or demographic profiles. Among those with UES abnormalities, the majority were either hypertensive (41.67%) or had impaired relaxation (37.5%) as compared to hypotensive (20.83%), although this did not reach statistical significance (P = 0.42). There was no specific association between treatment response and treatment type received; however, there was a significant association between UES abnormalities and treatment response. In patients with achalasia and concomitant UES abnormalities, 87.5% had poor treatment response, while only 12.5% had favorable response. In contrast, in patients with achalasia and no UES abnormalities, the majority (78.57%) had good treatment response, as compared to 21.43% with poor treatment response (P = 0.0001). After controlling for achalasia sub-type, those with UES abnormality had 26 times greater odds of poor treatment response than those with no UES abnormality (P = 0.009). Similarly, after controlling for treatment type, those with UES abnormality had 13.9 times greater odds of poor treatment response compared to those with no UES abnormality (P = 0.017).

CONCLUSION: The presence of UES abnormalities in patients with achalasia significantly predicted poorer treatment response as compared to those with normal UES function.

Key words: Upper esophageal sphincter; Achalasia; Motility; Dysphagia; Esophageal disorders

Core tip: Our study highlights how the presence of

Upper esophageal sphincter (UES) abnormalities in patients with achalasia significantly predicted poorer treatment response as compared to those with normal UES function, irrespective of the type of treatment received or achalasia sub-type. We believe this finding is novel and represents an opportunity to more fully characterize upper esophageal sphincter pathology in a clinical context.

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INTRODUCTION

Esophageal manometry has primarily been used to evaluate disorders of the esophageal body and lower esophageal sphincter. The introduction of high resolution esophageal manometry (HREM) has allowed the additional ability to assess the function of the upper esophageal sphincter (UES). While a wide spectrum of abnormalities such as alterations of resting UES pressures and impaired relaxation have been described in association with various motility disorders, the current Chicago Classification for manometric disorders[1] does not comment on UES findings. In addition, these abnormalities are often interpreted as incidental findings with no clearly defined clinical significance[2].

Manometric abnormalities of the UES have been documented in numerous settings, including as a function of aging[3-6]. They have also been reported in association with specific motility disorders and symptoms including achalasia[7-10], dysphagia[11-13], Parkinson's disease[14-16], oculopharyngeal muscular dystrophy[17], cricopharyngeal bar[18], globus[19], Zenker's diverticulum[20], and scleroderma[21]. However, the relationship and role of UES abnormalities in the context of motility disorders, specifically achalasia, remain unclear. While prior studies have demonstrated manometric UES abnormalities in achalasia[7-10], its clinical relevance and effects on therapeutic outcomes has not been fully characterized and remains poorly understood[22].

We hypothesized that UES abnormalities in association with achalasia may have significant clinical implications and may be useful as a predictor of treatment response. The primary aim of this study was therefore to assess the frequency and type of UES abnormalities in patients referred for HREM with a manometric diagnosis of achalasia. The secondary aims were to further characterize the correlation of specific UES abnormalities with achalasia sub-type and clinical characteristics and to additionally assess for differences in treatment response based on the presence or absence of UES abnormality.

MATERIALS AND METHODS

Subjects and study protocol

We performed a retrospective study of consecutive patients from October 2011 to November 2012 who underwent high resolution esophageal manometry at the Johns Hopkins Center for Neurogastroenterology and were subsequently diagnosed with Achalasia (Type Ⅰ, Ⅱ, or Ⅲ) defined as based per the current Chicago Classification. Patients with a manometric diagnosis that was consistent with achalasia were subsequently sub-divided into those with normal and abnormal UES function. Primary indications for HREM in these patients included dysphagia, atypical chest pain, cough, belching, globus, regurgitation, nausea and vomiting. The study protocol was approved by the John Hopkins University School of Medicine Institutional Review Board (IRB). Our protocol was in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Manometric protocol

Manometric studies were performed with the patients in the supine position after a minimum 6 h fasting period. A solid-state high-resolution manometer was used for all data collection (ManoScan360 High Resolution Manometry System, Sierra Scientific Instruments, and Los Angeles, CA). The manometric catheter has an outer diameter of 4 mm and 36 circumferential pressure sensors spaced 1 cm apart. The system is calibrated to record pressures between -20 and 600 mmHg, with fidelity of 2 mmHg. The catheter was positioned so that at least 2 distal sensors were in the stomach and 2 proximal sensors were located above the UES. The manometric protocol included a 5-min baseline recording, followed by 10 wet swallows of 5 cc water.

Manometric data analysis

All manometry studies were analyzed using ManoView software (*Sierra Scientific Instruments*) and were appropriately corrected for thermal sensitivity of the pressure-sensing elements using thermal compensation. The esophageal pressure topography plot of each swallow in the HRM study was subsequently analyzed based on the current Chicago Classification scheme[1]. Sub-classification of achalasia was defined based on the scheme put forth by Pandolfino *et al*[23] after the introduction of Chicago Classification: Type I representing classic achalasia with minimal esophageal contractility and low intraesophageal pressure, type Ⅱ representing absent peristalsis and panesophageal pressure elevations, and type Ⅲ representing lumen-obliterating esophageal spasm.

Definition of UES pressure and abnormalities

UES pressures were measured throughout the study prior to each of the 10 wet swallows and abnormalities recorded included: hypotensive upper esophageal sphincter pressure, hypertensive upper esophageal sphincter pressure, and impaired UES relaxation. UES resting pressure

during the first 5 min of the study (while establishing the baseline), was excluded from our study. While there is some discrepancy in the literature regarding normal UES baseline values, normal ranges were established based on a prior study that sought the UES pressures in 73 healthy subjects. The normal range was defined by the 5th and / or 95th percentile value of the parameters found[24]. Based on these values, our patients were divided into those with normal UES function and abnormal function including: impaired UES relaxation (residual pressure > 12 mmHg), hypertensive resting UES pressure (> 104 mmHg), and hypotensive resting UES pressure (< 34 mmHg). While there is currently no well-established normal range for UES pressure, for the purposes of this study, we used the normal ranges (as referenced above) put forth by GIVEN imaging for their high resolution esophageal manometry ManoView software (*Sierra Scientific Instruments*).

The frequency of UES abnormalities and sub-type of UES abnormality present (*e.g.,* hypotensive, hypertensive, or impaired relaxation) was evaluated in this population of patients with achalasia. Additionally, we looked at the association between sub-types of achalasia *(e.g.,* Ⅰ, Ⅱ, or Ⅲ) and the presence of specific UES abnormalities. In addition, clinical and demographic profiles were also examined and correlated with type of UES abnormality present including dominant presenting symptom, age, gender, race, co-morbid medical illness, psychiatric illness, and surgical history.

Lastly, we sought to determine whether or not the presence of an UES abnormality was predictive of either treatment received or treatment response in our patient population. Types of treatment included: endoscopic pneumatic dilation (PD), targeted endoscopic botulinum toxin (Botox) injections to the lower esophageal sphincter, medical therapy (*e.g.,* calcium channel blockers), Surgical myotomy with fundoplication, and Per Oral Endoscopic Myotomy (POEM). The majority of patients underwent surgical (*e.g.,* Heller myotomy) or endoscopic myotomy (*e.g.,* POEM) for definitive treatment. Only those patients deemed "higher risk" for invasive procedures were treated with PD, pharmacotherapy or LES botox injections. All treatment decisions were made by the primary gastroenterologist who evaluated the patient and discussed treatment options which each individual at the time of a clinical office visit. Also of note, individual therapeutic options were decided by the gastroenterologist and patient independent of the presence of a UES abnormality on their manometry study.

Treatment response was defined qualitatively by patients as being either "favorable" or "poor," as based on significant improvement in post-treatment dysphagia rates and other primary associated symptoms (*e.g.,* regurgitation, weight loss, chest pain) with satisfactory improvement in symptoms and/or Eckardt score. This response was assessed in each individual patient by a gastroenterologist during a clinical office visit. A single gastroenterologist subsequently reviewed charts to document outcome data; this individual was blinded to the presence or absence of UES abnormalities.

Statistical analysis

Counts and percentages are reported. Fisher's exact test was used to investigate the association between presence of UES abnormality and categorical variables of interest. Age was compared using a two-sample *t*-test. A multivariate logistic regression model was used to assess the relationship between presence of UES abnormality and treatment response, while controlling for the type of achalasia, given that Type Ⅱ achalasia is known to have the best treatment response. Two-sided *P*-values $\leqslant 0.05$ were considered statistically significant. All analyses were conducted using SAS v. 9.3 (SAS Institute; Cary, NC).

RESULTS

A total of 41 patients with a diagnosis of achalasia were identified during the study period, of which 24 (58.5%) had an upper esophageal sphincter abnormality present on their HREM. There were no significant differences between the groups in terms of age or gender. When comparing individuals with no UES abnormality to individuals with UES abnormality, there were no significant differences in terms of age or gender [mean age 55.81 *vs* 53.32 ($P = 0.6492$) and 53.94% male *vs* 50.00% respectively ($P = 1.0000$)]

Among those patients with UES dysfunction present, the majority of those with abnormalities had a hypertensive basal UES pressure (41.67%) followed by impaired UES relaxation (37.5%) and a hypotensive basal UES pressure (20.83%). Patients with achalasia were also significantly more likely to have either a hypertensive UES resting pressure or have impaired UES relaxation as compared to having low UES basal pressures (20.83% *vs* 79.17%, $P = 0.004$).

The majority of our cohort with UES abnormalities had type Ⅱ achalasia (Type Ⅱ 65% *vs* Type Ⅰ 20 % *vs* Type Ⅲ 15%), which was also the case in patients with no UES abnormalities (Type Ⅱ 56.25% *vs* Type Ⅰ 18.75% *vs* Type Ⅲ 25%). There was no significant association seen between sub-type of achalasia and the presence or absence of UES abnormality ($P = 0.8916$).There was no significant association between type of achalasia and subtype of UES abnormality (*e.g.,* hypertensive, hypotensive, or impaired relaxation, $p = 0.3345$) (Table 1).

There were no significant differences observed between presence or absence of UES abnormality and type of treatment that patients received (*e.g.,* endoscopic dilatation, endoscopic Botulinum toxin injections, medical therapy, POEM, or surgical myotomy) ($P = 0.40$). Similarly, there was no association when examining therapeutic treatment response when each treatment was compared individually (endoscopic dilatation, $P = 0.69$; endoscopic Botox, $P = 0.63$; medical therapy, $p = 0.21$; POEM, $p = 1.00$; surgical myotomy, $P = 0.08$). Additionally, there was no association between type of UES abnormality and specific treatment type of received ($P = 0.79$) (Table 2).

Table 1 Distribution of upper esophageal sphincter abnormality by achalasia sub-type

Type of achalasia	UES abnormality			*P*-value
	Hypertensive (%)	Hypotensive (%)	Impaired relaxation (%)	
Type Ⅰ	22.22	50	0.00	0.3345
Type Ⅱ	55.56	50	85.71	
Type Ⅲ	22.22	0	14.29	

UES: Upper esophageal sphincter.

With respect to treatment response, patients with achalasia and a UES abnormality present had a significantly poorer treatment response as compared to those with no UES abnormality present. Specifically, in patients with achalasia and a concomitant UES abnormality, 87.5% rated their treatment response as poor, while only 12.5% rated it favorable ($P < 0.0001$). In contrast, in patients with achalasia and no UES abnormality present, only 21.43% reported a poor treatment response while the majority (78.57%) rated it favorable ($P = 0.0001$) (Table 3). However, individual UES abnormality type was not significantly associated with treatment response ($P = 0.70$). In addition, after controlling for achalasia sub-type, those with UES abnormality had a 26 times greater odds of poor treatment response than those with no UES abnormality ($P = 0.0099$). Similarly, after controlling for treatment type, those with a UES abnormality present had a 13.9 times greater odds of poor treatment response compared to those without ($P = 0.0173$). There was no significant relationship observed when comparing treatment response with achalasia sub-type ($P = 0.2163$).

There was no significant association between initial dominant symptom presentation (dysphagia, chest pain, GERD, globus sensation, hiccups, or "other" dominant symptom) and presence or absence of UES abnormality ($P = 0.87$). Similarly, when examining these symptoms individually, there was no association between presence of UES abnormalities with any primary symptoms (dysphagia, $P = 0.7289$; chest pain, $P = 1.000$; GERD, $P = 0.5598$; globus sensation, $P = 1.000$; hiccups, $P = 1.0000$; other dominant symptom, $P = 1.000$).

The relationship between underlying medical co-morbidities with presence of absence of UES abnormalities was also assessed, and no significant associations were observed (diabetes, $P = 0.2072$; scleroderma, $P = 1.0000$; asthma, $P = 1.0000$; stroke, $P = 0.4146$; dementia, $P = 0.4146$; gastroparesis, $P = 1.0000$; achalasia, $P = 0.4328$). Additionally, we found no association between psychiatric disorders and presence or absence of UES abnormalities (psychiatric disorders, $P = 0.7364$; depression, $P = 1.0000$; anxiety, $P = 0.6293$; other psychiatric disorders [including bipolar disorder and schizophrenia], $P = 1.0000$). There was also no significant association observed between history of prior esophageal or other relevant surgeries and presence or absence of UES abnormality (History of any prior surgery, $P = 0.752$; larynx surgery, $P = 1.0000$; esophageal surgery, $P = 0.3725$; spine surgery, $P = 0.5024$; all additional surgeries, $P = 1.0000$).

DISCUSSION

The pathophysiology of disorders affecting the upper esophageal sphincter is incompletely understood. The advent of solid state, high resolution esophageal manometry has improved our understanding and ability to evaluate the UES and pharyngeal region. In the present study, upper esophageal sphincter abnormalities were not only a frequent finding in patients with achalasia, but additionally were useful in predicting treatment response. The association of UES abnormalities with treatment response remained even after adjusting for type of treatment received. Interestingly, among patients with achalasia, UES abnormalities were more common than normal UES function in this population. Further, the presence of UES abnormalities in patients with achalasia significantly predicted poorer treatment response when compared to those with normal UES function, irrespective of the type of treatment received or the sub-type of achalasia that was being treated. Similar to prior studies, the present study also demonstrated that in patients with UES abnormalities, Type Ⅱ achalasia was the most common sub-type[24-26]; however, there was no association observed between sub-type of achalasia and presence of UES dysfunction.

Malhi-Chowla *et al*[22] previously reported that UES abnormalities are a common incidental finding on manometric studies, even in the absence of abnormal radiographic signs or upper esophageal sphincter symptoms. These authors concluded that routine UES manometry with esophageal manometry was therefore not always useful, particularly when UES dysfunction was not suspected clinically. In contrast to their findings, with our assessment of clinical outcomes in a large group of patients with achalasia, the present study provides direct evidence that UES abnormalities may be clinically relevant, specifically in predicting treatment response in individuals with achalasia. As a result, our findings suggest a direct association between UES dysfunction and poorer outcomes in this patient population, and further provide support for careful manometic UES evaluation even when a motility disorder with a predominantly lower esophageal pathology (*i.e.,* achalasia) is suspected.

The finding that UES abnormalities in achalasia is strongly predictive of poorer treatment response suggests that this sub-population with UES dysfunction may have more severe disease with potentially more extensive and further proximal esophageal involvement. While prior studies have suggested that UES abnormalities appear to be associated with achalasia and other esophageal motility disorders[11-21], none of those studies directly assessed clinical significance or response to treatment.

Better treatment response in patients with type Ⅱ achalasia has been well described in several studies[26-28]. It is additionally well known that patients with type Ⅲ

Table 2 Type of treatment received based on upper esophageal sphincter abnormality sub-type

Treatment	UES abnormality			*P*-value
	Hypertensive (%)	Hypotensive (%)	Impaired relaxation (%)	
Pneumatic dilatation	0	25	11.11	0.3967
Endoscopic botox treatment	25	0	22.22	
Medical therapy	0	0	22.22	
POEM	12.5	0	11.11	
Surgical myotomy	62.5	75	33.33	

UES: Upper esophageal sphincter.

Table 3 Treatment response based on presence of upper esophageal sphincter abnormality

Treatment response	No UES abnormality	UES abnormality	*P*-value
Favorable	78.57%	12.50%	< 0.0001
Poor	21.43%	87.50%	

UES: Upper esophageal sphincter.

achalasia have the worst response to all therapies. However, even after controlling for type of achalasia, our results still demonstrated that treatment response was significantly better in all types of achalasia without UES abnormalities as compared to patients with concurrent achalasia and UES dysfunction. In other words, UES dysfunction appeared to independently predict treatment failure and normal UES function independently predicted better treatment response, irregardless of achalasia subtype.

UES dysfunction in achalasia has previously been described, specifically with impaired UES relaxation reported as the most common abnormality among patients with achalasia. Yoneyama *et al*[10] compared the UES manometric characteristics of 15 patients with diagnosis of achalasia as compared to 10 healthy volunteers and concluded that UES relaxation in patients with achalasia is incomplete. In the present study, we found a very high frequency of concomitant UES abnormalities among patients with achalasia (54%). Further, these individuals with UES abnormalities were more likely to have either impairment of UES relaxation or a hypertensive resting pressure as compared to being hypotensive. Although achalasia classically spares striated muscle, both prior literature and the results of the present study demonstrate a high frequency of upper esophageal sphincter involvement in this specific patient population.

In exploring what may account for this finding, it is plausible that increased UES pressure represents a compensatory or protective effect toward inadequate esophageal clearance in achalasia. Prior studies have also reported a reflexive hypertensive upper esophageal resting pressures after intraesophageal distension[29]. These investigators proposed that this may be a result of the UES serving as a dynamic barrier to esophagopharyngeal reflux and subsequent bronchial aspiration. Another possibility is that a neural feedback mechanism exists between UES relaxation and tension in the esophageal wall, such that increased resting pressure in the esophageal body transmits directly to the UES.

A paradoxical increase in UES pressure may also result from the loss of inhibitory neurons more proximally in patients with achalasia who may have more extensive esophageal involvement. A subset of patients with achalasia may also have more significant vagal involvement with Wallerian degeneration in the vagal fibers that supply the esophagus. In this context, the presence or severity of UES abnormalities may potentially be useful as a predictor to treatment response in achalasia. It is also possible that UES dysfunction in achalasia is simply a reflection of more severe disease and may reverse with treatment. In fact, prior studies have demonstrated that UES abnormalities disappear after pneumatic dilation[13], suggesting that reversal of UES dysfunction may be used as one of the predictors of treatment response. Lastly, although it is generally believed that the upper third of the esophagus, is composed primarily of striated muscle, this may not necessarily be the case in all individuals. Interestingly, in one autopsy study, smooth muscle fibers in the circular muscle up to the level of the upper esophageal sphincter were found in 45% of specimens[30].

Our study is the first to directly report on the potential clinical significance of UES abnormalities in treatment outcome in patients with achalasia; however, the authors acknowledge that there were significant limitations to the present study. First, this was a retrospective analysis which inherently limits the ability to draw causative conclusions. However, given the limited literature on UES abnormalities and clinical outcomes in patients with achalasia, it adds significant value in identifying key areas of further study in a larger, prospective evaluation. Another limitation is that treatment response was based on subjective evaluation by the patient of improvement in primary symptoms (and Eckardt scores were not assessed in all patients), which was collected by chart review based on the assessment of the clinical provider. A more objective measure such as a pre and post-treatment Eckardt score, barium esophogram, or repeat manometric study would have provided more objective outcome data; however, this was not possible given the retrospective nature of the study. In addition, further correlation with presence or resolution of UES abnormality post proce-

dure would have been ideal, but this was not feasible in this retrospective setting. Nevertheless, our subjective measure was able to reliably demonstrate a significant clinical difference. It is also important to note that this study took place at a tertiary care/motility referral center. Consequently, the results of this study may not be as generalizable to the general patient population. However, the demographics and presentation profile of our patient population appear largely similar to those in non-academic settings. Lastly, given that UES findings are not routinely reported on esophageal manometry studies and not formally included in any manometry classification systems at this time, it is likely that some studies that were interpreted as "normal," actually had UES abnormalities present. Thus, this study may even under-represent the true frequency of UES dysfunction among patients with achalasia.

In conclusion, our study illustrates that upper esophageal sphincter abnormalities in patients with achalasia have significant value in predicting treatment outcome. Our findings not only suggest a direct association between UES dysfunction and poorer outcomes in this population, but additionally provide support for manometic UES evaluation in all patients referred for HREM in whom an esophageal motility is suspected. Further, large scale studies are needed to determine whether specific UES abnormalities have additional prognostic value and may also clarify the underlying pathophysiologic mechanism driving the poorer outcomes seen in our study. Prospective evaluation is also needed to further delineate the underlying mechanism and natural history of UES dysfunction in achalasia in order to optimize therapeutic treatment modalities.

COMMENTS

Background

High resolution esophageal manometry has allowed the ability to assess the upper esophageal sphincter (UES). However, UES abnormalities are often interpreted as incidental findings with no defined clinical significance.

Research frontiers

The way in which UES abnormalities impact clinical outcomes in achalasia is unknown. We hypothesized that UES abnormalities have clinical significance and may predict treatment response in patients with achalasia.

Innovations and breakthroughs

The authors found that UES abnormalities were associated with worse treatment outcomes in achalasia patients. Prior studies do not focus on specific clinical outcomes.

Applications

These results, in combination with future studies, could aid in identifying which patients are more likely to succeed with achalasia treatment and could further direct treatment of UES conditions.

Terminology

UES refers to the upper esophageal sphincter.

Peer review

This manuscript assesses the function of UES in patients with achalasia. It is interesting. Manuscript is well written and easy to follow.

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