Achalasia and Obstructive Motor Disorders Are Not Uncommon in Patients With Eosinophilic Esophagitis

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BACKGROUND: **An association has been reported between achalasia and eosinophilic esophagitis (EoE). We performed a retrospective study of high-resolution manometry (HRM) patterns in a large cohort of patients with EoE.**

MATERIAL AND METHODS: **We collected data from consecutive patients with a new diagnosis of EoE from 2012 through 2019 undergoing HRM during the initial assessment at different centers in Italy. Demographic, clinical, endoscopic and histological characteristics were recorded at baseline and during management. Diagnoses of EoE and esophageal motility disorders were made according to established criteria. Treatments offered included proton pump inhibitors and topical steroids for EoE, and pneumatic dilation and myotomy for achalasia. Response to therapy was defined as less than 15 eosinophils per high power field in esophageal biopsies.**

RESULTS: **Of 109 consecutive patients (mean age 37 years, 82 male), 68 (62%) had normal findings from HRM. Among 41 patients with motor disorders, 24 (59%) had minor motor disorders and 17 (41%) presented with major motor disorders, including 8 with achalasia (1 with type 1, 4 with type 2, and 3 with type 3). Achalasia and nonachalasia obstructive motor disorders had 14.7% prevalence among patients with EoE. Achalasia was more frequent in women, with longer diagnostic delay and abnormal esophagogram ($P < .05$) compared with EoE without achalasia or obstructive motor disorders. Clinical features and endoscopic findings did not differ significantly between patients with EoE with vs without achalasia and obstructive motor disorders. A higher proportion of patients without achalasia and obstructive motor disorders responded to topical steroids than patients with these features ($P < .005$). Invasive achalasia management was required for symptom relief in 50% of patients with achalasia and obstructive motor disorders.**

CONCLUSION: **Achalasia and obstructive motor disorders are found in almost 15% of patients with EoE—esophageal eosinophilia might cause these disorders. Patients with EoE who does not respond to standard treatments might require targeted muscle disruption**

Keywords: Inflammation; Manometry; Obstructive Motility Disorders; Esophagus.

Abbreviations used in this paper: **DES, distal esophageal spasm; EGD, esophagogastroduodenoscopy; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; EoE, eosinophilic esophagitis; eos/HPF, eosinophils per high-power field; HRM, high-resolution manometry; IRP, integrated relaxation pressure; PPI, proton pump inhibitor.**

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Eosinophilic esophagitis (EoE) is a chronic immune- and antigen-mediated disorder characterized by esophageal symptoms and eosinophilic inflammation,[1,2] in which antigens, mainly of food origin, stimulate a Th2-mediated immune response that recruits eosinophils into the esophagus.[3] Once there, eosinophils produce a plethora of inflammatory cytokines, resulting in fibrotic remodeling of the esophageal wall, and leading to esophageal dysfunction and symptoms.[1] Because eosinophils have been isolated from esophageal muscle biopsies, and can release neurotoxic products, they are suspected to play a role in achalasia pathogenesis.[4,5] Indeed, eosinophilic inflammation of the esophageal muscularis propria and mucosal layer have been reported in achalasia.[6–10]

The easy availability of esophagogastroduodenoscopy (EGD) and high-resolution manometry (HRM) in clinical practice allows earlier and precise investigation of dysphagia.[11] Although esophageal motility abnormalities ranging from hypo- to hypercontractile disorders and achalasia have been reported in EoE,[4,12–16] their relationship with EoE remains poorly understood. We hypothesized that a true association exists in some instances via shared pathogenesis through eosinophilic infiltration. Our primary aim was to evaluate the overlap between EoE and esophageal obstructive motor disorders, including achalasia. Secondary aims were to assess the clinical course and the response to treatment in these cohorts.

What You Need to Know

Background

Eosinophilic esophagitis (EoE) is characterized by esophageal symptoms and eosinophilic inflammation of esophageal mucosa. Eosinophils have recently been implicated in the pathogenesis of achalasia and esophageal obstructive motility disorders.

Findings

Achalasia and obstructive motility disorders were identified in approximately 15% of patients with EoE. Clinical and endoscopic findings were almost identical between patients with EoE with and without achalasia and obstructive motility disorders; the diagnostic delay was significantly longer for patients with EoE with achalasia.

Implications for patient care

Coexistence of achalasia and obstructive motility disorders requires disease-specific management for resolution of dysphagia. Esophagography and high-resolution manometry can facilitate diagnosis of motility disorders in patients with EoE—especially when symptoms persist despite treatment.

Materials and Methods

Study Population

We evaluated consecutive patients with a new diagnosis of EoE who underwent HRM during initial evaluation at academic institutions in Padua, Genoa, Pisa, and Naples, between 2012 and 2019. HRM was added to the diagnostic work-up after evidence of overlap between achalasia and EoE.[6] The study was performed according to the Declaration of Helsinki and was approved by the local ethics committee (Identifier: Cesc 3312/AO/14). Part of the reported data has been previously published elsewhere.[17–19] All patients provided written informed consent before data collection.

EGD and Esophagogram

Each patient presented with esophageal symptoms (dysphagia or food impaction). At EGD, 2 biopsy samples each from the proximal, mid, and distal esophagus, and samples from the stomach and duodenum were obtained. Gross esophageal mucosal characteristics were recorded and endoscopic reference score was calculated,[20] which rates the severity of edema (0–1), rings (0–3), exudates (0–2), furrows (0–2), and strictures (0–1). A diagnosis of EoE required presence of ≥15 eosinophils per high-power field (eos/HPF) on biopsies from the mid and proximal esophagus.[21] Other causes of esophageal eosinophilia were excluded.[22] Each patient underwent an esophagogram to evaluate for transit abnormalities, strictures, dilated esophagus, esophageal stasis, bird's beak appearance, tortuous esophagus, and tertiary contractions.

High-Resolution Esophageal Manometry

All patients underwent HRM for inclusion, performed according to the Italian National Guidelines,[23] with manometric diagnoses according to Chicago Classification version 3.0.[24] Achalasia required abnormal median integrated relaxation pressure (IRP), and was subtyped based on absence (type 1) or presence of ≥20% esophageal panesophageal pressurization (type 2), or ≥20% premature contractions (type 3). Nonachalasia obstructive motility disorders included distal esophageal spasm (DES) (≥20% premature contractions with normal IRP), jackhammer esophagus (≥20% sequences with distal contractile integral >8000 mm Hg/cm/s and normal IRP), and esophagogastric junction (EGJ) outflow obstruction (EGJOO) (abnormal IRP without achalasia or structural EGJ stenosis). ManoScan Acquisition Software and ManoView Analysis Software (Medtronic, Minneapolis, MN) were used for HRM acquisition and interpretation.

Clinical Assessment

Demographic and clinical characteristics were extracted from the initial presentation. A 4-point Likert-type scale was used to characterize esophageal and exraesophageal symptoms, as previously reported.[19,21] Dysphagia was defined as dominant when the Likert-type score was >2. Dysphagia and reflux symptoms were further assessed using the Dysphagia Symptom Questionnaire and Gastroesophageal Reflux Disease Questionnaire.[19,21] The Eckardt score was recorded in all patients, despite validation only in achalasia. This score attributes 0–3 points to 4 symptoms (dysphagia, regurgitation, chest pain, and weight loss), with final scores ranging from 0 to 12.

All patients diagnosed with EoE initially underwent 8 weeks of double-dose proton pump inhibitor (PPI) treatment (ie, pantoprazole 40 mg twice a day, esomeprazole 40 mg twice a day, or rabeprazole 20 mg twice a day), and repeat EGD to assess endoscopic and histological response. In the absence of histological response (ie, <15 eos/HPF), topical steroid therapy (fluticasone or budesonide, 2 mg daily) or 6-food elimination diet was administered, with subsequent repeat EGD. When strictures were found, endoscopic dilation was performed. Symptoms, endoscopic and histological features were recorded during follow-up.

In the 16 patients with achalasia or obstructive motor disorders, additional detailed clinical history, diagnostic delay, comorbidities, diagnostic evaluation, and response to therapy were obtained. Specific achalasia treatments were administered when dysphagia persisted (Eckardt score >3 or Likert score >2), and included laparoscopic surgical myotomy (laparoscopic Heller myotomy) or pneumatic dilation according to availability and experience at each center.

Statistical Analysis

Differences in proportions were compared using the chi-square or Fisher's exact test as appropriate. Unless otherwise specified, data are presented as median and range values. When data were not normally distributed, differences between groups were compared using Kruskal-Wallis or Mann-Whitney tests. Differences were considered statistically significant when $P < .05$.

Results

Of 186 EoE patients identified, 77 were excluded (declined HRM, prior EoE diagnosis and therapy, severe strictures). The final study cohort consisted of 109 consecutive patients (mean 37 years of age, 82 male) with a new EoE diagnosis, complete clinical data and interpretable HRM (Table 1). None of the patients were taking opiate medications. Obstructive symptoms including dysphagia (90%) and bolus impaction (67%) were frequent, whereas gastroesophageal reflux disease–like symptoms were less common (40%). Endoscopic fibrosis (ie, rings, narrowing) and inflammation (ie, edema, whitish exudates, linear furrows) were found in 69% and 80%, respectively, with esophageal strictures in 16%. Most patients responded to PPI or topical steroid therapy (92.68%); only 2 patients underwent 6-food elimination diet alone without response. Among the 101 responders, 13 patients underwent endoscopic dilation along with medical therapy (n = 4 with PPI and n = 9 with steroids).

High-Resolution Manometry

A normal HRM study was observed in 68 (62%) patients (Figure 1). Of the remaining 41 patients, 24 (59%) had a minor motor disorder (ineffective esophageal motility = 23, fragmented peristalsis=1), while 17 (41%) had a major motility disorder (achalasia type 1 = 1, type 2 = 4, type 3 = 3, DES = 1, jackhammer esophagus=2, EGJOO=5, absent contractility = 1). Eventually, 8 (7.3%) patients had achalasia and 8 (7.3%) had non-achalasia obstructive motor disorders, for a total of 16 (14.7%) patients with obstructive motor pathophysiology.

EoE Patients With and Without Achalasia and Other Obstructive Motility Disorders

Upon comparing clinical characteristics (Table 1), more women were noted in EoE with achalasia and obstructive motility disorders group compared with those without ($P = .011$), while other demographic features, diagnostic delay, and clinical, endoscopic, and histologic findings were similar between the 2 cohorts ($P \geq .1$ for each comparison). Abnormalities on esophagogram were seen more often in achalasia and obstructive motility disorders ($P < .001$). While PPI response was similar ($P = .104$), patients with achalasia or other obstructive motility disorders responded significantly less to topical steroids ($P = .005$) (Figure 2).

Achalasia patients resembled those with other obstructive motility disorders, without differences in demographic features, symptoms, endoscopic and histologic features ($P \geq .23$ for each comparison) (Table 2). However, diagnostic delay was significantly longer in achalasia patients compared with nonachalasia obstructive motility disorders ($P = .038$), and with EoE without obstructive motor disorders or achalasia ($P = .024$). Diagnostic delay trended toward significance ($P = .1$) when EoE with both achalasia and obstructive motor disorders were compared with EoE without these motility disorders. There were no differences in PPI and topical steroid response between achalasia and other obstructive motor disorders ($P = 1$ and $P = .592$, respectively) (Figure 2).

Table 1. Baseline Demographics, Clinical Features, and Investigation Details Between Patient Cohorts

	All Patients	EoE patients With Achalasia or Nonachalasia Obstructive Motor Disorders	EoE Patients Without Achalasia or Nonachalasia Obstructive Motor Disorders	
	n = 109	n = 16	n = 93	*P* Value
Age at diagnosis, y	34 (12-73)	30.5 (16-73)	34 (12-68)	.540
Female	17 (25%)	8 (50%)	19 (20%)	.011[a]
BMI, kg/m^2	22.5 (15-42)	22 (19-26)	22.5 (15-42)	.348
Diagnostic delay, y	2 (0-20)	4 (1-18)	2 (0-20)	.102
Allergy	65 (60%)	11 (69%)	54 (58%)	.421
Obstructive symptoms	103 (95%)	15 (94%)	88 (95%)	1.0
GERD-like symptoms	44 (40%)	4 (25%)	40 (43%)	.270
Dominant dysphagia	96 (88%)	15 (94%)	81 (87%)	.687
Eckardt score	3 (1-8)	3.5 (2-7)	3 (1-8)	.307
Eosinophil count	57 (20-130)	51 (20-110)	58 (20-130)	.318
EREFS score	3 (0-6)	3 (0-6)	3 (0-6)	.262
Abnormal esophagogram	30 (28%)	11 (69%)	19 (20%)	<.001[a]

Values are mean (range) or n (%).
BMI, body mass index; EoE, eosinophilic esophagitis; EREFS, endoscopic reference score.
[a]•••.

Follow-Up and Outcome in EoE With Achalasia and Obstructive Motor Disorders

Of the 8 achalasia patients, most were women, with a long history of symptoms and endoscopic evaluations before EoE diagnosis (Table 3). Esophagograms suggested achalasia in 75% of cases. One achalasia patient had histologic response and partial clinical response to PPI therapy, but dysphagia resolved after pneumatic dilation. Topical steroids were effective in 5 of the remaining patients, but 2 required achalasia management to resolve obstructive symptoms. Finally, 2 patients did not respond to medical therapies, and required invasive achalasia management (Table 3); topical steroids were used for residual eosinophilia.

Of the 8 patients with nonachalasia obstructive motility disorders, 5 had EGJOO (Table 4). One had clinical improvement and histological resolution of eosinophilia after PPI therapy, and another obtained deep remission with topical steroids. Of the remaining 3 with EGJOO, only 1 achieved histological remission with topical steroids, but all 3 required pneumatic dilation for dysphagia resolution; residual eosinophilic infiltration was effectively treated with topical steroids in 2 patients. The 2 patients with jackhammer esophagus had clinical and histological remission with medical therapy, one with PPI and the other with topical steroids. Finally, 1 patient with DES did not achieve clinical and histological remission with medical therapy, likely owing to poor compliance to daily therapy (Table 4).

After mean follow-up of 30 months, clinical, endoscopic and histological benefit from therapy was observed in 15 of 16 (94%) patients with achalasia and obstructive motor disorders.

Discussion

In this multicenter study evaluating a large cohort of EoE patients, we reported that achalasia is not an uncommon finding in EoE, detected in 7.3% of patients evaluated with HRM. When obstructive major motility disorders with an obstructive component were also included, the frequency increased to 14.7%. We showed that clinical features of EoE patients with achalasia and obstructive motor disorders were almost identical to those without these motility disorders, indicating that dysphagia induced by motor disorders can overlap or mimic that related to EoE. In our opinion, this is clinically relevant, because most patients with obstructive motor disorders required disease-specific invasive management in addition to usual EoE treatments for symptom relief. We conclude that dedicated dysphagia evaluation with both esophagogram and HRM is needed when symptoms persist despite EoE management.

Anatomical and structural changes identified on EGD, such as rings, strictures, and narrow caliber lumen, may explain dysphagia, particularly food impaction, which is more specific for EoE than achalasia. However, dysphagia may occur even without endoscopic findings, when the mechanism is unclear. In these circumstances the possibility that a hidden esophageal motility disorder, including achalasia, could be involved in symptom generation has been increasingly recognized[4,12–15] and reported in up to 40% of EoE patients, although supporting data are limited to case reports and small retrospective series.[13,14,25–27] We confirm a similar frequency of motility disorders (38%), with 16% demonstrating major motility disorders according to Chicago Classification version 3.0.

More significantly, our data indicate that 1 in 7 patients with EoE may have an obstructive motor process, and 1 in 14 may have overt achalasia. Considering that the estimated prevalence of achalasia in the general population is 10-16 cases per 100,000 individuals,[28] our results are supportive of a potential causal link with EoE. Clinical presentation was identical to that of EoE without obstructive motor disorders, except for a longer diagnostic delay, particularly with achalasia. Most patients with achalasia and obstructive motility disorders required specific management targeting the obstruction in addition to usual EoE treatment. Our data highlight the fact that dysphagia in EoE patients may not always be explained by structural or anatomical abnormalities, and indicate the need for specific treatment when symptoms persist.[6,14,15,29] We agree with the current guidelines for EoE management when endoscopic or histologic criteria for diagnosis are fulfilled, but our findings highlight the importance of further evaluation for possible obstructive motor disorders, when symptoms do not improve with standard EoE management.

Since the late 1970s, single case reports have documented eosinophilic infiltrate in esophageal muscle layers of surgically treated achalasic patients,[8,9,30] rather than mucosal eosinophil infiltration characteristic of EoE.[4,31] In the last decade, refined EoE diagnostic criteria have allowed recognition of atypical sites of eosinophil infiltration in presence of motor abnormalities, including achalasia.[30,32] Spechler et al[4] synthesized these concepts into 3 plausible pathophysiological relationships between achalasia and EoE. The first considers stasis of retained food material causing mucosal inflammation with secretion of chemokines, which in turn attract eosinophils. This concept is not supported by the fact that eosinophilia is almost always under 15 eos/HPF and does not necessarily resolve following laparoscopic Heller myotomy, which should resolve stasis.[33] Moreover, in our patients, eosinophilia persisted in 4 patients with achalasia or obstructive motor abnormalities despite complete LES disruption, whereas medical therapy resolved the inflammation in 4 patients prior to definitive management. Therefore, our data are mixed and cannot exclude that food stasis facilitated the initiation of esophageal inflammation.

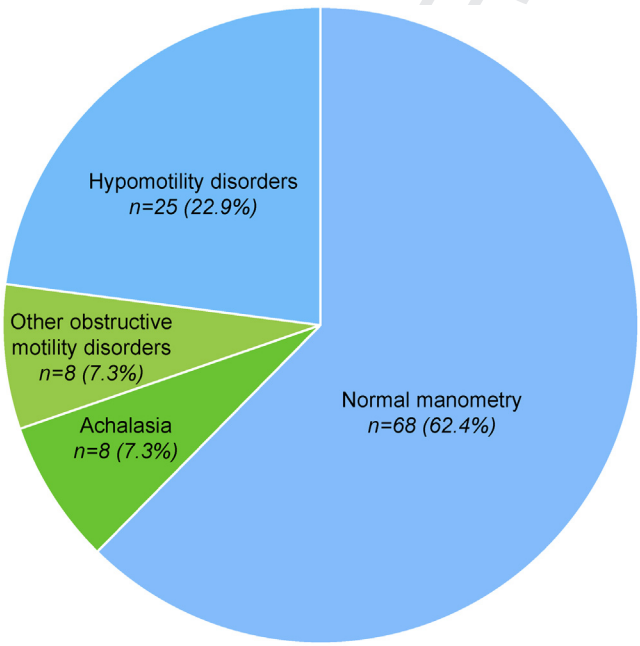

Figure 1. HRM patterns in patients with EoE.

The second hypothesis suggests that eosinophils located in the muscular layer release neurotoxins that destroy esophageal intramural neurons in Auerbach's plexus, thus causing the inhibitory neural dysfunction typical of achalasia. This is supported by the finding of eosinophilic infiltrate adjacent the remaining myenteric ganglion cells in esophageal muscle biopsies obtained during POEM.[5] This hypothesis, however, requires that symptomatology and manometric abnormalities are irreversible, whereas there are reports of clinical, manometric, and histological remission after medical management alone.[4,6,32] Resolution of dysphagia with medical therapies in our patients suggests that symptoms and manometric abnormalities can be reversible, at least in part, by likely reducing the cytokine milieu produced by eosinophils rather than neurotoxic damage. Consequently, one could question whether eosinophil inflammation of esophageal myenteric plexus necessarily induces permanent destruction of local intramural neurons in patients with achalasia and other obstructive motor disorders.

The third hypothesis suggests that eosinophilic products can cause achalasia-like motility abnormalities, which may potentially resolve after treatment. Eosinophils are known to produce substances with proinflammatory, myoactive, neuroactive, and profibrotic action. Therefore, they can mediate both the fibrotic degeneration of superficial layers and the modulation of contractile activity of the esophageal smooth muscle.[4] In keeping with this hypothesis, there are several reports of normalization of dysmotility in EoE patients after topical steroid treatment,[4,6,15,16] which improved symptoms with resolution of eosinophilia more often than PPI therapy in our patients as well. While there could be various pathophysiological mechanisms underlying the association between achalasia and EoE, our data seem to support the third hypothesis, even though firm conclusions cannot be drawn because of the lack of consistent HRM data following EoE management.

The longer diagnostic delay in EoE-achalasia patients is consistent with delayed diagnosis of achalasia in general. However, radiological abnormalities compatible with achalasia or other obstructive motor disorders were evident in the majority of patients even prior to manometric confirmation. This emphasizes the value of esophagogram in these patients, in that it can also identify esophageal strictures.[34] Furthermore, clinical, endoscopic, and histological findings in EoE patients with achalasia and obstructive motor disorders were almost

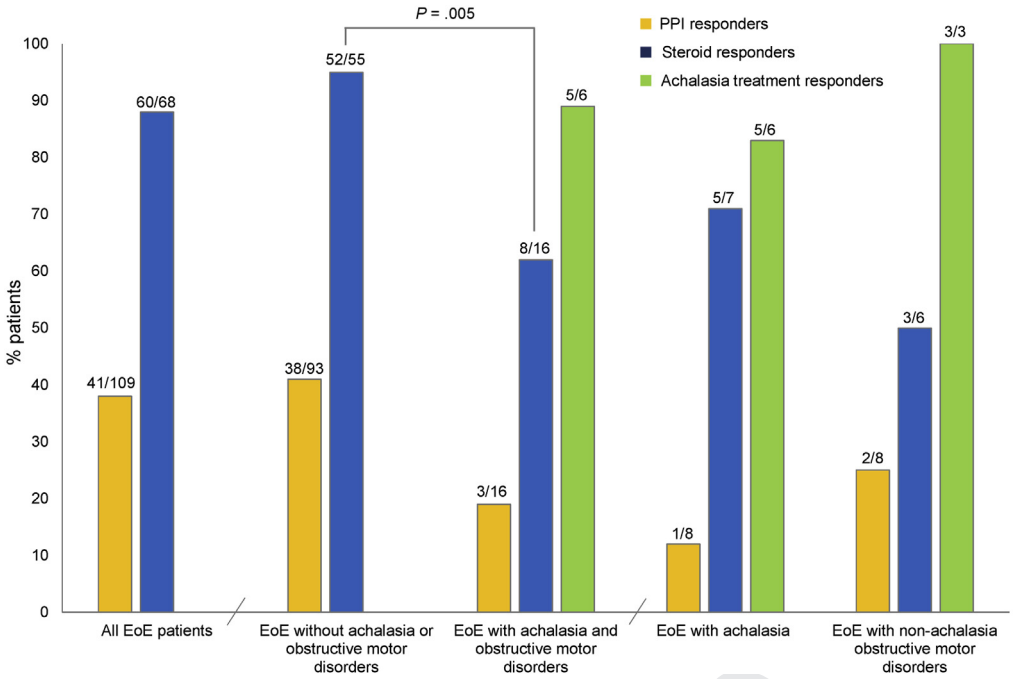

Figure 2. Comparison of response to therapy between the study groups. Topical steroid therapy offered to patients refractory to PPI was more successful in absence of achalasia or nonachalasia obstructive motor disorders ($P = .005$). Achalasia therapies were used in case of nonresponse to PPIs and topical steroid use. All other achalasia and nonachalasia obstructive motor disorder patients treated with achalasia-specific therapy had a good symptomatic response.

identical to the broader cohort without these motor abnormalities, thus underlining the value of an accurate assessment of dysphagia. The significance of a higher prevalence of women in the EoE-achalasia cohort is unclear. Autoimmunity, thought to be the basis for achalasia pathophysiology,[35] is seen more often in women. Furthermore, immunosuppressive therapy (ie, steroids) was effective and supportive of this autoimmune hypothesis. Nevertheless, our small patient number does not allow reliable conclusions regarding gender effect. Finally, we observed that both disorders require specific disease-related treatments, although a minority of patients achieve symptom improvement without the need of invasive treatments.

Table 2. Demographics, Clinical Features, and Investigation Details Between EoE Patients With Achalasia and Those With Nonachalasia Obstructive Motor Disorders

	EoE Patients With Achalasia	EoE Patients With Nonachalasia Obstructive Motor Disorders	
	n = 8	n = 8	*P* Value
Age at diagnosis, y	24 (16-73)	32.5 (19-45)	.798
Female	5 (62.5%)	3 (38%)	.619
BMI, kg/m^2	21.2 (20-26)	23.3 (19-25)	.234
Diagnostic delay, y	6 (1-8)	1.5 (1-10)	.038[a]
Allergy	5 (63)	6 (75%)	1.0
Obstructive symptoms	7 (87%)	8 (100%)	1.0
GERD-like symptoms	3 (37%)	1 (12%)	.569
Dominant dysphagia	7 (87%)	8 (100%)	1.0
Eckardt score	3.5 (2-7)	3.5 (2-4)	.721
Eosinophil count	62.5 (20-110)	45.5 (28-80)	1.0
EREFS score	3 (0-5)	3.5 (1-6)	.798
Abnormal esophagogram	6 (75%)	5 (63%)	1.0

Values are mean (range) or n (%).
BMI, body mass index; EoE, eosinophilic esophagitis; EREFS, endoscopic reference score; GERD, gastroesophageal reflux disease.
[a]•••.

Our work presents some limitations. First, despite multicenter consecutive patient enrollment, the sample size of achalasia and obstructive spastic disorders is unfortunately limited, given the discretional use of HRM as nonroutine test in EoE patients. In addition, we cannot exclude the potential for selection or referral bias, given that the centers involved have expertise in diagnosis and management of esophageal motor disorders. Thus, our sample size may have been skewed by highly symptomatic or more compliant patients who consented to HRM. However, this does not underestimate the relevance of achalasia diagnosis in EoE patients. Second, manometric reassessment was performed only in 2 of 8 achalasia patients after EoE treatment, thus limiting long-term analysis of the effect of EoE treatment on motility abnormalities. Another limitation was the partial information we had from histology as there are some studies suggesting the utility of full-thickness biopsy samples that include deeper layers of the esophageal wall in EoE patients. Finally, we combined achalasia spectrum disorders with other obstructive motor disorders (including EGJOO) to obtain the overall prevalence of 14.7%, in concert with modern concepts of obstructive pathophysiology in these disorders.[36] We note that the prevalence of these obstructive motor disorders in EoE is

Table 3. Characteristics of EoE Patients with Achalasia

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age at diagnosis, y	68	16	73	22	21	50	26	19
Sex	F	M	F	M	M	F	F	F
Diagnostic delay, y	18	10	15	6	5	3	6	2
History of allergy	No	Allergic dermatitis and rhinitis	No	Allergic rhinitis	Allergic conjunctivitis	No	Allergic dermatitis	Allergic dermatitis
Main symptoms	Dysphagia	Dysphagia	Regurgitation	Dysphagia and globus	Dysphagia and odynophagia	Dysphagia and heartburn	Dysphagia and food impaction	Dysphagia
EREFS score	4	5	3	3	3	0	4	1
HRM: achalasia subtype	E1R1E1F0S1 type II	E1R2E1F1S0 type III	E1R0E1F0S1 type I	E0R1E1F0S1 type III	E1R1E1F0S0 type II	E0R0E0F0S0 type III	E1R2E0F0S1 type II	E1R0E0F0S0 type II
Esophagogram	Dilated esophagus, narrowed EGJ	Delayed esophageal emptying	Esophageal stasis, narrowed EGJ	Narrowed EGJ	Dilated esophagus, narrowed EGJ	Normal	Narrowed EGJ	Normal
PPI response	Yes	No	No (intolerant)	No	No	No	No	No
Topical steroid response	NA	Yes	Yes, only after achalasia therapy	Yes	Yes	Yes, only after achalasia therapy	Yes	Yes
EoE treatment outcome based on symptoms and histology	PPI responder	Steroid responder	PPI and steroid refractory[a]	Steroid responder	Steroid responder	PPI and steroid refractory[a]	Steroid responder	Steroid responder
Achalasia therapy	PD	Not required	LHM	Not required	PD and LHM	PD	Not required	LHM
Achalasia treatment outcome	Responder to PD	NA	Responder to LHM	NA	Responder to LHM	Responder to PD	NA	Responder to LHM
HRM after EoE therapy	Not done	Not done	Not done	EGJOO	Not done	Not done	Not done	Achalasia type II

EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; EoE, eosinophilic esophagitis; EREFS, endoscopic reference score; F, female; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; LHM, laparoscopic Heller myotomy; M, male; PD, pneumatic dilation; PPI, proton pump inhibitor.

[a]Both patients became steroid responsive after achalasia treatment.

Table 4. Clinical Characteristics of EoE Patients With Nonachalasia Obstructive Motor Disorders

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age at diagnosis, y	19	32	29	37	45	40	22	33
Sex	F	M	M	M	M	F	M	F
Diagnostic delay, y	1	10	1	2	5	1	3	1
History of allergy	No	Allergic asthma and rhinitis	Allergic asthma and rhinitis	Allergic rhinitis	No	Allergic dermatitis and rhinitis	Allergic asthma	Allergic rhinitis
Main symptoms	Dysphagia	Dysphagia	Dysphagia	Dysphagia	Dysphagia	Dysphagia	Dysphagia and Heartburn	Dysphagia
EREFS score	1 E0R1E0F0S0	4 E0R1E2F1S0	2 E0R2E0F0S0	3 E1R2E0F0S0	4 E1R1E0F1S1	4 E1R1E1F0S1	6 E1R1E2F1S1	1 E1R0E0F0S0
HRM: spastic disorder type	EGJOO	DES	EGJOO	Jackhammer	EGJOO	EGJOO	EGJOO	Jackhammer
Esophagogram	Delayed emptying, narrowed EGJ	Normal	Normal	Normal	Narrowed EGJ	Narrowed EGJ	Narrowed EGJ	Tertiary contractions
PPI response	Yes	No (poor compliance)	No	No	No	No	No	Yes
`Topical steroid response	NA	No (poor compliance)	Yes	Yes	Yes	Yes, only after dilation therapy	Yes, only after dilation therapy	NA
EoE treatment outcome based on symptoms and histology	PPI responder	PPI and steroid refractory	Steroid responder	Steroid responder	Steroid responder	PPI and steroid refractory[a]	PPI and steroid refractory[a]	PPI responder
Achalasia therapy	Not required	Noncompliant	Not required	Not required	PD	PD	PD	Not required
Achalasia treatment outcome	NA	NA	NA	NA	Responder to PD	Responder to PD	Responder to PD	NA
HRM after EoE therapy	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done

DES, diffuse esophageal spasm; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; EoE, eosinophilic esophagitis; EREFS, endoscopic reference score; F, female; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; LHM, laparoscopic Heller myotomy; M, male; NA, not applicable; PD, pneumatic dilation; PPI, proton pump inhibitor.

[a]Both patients became steroid responsive after PD.

>10% even if EGJOO is excluded. While EGJOO may have heterogenous etiologies, and spastic motor disorders (DES, jackhammer esophagus) may not always have obstructive components, we documented abnormal bolus transit in all instances, clinical features were similar between those with and without traditional achalasia features, and management similar to achalasia was effective in most instances, indicating that all these disorders had an obstructive element. Nevertheless, we feel that our study introduces an important concept of the need to evaluate the presence of achalasia and obstructive motor disorders in EoE patients, especially those with persisting symptoms. In fact, symptom response, including that to EoE therapies, depends on adequate management of abnormal esophageal emptying in many of these patients.

In conclusion, in this first study aimed at evaluating the prevalence of achalasia and obstructive motor disorders in EoE patients, we report achalasia in 7.3% and a total of obstructive motility disorders in 14.7% of our cohort, with almost identical clinical, endoscopic and histological features compared with EoE patients without these disorders. Variability in manometric patterns, epidemiological characteristics and response to therapy suggest that this relationship is not unequivocal, and the exact pathophysiology remains to be elucidated. Our findings indicate the need for carefully collecting clinical symptoms and the use of expanded esophageal diagnostic procedures as part of the diagnostic workup, particularly when symptoms persist in EoE patients. Finally, we demonstrate that patients with concurrent EoE and achalasia or obstructive esophageal motility disorders may not only respond to common medical therapies, but also require invasive intervention. We conclude that the association of EoE with achalasia and obstructive motor disorders requires further prospective investigation.

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Conflicts of interest
The authors disclose no conflicts. Q1