Review paper

High-resolution manometry in diagnostics and evaluation of therapy effectiveness in patients with eosinophilic esophagitis – underestimated breakthrough or dead end?

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Abstract

Eosinophilic esophagitis (EoE) is a chronic disease with non-specific symptoms, among which dysphagia is a prevailing one. The observed increase of EoE rate, its chronic and recurrent character, as well as invasive follow-up examination (periodical panendoscopy with specimen collection for histopathology), compel optimization of both the diagnostics algorithm and disease monitoring through searching for new, unique methods and tools so far not applied, including high-resolution manometry (HRM). Mentioned investigations result from advances in comprehension of disease pathogenesis, in which it is suggested that development of a chronic inflammatory reaction of the esophageal wall may lead to consecutive fibrosis and motility disorders. In research published to date one manometric pattern characteristic for EoE was not obtained, whereas the obtained inconsistent and at times contradictory results do not correlate either with symptoms exacerbation or endoscopic scan. Numerous constraints of discussed studies as well as current knowledge in disease etiopathology and esophagus biomechanics prompt further investigation of HRM significance in diagnostics and therapy monitoring of patients with EoE.

Introduction

In recent years a significant increase in the number of reported eosinophilic esophagitis (EoE) has been observed. It has been estimated that over the last two decades disease prevalence has increased 30-fold, and the frequency of occurrence varies between 13 and 49 cases out of 100 000 inhabitants. Thus, EoE is classified in the group of diseases constituting an common clinical problem [1–3]. As research shows that occurrence dynamics exceeds the increase of diagnostic test frequency 20-fold, consequently increased recognition does not solely result from improved disease identification, its more effective detection or establishment of unambiguous diagnostic criteria, but from existing environmental changes (hypotheses concern changes in food and airborne allergens, reduction of *Helicobacter pylori* infections, increase in administration of proton pump inhibitors, as well as exposure to dangers in early lifetime that might influence microbiome modifications) [2, 4, 5].

The EoE is a chronic disease with non-specific symptoms that may vary depending on patients' age. Due to early occurrence of signs and their distinctness in adults and children, EoE was originally regarded as an exclusively pediatric issue, whereas dysphagia in adult patients, episodes of food impaction, pyrosis or retrosternal chest pain were treated as gastroesophageal reflux disease (GERD) [1, 3, 6]. Today it is assumed that undiagnosed EoE may constitute 10% of cases of so-called reflux disease refractory to treatment [7].

Due to the chronic process and recurrent disease character patients require constant gastroenterological monitoring including follow-up examinations that will allow one to evaluate the effectiveness of conducted treatment, which in accordance with present standards means periodical panendoscopy with specimen collection for histopathology [1]. Invasive clinical tests in re-

lation to disease symptoms, which frequently do not respond to standard treatment, significantly downgrade patients' quality of life [8], yet simultaneously stimulate numerous groups of researchers to investigate alternative diagnostic methods and EoE therapies.

Eosinophilic esophagitis diagnostics

The latest UEG, EAACI ESPHAGAN and EUREOS (2017) guidelines define EoE as a chronic esophageal disease with an immunological background, clinically distinguished as esophageal dysfunctions with swallowing disorders, and histologically distinguished as inflammatory infiltration of the esophagus wall with predominant eosinophils [1]. Definition modification arises from changes referring to suspected disease etiology, and consequently they modify the previous diagnostic approach. Until now, besides clinical and histological EoE features diagnostic criteria involved an 8-week trial of treatment with proton-pump inhibitors (PPIs) with a complete therapeutic dosage applied twice a day. Patients with an improved clinical and histopathological response following 8-week therapy were not diagnosed with EoE; however, they were classified as patients with proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE), or as patients with diagnosed GERD with esophageal eosinophilia connected with hydrochloric acid [3]. Since it still remains unknown whether the immunological response in the esophagus wall in predisposed patients is triggered as reaction to food and airborne allergens, hydrochloric acid or a combination of the two, the term 'antigene' was removed from the valid disease definition, and application of PPIs was classified as a therapeutic method, not a diagnostic EoE [1, 9]. Differential diagnostics is still perceived as a necessary procedure in EoE identification. It is maintained and emphasized as a procedure to exclude systemic and topical causes of esophageal eosinophilia other than EoE (including eosinophilic gastritis and enteritis, Leśniowski-Crohn disease, parasitic infection, achalasia, hypereosinophilic syndrome, hypersensitivity to medicines, connective tissue diseases, vasculitis, graft-versus-host disease, pemphigus) [1].

Changes in present guidelines also refer to histological identification of EoE. The required description in esophagus biopsy specimen ≥ 15 eosinophilia per high power field magnification (in the area ~0.3 mm^2) remained unaltered; however, the number of biopsies was increased from 2–4 (suggested in numerous guidelines including ACG from 2013) to a minimum of 6 from at least two different parts of the esophagus (distal and proximal half of the esophagus) [1, 3, 10, 11]. Recommended sites for esophagus endoscopic biopsy ought to be the areas with macroscopic changes such as circular folds, mucous membrane rings (esophagus trachealization), longitudinal furrows, white exudates, lack of vascular pattern, hyperemia, mucosa edema, or stricture [1]. Correct scan of esophagus mucous membrane does not rule out detection (it is estimated that in approximately 10% of adult patients EoE might proceed without visible macroscopic changes), which is why in the case of clinical signs it is advisable to collect the specimen from esophagus mucosa not subject to macroscopic changes [1, 12]. In the opinion of some authors recognition cannot be excluded from specimens with the number of eosinophils between 1 and 14 in a high-power field. They also state that repeated histopathological evaluation of such specimens in 22% of cases will allow errors to be avoided and enable assessment of eosinophils in order to meet histological criteria indispensable for EoE detection [13].

Although endoscopy with specimen collection for histopathology is an invasive procedure with numerous restrictions relating to financial expenditures, time consumption, significant impact of the human factor, uneven position of lesions (false negative results), or diversity and quality of endoscopic and microscopic equipment (for example high power field (HPF) magnification), is not only a diagnostic method for EoE, but also a monitoring one [1, 13]. The latest guidelines referring to monitoring of therapy effectiveness in patients with EoE demand endoscopic and histopathological follow-up examination already implemented in 6–12 weeks following therapy commencement, but also in case of modification of the therapeutic approach or medicine dosage due to disease exacerbation or symptoms recurrence [1, 14, 15]. Evaluation of clinical signs exacerbation is generally insufficient because a constant correlation of symptoms scale and inflammatory reaction in the histopathological scan was not reported [1, 16]. Endoscopic examination in dysphagia diagnostics is highly advised out of consideration for its potential organic background, yet due to the invasive character of endoscopic tests combined with biopsy specimen collection, as well as possible complications and patients' concerns, it seems to be justified to reduce the frequency of endoscopic follow-up tests. On the other hand, reduction of these procedures might delay therapeutic decisions such as modification of patient diet or medicine dosage, and consequently it might have an impact on obtaining and sustaining remission [15]. Since UEG, EAACI ESPHAGAN and EUREOS (2017) guidelines due to insufficient evidence neither recommend other monitoring methods in remission of esophageal inflammatory changes (scanning studies, laboratory tests) nor advise

esophagus functional tests including high-resolution manometry, it is necessary to conduct research aiming at investigation for an effective, less invasive and well-tolerated method monitoring response to treatment [1, 17, 18].

Pathogenesis of esophageal motility disorders in eoe and their monitoring

Significant changes in the present diagnostic algorithm and further investigation for other promising methods and tools facilitating EoE detection and monitoring are the result of the latest progress in understanding disease pathogenesis [5].

Many interfering mechanisms, environmental factors, genetic and ontogenetic immunological features participate in EoE development. In predisposed patients a chronic inflammatory reaction of the esophageal wall with predominant eosinophilia develops. It has not been unequivocally determined whether the immunological process is solely triggered in response to airborne and food allergens, or in consequence of hydrochloric acid effects as well. However, the latest research suggests that exposure to acid reflux might interfere with esophageal mucous membrane integrity, thus facilitating transfer of interepithelial allergens [1, 19].

Exposure to allergens induces a Th2-mediated response and leads to increase in interleukins 13 and 4, thereby increasing the concentration of eotaxin 3, which entails migration of eosinophils to esophagus, induction of tissue remodeling combined with collagen deposition, angiogenesis, as well as damage of the epithelium barrier via desmoglein 1 degradation [5, 20]. As it is induced by IL-13, interleukin 5 affects eosinophil migration and their degranulation with release of many proteins and mediators, especially major basic proteins (MBP), eosinophilic cation protein, eosinophilic peroxidase, eosinophilic neurotoxin, TGF-β, interleukin 13, and the factor activating platelets [20]. Although all the factors play an important role in tissue damage and remodeling, a crucial role belongs to major basic protein that stimulates fibroblast activity and proliferation, direct epithelium damage, and mast cell degranulation with release of proteolytic enzymes and TGF-β, which has an influence on disruption of esophageal mucosal barrier, fibrosis, remodeling of esophageal mucosa and deterioration of smooth muscle functioning [20]. At present, esophagus remodeling is evaluated with histological parameters of epithelium, including hypertrophy and elongation of stratum basale papillae, broadening of the intercellular space as well as fibrosis of stratum basale of the mucosal membrane [1, 5]. Development of an inflammatory reaction leads to fibrosis and esophageal motility disorders [21, 22].

High-resolution manometry

A modern tool aiming at differentiation of neuromotor dysfunction from functional dysphagia is high-resolution manometry (HRM) involving precise measurement of real segmental pressure in reference to bolus dynamic movement, with the possibility of correlation of all components beginning with the superior esophageal sphincter, through trunk parameters with contribution of functions of both gastroesophageal connection and diaphragm branches.

The HRM was introduced into clinical practice in the year 2000. Since that time a few both prospective as well as retrospective studies have been published with the objective to establish manometric pattern characteristic for EoE patients.

It is estimated that irregularities in the manometric record occur in 20–76% of patients with EoE [23–29]. Among motility disorders mentioned in Chicago classification criteria the most frequently quoted were the patterns of weak peristalsis (17–27%), frequent failed peristalsis (7–12%) [23–27], as well as functional esophagogastric junction (EGJ) obstruction, rapid contraction with normal latency, absent peristalsis, hypertensive peristalsis [23], or even Jackhammer esophagus [25]. Although esophageal motility disorders occurred more frequently in patients with EoE than in control groups, both frequency and type of described manometric irregularities were similar to those observed in patients with GERD [23, 24], and in the case of patients with PPI-REE proved to be nearly identical, which might indicate that both diseases share similar pathogenetic mechanisms [29]. Yet, as opposed to patients with GERD, patients with EoE are symptomatically more prone to exposure to abnormal bolus pressurization in the esophagus (20–48%), such as early pan-esophageal pressurizations (15–17%) or compartmentalized esophageal pressurizations (5–19%) [23, 26, 28]. It was specified that pan-esophageal pressurizations correlate with episodes of bolus impaction in this group of patients, but do not correlate with dysphagia occurrence [28]. Another study did not find a connection between deterioration of signs and manometric features, yet it defined disease duration as a risk factor responsible for esophageal motility disorders. In this research frequency of irregularities described in HRM rose from 36% in the first 5 years of disease duration to 83% in the case of patients suffering for at least 16 years [24]. Along with disease duration and progression of changes evolving from chronic inflammation and resulting in esophageal wall fibrosis [21, 22], in accordance with the endoscopic reference system (EREFS), there were distinguished inflammatory and fibrostenotic subtypes of EoE [30]. Some authors claim that manometric features

also differentiate between these two subtypes. It was confirmed that patients with EoE have increased intrabolus pressure (IBP) [23], but patients with fibrostenotic subtype in HRM have not only significantly higher IBP (determined cut-off value in phenotype differentiation up to 16 mm Hg) but also a larger reduction of medium IBP following administration of site steroid therapy than in the case of patients with inflammatory subtype [25, 26]. At the same time, there are reports of no meaningful manometric differences between subtypes in EoE [27]. Apart from higher IBP values, patients with EoE reported essentially higher resting pressure of the EGJ and the UES, and more breaks of the peristaltic wavefront in the 20 mm Hg and in the 30 mm Hg isobaric contour, which proves ineffectual motoric function in this group of patients. However, no relation was confirmed between these irregularities and noticeable discomfort during swallowing [27].

Although no single optimal HRM parameter was defined to monitor the response to treatment, still regardless of the EoE subtype, in the group of patients with incorrect esophageal motility diagnosed prior to treatment, histological and clinical remission correlates with recovery from esophageal motility disorders [26].

Conclusions

With regard to the increased number of EoE reported cases there is a continued effort to optimize the invasive nature of present diagnostic workup and to monitor the disease through exploration of unique methods and diagnostic tools involving HRM. Insufficiently acknowledged and regularly updated alleged disease pathophysiology indicates that development of a chronic inflammatory reaction of the esophageal wall may entail subsequent fibrosis and motility disorders.

Although to date seven research studies devoted to investigation of HRM significance in diagnostics of EoE patients' therapy monitoring have been published, due to obtaining incoherent and sometimes contradictory results, a manometric pattern for EoE has not been established yet. Studies have numerous constraints resulting from, among other factors, changes in disease definition, modifying precise criteria for including and excluding patients from projects. Unquestionable drawbacks of all projects taking into consideration manometric evaluation in patients with EoE conducted so far are the small study group of 20 to 52 patients with EoE (including patients with PPI-REE) [23–29], as well as differences in gender distribution and participants' age. The impact of mentioned drawbacks must be taken into account when considering esophageal motility disorders [23, 24]. What is more, constraints also emerge as far as research conduct is concerned. Not all the projects included a control group [26], and patient position was not described during HRM examination [25, 28]. Only a few projects considered the potential therapeutic influence of gastroscopy in scheduling succession of conducted procedures in time [25], or introduced a break between tests [28] in order not to decrease the diagnostic effect or compromise the HRM result. Most of the researchers collected specimens from the stomach and duodenum in order to eliminate other EoE causes [26–29], and only a few took into account possible interference of EoE with GERD [23], verifying with histopathological tests specimens of esophageal mucosa in patients with GERD [29] or excluding pathological reflux with 24-hour pH-metry with impedance evaluation in patients with EoE [24, 26]. In the light of increasing significance of hydrochloric acid in EoE etiopathogenesis it might undoubtedly contribute to obtained test results. The lack of objectification of results correlated with HRM, the data obtained from the patient, related to occurrence and exacerbation of signs, as well as disease duration and diagnostic delay due to application of unvalidated questionnaires, seem to be considerable constraints [26]. Bearing in mind the fact that dysphagia evaluation in EoE depends on type and texture of foods, and discomfort is generally related to solid food swallowing, water swallowing during manometric examination may serve as an explanation of lack of an essential correlation between dysphagia exacerbation and manometric results [27].

To conclude, HRM results in patients with EoE are non-specific and incoherent, and moreover do not correlate with dysphagia exacerbation and endoscopic signs. Numerous constraints of discussed studies as well as present knowledge on etiopathology and esophageal biomechanics encourage further investigation. However, significance of HRM in diagnostics and monitoring of EoE patients may not be unequivocally ignored.

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Conflict of interest

The authors declare no conflict of interest.

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