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Esophageal eosinophilia and esophageal diseases in children. Are the limits clear?

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Title: Esophageal eosinophilia and esophageal diseases in children. Are the limits clear?

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Keywords: Esophageal eosinophilia, eosinophilic esophagitis, gastroesophageal reflux disease, esophageal motility disorders, paediatrcs, high resolution manometry.

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Abstract:

Gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), and esophageal motility disorders are among the most common diseases accompanying esophageal eosinophilia. These have similarities and their limits are frequently not well-defined; they can even overlap. This article reviews the main characteristics that resemble and differentiate them; exposing areas of controversy and gaps in the knowledge we have about them. In the case of a patient with symptoms of esophageal dysfunction, it is suggested to carry out integral analysis of the clinic, the diagnostic tests carried out, including histology, and to individualize each case before reaching a definitive diagnosis. Future research, including pediatric age, is required to assess eosinophilic infiltration of the different layers of the esophagus and its pathophysiological implications.

Introduction:

Under normal physiological conditions, eosinophils are present throughout the gastrointestinal tract distal to the squamous esophagus, which the esophagus is normally lacking.[1] Several conditions have been associated with infiltration of eosinophils into the esophagus or esophageal eosinophilia, many are rare or have distinctive clinical features (eosinophilic gastritis, gastroenteritis or colitis with esophageal involvement; hypereosinophilic syndrome; Crohn's disease with esophageal involvement; infections; connective tissue disorders; hypermobility syndromes; autoimmune disorders and vasculitis; dermatologic conditions with esophageal involvement; drug hypersensitivity reactions; pill esophagitis; graft-versus-host disease; some Mendelian disorders).[2] However, we also find frequent esophageal diseases with the presence of eosinophils in esophageal histology, such as gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), and even esophageal motility disorders. We will make reference to these three groups in this article, as they are common diseases in clinical practice, which can overlap and sometimes we are unable to define the limits between them. There have been consensus and multiple investigations on these entities separately, but many aspects may still need to be clarified. The intention of this review is to offer a joint approach to these three conditions, with so many similarities and sometimes not well defined limits, emphasizing the main characteristics that resemble and differentiate them.

Definitions:

EoE is a chronic, inflammatory, local disease of immunological origin and mediated by antigens, usually food. Eosinophilic infiltration of the esophagus in 1978 was initially described in biopsies of a patient diagnosed with achalasia. It has been recognized as a clinicopathological entity since Dr. DeMeester's report in 1993, but the general recognition of this new disorder was in the current new millennium. Since then it has been reported in adults and children.[3] [4] It is predominantly inflammatory during childhood (inflammatory phenotype) and with progression to fibrosis in adulthood (fibrostenosing phenotype), characterized by signs and symptoms of esophageal dysfunction related to eosinophilic inflammation limited to the esophagus. [5] According to

the latest International Consensus update on the diagnostic criteria for eosinophilic esophagitis, **suspicion of EoE** was defined as symptoms of esophageal dysfunction (concomitant atopic conditions can increase suspicion of EoE) and at least 15 eosinophils/hpf (high- power field) or approximately 60 eosinophils/mm^2 in esophageal biopsy. Confirmed EoE was defined as symptoms of esophageal dysfunction and at least 15 eosinophils/hpf or approximately 60 eosinophils/mm^2 on esophageal biopsy (eosinophilic infiltration should be limited to the esophagus) after evaluation of other causes of esophageal eosinophilia.[2] In this consensus, in addition to reflecting that it is the same disease in children and adults, so it is applicable in both age groups, it emphasizes the need to evaluate the conditions that could contribute to esophageal eosinophilia instead of requiring your exclusion. This allows the diagnosis of EoE to coexist with that of GERD and other conditions.

The NASPGHAN and ESPGHAN pediatric gastroesophageal reflux (GER) clinical practice guidelines define GER as the passage of gastric contents into the esophagus with or without regurgitation and vomiting; GERD occurs when GER leads to problematic symptoms and / or complications.[6] However, GERD shares symptoms and complications with EoE, making it difficult to delimit this condition. It also shares symptoms with some motility disorders, both may be present in the same patient. Therefore, a definition based on symptoms that can be shared with other conditions may not be completely clear.

The diagnosis of esophageal motility disorders is based on alterations present in esophageal manometry, since 2000 conventional manometry has been gradually replaced by high resolution manometry (HRM), which is currently the “gold standard” for diagnosis,[7] through the Chicago classification (CC), first published in 2008, its last update was in 2015, version 3.0.[8] The CC provides uniformity in diagnoses, consisting of a hierarchical analysis which focuses initially on disorders with esophagogastric junction (EGJ) outflow obstruction, later on major disorders of peristalsis, and finally on minor disorders of peristalsis.[9] [10] The CC was performed based on the metric from studies carried out in a healthy adult population, so it may have its limitations in the pediatric population. Limitations for obtaining similar studies on a healthy pediatric

population are of ethical nature.[11] Studies have been carried out to evaluate the metric in symptomatic children depending on parameters such as esophageal length, age, but still without definitive conclusions.[12] Being a diagnosis based on manometric alterations, it leaves a gap open for other alterations that could coexist.

Clinical aspects:

In pediatric age, diagnostic guidance based on symptoms is even more difficult, especially at younger ages, when symptoms are less specific, and generally reported by caregivers, depending on their interpretation.

EoE is not suspected at the clinical level when there are symptoms of esophageal dysfunction, which could manifest themselves in various ways, including dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain and malnutrition. Atopic comorbidities such as asthma, atopic dermatitis, or immediate food allergies should increase the clinical index of suspicion. In younger children the most common symptoms are those similar to gastroesophageal reflux, vomiting, abdominal pain, food refusal, and failure to thrive. In older children, adolescents and adults, dysphagia to solids, food impaction and chest pain not associated with swallowing are more frequently reported.[13] The presence of esophageal eosinophilia on histological examination without further consideration of the clinical presentation is not a diagnosis of EoE.[2]

Because these symptoms are nonspecific, patients should be treated as clinically indicated. EoE presents a wide range of symptoms, the diagnostic algorithm cannot anticipate all clinical possibilities, and provides scope for appropriate evaluation.

Among the most frequent symptoms that may be associated with GERD in infants and children we find the general manifestations (irritability, food refusal, failure to thrive), gastrointestinal manifestations (heartburn, regurgitation / vomiting, retrosternal chest pain, dysphagia, epigastric pain) and manifestations at the airway level (cough, stridor, wheezing, apnea episodes, asthma, pneumonia).[6] [14] [15] Given that the symptoms of GERD are not specific, “red flags” or warning signs have been defined to guide the

need for research to rule out complications of GERD and underlying disorders with similar symptoms.[6]

Esophageal motility disorders also show a spectrum of symptoms similar to EoE and GERD, including weight loss (nonspecific symptom predictive of abnormal MAR), feeding difficulties, dysphagia, vomiting, manifestations of GERD, respiratory symptoms, chest pain, failure to thrive, among others.[16] In disorders of obvious clinical significance such as achalasia, more nonspecific symptoms are described in younger children, such as vomiting, anorexia, chronic cough, which often delays diagnosis.[17 18] In esophageal motor conditions, allergic disorders have also been reported among the most frequent comorbidities.[11]

According to the above, many of the clinical manifestations are similar in the three entities, which makes clinical-based differential diagnosis difficult, and diagnostic procedures should be performed when indicated. (Table 1)

Endoscopic aspects:

Esophagogastroduodenoscopy (EGD) may have specific characteristics, but it may also be normal in EoE and GERD.

In the EoE, an endoscopic reference score was developed: EREFS (Edema, Rings, Exudates, Furrows, Strictures) that gives a score according to the degree of severity of the results.[19] The finding of mucosa on crepe paper and mucous friability are also described.[3 20 21]

In the case of GERD, it does not have a “gold standard” test. EGD is recommended if the complications of GERD need to be assessed and if underlying mucosal disease is suspected before intensification of therapy. The probability of having erosive esophagitis caused by reflux varies from 15 to 71% between studies, so a normal endoscopy does not necessarily rule out the possibility of GERD.[6 22] When GERD is erosive, its diagnosis is facilitated, the most used classification is that of Los Angeles.[23] There are, of course, other complementary tests, such as pHmetry / pHmetry-Impedanciometry to support the diagnosis of GERD in necessary cases.

For the diagnosis of esophageal motility disorders, anatomic causes must be excluded by means of a contrast study of the esophagus and / or EGD.[7] [18] Therefore, upper digestive endoscopy should be normal, which, as we have mentioned, does not exclude the presence of esophageal disease. If there is EoE or GERD, and esophageal manometry is performed, we can find the diagnosis of motor disorders in these entities.

Histological aspects:

Although there are aspects that could help differentiate GERD and EoE from the histological point of view, there are some cases that are histologically indistinguishable, and as we have said previously, both conditions can overlap. It is also more complex if samples are only taken from the distal third of the esophagus, since this is the most affected in GERD, while in EoE the entire esophagus is affected in patches. Also in severe cases of GERD, more proximal areas can be affected.[24] A study of EoE in pediatric age showed a denser eosinophilic infiltrate in the distal esophagus relative to the middle esophagus.[25] Eosinophil levels in EoE patients are reported to vary widely by patient, in the same patient by biopsy sample, and in the same biopsy by hpf analysis.[24] Therefore, in all cases where EoE is a clinical possibility, even when visualizing the normal mucosa, multiple biopsy samples of 2 or more esophageal levels, directed to areas of apparent inflammation, are recommended to increase diagnosis.[2] In the histological study, in addition to the peak of the eosinophil count, a histological score (EoEHSS) has recently been developed. This provides more histological elements to evaluate and has been shown to be superior in the diagnosis of EoE and in therapeutic decision-making.[26] [27] [28]

In GERD, the characteristic histological changes are: polymorphonuclear leukocyte infiltrate, intraepithelial eosinophils, hyperplasia of the basal area and elongation of the papillae.[22] These changes are also mentioned in the EoE.[21] The absence of histological changes does not exclude GERD.[6] (Table 1)

Manometric aspects:

The association of motility disorders with esophageal eosinophilia in the different layers of the esophagus has been described for decades.[4]

No specific manometric pattern has been identified for EoE.[29] Variable motor abnormalities, both hypocontractile and hypercontractile, were described with conventional esophageal manometry.[4 30] After the use of the HRM with the CC, they have continued being reported. Because esophageal manometry is not required for the diagnosis of EoE, and occasionally patients diagnosed with an esophageal motor disorder have not previously undergone esophageal histological study, and sometimes not even EGD, the establishment of association may be lost between EoE and esophageal motility disorders.

In cases where achalasia and eosinophilic infiltration of the esophageal mucosa has been diagnosed, it is unclear when the motility disorder is due to esophageal eosinophilia or vice versa. Thomas Frieling et al. propose that achalasia and esophageal eosinophilic infiltration are not different clinical entities. They present an adult case with EoE, achalasia, without a history of atopy, and without response to steroids, there was a clinical response after esophageal dilation. They suggest that eosinophilic infiltration is secondary to achalasia.[29] Also, in a Canadian study they report esophageal eosinophilia at the mucosa level, which was even maintained and increased in several patients after laparoscopic Heller myotomy, despite good clinical response to Surgery.[31] However, other authors presented a patient with both findings and response to steroid therapy.[32] An adult was also described with “Jackhammer esophagus” associated with EoE, in response to steroid treatment of mucosal eosinophilic infiltration, but persistence of the motor disorder, so a peroral endoscopic myotomy (POEM) was performed, with good subsequent evolution. A sample of the esophageal muscle tissue was taken during POEM and eosinophilic infiltration was also verified at this level.[33] EoE is mentioned as one of the causes of EGJ outflow obstruction.[34] A Japanese study in adults diagnosed with primary esophageal motor disorder in which secondary causes, including EoE, were excluded. Biopsy of the muscularis propria during peroral endoscopic myotomy (POEM) and eosinophilic infiltration was reported in patients with Jackhammer esophagus.[35] Sato H et al. in an interesting study, they describe the heterogeneous infiltration of those eosinophils in the esophagus, at the level of the mucosa, submucosa and the muscularis propria. EoE was associated with failed peristalsis, as was subepithelial eosinophilic esophagitis. The presence of

eosinophils in esophageal muscle tissue is called eosinophilic esophageal myositis, and was associated with hypercontractile esophagus. They found differences in these three patterns of esophageal eosinophilic disorders in cytokine profiles.[36] The study of the different esophageal layers has become more accessible with the introduction of POEM.

GERD suggests using manometric studies when a motility disorder is suspected. The alterations associated with gastroesophageal reflux are dysfunction of the gastroesophageal junction and alterations in the motility of the esophageal body, mainly ineffective esophageal motility.[16 37 38]

The relationship between esophageal motility disorders with esophageal eosinophilia and GERD requires new research, mainly in the pediatric age, since most of the research is carried out in the adult population.

Treatment-related aspects:

GERD was previously distinguished from other diseases and from EoE by its clinical response to proton pump inhibitor (PPI) therapy. Then it was found that there was a group that histologically met the criteria for EoE but also responded to this treatment and was called PPI-responsive esophageal eosinophilia (PPI-REE). In the last diagnostic consensus of EoE, the PPI-REE was included in the EoE, since they verified that it was the same disease. Because of this, an IBP assay is not required for the diagnosis of EoE in this algorithm.[2] We cannot differentiate EoE and GERD by the response to PPI therapy, since it has been suggested that it has an anti-inflammatory effect.[39]

Some aspects in relation to the pathophysiology

Apparently, the explanation for the similarity in the symptoms and many aspects of the diseases treated is in the pathophysiology. New hypotheses related to mechanisms of inflammation and cytokine release have been developed to explain the abnormalities. In the case of GERD, a new concept has been proposed that states that it is not reflux that directly damages the epithelium, but rather stimulates epithelial cells to release cytokines that induce proliferative changes and attract T lymphocytes and other

inflammatory cells that end up damaging the mucosa.[39] In the case of EoE, it is known that there is an abnormal immune reaction mediated by Th2 interleukins, in which there is a recruitment of eosinophils, inflammatory cytokines are released and the degranulation products released by the eosinophils contribute to epithelial injury.

Regarding motility disorders, Spechler has proposed that EoE, similar to what occurs in eosinophilic gastroenteritis, could have forms with mucous predominance and forms with muscular predominance; the predominantly muscular form could cause a variety of esophageal motor disorders, including achalasia. Some eosinophil products can cause esophageal muscle contraction (Thromboxane B2, Leukotriene D4), others cause muscle relaxation (IL-6, IL-13), fibrosis (TGF-β, IL-13). They can also secrete neuroactive products, or others that destroy esophageal intramural neurons.[40]

Conclusions:

The clinical similarity between GERD, EoE, and esophageal motility disorders, along with the possibility that they may overlap, require great attention from the physician. It should be remembered that other entities may be underdiagnosed in the clinical context of GERD. In the presence of symptoms of esophageal dysfunction, we recommend that if an EGD is to be performed, always take esophageal biopsy samples in distal and middle thirds, even if there are no endoscopic alterations, nor have EoE been initially considered. To assess the results of HRM in conjunction with those of EGD and esophageal histology. Before reaching a definitive diagnosis, carry out a comprehensive clinical analysis, the diagnostic tests performed, including esophageal histology, and individualize each case.

Some of the esophageal motility disorders still have an uncertain clinical significance. They can constitute a heterogeneous group of disorders with different pathophysiologies. Therefore, the treatment must be individualized. Perhaps we should rethink the hitherto known as "primary esophageal motor disorders." The definition of EoE may need to be more encompassing, including, in addition to mucosal eosinophilia, submucosal, muscular and mucosal infiltration. The relationship between esophageal eosinophilia and motility disorders needs to be clarified. Future research, including

pediatric age, is required to assess eosinophilic infiltration of the different layers of the esophagus and its pathophysiological implications.

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Table 1: Main similarities and differences between Eosinophilic esophagitis (EoE), Gastroesophageal reflux disease (GERD) and esophageal motility disorders.

<table>
<tr><th colspan="2">Aspects</th><th>EoE</th><th>GERD</th><th>Esophageal motility disorders</th></tr>
<tr><td colspan="2" rowspan="2">Definition</td><td colspan="2">Symptoms are mentioned in both definitions and may be common. Some complications of GERD are also common to EoE</td><td rowspan="2">Based mainly on manometric parameters, so it does not exclude other aspects</td></tr>
<tr><td>Generally higher number of eosinophils on biopsy</td><td>Some complications are typical of GERD (Barrett's esophagus)</td></tr>
<tr><td colspan="2" rowspan="2">Clinical aspects</td><td colspan="3">Symptomatology compatible (symptoms of esophageal dysfunction)</td></tr>
<tr><td>More frequent history of atopy</td><td colspan="2">There may also be atopy and respiratory manifestations</td></tr>
<tr><td colspan="2" rowspan="3">Upper Digestive Endoscopy</td><td colspan="3">Can be normal</td></tr>
<tr><td>Endoscopic reference score (EREFS: Edema, Rings, Exudates, Furrows and Strictures)</td><td>Los Angeles classification for erosive esophagitis; stenosis, esophageal metaplasia, etc.</td><td rowspan="2">Organic causes of dysphagia are excluded</td></tr>
<tr><td>Involvement throughout the esophagus</td><td>Distal involvement</td></tr>
<tr><td rowspan="4">Histology[24]</td><td>General features</td><td colspan="2">Eosinophilic infiltration, basal cell hyperplasia, dilated intercellular spaces, elongation of the papillae</td><td rowspan="4">Findings compatible with GERD, with EoE and eosinophilic infiltration of the submucosa and the muscularis propria have been described</td></tr>
<tr><td>Eosinophil number</td><td>≥15 eos/hpf</td><td>Usually less, although in some cases it can reach 15 eos/hpf</td></tr>
<tr><td>Location of eosinophil infiltration</td><td>Patched along the esophagus</td><td>More intense in distal esophagus</td></tr>
<tr><td>Eosinophilic</td><td>Frequent</td><td>Rare</td></tr>
</table>

	abscesses			
	Eosinophils degranulated	Frequent	Infrequent	
	Erosion / ulcer	Rare	May be present	
	Damage and loss of superficial squamous cells	Useful if present	Rare	
Esophageal manometry		It can be pathological		With alterations
Treatment		There may be a good response to IBP		
		Response to other therapies (steriodes, diet)	Other treatments depending on the evolution and severity	Treatment depending on the type of disorder. Steroid response has been described in some cases
Observations		They can overlap		
		New hypotheses in pathophysiology related to mechanisms of inflammation and cytokine release		

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Title: Esophageal eosinophilia and esophageal diseases in children. Are the limits clear?

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Abstract

Gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), and esophageal motility disorders are among the most common diseases accompanying esophageal eosinophilia. They have similarities and their limits are frequently not well-defined; in fact, there is a possibility of overlapping. This article reviews the main characteristics relating to their similarities and differences, highlighting existing controversies among these diseases, in addition to current knowledge about them. In the case of a patient with symptoms of esophageal dysfunction, it is suggested to carry out an integral analysis of the clinical features and diagnostic test results, including histology, while individualizing each case before confirming a definitive diagnosis. Future investigation, which should include pediatric patients, it is necessary to assess eosinophilic infiltration in the various layers of the esophageal tissue, along with its clinical and pathophysiological implications.

Introduction

Under normal physiological conditions, eosinophils are present throughout the gastrointestinal tract distal to the squamous esophagus, so the esophagus normally lacks these.[1] Several conditions are associated with the infiltration of eosinophils within the esophagus, or esophageal eosinophilia (Box 1), many of which are uncommon or may present distinctive clinical characteristics.[2] However, in the clinical setting, there are some frequent esophageal diseases with the evidence of eosinophils presented on esophageal histology, such as gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), and even esophageal motility disorders.

EoE is the most distinctive as it relates to the presence of significant mucosal esophageal eosinophilia, but other disorders must be considered in the differential diagnosis. Eosinophilic gastroenteritis with esophageal involvement should be evaluated with the study of gastric and duodenal biopsy samples. Hypereosinophilic syndrome should be considered when the peripheral blood eosinophil count is >1500 x 10^9 cells/L. Children who have inflammatory bowel disorders, including celiac disease or Crohn's disease, can have eosinophil-predominant esophageal inflammation. However, a diagnosis of EoE is not appropriate when another condition could account for the histological changes. Treatment should be initiated for the presumed primary etiology, with monitoring of the esophageal inflammation. If esophageal eosinophilia persists after the primary disease is controlled, EoE could be diagnosed as an overlapping condition. EoE has also been associated with connective tissue diseases, perhaps due to a shared pathogenic mechanism. It can also present with other unrelated medical conditions. Many other causes of esophageal eosinophilia are relatively rare and can be excluded with a comprehensive medical history and laboratory tests, however, in the case of GERD it can be more complex. Also, there are various reports of association of esophageal eosinophilic infiltration and esophageal motility disorders, with recent studies based on its pathophysiology.[2 3] It is to these three disorders (EoE, GERD and esophageal motility disorders) that we will make reference to in this article, since they are common diseases in clinical practice, which can overlap and sometimes their limits are not well defined. There have been some consensuses and multiple investigations in

regards on these diseases separately, but many aspects may still need to be clarified. The intention of this review is to offer a joint approach to these three conditions, with many similarities and sometimes their limits are not so well-defined, emphasizing their main characteristics that make they may be similar and be different.

Definitions

EoE is a chronic, inflammatory, local disease of immunological origin and mediated by antigens, usually food. Eosinophilic infiltration of the esophagus was initially described in 1978 in biopsies of a patient that was diagnosed with achalasia.[4] Eosinophilic infiltration was initially considered a consequence of GERD. It has been recognized as a clinicopathological entity from a report made in 1993.[5] Subsequently, the response to dietary therapy was identified,[6] but the general recognition of this new disorder was in the current new millennium. Since then it has been reported in adults and children.[7 8] It is predominantly inflammatory during childhood (inflammatory phenotype) and with progression to fibrosis in adulthood (fibrostenosing phenotype), characterized by signs and symptoms of esophageal dysfunction related to eosinophilic inflammation limited to the esophagus.[9] According to the latest International Consensus update on the diagnostic criteria for eosinophilic esophagitis, **suspicion of EoE** was defined as symptoms of esophageal dysfunction (concomitant atopic conditions can increase suspicion of EoE) and at least 15 eosinophils/high-power field (hpf) or approximately 60 eosinophils/mm^2 in esophageal biopsy. **Confirmed EoE** was defined as symptoms of esophageal dysfunction and at least 15 eosinophils/hpf or approximately 60 eosinophils/mm^2 on esophageal biopsy (eosinophilic infiltration should be limited to the esophagus), after evaluation for other causes of esophageal eosinophilia.[2] In this consensus, in addition to reflecting that it is the same disease in children and adults, so it is applicable in to all ages, was emphasized the need to evaluate for conditions that might contribute to esophageal eosinophilia rather than require their exclusion. This allows the diagnosis of EoE to coexist with that of GERD and other conditions.

The NASPGHAN and ESPGHAN Pediatric Gastroesophageal Reflux (GER) Clinical Practice Guidelines defines GER as the passage of gastric contents into the esophagus with or without regurgitation and vomiting. GERD is when GER leads to troublesome

symptoms and/or complications.[10] However, GERD shares symptoms and complications with EoE, making it difficult to delimit this condition. It also shares symptoms with some motility disorders, both entities may be present in the same patient. Therefore, a definition based on symptoms that can be shared with other conditions may not be completely clear. (Table 1)

The diagnosis of esophageal motility disorders is based on alterations present in esophageal manometry. Conventional manometry has been gradually replaced by high resolution manometry (HRM), which is currently the "gold standard" for diagnosis. The Chicago Classification (CC), that defines esophageal motility disorders, was first published in 2008, and its last update was in 2015 (version 3.0).[11 12] The CC provides uniformity in diagnoses, consisting of a hierarchical analysis, it is initially focuses on disorders within esophagogastric junction (EGJ) outflow obstruction (achalasia, EGJ outflow obstruction) , later on major disorders of peristalsis (diffuse esophageal spasm, Jackhammer esophagus, absent contractility) and finally minor disorders of peristalsis (ineffective motility, fragmented peristalsis).[13 14] The CC was performed based on the metric from studies carried out in a healthy adult population, therefore it may have limitations in the pediatric population. The limitation for obtaining similar studies in a healthy pediatric population is an ethical considerations.[15] Studies have been carried out to evaluate the metric in symptomatic children depending on parameters such as esophageal length and age, but still without definitive conclusions.[16] Being a diagnosis based only on manometric alterations, it leaves an open gap for other pathologies that could coexist.

Clinical aspects

In pediatric patients, diagnostic guidance based on symptoms is difficult, especially at younger ages, when symptoms are more nonspecific, and generally reported by caregivers, and therefore depend on their interpretation.

EoE is suspected clinically when there are symptoms of esophageal dysfunction, which could manifest themselves in various ways, including dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain and malnutrition. Atopic comorbidities such as

asthma, atopic dermatitis, or immediate food allergies should increase the clinical index of suspicion. In younger children, the most common symptoms are those similar to gastroesophageal reflux, in addition to vomiting, abdominal pain, food refusal, and failure to thrive. In older children, adolescents and adults, dysphagia to solids, food impaction and chest pain not associated with swallowing are more frequently reported.[17] The presence of esophageal eosinophilia on histological examination without further consideration of the clinical presentation of is not a diagnosis of EoE. Because these symptoms are nonspecific, therefore patients should be treated as clinically indicated. The diagnostic algorithm cannot anticipate all clinical possibilities, and provides scope for appropriate evaluation. [2]

Among the most frequent symptoms that may be associated with GERD in infants and children we find the general manifestations (irritability, food refusal, failure to thrive), gastrointestinal manifestations (heartburn, regurgitation / vomiting, retrosternal chest pain, dysphagia, epigastric pain) and manifestations of the airway (cough, wheezing, stridor, apnea episodes, asthma, pneumonia).[10 18 19] Given that the symptoms of GERD are not specific, “red flags” or warning signs have been defined to guide the need for research studies to rule out complications of GERD and underlying disorders with similar symptoms. It should be noted that GER in infants is very common, and is usually self-limiting. In the presence of an infant with recurrent regurgitation, a thorough history and physical examination with attention to warning signals suggesting other diagnoses is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER. In the absence of warning signs, diagnostic testing and/or therapies including acid suppression are not needed if there is no impact of the symptoms on feeding, growth or acquisition of developmental milestones. It is recommended to refer to the pediatric gastroenterologist when in infants or children there are alarm signs or symptoms suggesting an underlying gastrointestinal disease.[10]

Esophageal motility disorders also show a spectrum of symptoms similar to EoE and GERD, including weight loss (nonspecific symptom predictive of abnormal HRM), feeding difficulties, dysphagia, vomiting, manifestations of GERD, respiratory symptoms, chest pain, failure to thrive, among others.[20] Clinical significant disorder such

as achalasia, more nonspecific symptoms are described in younger children, such as vomiting, anorexia, chronic cough, which often delays diagnosis.[21 22] In esophageal motility disorders, allergic disorders have also been reported among the most frequent comorbidities.[15]

According to the above, many of the clinical manifestations are similar in the three entities (Table 1), which makes clinical-based differential diagnosis difficult, and diagnostic procedures should be performed when indicated.

Endoscopic aspects

Upper digestive endoscopy or esophagogastroduodenoscopy (EGD) may have specific features but may also be normal in EoE and GERD. (Table 2)

In the EoE, an endoscopic reference score has been developed: EREFS (Edema, Rings, Exudates, Furrows, Strictures) that gives a score according to the degree of severity of the finding.[23] The findings of mucosa on crepe paper and mucous friability are also described.[7 24 25]

In the case of GERD, it does not have a gold standard test. EGD is recommended if the complications of GERD need to be assessed and if underlying mucosal disease is suspected before intensification of therapy. The probability of having erosive esophagitis caused by reflux varies from 15 to 71% between studies, so a normal endoscopy does not necessarily rule out the possibility of GERD.[10 26] When GERD is erosive, the diagnosis of this is facilitated, the most used classification is Los Angeles classification.[27] There are, of course, other complementary tests, such as pH-metry and multichannel intraluminal impedance to support the diagnosis of GERD in necessary cases.

For the diagnosis of esophageal motility disorders, anatomic causes of the symptoms must have been excluded by means of a contrast study of the esophagus and/or EGD.[7 22] Therefore, EGD should be normal, which does not exclude the presence of esophageal disease. If there is EoE or GERD, and esophageal manometry is performed, we can find the diagnosis of motor disorders in these entities.

Histological aspects

Although there are aspects that could help differentiate GERD and EoE from the histological point of view, there are some cases that are histologically indistinguishable and both conditions can overlap. (Table 2) It is also more complex if samples are only taken from the distal third of the esophagus, since this is the most affected in GERD, while in EoE the entire esophagus is affected in patches. In addition, in severe cases of GERD, more proximal areas can be affected.[28] A study of EoE performed in pediatric age showed a denser eosinophilic infiltrate in the distal esophagus relative to the middle esophagus.[29] Eosinophil levels in EoE are reported to vary widely by patient, in the same patient per biopsy sample, and in the same biopsy by hpf analysis.[28] Therefore, in all cases where EoE is a clinical possibility, even when visualizing the normal mucosa, multiple biopsy samples of 2 or more esophageal levels, directed to areas of apparent inflammation, are recommended to increase diagnostic performance.[2] In the histological study, in addition to the peak of the eosinophil count, a histological score (EoEHSS) has been developed recently. This provides more histological elements to evaluate EoE and has been shown to be superior in the diagnosis of EoE and in therapeutic decision-making.[30-32]

In GERD, the characteristic histological changes are: polymorphonuclear leukocyte infiltrate, intraepithelial eosinophils, hyperplasia of the basal area and elongation of the papillae.[26] These changes are also mentioned in the EoE.[25] The absence of histological changes does not exclude GERD.[10]

Manometric aspects

No specific manometric pattern for EoE has been identified.[33] Variable motor abnormalities, both hypocontractile and hypercontractile, were described with conventional esophageal manometry.[8] [34] After the use of HRM with CC, they have continued to report, even with a favorable response to steroid therapy.[35] Because the performance of esophageal manometry is not required for the diagnosis of EoE, and sometimes patients diagnosed with an esophageal motor disorder have not previously undergone an esophageal histological study, sometimes not even an EGD, this can lead to the loss of the association between EoE and esophageal motility disorders.

In GERD it is suggested to use manometric studies when a motility disorder is suspected.[10] The alterations associated with gastroesophageal reflux are dysfunction of the EGJ and alterations in the motility of the esophageal body, mainly ineffective esophageal motility.[20 36 37]

The association of motility disorders with esophageal eosinophilia in the different layers of the esophagus has been described for decades.[8] In relation to achalasia, the association with mucosal eosinophilia (EoE) is uncommon, but there are several publications about the association with eosinophilic infiltration of the esophageal muscular tissue. The first report of esophageal eosinophilic infiltration was in California, precisely in a patient with achalasia.[4] In 1989 an adult with achalasia and gastric adenocarcinoma without esophageal involvement was reported in Denmark, who underwent surgery, and the distal esophagus shows eosinophilic infiltration in all layers of the esophageal wall.[38] Subsequent to this report, these investigators published 9 cases of primary achalasia that Heller's myotomy was performed, and esophageal eosinophilia was evidenced in biopsies of esophageal muscularis propria.[39] In 1994 a study of 42 patients with achalasia who underwent esophagectomy was performed, all cases presented eosinophils and lynphocytes infiltrating the myenteric plexus, with eosinophilia involving the muscularis propria in 52%.[40] Similar findings were later described in esophageal muscle- biopsy specimens taken during Heller myotomy, with presence in addition to T lymphocytes.[41] Other studies also describe the association between achalasia and esophageal eosinophilic infiltration.[42-45]

It is not clear when the motility disorder is due to esophageal eosinophilia or vice versa. Thomas Frieling et al. propose that achalasia and esophageal eosinophilic infiltration are not different clinical entities. They investigated an adult patient with EoE and achalasia, without any prior history of atopy, and without response to steroid treatment, but there was a clinical response after esophageal dilation. They suggest that eosinophilic infiltration is secondary to achalasia.[33] Also, in a Canadian study; it has been reported esophageal mucous eosinophilia in patients diagnosed with achalasia. In these patients the eosinophilic infiltration was maintained, and increased in some of these cases, after laparoscopic Heller myotomy, despite a good clinical response to

surgery.[46] However, other authors reported a patient with achalasia and EoE with a response to steroid therapy.[47] Mandaliya et al. reported 4 cases of EoE and achalasia, with partial response to steroid therapy in one case of vigorous achalasia.[44] Hejazi et al. also described a case of EoE and vigorous achalasia with favorable response to steroids.[45] The study of the different esophageal layers is made more accessible with the introduction of peroral endoscopic myotomy (POEM) as a treatment option, and with this, the performance of the peroral esophageal muscle biopsy (POEM-b). Tanaka et al. described an adult with "Jackhammer esophagus" (JE) associated with EoE, with good response to steroid treatment of mucosal eosinophilic infiltration, but with persistent motor disorder, therefore POEM was performed, with good subsequent evolution. POEM-b confirmed eosinophilic infiltration in the muscularis propria.[48] EoE is mentioned as one of the causes of EGJ outflow obstruction.[49] In a Japanese study, carried out in adults diagnosed with different primary esophageal motor disorders in which EoE and others secondary causes of dysmotility were excluded, who received POEM treatment and POEM-b was performed, eosinophilic infiltration in the esophageal muscle was reported in 3 patients with JE and one with nutcracker esophagus.[50] Funaki et al. reported marked efficacy with steroid treatment of 3 patients with JE, 2 of them with EoE.[51] Sato H. et al. described the heterogeneous infiltration of eosinophils in the esophagus, in the mucosa, submucosa and muscularis propria. EoE and subepithelial eosinophilic esophagitis (sEoE) were associated with failed peristalsis. Increased cytokine expression was identified in the esophageal epithelium in EoE: eotaxin-3, interleukin (IL) -5, IL-13, C-C chemokine receptor type-3 (CCR3), Calpain 14. In 1 case of sEoE was an identified elevated level of serum immunoglobulin E. The presence of eosinophils in the esophageal muscle tissue diagnosed by POEM-b is named as eosinophilic esophageal myositis, and was associated with hypercontractile esophagus. In the esophageal epithelium of these patients, no increase in eosinophils or cytokine overexpression was observed, but in muscle tissue, there was eosinophilia and eotaxin-3 and CCR3 overexpression. The research has as limitations that it was a small-size pilot study and the use of patients with achalasia as a control group.[52]

The relationship between esophageal motility disorders with esophageal eosinophilia and GERD require new researches, mainly in pediatric patients because most of the researches were completed within the adult population.

Treatment-related aspects

In managing infants with GERD, it is initially recommended non-pharmacological treatment such as avoid overfeeding, thickened feeds and continuous breastfeeding in breastfed infant. If there is no improvement, consider 2-4 weeks of a protein hydrolysate or aminoacid-based formula, or in breastfed infant: elimination of cow's milk in maternal diet. In children and adolescents, the initial recommendation is also lifestyle and dietary education. If there is no improvement pharmacological treatment is recommended: acid suppression for 4-8 weeks, preferably with proton pump inhibitors (PPIs). Refer to the pediatric gastroenterologist when patients are refractory to optimal treatment and cannot be permanently weaned from pharmacological treatment within 6-12 months.[10]

GERD was previously distinguished from other diseases and from EoE by clinical response to PPI therapy. Then it was found that there was a group that histologically met the criteria for EoE but also responded to this treatment and was termed PPI-responsive esophageal eosinophilia (PPI-REE). In the last diagnostic consensus of EoE, PPI-REE was included in EoE because studies had shown it was the same disease.[2] To understand this, it is necessary to mention some aspects of the pathophysiology of EoE. The abnormalities found in cases of EoE are increased esophageal mucosa permeability, it may be responsible for entry of food and environmental allergens into subepithelial tissues and induce allergic reactions following eosinophil infiltration. These allergens then stimulate a Th2-type immune response with increased production of Th2-type cytokines, including IL-13 and IL-4, which increases eosinophil accumulation in the esophagus through stimulation of eotaxin-3 production by esophageal epithelial cells.[53 54] Cheng et al. showed that in EoE and GERD cell lines, IL-4 and IL-13 activated the eotaxin-3 promoter. Similar levels of eotaxin-3, and omeprazole blocks that eotaxin-3 expression, were observed in both diseases. PPI might have eosinophil-reducing effects independent of effects on acid reflux, and that response to PPI does not distinguish EoE from GERD.[55] A molecular EoE diagnostic

panel (EDP) was identified, that is composed of 94 EoE genes and distinguishes patients with EoE from control subjects. Applying EDP, similar expression patterns were demonstrated in EoE and PPI-REE, indicating that PPI-REE is a condition within the same spectrum as EoE.[56] Due to this, a test with PPI is not required for the diagnosis of EoE in the diagnostic algorithm of the mentioned disease.[2] And we cannot distinguish GERD and EoE by their response to PPI therapy. (Table 3)

Some aspects in relation to the pathophysiology

Apparently, the explanation for the similarity in the symptoms and many aspects of the referred diseases is included within the pathophysiology. New hypotheses related to the mechanisms of inflammation and cytokine release have been developed to explain the abnormalities. In the case of GERD, a new concept has been proposed, stating that it is not reflux that directly damages the epithelium, but rather stimulates epithelial cells to release cytokines that induce proliferative changes and attract T lymphocytes and other inflammatory cells that they end up damaging the mucosa.[54] In EoE, it is known that there is an abnormal immune reaction mediated by Th2 interleukins, in which there is a recruitment of eosinophils, inflammatory cytokines are released and the degranulation products released by the eosinophils contribute to epithelial damage.[24] By having similar pathophysiological mechanisms, mediated by cytokines, other similarities in GERD and EoE could be justified.[54]

EoE is defined by the infiltration of eosinophils into the esophageal mucous layer. Because of this, and for of the invasiveness and difficult access to the rest of the layers of the esophageal wall, these are generally not studied. Esophageal biopsies that are limited to the evaluation of the esophageal epithelium are an inadequate means to assess overall, clinical disease severity in EoE.[57] However, in a study carried out in patients with EoE, the authors reported activated eosinophils in all esophageal layers.[58]

Several studies have proposed hypotheses to explain the association of achalasia and other motility disorders with esophageal eosinophilia. From weak evidence that the esophageal stasis of achalasia causes eosinophilia mucosa,[33 42 46] to the esophageal eosinophilia causes motility abnormalities through the release of cytokines and neurotoxic eosinophil secretory products.[39 41 58-61]

Spechler has proposed that EoE, similar to what occurs in eosinophilic gastroenteritis, could have forms with a predominance of mucosa and forms with a predominance of muscle; the predominantly muscular form could cause a variety of esophageal motor disorders, including achalasia. Some eosinophil products can cause esophageal muscle contraction (Thromboxane B2, Leukotriene D4), others cause muscle relaxation (IL-6, IL-13), fibrosis (TGF-β, IL-13). They can also secrete neuroactive products, or others that destroy esophageal intramural neurons.[62]

Conclusions

The clinical similarity between GERD, EoE and esophageal motility disorders, along with the possibility that they may overlap, requires great attention from the physician. It should be remembered that other entities may be underdiagnosed in the clinical context of GERD. We recommend, in the presence of symptoms of esophageal dysfunction, if an EGD is to be performed, always take esophageal biopsy samples in the distal and middle/upper thirds, even if there are no endoscopic alterations, nor have EoE been initially considered. The results of HRM should be evaluated in conjunction with those of EGD and esophageal histology. Before reaching a definitive diagnosis, carry out a comprehensive analysis of the clinic, the diagnostic tests performed, including esophageal histology; and individualize each case with esophageal motor disorder.

Some of the esophageal motility disorders still have an uncertain clinical significance. They can constitute a heterogeneous group of disorders with different pathophysiologies. Therefore, the treatment must be individualized. Perhaps we should rethink the hitherto known as "primary" esophageal motor disorders. The definition of EoE may need to be more comprehensive, including in addition to mucosal eosinophilia, submucosal and muscular eosinophilic infiltration. The relationship between esophageal eosinophilia and motility disorders needs to be clarified. Future research, including pediatric patients, is required to assess eosinophilic infiltration of the different layers of the esophagus and its pathophysiological implications. The performance of POEM-b and genetic studies would be useful in this regard.

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Box 1: Conditions associated with esophageal eosinophilia.[2]

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- GERD
- Achalasia and other disorders of esophageal involvement
- Hypereosinophilic syndrome
- Crohn's disease with esophageal involvement
- Infections (fungal, viral)
- Connective tissue disorders
- Hypermobility syndromes
- Autoimmune disorders and vasculitides
- Dermatologic conditions with esophageal involvement
- Drug hypersensitivity reactions
- Pill esophagitis
- Graft-versus-host disease
- Mendelian disorders (Marfan syndrome type II, hyper-IgE syndrome, PTEN hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting syndrome)

Table 1: Main similarities and differences between eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD) and esophageal motility disorders in terms of concept and clinical aspects.

<table>
<tr><th>Aspects</th><th>EoE</th><th>GERD</th><th>Esophageal motility disorders</th></tr>
<tr><td rowspan="2">Definition[2] [10 11]</td><td colspan="2">Symptoms are mentioned in both definitions and may be common. Some complications of GERD are also common to EoE

Histology is important in EoE definition, in both diseases there is eosinophilia mucosa</td><td rowspan="2">Based mainly on manometric parameters, so it does not exclude other aspects</td></tr>
<tr><td>Generally higher number of eosinophils on biopsy</td><td>Some complications are typical of GERD (Barrett's esophagus)</td></tr>
<tr><td rowspan="2">Clinical aspects</td><td colspan="3">Symptomatology compatible (symptoms of esophageal dysfunction)</td></tr>
<tr><td>More frequent history of atopy</td><td colspan="2">There may also be atopy and respiratory manifestations</td></tr>
</table>

Table 2: Some aspects of diagnostic test in eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD) and esophageal motility disorders.

Diagnostic tests		EoE	GERD	Esophageal motility disorders
Upper Digestive Endoscopy		Can be normal		
		Endoscopic reference score (EREFS: Edema, Rings, Exudates, Furrows and Strictures)	Los Angeles classification for erosive esophagitis; stenosis, esophageal metaplasia, etc.	Organic causes of dysphagia should be excluded
		Involvement throughout the esophagus	Distal involvement	
Histology[28]	General features	Eosinophilic infiltration, basal cell hyperplasia, dilated intercellular spaces, elongation of the papillae		Findings compatible with GERD, with EoE and eosinophilic infiltration of the submucosa and the muscularis propria have been described
	Eosinophil number	≥15 eos/hpf	Usually less, although in some cases it can reach 15 eos/hpf	
	Location of eosinophil infiltration	Patched along the esophagus	More intense in distal esophagus	
	Eosinophilic abscesses	Frequent	Rare	
	Eosinophils degranulated	Frequent	Infrequent	
	Erosion / ulcer	Rare	May be present	
	Damage and loss of superficial squamous cells	Useful if present	Rare	
Esophageal manometry		It can be pathological		With alterations

Table 3: Aspects related to treatment in eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD) and esophageal motility disorders.

	EoE	GERD	Esophageal motility disorders
Treatment	There may be a good response to IBP		
	Response to other therapies (steroids, diet)	Non-pharmacological treatment is initially indicated Other treatments depending on the evolution and severity	Treatment depending on the type of disorder Steroid response has been described in some cases with esophageal eosinophilia

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Esophageal eosinophilia and esophageal diseases in children. Are the limits clear?

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Abstract

Gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), and esophageal motility disorders are among the most common diseases accompanying esophageal eosinophilia. They have similarities and their limits are frequently not well-defined. This article reviews the main characteristics relating to their similarities and differences, highlighting existing controversies among these diseases, in addition to current knowledge. In the case of a patient with symptoms of esophageal dysfunction, it is suggested to carry out an integral analysis of the clinical features and diagnostic test results, including histology, while individualizing each case before confirming a definitive diagnosis. Future investigation in pediatric patients is necessary to assess eosinophilic infiltration in the various layers of the esophageal tissue, along with its clinical and pathophysiological implications.

Introduction

Under normal physiological conditions, eosinophils are present throughout the gastrointestinal tract distal to the squamous esophagus, so the esophagus normally lacks these.[1] Several conditions are associated with the infiltration of eosinophils within the esophagus, or esophageal eosinophilia (Box 1), many of which are uncommon or may present distinctive clinical characteristics.[2] However, in the clinical setting, there are some frequent esophageal diseases with the evidence of eosinophils presented on esophageal histology, such as gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), and even esophageal motility disorders.

EoE is the most distinctive as it relates to the presence of significant mucosal esophageal eosinophilia, but other disorders must be considered in the differential diagnosis. Eosinophilic gastroenteritis with esophageal involvement should be evaluated with the study of gastric and duodenal biopsy samples. Hypereosinophilic syndrome should be considered when the peripheral blood eosinophil count is >1500 x 10^9 cells/L. Children who have inflammatory bowel disorders, including celiac disease or Crohn's disease, can have eosinophil-predominant esophageal inflammation. However, a diagnosis of EoE is not appropriate when another condition could account for the histological changes. Treatment should be initiated for the presumed primary etiology, with monitoring of the esophageal inflammation. If esophageal eosinophilia persists after the primary disease is controlled, EoE could be diagnosed as an overlapping condition. EoE has also been associated with connective tissue diseases, perhaps due to a shared pathogenic mechanism. It can also present with other unrelated medical conditions. Many other causes of esophageal eosinophilia are relatively rare and can be excluded with a comprehensive medical history and laboratory tests, however, in the case of GERD it can be more complex. Also, there are various reports of association of esophageal eosinophilic infiltration and esophageal motility disorders, with recent studies based on its pathophysiology.[2 3] It is to these three disorders (EoE, GERD and esophageal motility disorders) that we will make reference to in this article, since they are common diseases in clinical practice, which can overlap and sometimes their limits are not well defined. There have been some consensuses and multiple investigations in

regards on these diseases separately, but many aspects may still need to be clarified. The intention of this review is to offer a joint approach to these three conditions, with many similarities and sometimes their limits are not so well-defined, emphasizing their main characteristics that make they may be similar and be different.

Definitions

EoE is a chronic, inflammatory, local disease of immunological origin and mediated by antigens, usually food. Eosinophilic infiltration of the esophagus was initially described in 1978 in biopsies of a patient that was diagnosed with achalasia.[4] Eosinophilic infiltration was initially considered a consequence of GERD. It has been recognized as a clinicopathological entity from a report made in 1993.[5] Subsequently, the response to dietary therapy was identified.[6] The general recognition of this new disorder was in the current millennium, when it has been reported in adults and children.[7] [8] It is predominantly inflammatory during childhood (inflammatory phenotype) and with progression to fibrosis in adulthood (fibrostenosing phenotype), characterized by signs and symptoms of esophageal dysfunction related to eosinophilic inflammation limited to the esophagus.[9] According to the latest International Consensus update on the diagnostic criteria for eosinophilic esophagitis, **suspicion of EoE** was defined as symptoms of esophageal dysfunction (concomitant atopic conditions can increase suspicion of EoE) and at least 15 eosinophils/high-power field (hpf) or approximately 60 eosinophils/mm^2 in esophageal biopsy. **Confirmed EoE** was defined as symptoms of esophageal dysfunction and at least 15 eosinophils/hpf or approximately 60 eosinophils/mm^2 on esophageal biopsy (eosinophilic infiltration should be limited to the esophagus), after evaluation for other causes of esophageal eosinophilia.[2] In this consensus, there is recognition that it is the same disease in children and adults. The need to evaluate for conditions that might contribute to esophageal eosinophilia has been recognized. This allows the diagnosis of EoE to coexist with that of GERD and other conditions.

The NASPGHAN and ESPGHAN Pediatric Gastroesophageal Reflux (GER) Clinical Practice Guidelines defines GER as the passage of gastric contents into the esophagus with or without regurgitation and vomiting. GERD is when GER leads to troublesome

symptoms and/or complications.[10] However, GERD shares symptoms and complications with EoE, making it difficult to distinguish these conditions. It also shares symptoms with some motility disorders and both entities may be present in the same patient. Therefore, a definition based on symptoms that can be shared with other conditions may not be completely clear. (Table 1)

The diagnosis of esophageal motility disorders is based on alterations present in esophageal manometry. Conventional manometry has been gradually replaced by high resolution manometry (HRM), which is currently the "gold standard" for diagnosis. The Chicago Classification (CC), that defines esophageal motility disorders, was first published in 2008, and its last update was in 2015 (version 3.0).[11 12] The CC provides uniformity in diagnoses, consisting of a hierarchical analysis, it initially focuses on disorders within esophagogastric junction (EGJ) outflow obstruction (achalasia, EGJ outflow obstruction), later on major disorders of peristalsis (diffuse esophageal spasm, Jackhammer esophagus (JE), absent contractility) and finally minor disorders of peristalsis (ineffective motility, fragmented peristalsis).[13 14] The CC was based on manometric studies carried out in a healthy adult population, therefore it may have limitations in the pediatric population. The limitation for obtaining similar studies in a healthy pediatric population is an ethical consideration.[15] Studies have been carried out to evaluate manometric parameters in symptomatic children depending on factors such as esophageal length and age, but still without definitive conclusions.[16] Being a diagnosis based only on manometric alterations, it leaves an open gap for other pathologies that could coexist.

Clinical aspects

In pediatric patients, diagnostic guidance based on symptoms is difficult, especially at younger ages, when symptoms are more nonspecific, and generally reported by caregivers, and therefore depend on their interpretation.

EoE is suspected clinically when there are symptoms of esophageal dysfunction, which could manifest themselves in various ways, including dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain and malnutrition. Atopic comorbidities such as

asthma, atopic dermatitis, or immediate food allergies should increase the clinical index of suspicion. In younger children, the most common symptoms are those similar to gastroesophageal reflux, in addition to vomiting, abdominal pain, food refusal, and failure to thrive. In older children, adolescents and adults, dysphagia to solids, food impaction and chest pain not associated with swallowing are more frequently reported.[17] Because these symptoms are nonspecific, patients should be treated as clinically indicated. The diagnostic algorithm cannot anticipate all clinical possibilities, and provides scope for appropriate evaluation. [2]

Among the most frequent symptoms that may be associated with GERD in infants and children are general manifestations (irritability, food refusal, failure to thrive), gastrointestinal manifestations (heartburn, regurgitation / vomiting, retrosternal chest pain, dysphagia, epigastric pain) and manifestations of the airway (cough, wheezing, stridor, apnea episodes, asthma, pneumonia).[10 18 19] Given that the symptoms of GERD are not specific, “red flags” or warning signs have been defined to guide the need for research studies to rule out complications of GERD and underlying disorders with similar symptoms. It should be noted that GER in infants is very common, and is usually self-limiting. In the presence of an infant with recurrent regurgitation, a thorough history and physical examination with attention to warning signals suggesting other diagnoses is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER. In the absence of warning signs, diagnostic testing and/or therapies including acid suppression are not needed if there is no impact of the symptoms on feeding, growth or acquisition of developmental milestones. Referral to the pediatric gastroenterologist is recommended when in infants or children there are warning signs or symptoms suggesting an underlying gastrointestinal disease.[10]

Esophageal motility disorders also show a spectrum of symptoms similar to EoE and GERD, including weight loss (nonspecific symptom predictive of abnormal HRM), feeding difficulties, dysphagia, vomiting, manifestations of GERD, respiratory symptoms, chest pain, failure to thrive, among others.[20] More nonspecific symptoms are described in younger children, such as vomiting, anorexia, chronic cough, which often

delays diagnosis.[21 22] In esophageal motility disorders, allergic disorders have also been reported among the most frequent comorbidities.[15]

Many of the clinical manifestations are similar in the three entities (Table 1), which makes clinical-based differential diagnosis difficult, and diagnostic procedures should be performed when indicated.

Endoscopic aspects

Upper digestive endoscopy or esophagogastroduodenoscopy (EGD) may have specific features but may also be normal in EoE and GERD. (Table 2)

In the EoE, an endoscopic reference score has been developed: EREFS (Edema, Rings, Exudates, Furrows, Strictures) that gives a score according to the degree of severity of the finding.[23] The findings of mucosa on crepe paper and mucous friability are also described.[7 24 25]

In the case of GERD, it does not have a gold standard test. EGD is recommended if the complications of GERD need to be assessed and if underlying mucosal disease is suspected before intensification of therapy. The probability of having erosive esophagitis caused by reflux varies from 15 to 71% between studies, so a normal endoscopy does not necessarily rule out the possibility of GERD.[10 26] When GERD is erosive, the diagnosis of this is facilitated, the most used classification is Los Angeles classification.[27] There are, of course, other complementary tests, such as pH-metry and multichannel intraluminal impedance to support the diagnosis of GERD in necessary cases.

For the diagnosis of esophageal motility disorders, anatomic causes of the symptoms must have been excluded by means of a contrast study of the esophagus and/or EGD.[7 22] Therefore, EGD should be normal, which does not exclude the presence of esophageal disease. If there is EoE or GERD, and esophageal manometry is performed, we can find the diagnosis of motor disorders in these entities.

Histological aspects

Although there are aspects that could help differentiate GERD and EoE from the histological point of view, there are some cases that are histologically indistinguishable and both conditions can overlap. (Table 2) It is also more complex if samples are only taken from the distal third of the esophagus, since this is the most affected in GERD, while in EoE the entire esophagus is affected in patches. In addition, in severe cases of GERD, more proximal areas can be affected.[28] A study of EoE performed in pediatric age showed a denser eosinophilic infiltrate in the distal esophagus relative to the middle esophagus.[29] Eosinophil levels in EoE are reported to vary widely by patient, in the same patient per biopsy sample, and in the same biopsy by hpf analysis.[28] Therefore, in all cases where EoE is a clinical possibility, even when visualizing the normal mucosa, multiple biopsy samples of 2 or more esophageal levels, directed to areas of apparent inflammation, are recommended to increase diagnostic performance.[2] In the histological study, in addition to the peak of the eosinophil count, a histological score (EoEHSS) has been developed recently. This provides more histological elements to evaluate EoE and has been shown to be superior in the diagnosis of EoE and in therapeutic decision-making.[30-32]

In GERD, the characteristic histological changes are: polymorphonuclear leukocyte infiltrate, intraepithelial eosinophils, hyperplasia of the basal area and elongation of the papillae.[26] These changes are also mentioned in EoE.[25] The absence of histological changes does not exclude GERD.[10]

Manometric aspects

No specific manometric pattern for EoE has been identified.[33] Variable motor abnormalities, both hypocontractile and hypercontractile, were described with conventional esophageal manometry.[8 34] After the use of HRM with CC, they have continued to report, even with a favorable response to steroid therapy.[35]

In GERD it is suggested to use manometric studies when a motility disorder is suspected.[10] The alterations associated with gastroesophageal reflux are dysfunction of the EGJ and alterations in the motility of the esophageal body, mainly ineffective esophageal motility.[20 36 37]

The association of motility disorders with esophageal eosinophilia in the different layers of the esophagus has been described for decades.[8] In relation to achalasia, the association with mucosal eosinophilia only (EoE) is uncommon, but there are several publications about the association with eosinophilic infiltration of the different esophageal tissues, especially muscularis propria.[4 38-45]

It is not clear when the motility disorder is due to esophageal eosinophilia or vice versa. In a study, a decrease in esophageal eosinophilia is described after the therapy of motility disorder,[33] or just clinical improvement.[46] However, other authors reported a patients with achalasia and EoE with a response to steroid therapy,[47] mainly vigorous achalasia.[44 45] Improvement of esophageal eosinophilia has also been described with the use of steroids in JE.[48 49]

Sato H. et al. described the heterogeneous infiltration of eosinophils in the esophagus in the mucosa, submucosa and muscularis propria. The presence of eosinophils in the esophageal muscle tissue is named as eosinophilic esophageal myositis, and was associated with hypercontractile esophagus. In the esophageal epithelium of these patients, no increase in eosinophils or cytokine overexpression was observed, but in muscle tissue, there was eosinophilia, eotaxin-3 and C-C chemokine receptor type-3 overexpression. The research has limitations as it was a small-size pilot study and the use of patients with achalasia as a control group.[50]

The relationship between esophageal motility disorders with esophageal eosinophilia and GERD require new researches, mainly in pediatric patients because most of the researches were completed within the adult population.

Treatment-related aspects

In managing infants with GERD, non-pharmacological treatment such as avoiding overfeeding, thickened feeds and continuous breastfeeding in breastfed infant are initially recommended. If there is no improvement, consider 2-4 weeks of a protein hydrolysate or aminoacid-based formula, or in breastfed infant: elimination of cow's milk in maternal diet. In children and adolescents, the initial recommendation is also lifestyle and dietary education. If there is no improvement pharmacological treatment is

recommended: acid suppression for 4-8 weeks, preferably with proton pump inhibitors (PPIs). Refer to the pediatric gastroenterologist when patients are refractory to optimal treatment and cannot be permanently weaned from pharmacological treatment within 6-12 months.[10]

GERD was previously distinguished from other diseases and from EoE by clinical response to PPI therapy. Then it was found that there was a group that histologically met the criteria for EoE but also responded to this treatment and was termed PPI-responsive esophageal eosinophilia (PPI-REE). In the last diagnostic consensus of EoE, PPI-REE was included in EoE because studies had shown it was the same disease.[2] To understand this, it is necessary to mention some aspects of the pathophysiology of EoE. The abnormalities found in cases of EoE are increased esophageal mucosa permeability. It may be responsible for entry of food and environmental allergens into subepithelial tissues and induce allergic reactions following eosinophil infiltration. These allergens then stimulate a Th2-type immune response with increased production of Th2-type cytokines, including IL-13 and IL-4, which increases eosinophil accumulation in the esophagus through stimulation of eotaxin-3 production by esophageal epithelial cells.[51 52] Cheng et al. showed that in EoE and GERD cell lines, IL-4 and IL-13 activated the eotaxin-3 promoter. Similar levels of eotaxin-3 were observed in both diseases. PPI might have eosinophil-reducing effects independent of effects on acid reflux, and that response to PPI does not distinguish EoE from GERD.[53] A molecular EoE diagnostic panel (EDP) was identified, that is composed of 94 EoE genes and distinguishes patients with EoE from control subjects. Applying EDP, similar expression patterns were demonstrated in EoE and PPI-REE, indicating that PPI-REE is a condition within the same spectrum as EoE.[54] Due to this, a test with PPI is not required for the diagnosis of EoE in the diagnostic algorithm of the mentioned disease.[2] And we cannot distinguish GERD and EoE by their response to PPI therapy. (Table 3)

Some aspects in relation to the pathophysiology

New hypotheses related to the mechanisms of inflammation and cytokine release have been developed to explain the abnormalities. In the case of GERD, a new concept has been proposed, stating that it is not reflux that directly damages the epithelium, but

rather stimulates epithelial cells to release cytokines that induce proliferative changes and attract T lymphocytes and other inflammatory cells that they end up damaging the mucosa.[52] In EoE, it is known that there is an abnormal immune reaction mediated by Th2 interleukins, in which there is a recruitment of eosinophils, inflammatory cytokines are released and the degranulation products released by the eosinophils contribute to epithelial damage.[24] By having similar pathophysiological mechanisms, mediated by cytokines, other similarities in GERD and EoE could be justified.[52]

EoE is defined by the infiltration of eosinophils into the esophageal mucous layer. Because of this, and for of the invasiveness and difficult access to the rest of the layers of the esophageal wall, these are generally not studied. Esophageal biopsies that are limited to the evaluation of the esophageal epithelium are an inadequate means to assess overall, clinical disease severity in EoE.[55] However, in a study carried out in patients with EoE, the authors reported activated eosinophils in all esophageal layers.[56]

Several studies have proposed hypotheses to explain the association of achalasia and other motility disorders with esophageal eosinophilia. From weak evidence that the esophageal stasis of achalasia causes eosinophilia mucosa,[33 42 46] to the esophageal eosinophilia causes motility abnormalities through the release of cytokines and neurotoxic eosinophil secretory products.[39 41 56-59]

Spechler has proposed that EoE, similar to what occurs in eosinophilic gastroenteritis, could have forms with a predominance of mucosa and forms with a predominance of muscle; the predominantly muscular form could cause a variety of esophageal motor disorders, including achalasia. Some eosinophil products can cause esophageal muscle contraction (Thromboxane B2, Leukotriene D4), others cause muscle relaxation (IL-6, IL-13), fibrosis (TGF-β, IL-13). They can also secrete neuroactive products, or others that destroy esophageal intramural neurons.[60]

Conclusions

The clinical similarity between GERD, EoE and esophageal motility disorders, along with the possibility that they may overlap, requires great attention from the physician. It should be remembered that other entities may be underdiagnosed in the clinical context

of GERD. We recommend, in the presence of symptoms of esophageal dysfunction, if an EGD is to be performed, always take esophageal biopsy samples in the distal and middle/upper thirds, even if there are no endoscopic alterations, nor have EoE been initially considered. The results of esophageal manometry should be evaluated in conjunction with those of EGD and esophageal histology. Before reaching a definitive diagnosis, carry out a comprehensive analysis of the clinical symptoms and the diagnostic tests performed, including esophageal histology.

Future research, including pediatric patients, is required to assess eosinophilic infiltration of the different layers of the esophagus and its pathophysiological implications.

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Box 1: Conditions associated with esophageal eosinophilia.[2]

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- GERD
- Achalasia and other disorders of esophageal involvement
- Hypereosinophilic syndrome
- Crohn's disease with esophageal involvement
- Infections (fungal, viral)
- Connective tissue disorders
- Hypermobility syndromes
- Autoimmune disorders and vasculitides
- Dermatologic conditions with esophageal involvement
- Drug hypersensitivity reactions
- Pill esophagitis
- Graft-versus-host disease
- Mendelian disorders (Marfan syndrome type II, hyper-IgE syndrome, PTEN hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting syndrome)

Table 1: Main similarities and differences between eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD) and esophageal motility disorders in terms of concept and clinical aspects.

<table>
<tr><th>Aspects</th><th>EoE</th><th>GERD</th><th>Esophageal motility disorders</th></tr>
<tr><td rowspan="2">Definition[2] [10 11]</td><td colspan="2">Symptoms are mentioned in both definitions and may be common. Some complications of GERD are also common to EoE

Histology is important in EoE definition, in both diseases there is eosinophilia mucosa</td><td rowspan="2">Based mainly on manometric parameters, so it does not exclude other aspects</td></tr>
<tr><td>Generally higher number of eosinophils on biopsy</td><td>Some complications are typical of GERD (Barrett's esophagus)</td></tr>
<tr><td rowspan="2">Clinical aspects</td><td colspan="3">Symptomatology compatible (symptoms of esophageal dysfunction)</td></tr>
<tr><td>More frequent history of atopy</td><td colspan="2">There may also be atopy and respiratory manifestations</td></tr>
</table>

Table 2: Some aspects of diagnostic test in eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD) and esophageal motility disorders.

Diagnostic tests		**EoE**	**GERD**	**Esophageal motility disorders**
Upper Digestive Endoscopy		Can be normal		
		Endoscopic reference score (EREFS: Edema, Rings, Exudates, Furrows and Strictures)	Los Angeles classification for erosive esophagitis; stenosis, esophageal metaplasia, etc.	Organic causes of dysphagia should be excluded
		Involvement throughout the esophagus	Distal involvement	
Histology[28]	General features	Eosinophilic infiltration, basal cell hyperplasia, dilated intercellular spaces, elongation of the papillae		Findings compatible with GERD, with EoE and eosinophilic infiltration of the submucosa and the muscularis propria have been described
	Eosinophil number	≥15 eos/hpf	Usually less, although in some cases it can reach 15 eos/hpf	
	Location of eosinophil infiltration	Patched along the esophagus	More intense in distal esophagus	
	Eosinophilic abscesses	Frequent	Rare	
	Eosinophils degranulated	Frequent	Infrequent	
	Erosion / ulcer	Rare	May be present	
	Damage and loss of superficial squamous cells	Useful if present	Rare	
Esophageal manometry		It can be pathological		With alterations

Table 3: Aspects related to treatment in eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD) and esophageal motility disorders.

	EoE	GERD	Esophageal motility disorders
Treatment	There may be a good response to PPI		
	Response to other therapies (steroids, diet)	Non-pharmacological treatment is initially indicated Other treatments depending on the evolution and severity	Treatment depending on the type of disorder Steroid response has been described in some cases with esophageal eosinophilia

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SEDO: Planned the study, searched and selecting articles in the PubMed and Cochrane Library search engines, performed analysis and interpretation of data, writing of the manuscript, approval of final version and responsible for overall content.

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