



Eosinophilic gastroenteritis: epidemiology, diagnosis, and treatment

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Purpose of review

Although several reviews concerning diagnosis and treatment of eosinophilic esophagitis (EoE) have been presented, there are few in regard to eosinophilic gastroenteritis (EGE). Fortunately, findings related to epidemiology, as well as diagnosis and treatment of this disease have recently been increasing.

Recent findings

The rates of incidence of both EoE and EGE have been reported to be increasing. For accurate diagnosis, plasma concentrations of thymic stromal lymphopoietin and IL-33 may be useful as biomarkers, though consensus has not been reached, while increased eosinophil infiltration in gastrointestinal tissue remains a critical factor. Topical glucocorticoid administration, an elimination diet, and molecular target therapy with neutralizing antibodies are potentially effective therapies that have recently been evaluated.

Summary

As seen with other allergic diseases, EGE seems to be increasing. Several research projects regarding diagnosis and treatment of the disease are currently in progress.

Keywords

elimination diet, eosinophilia, IL-13, IL-5, proton pump inhibitor

INTRODUCTION

Eosinophilic gastrointestinal disorders (EGIDs) are Th2 allergic diseases characterized by dense infiltration of eosinophils in the gastrointestinal tract and symptoms originating from that location. They can be divided into two diseases based on the gastrointestinal site of eosinophil infiltration, eosinophilic esophagitis (EoE), which only shows esophageal eosinophil infiltration and no pathological eosinophil infiltration in other parts of the gastrointestinal tract, and eosinophilic gastroenteritis (EGE), which demonstrates pathological dense eosinophil infiltration in the gastrointestinal tract irrespective of esophageal involvement. EGE is further divided into three subtypes, eosinophilic gastritis, eosinophilic enteritis, and eosinophilic colitis, based on the involved gastrointestinal tract segment. Furthermore, EoE, gastritis, enteritis, and colitis frequently overlap, and pathological eosinophil infiltration can be observed in more than one segment.

The rates of incidence and prevalence of EGE are reported to be increasing in some areas of the world. Different from EoE, EGE is usually accompanied by peripheral eosinophilia and other diseases accompanied by eosinophilia, such as eosinophilic granulomatosis with polyangiitis (EGPA) and

hypereosinophilic syndrome, must be ruled out before confirming its diagnosis. Glucocorticoid administration is the standard treatment for EGE and widely used, though several new options are being developed, and may improve the therapeutic effects and long-term prognosis of affected patients. In this study, a review of recent findings related to epidemiology, diagnosis, and treatment of EGE are described.

EPIDEMIOLOGY

Although EGE is considered to be a rare disease, along with the increasing prevalence of other allergic diseases, such as bronchial asthma and allergic rhinitis, the number of reported cases is increasing [1]. In the United States, the number of cases with

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KEY POINTS

- The incidence of EGE seems to be increasing in most parts of the world.
- Different from EoE, there is no age or sex preponderance for EGE.
- The value of serum biomarkers for diagnosis of EGE remains to be demonstrated.
- Investigations are currently underway regarding the therapeutic effects of topical glucocorticoid administration, elimination diets, and use of neutralizing antibodies.

EGE diagnosed in tertiary referral centers was recently reported to be increasing [2[¶]]. The recent prevalence of EGE in western countries ranges from 5 to 8 per 100 000 of the general population, lower than that of EoE, which is 50 per 100 000 of the general population [3]. As for Japan, the prevalence of EGE was reported to be higher as compared to EoE [4], though that of the latter is rapidly increasing and has recently reached a level similar to EGE.

The median age of patients with EGE ranges from 30 to 50 years old, similar to that of those with EoE, while the prevalence of EoE has an age dependent distribution and a clear peak at 30–50 years old. On the other hand, the prevalence of EGE has not been found to have age dependent changes in either western countries or Japan, though the prevalence of cases with intestinal involvement tends to be increased in childhood [5]. While sex difference in EGE cases is not clear, the number of female patients may tend to be higher, different from EoE, which has a clearly higher prevalence in males at approximately 80%. EoE and EGE are recognized as Th2 type delayed allergic diseases, and share the same pathogenesis, as well as several clinical and laboratory characteristics. However, differences in epidemiological data between them, such as age distribution and sex differences, suggest similar but different pathogeneses for these two EGIDs.

DIAGNOSIS

Symptoms experienced by patients with EGE are not specific and differ depending on the involved segments. Those with gastric diseases mainly note epigastralgia and nausea, while patients with intestinal or colonic involvement are generally affected by abdominal pain and diarrhea [6]. Furthermore, dysphagia and heartburn frequently occur in patients with esophageal eosinophil infiltration in addition to gastrointestinal involvement, while those with a

significant volume of ascites sometimes complain about abdominal fullness. Physical examination findings rarely reveal specific signs useful for diagnosis, though abdominal tenderness and ascites, as well as signs of other atopic diseases, such as atopic dermatitis and bronchial asthma, are sometimes observed.

Laboratory test results are helpful for diagnosis. The peripheral blood leukocyte number is raised in many cases, while eosinophil number is reported to be elevated in 80% of cases with EGE [6]. Moreover, peripheral eosinophilia grade has been shown to be significantly elevated in the small intestine as compared with other sites [6,7]. Patients with mucosal or subserosal involvement are known to have more remarkable eosinophilia than those predominantly with muscle involvement. Peripheral eosinophil number is considered to be one of the signs of disease severity, with an absolute eosinophil number in peripheral blood less than 1500 considered to indicate a mild, 1500–5000 a middle grade, and over 5000 a severe condition. Patients with higher peripheral eosinophil numbers tend to develop various types of eosinophilia-related complications. For example, approximately half of those with severe eosinophilia are reported to have cardiac involvement, including endocarditis, myocarditis, and intracardiac mural thrombosis [8]. In these cases, elevated levels of creatinine phosphokinase, lactate dehydrogenase, and troponin T, as well as an activated coagulation system can be identified.

In addition, an elevated total IgE concentration is observed in more than 70% of affected patients, while increased IgE concentrations in response to various types of food and airborne antigens can also be found, though their diagnostic role remains unclear [9]. Furthermore, some investigators have reported that elevated peripheral thymic stromal lymphopoietin and IL-33 concentrations are helpful for diagnosis and grading of EGE severity, at least in infants [10]. However, other studies have suggested a limited role for peripheral cytokine and chemokine measurements in regard to EGID diagnosis [11].

Chest radiograph examination results rarely show lung involvement, though can suggest eosinophil pulmonary infiltration in severe cases. However, when pulmonary involvement is found, other diseases, including hypereosinophilic syndrome, systemic parasitic infection, and EGPA, must be considered. ECG and cardiac ultrasonographic findings may suggest the presence of endocarditis or myocarditis, while abdominal computed tomography and ultrasonography frequently show ascites and segmental wall thickening of the involved gastrointestinal tract.

Endoscopy is mainly useful as a method for obtaining gastrointestinal mucosal tissue samples for histopathological examination, though the findings are not adequate for diagnosis. Studies have noted that less than 10% of involved gastrointestinal segments show endoscopically identifiable abnormalities [1,12]. Even when abnormal findings are revealed in an endoscopic examination, they are mainly nonspecific, such as edema, erythema, erosions, or ulcers [13]. On the contrary, different from EoE with characteristic endoscopic abnormalities, including longitudinal furrows, white plaques, and rings, an endoscopic examination is not adequate for diagnosis of EGE.

Histopathological identification of dense eosinophil infiltration is a critical diagnostic clue indicating EGE. Although healthy individuals demonstrate eosinophil infiltration in gastrointestinal mucosa, endoscopic biopsy findings of a normal esophageal epithelial layer will indicate no eosinophil infiltration, whereas that is present in the stomach, intestines, and colon of healthy normal individuals. In fact, the grade of eosinophil infiltration in different segments of the gastrointestinal tract in normal individuals has been reported by several investigators [14,15]. Nearly all related studies have suggested that mucosal eosinophil density is highest in the distal ileum and right-side colon, and can reach a level of 20 eosinophils/ $\times 400$ high power field (HPF) [16[¶]]. On the oral and anal sides of these densely infiltrated segments, eosinophil infiltration is decreased to less than 5 eosinophils/HPF in the rectum and less than 10 eosinophils/HPF in the stomach. Therefore, for accurate diagnosis of EGE, an abnormal level of eosinophil infiltration must be evaluated based on the involved segments of the gastrointestinal tract. In addition to increased infiltration of eosinophils, eosinophil degranulation, mast cell infiltration, and eosinophil infiltration in the epithelial layer are regarded as abnormal findings and potentially useful for diagnosis. Although a number of methods for simple assessment of eosinophil infiltration have been reported, none are adequately reliable because of size variations of the microscopic fields and possible degranulation of activated eosinophils, making histological identification of degranulated eosinophils difficult [15,16[¶]]. It is necessary to obtain several biopsy samples because of the patchy distribution of pathological eosinophil infiltration in gut mucosa.

No consensus has been reached concerning diagnostic criteria for EGE. However, many investigators consider that the presence of gastrointestinal symptoms, in addition to evidence of increased infiltration and activation of eosinophils only in the gastrointestinal tract are necessary for diagnosis.

TREATMENT

No prospective randomized controlled study regarding treatment of EGE has been conducted, mainly because of its low prevalence. Antiallergic drugs, proton pump inhibitors (PPI), glucocorticoids, and elimination diet, as well as newly developed molecular targeted drugs including neutralizing antibodies against various cytokines and their receptors are currently employed for treatment of EGIDs including EGE.

Histamine H1 receptor antagonists are widely used antiallergic drugs for treatment of mild EGE cases, though their therapeutic effects have yet to be confirmed and evidence regarding their role for treatment of EGE has not been presented. In addition to histamine H1 receptor antagonists, leukotriene receptor antagonists are used for treatment, with several case reports and series concerning their therapeutic effects published. However, evidence demonstrating the effects of leukotriene receptor antagonists is quite low, because of lack of a prospective randomized controlled study. In addition, many of those case reports and series did not show histological improvement, but rather used subjective symptoms for evaluation of therapeutic effects. Since subjective symptoms are prone to various biases, results dependent on symptom improvement unfortunately have limited value.

PPIs are widely used as first-line therapeutic drugs for treatment of EoE [17]. Several randomized prospective studies have clarified those therapeutic effects and found that more than 50% of EoE patients can be successfully controlled by a continuous administration, whereas evidence of such effects for EGE is unfortunately scant [18]. PPIs are used for treatment of eosinophilic gastritis and duodenitis based on an expected anti-inflammatory action toward Th-2 immune response, as well as the assumption that inhibition of gastric acid secretion will suppress gastroduodenal mucosal damage and inflammation, though supporting findings have not been shown [19]. When ulcerated lesions are present in the stomach and duodenum, PPI administration may be effective for endoscopic healing of ulcers. On the other hand, some investigators have suggested possible aggravating effects of PPIs for EGID treatment. Several different food allergens that are composed of peptides can be digested and degraded by pepsin, a gastric protease that is enzymatically active only in an acidic environment under pH 3.0. Therefore, administration of a potent acid inhibitor prevents effective degradation of food allergens, and may induce or aggravate food antigen-induced allergic reactions. Indeed, serum food allergen specific IgEs were reported to be elevated after a 3-month administration of acid inhibitors

[20]. In addition, experimental animals were found to develop food allergen-induced allergic reactions more easily with PPI administration. Furthermore, PPIs are reported to increase the permeability of gastrointestinal mucosa and may also enhance mucosal penetration of food antigens, resulting in food-induced allergic reactions. Therefore, indiscriminate administration of PPIs to patients with EGE is considered to be inappropriate.

Glucocorticoids are the most widely prescribed type of drug for EGE, even without evidence obtained from a prospective controlled study. Systemic administration of prednisolone is a conventional therapeutic option that has been well reported. A majority of patients treated at a dose of 30–40 mg/day showed a favorable response and achieved remission status, though with a decreased dose, more than 50% of patients who attained remission showed exacerbation [21,22*,23]. Therefore, many patients with EGE require a continuous administration of prednisolone and suffer from various adverse side-effects as a result. Topical glucocorticoids that are degraded very rapidly in the liver are known to show limited adverse effects including adrenal suppression. Budesonide and fluticasone are two of the major topical glucocorticoids available, and evidence showing their therapeutic effects for treatment of EoE is high, which is different from EGE [24]. Over 70% of patients with EoE can be successfully controlled by oral administration of budesonide or fluticasone. Although their therapeutic effects for EGE have not been established, several case reports and case series have suggested beneficial effects of topical glucocorticoid administration. Notably, enteric coated budesonide is considered to be effective for controlling eosinophil inflammation in the distal intestine and colon.

The value of an elimination diet for treatment of EoE has been repeatedly reported. Wheat, milk products, soy, egg, nuts, and fish are foods that frequently cause allergic inflammation in the esophagus. Following elimination of all those foods from the diet of patients with EoE, 70% were reported to show significant improvement. Next, after returning them one by one into the regular diet, the responsible food causative of allergic inflammation could be identified. According to reports from western countries, wheat and milk are two of the major responsible foods that can cause EoE. When the responsible food is eliminated from the diet, long-term control of the disease is possible. While the value of an elimination diet has been established for treatment of EoE, that for treatment of EGE has yet to be confirmed, though several case reports and case series have suggested the value of an elimination or elemental diet for treatment of affected

patients [25]. However, those case series have some limitations, as the quality of the elimination diets employed may not have been high enough for an accurate evaluation. Complete elimination of a specific diet component is very difficult to achieve on an outpatient basis, since wheat, milk, soy, and eggs are contained in several types of processed foods, thus complete elimination must be conducted under complete control of a dietician. Moreover, the endpoints employed for evaluating the therapeutic effects of elimination diet are frequently symptom improvement but not histological improvement, possibly due to difficulties with repeated small intestinal endoscopic observations. Because of these limiting factors, the true value of an elimination diet for treatment of EGE has not yet been clarified.

We recently summarized findings of 10 glucocorticoid-resistant EGE patients who were treated with a six-food elimination diet and attempted to identify the responsible food by returning the eliminated foods one-by-one. The endpoint of the study was the combination of histopathological improvement and symptom resolution. All of the elimination diets were prepared by hospital dieticians and the patients were treated on an in-patient basis in a hospital ward. The food responsible for gastrointestinal inflammation was identified in eight of those 10 patients and the results suggested the potential role of an empirical six-food elimination diet followed by returning the eliminated foods one by one as a therapeutic option for glucocorticoid-resistant EGE.

Recently, molecular target therapy against cytokines, which have important roles in EGID development, has been used as a possible advanced treatment option with administration of neutralizing antibodies. For EoE cases, anti-TNF and anti-IgE antibodies were found to be not effective, whereas anti-IL-5, anti-IL-13, and anti-IL4/13 receptor antibodies showed effectiveness [26–28]. Those findings indicated relief of symptoms as well as histopathological eosinophil infiltration by neutralizing antibody administration. In addition, another study reported that the anti $\alpha 4\beta 7$ integrin antibody was effective for some EGE cases, though the cohort had a limited number [29].

CONCLUSION

The prevalence of EGE is lower than that of EoE, though that of both is reported to be increasing. Achievement of accurate diagnosis of EGE is more complicated, mainly because of the varying density of eosinophil infiltration in different segments of the gastrointestinal tract in healthy normal

individuals. In addition, a significant overlap exists between the concept of EGE and that of hypereosinophilic syndrome, and precise definitions of these two diseases based on recent research results using molecular analysis of eosinophil proliferation are necessary. Based on clinical experience, first-line treatment for EGE remains solely glucocorticoid administration, as no reliable prospective randomized double-blind study of an effective therapy has been presented. Furthermore, the effects of topical glucocorticoid administration, an elimination diet, and molecular target therapy using a neutralizing antibody need to be clarified by appropriate clinical research investigations.

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