CURRENT APPROACHES TO EOSINOPHILIC GASTROENTERITIS AND ITS NUTRITIONAL INTERVENTIONS

EOZİNOFİLİK GASTROENTERİT HASTALIĞININ BESLENME TEDAVİSİ

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ÖZET

Eozinofilik gastroenterit (EGE), ağırlıklı olarak mide ve ince bağırsakta eozinofillerin inflamasyonu ile karakterize bir sindirim sistemi hastalığıdır. Nadir görülmesi, teşhis ve tedavisinin zor olması EGE'nin oldukça karmaşık bir hastalık olarak değerlendirilmesine yol açar. Eozinofilik infiltrasyonu azaltmak ve uzun vadede ciddi komplikasyonlara neden olabilen gastrointestinal belirtileri önlemek tedavinin temelini oluşturur. Mevcut tedaviler arasında diyet, farmakolojik ve cerrahi tedavi bulunur. EGE'nin hangi sebeple ortaya çıktığı kesin olmamakla birlikte gıda hassasiyeti gibi alerjik bir nedenden kaynak alabileceği, gıda alerjenlerinin hastaların gastrointestinal kanalında Th2 tipi hücresel yanıtı arttırarak etki edeceği düşünülmektedir. Fazla kilonun ve D vitamini eksikliğinin EGE için bir risk faktörü olabileceği konusu tartışmalıdır. Bu iki etkenin pro-inflamatuar sitokinleri artttıran, antiinflamatuar sitokinleri azaltan dolayısıyla hücresel yanıtın Th2 tipine doğru eğilim göstermesine neden olan süreçleri meydana getirdiği bilinmektedir. Bu süreçlerle birlikte bağışıklık sisteminin toleransının düştüğü, astım ve alerji gibi hastalıklara neden olduğu dolayısıyla EGE gelişimine uygun ortamın meydana geldiği tahmin edilmektedir. Özellikle son yayınlarda hastalığın tedavisinde sıklıkla diyet yaklaşımlarının üzerinde durulmaktadır. Diyet yaklaşımlarının temel amacı; hastalığın şiddetini arttıran gıdaları beslenmeden çıkarıp, hastanın alerjenlere maruz kalmasını önleyerek semptomlarını azaltmaktır. Diyetler elemental diyet, ampirik eliminasyon diyetleri ve alerji testine dayalı eliminasyon diyeti olarak sınıflandırılmaktadır. Farmakolojik tedavi ana tedavi olmakla birlikte hastalar genellikle steroidlere cevap verirler ne var ki uzun süreli kullanımı ciddi yan etkilere neden olabilir. Bu yüzden son dönemde farklı ajanların kullanılması ve kombine tedavi önerilmektedir. Cerrahi tedavi en son aşamada düşünülmektedir. Bununla birlikte opere olan hastaların bile büyük çoğunluğunda tekrar nüks görülmektedir. Tanı ve tedavisi oldukça karmaşık olan EGE günümüzde gittikçe artan bir insidansa sahiptir. Bu çalışmada EGE'nin tedavi yöntemlerini, beslenmeyle olan ilişkisini ve diyet tedavisinin önemini araştırmak amaçlanmıştır. Ayrıca hastalığın tedavisinde kullanılan farklı diyet yaklaşımları sınıflandırılarak mevcut literatür eşliğinde vaka serileri değerlendirilmiştir.

ABSTRACT

Eosinophilic gastroenteritis (EGE) is a digestive system disease characterized by inflammation of the eosinophils predominantly in the stomach and small intestine. Being rare and difficult to diagnose and treat causes EGE to be evaluated as a very complex disease. The mainstay of treatment is to reduce eosinophilic infiltration and prevent gastrointestinal symptoms that can cause serious complications in the long term. Present treatments include diet, pharmacological and surgical treatment. Although the etiology of EGE is uncertain, it is thought to be caused by food sensitivity, especially food allergens, by increasing the Th2 type cellular response in the gastrointestinal tract of patients. It is debated that overweight and vitamin D deficiency may be a risk factor for EGE. All of these generate processes that increase pro-inflammatory cytokines and decrease anti-inflammatory

cytokines, thus causing a Th2-type cellular response. Also, it is thought that lowered immune system tolerance and diseases such as asthma/ allergies may also support the development of EGE. Especially, in the last publications, dietary approaches are frequently emphasized in the treatment of the EGE. The main purpose of dietary approaches is to reduce the symptoms of the patient by removing the nutrients that increase the severity of the disease from the diet and preventing the patient from being exposed to allergens. Diets are applied as elemental diet, empirical elimination diet, and allergy testing directed elimination diet. Even though, pharmacological treatment is the main treatment patients generally respond well to steroids. However, long term use of steroids can cause serious side effects. Therefore, recently the use of different agents and combined treatments are recommended. Surgical treatment is considered at the last stage. In addition to this, recurrence is seen in most of the operated patients. EGE, which diagnosis and treatment are quite complex, has an increasing incidence today. In this study, it is aimed to present the treatment methods of EGE, its relationship with nutrition and the importance of diet treatment. In addition, different dietary approaches used in the treatment of the disease were classified, and case series were evaluated in the light of the current literature.

Keywords: Eosinophilic gastroenteritis, diet treatment, food sensitivity

1. INTRODUCTION

Eosinophilic gastroenteritis (EGE) is a rare inflammatory disease characterized by infiltration of eosinophils in the gastrointestinal system in the absence of known secondary causes for eosinophilia (Rotherberg, 2004). Although EGE mostly shows symptoms in the stomach and small intestine, it can involve any part of the gastrointestinal system from the esophagus to the rectum. Known secondary causes for eosinophilia are such as parasitic infections, malignancies, drug hypersensitivity reactions, and hypereosinophilic syndrome. EGE was first identified by a surgeon eighty years ago (Kaijser, 1937). Afterward, the disease was divided into subtypes, and the symptoms were detected to vary according to the affected layer and the diagnosis criteria were determined (Klein et al., 1970; Talley et al., 1990). The diagnosis criteria of the disease renewed ten years ago (Chang et al., 2010). It is thought that the clinical appearance and symptoms may also change depending on the depth and location of the gastrointestinal region, which is inflamed by eosinophils (Klein et al., 1970). Because of this opinion, EGE was divided into three subtypes mucosal, muscular, and serosal. It has been reported that mucosal involvement is observed more frequently than muscular and serosal involvement, and nowadays the incidence of the disease in the mucosal layer has increased even more (Talley et al., 1990; Chang et al., 2010).

2. EPIDEMIOLOGY AND PREVALENCE OF EOSINOPHILIC GASTROENTERITIS

EGE can show symptoms in all age groups and can occur in any period of life (Talley et al., 1990; Chang et al., 2010). It is stated that EGE usually occurs between the 30 to 50 age range that it can occur both in men and women. However, it is also stated that it affects men a little more (Chang et al., 2010). In most studies, it was pointed out that the disease was more common in the Caucasian race and that the education level of most of the patients was high. EGE is a very rarely seen and hard to diagnose disease that is why the prevalence of the disease is not clearly known. According to the estimates in the national database, its prevalence was found to be 8.4-28 per 100,000 (Spergel et al., 2011; Jensen et al., 2016). According to the study published in the United States in 2017, it was detected that the prevalence of EGE can show differences between regions (Spergel, et al., 2011). It has been notified that the prevalence in the Northeast and west is significantly higher than in the South and the Midwest. Another reason for the regional difference in EGE prevalence is thought to be a genetic predisposition. In a 10- year study conducted in the United States, it was established that as age increases, the prevalence decreases with age, it is more common in pediatric patients than adult

patients, and the incidence of the disease increases, especially in children under 5 years of age (Jensen et al., 2016).

3. PATHOPHYSIOLOGY OF EOSINOPHILIC GASTROENTERITIS

Even though the pathogenesis of the disease is complex and uncertain, it is a predominant view caused by environmental factors and food allergies. The majority of the cases are atopic, the presence of food sensitivity, as well as symptoms such as asthma, eczema, rhinitis accompanying allergic conditions, increased IgE antibody levels against a specific food, positive skin prick test (DPT) against food allergens, RAST (radioallergosorbent test) responses also, some positive eradicative diets are the results that confirm the view that pathogenesis may be caused by environmental factors and food allergies (IgE – mediated allergic mechanism) (Khan, 2005; Chang et al., 2010; Reed et al., 2015). Genetic factors are also thought to play a role. In a study, it was found that 10% of individuals diagnosed with EGE had a family history (Guajardo et al., 2002). The metabolic pathway through which eosinophils increase in the gastrointestinal tract and cause inflammation is still unclear (Desreumaux et al., 1996). It is thought that it may derive from Th2 type cellular response. Th2 type cytokines (IL-3, IL-5), chemokines (eotaxin) and GM-CSF (granulocyte – macrophage colony stimulating factor) cause eosinophil accumulation and activation in the gastrointestinal system. Activated eosinophils increase the inflammatory response through pro-inflammatory cytokines and cytotoxic granules that cause tissue damage. Eotaxin, a chemokine, plays a critical role in the pathogenesis of EGE by causing allergic inflammation and the accumulation of eosinophils (Hogan, Mishra, Brandt, Foster & Rothenberg, 2000). Evidence of this is that an animal study demonstrated a reduced accumulation of eosinophils in the small intestine of mice genetically deprived of eotaxin. In experimental animal studies, the continuation of the disease with allergen stimulation and the higher plasma levels of IL-5 and IL-15 in patients with EGE in Japan compared to the control group are the results that support the view that Th2 type inflammation plays a role in the pathogenesis of EGE (Desreumaux et al., 1996; Hogan et al., 2000; Kinoshita et al., 2013). In other words, both IgE-mediated food sensitivity and delayed Th2-type cellular response are thought to play a role in the pathogenesis of the disease. The absence of concomitant allergic conditions such as atopy in some cases, lack of response to dietary elimination, the appearance of anaphylactic reactions to food in a minority of patients makes it question that non- IgE mechanisms (autoimmunity) may be involved in the pathogenesis (Rothenberg, 2004).

3.1. Relationship Between Obesity and Eosinophilic Gastroenteritis

In literature, it is apparent that obesity has a positive relation with asthma, allergy, and atopic diseases (Festa et al., 2011). Obesity, even if its percentage is low, is a chronic inflammatory state. The increase in pro-inflammatory cytokines such as IL-6, IL-18, CRP, TNF-a in obese individuals and their levels decrease as weight lost is proof of this hypothesis. Increased white adipose tissue can be shown as the source of pro- inflammatory cytokines, as it secretes various adipokines associated with inflammation (Hersoug & Linneberg, 2007). Various bioactive mediators are secreted from the white adipose tissue. These mediators secreted are called adipokines. Their numbers increase with the obesity. Some examples for adipokines are leptin, adiponectin, cytokines (e.g. TNF- a, IL-6), chemokines (e.g.monocyte chemoattractant protein-1 (MCP-1) and growth factors **(**Trayhurn, 2005; Hersoug & Linneberg, 2007). It is thought that there is a link between adipocytes and the immune system and that preadipocytes can exhibit phagocytic activity in the circulation like macrophages (Hersoug & Linneberg, 2007). Leptin, secreted from white adipose tissue, increases energy expenditure in metabolism by affecting the hypothalamus and plays a role in suppressing hunger. As the white adipose tissue increases, leptin produced from adipocytes begins to increase. Excess leptin suppresses the immune system by increasing the production of pro-inflammatory cytokines (IL-6, CRP, TNF-α) from macrophages and preventing the proliferation of regulatory T cells along with IL-6 (Trayhurn, 2005; Hersoug& Linneberg, 2007). As the adipose tissue increases, the level of adiponectin decreases. Decreased adiponectin reduces the production of IL-10, which acts as an anti-

inflammatory cytokine in the immune system (Fiorentino et al., 1991). TNF-α, another mediator secreted from white adipose tissue, causes obesity and asthma with the same inflammatory response TNF-α tends towards the Th2 cytokine profile with proinflammatory mediators (IL-4, IL-5) as well as causing bronchial hyperreactivity and asthma. (Weiss & Litonjua, 2007). With obesity, processes that increase the inflammatory response and reduce the anti-inflammatory response occur (Festa et al., 2011). The tolerance of the immune system lowers (Hersoug, & Linneberg, 2007). The immune system, which tends towards the Th2 cytokine profile, prepares the ground for the development of other diseases related to the immune system such as asthma and allergies (Trayhurn, 2005; Fiorentino et al., 1991; Weiss & Litonjua, 2007). This situation calls into question that obesity may cause a decrease in immune system tolerance and excess weight may be involved in the pathogenesis of EGE indirectly through the immune system and maybe a risk factor for its development.

3.2. Relationship Between Vitamin D and Eosinophilic Gastroenteritis

According to a study conducted in the United States in 2015, the EGE is more common in the northern states compared to the southern states (Spergel et al., 2011). It has been thrown out for consideration that besides the genetic factor, vitamin D may also play a role as the cause of regional differences. Vitamin D has an immunomodulation effect (Weiss & Litonjua, 2007). It exerts this effect by decreasing various pro-inflammatory cytokines in the immune system (eg.IL-12) and increasing anti-inflammatory cytokines (eg.IL-10). In addition to this, T cells are involved in balancing regulatory function. Vitamin D deficiency provides a suitable environment for the failure of T cells to fulfill their functions, decrease in immunomodulatory effects and decrease in immune tolerance, deterioration of the balance between Th1 and Th2, and the development of allergic and autoimmune diseases. Other causes for vitamin D deficiency are wearing long-sleeved clothes, sunscreen, and intake of foods containing insufficient vitamin D in the diet (Özdemir & Karavaizoğlu, 2018). In the current reports, no definitive opinion has been proven that vitamin D supplements provide benefits on allergic diseases. It has been concluded that people with low vitamin D have more allergic sensitivity, vitamin D supplementation prevents attacks in asthmatic patients and eczema. On the other hand, it is beneficial in patients with chronic urticaria indirectly, so vitamin D can prevent food allergy. Vitamin D can be suggested as the reason why EGE is more common in northern states because of the regional differences. (Spergel et al., 2011). Vitamin D deficiency may be a risk factor for EGE indirectly with inflammatory processes by decreasing the tolerance of the immune system, increasing the susceptibility to allergic diseases and disrupting the balance between Th1 and Th2 (Weiss & Litonjua, 2007; Spergel et al., 2011; Özdemir & Karavaizoğlu, 2018).

4. CLINICAL SYMPTOMS IN EOSINOPHILIC GASTROENTERITIS

It has been reported that clinical symptoms vary according to the location and depth of the area of inflammation, so EGE is divided into three as mucosal, muscular, and serosal layer disease (Klein et al., 1970). It was stated that more than half of the cases with mucosal layer disease had food sensitivity and allergies, however, food sensitivity and allergies were not detected in patients with muscular and serosal layer disease (Talley et al., 1990). In addition, gastrointestinal manifestations in patients with mucosal and muscular layer involvement may be confused with functional bowel disease. The most common symptoms in patients with mucosal involvement are abdominal pain, nausea-vomiting, diarrhea, bloody stools, malabsorption, and protein-losing enteropathy (Lucendo & Arias, 2012). While the prevalence of mucosal involvement is 45-80% compared to previous publications, it varies between 88-100% in new publications (Chang et al., 2010; Lucendo & Arias, 2012). Abdominal pain, nausea-vomiting, stenosis in the outlet of the stomach and small intestine wall, and small intestine obstruction are observed in patients with EGE in the muscular layer involvement. The prevalence of muscular layer involvement is 12-30% (Lucendo & Arias, 2012). Serosal layer involvement is less common, but its frequency can vary between 12.5% and 39%. The number of eosinophils in peripheral blood increased compared to other layers. Serosal involvement can cause inflammation in the peritoneum layer, ascites in more severe patients, peritonitis, pleural effusion with ascites, small

intestine perforation (Lucendo & Arias, 2012; Ingle & Hinge Ingle, 2013). It is also expressed that involvement in the bile ducts and pancreas can be observed less frequently. Clinical signs are jaundice, cholestasis, changes in liver function tests and enlargement of bile ducts.

5. DIAGNOSIS METHODS OF EOSINOPHILIC GASTROENTERITIS

For the diagnosis of the disease, the important criteria have been determined, which are the presence of acute or recurrent gastrointestinal symptoms, prominent biopsies with eosinophilic infiltration in one or more areas of the gastrointestinal tract, absence of parasite infection, and absence of eosinophilic inflammation in organs other than the gastrointestinal tract (Talley et al., 1990).

5.1. Complete Blood Count

After the history of the patient is taken, the laboratory findings supporting the diagnosis should be examined carefully. Complete blood count has an important role in the diagnosis of this rare and difficult disease. Although high eosinophil level in peripheral blood is an important criterion in the diagnosis of the disease, it was found in a clinical study that at least 20% of the cases did not have a high level of eosinophils in the blood (Talley et al., 1990). Hypereosinophilia in peripheral blood ceases is to be a universal diagnostic criterion in the diagnosis of EGE. Consequently, the diagnosis of EGE cannot be ruled out in cases where there is no high level of eosinophils in the blood and are evident with various undiagnosed gastrointestinal symptoms. A case series has been published comparing 2 groups with high blood eosinophils with a diagnosis of EGE and characterized by unexplained gastrointestinal symptoms (Chang et al., 2010). According to the results, it was indicated that all of the group diagnosed with EGE had high levels of eosinophils and no clinical difference was observed between the hyper eosinophilic groups. Therefore, hypereosinophilia, which is not accepted as a universal diagnostic criterion, contradicts with this study. The probable reason for contradicting current sources is that most patients have a history of atopy, such as allergy, eczema, asthma, and allergic rhinitis, and these symptoms commonly cause hypereosinophilia. According to these two different views, it was understood that hypereosinophilia is not a universal diagnostic criterion, but a finding that should be taken into account and should be approached with suspicion (Talley et al., 1990; Chang et al., 2010). The number of eosinophils in the blood of the patients varies according to the layer involved (Ingle & Hinge Ingle, 2013). Normally, the eosinophil count below 500 µL is 2000 eosinophils/µL in mucosal involvement, 1000 eosinophils/µL in muscular involvement, and 8000 eosinophils/µL in serosal involvement. Mucosal involvement is moderate, muscular involvement is mild, serosal involvement has a severe eosinophil level.

In order to determine the protein loss Alpha-1 antitrypsin levels should be measured (Ingle & Hinge Ingle, 2013). It was observed that alpha-1 antitrypsin level in the stools of patients with EGE was much higher than normal values. Steatorrhea is also present in 30 % of the patients. It has been marked that Charcot- Leyden crystals, which are residues of eosinophil degranulation, are frequently found in the stools of the patients (Rothenberg, 2004). Although serum IgE is high in most patients, a decrease in immunoglobulin levels may occur as a result of protein loss (Ingle & Hinge Ingle, 2013; Mori et al., 2013). While the sedimentation rate increases in some cases, it may remain normal in some cases and generally increases moderately. Results such as abnormalities in liver function tests and prolongation of prothrombin time can also be observed. EGE is generally a protein-losing disease and patients' serum albumin levels may decrease (Ingle & Hinge Ingle, 2013; Mori et al., 2013; Rached & Hajj 2016). With the prolongation of the disease malabsorption may occur. In connection with protein loss and steatorrhea hypoalbuminemia, iron deficiency anemia, inability to absorb fat-soluble vitamins such as ADEK, can cause problems such as weight loss, growth retardation, growth retardation, amenorrhea and food rejection in children and adolescents (Ingle & Hinge Ingle, 2013; Mori et al., 2013; Reed et al., 2015; Rached & Hajj, 2016).

Eosinophils are important immune cell elements found in the gastrointestinal system and hematopoietic organs (Rothenberg, 2004). It has functions such as protecting the gastrointestinal

system against parasitic infections. Eosinophils can be found in the lamina propria of other gastrointestinal tract regions (stomach, small intestine, colon and cecum) except esophagus in healthy people. When the inflammatory response begins, the number of eosinophils increases and accumulates in different numbers according to the departments in the gastrointestinal system. The presence of eosinophils 20 per high power field (HPF) under the microscope has been indicated as an increase in eosinophils in the gastrointestinal system (Talley et al., 1990; Chang et al., 2010). In a study, the region with the highest eosinophil counts in 44 patients with a diagnosis of EGE was described as the colon (Reed et al., 2015).

5.2. Radiology

Differences in radiology were not detected in at least 40% of the patients, so imaging methods were not found sufficient for the diagnosis of EGE (Ingle & Hinge Ingle, 2013; Mori et al., 2013). During computed tomography, there may be irregular thickening in the distal stomach and proximal small intestine folds, but this is not a special case for EGE (Chen et al., 2013). Because irregular folds during imaging can also occur in diseases such as inflammatory bowel disease, ménétrier disease, lymphoma, and scirrhous. Significant mucosal folds may occur in the colon and the small intestine may expand when the thickness of the mucosal folds is increased (Ingle & Hinge Ingle, 2013). In muscular layer involvement, thickening of the stomach wall, narrowing of the distal antrum, and ascites can be detected in patients with serosal involvement. High levels of eosinophils in paracentesis fluid may simplify diagnosis.

5.3. Endoscopy

The endoscopic view is not characteristic for the diagnosis of EGE (Mori et al., 2013; Rached & Hajj, 2016). It is characterized by endoscopic appearance, friable mucosa with erythema, nodules, polyps, and sometimes ulcers (Chen et al. 2003). When eosinophilic inflammation is limited, epithelial cell necrosis and villous atrophy can be observed (Ashitani et al., 2019). In some cases, complete loss of villi, involvement of more than one layer, submucosal edema and fibrosis can be detected, and this can be explained by the persistence of inflammation in the disease. For the correct diagnosis of EGE, there must be distinct tissues that are inflamed by eosinophils (Chen et al., 2003). The distributions in tissues evident with eosinophilic infiltration may be irregular or can be diagnosed despite the normal appearance on endoscopy (Ashitani et al., 2019). Hence, a definitive diagnosis can be made by performing more than one biopsy. Even if the biopsy result is negative, if EGE is suspected, re-endoscopy may be beneficial. If needed, colonoscopy, gastro duodenoscopy, if the disease is in the small intestine, laparotomy or laparoscopic full-thickness biopsies are other diagnostic methods for diagnosing the disease (Khan, 2005, Rached & Hajj, 2016, Chen et al. 2003, Ashitani et al., 2019).

5.4. Differential Diagnosis

After there is certainly eosinophilic inflammation in the gastrointestinal system, secondary causes causing the eosinophilia should be identified and excluded. Laboratory findings, imaging, endoscopy, and histological evidence are extremely important for correct diagnosis.

Table 1. Other diseases causing eosinophilic inflammation in the gastrointestinal system.

Parasitic Infections		
Ancylostoma caninum	*Giardia lamblia*	*Anisakis*
Strongyloides stercoralis	*Fascilo hepatica*	*Ascaris*
Eustoma rotundatum	*Trichinella spiralis*	*Trichuris*
Enterobius vermicularis	*Toxocara canis*	*Schistosomiasis*
Medicines Gemfibrozil, enalapril, carbamazepine, clofazimine, co-trimoxazole and gold salts		
Cow’s milk allergy, food allergy, gluten – sensitive enteropathy		

Vasculitis and Connective Tissue Diseases Churg-Strauss syndrome, polyarteritis nodosa, scleroderma, dermatomyositis and polymyositis
Hypereosinophilic syndrome
Malignancies Lymphoma, leukemia
Inflammatory Bowel Disease Crohn Disease, ulcerative colitis
Organ Transplantations

6. TREATMENT OPTIONS OF EOSINOPHILIC GASTROENTERITIS

Effective treatments include diet, pharmacological, and surgical treatment. Pharmacological treatment includes corticosteroids, mast cell stabilizers, various agents such as leukotriene receptor antagonists, dietary therapies (elimination diets and amino acid-based elemental diet) and surgical treatment.

6.1. Diet Therapy

Despite the fact that the efficacy of dietary treatments has been proven more in eosinophilic esophagitis, which is one of the eosinophilic gastrointestinal disorders, it has been reported that it has been tried several times to create an alternative treatment in patients with EGE and that dietary treatments have an important role in controlling the disease (Lucendo et al., 2015). In a systematic review examining the feasibility of dietary therapies, it was stated that the majority of patients were of the mucosal type, and that the mucosal layer, which is known to be more associated with food allergies, responded better to diet, and layers that were less associated with food allergy, such as the muscular and serosal type, had less response to diet (Talley et al., 1990; Lucendo, et al., 2015). In the treatment of EGE, various types of diets are being tried. These recommended treatments include:

A) Elimination diet based on the allergy test

B) Elemental Diet: It is divided into two as amino acid-based elemental diet and semi – elemental diet, usually amino acid- based formulas are used.

C) Empiric Elimination Diet: In this study, a six-food elimination diet (SFED), a multi-food elimination diet, and a two-food elimination diet were examined. Different types of empirical elimination diets, such as the seven-food elimination diet and the four-food elimination diet, are also applied to patients (Lucendo et al., 2015).

6.1.1. Elimination Diet Based on the Allergy Test

Allergen-specific IgE antibody levels, DPT and patch tests are used to determine the food that causes the allergy in the patient (Lucendo et al., 2015). The purpose of these tests is to identify the food that causes the allergy by various tests and to remove it from the patient's diet. Elimination diet based on allergy tests is preferred because it is difficult to comply with the amino acid-based elemental diet and to be able to apply diet therapy to more patients. The use of DPT is the evaluation according to the changes in the skin after waiting for a while after applying the allergen-containing fluids to the patient's skin by dropping them under the skin (Chen & Kao, 2017). On the other hand, it has been reported that there are very few studies on the use of allergy tests to exclude foods from the diet, clinical symptoms resolved in patients, but only a 9-year-old pediatric case showed histological improvement in post-treatment biopsies (Basilious & Liem 2011; Lucendo et al., 2015). In a case report, a 26-year-old female patient diagnosed with eosinophilic enteritis had an allergy test (Lamendola et al., 2012). Related food was excluded from the diet and an elimination diet was applied.

It was observed that the elimination diet provided recuperation and the patient's symptoms were resolved. However, data on the pathological eosinophil count after diet therapy is lacking. It is unknown whether it provides histological improvement or not. It has been found that there are no sensitive and specific tests to find the food that aggravates the disease (Lucendo et al., 2015). False positivity rates may appear. Even though serum IgE antibody levels are high in most patients diagnosed with EGE, the use of serum IgE, DPT and patch tests in the evaluation of food allergies has not been definitively confirmed. The reason for this is that delayed non-IgE-mediated inflammatory response plays a more dominant role in pathogenesis than IgE-mediated response (Sasaki et al., 2019).

6.1.2. Elemental Diet

While applying an elemental diet, patients are fed an artificial formula that does not contain any antigen and contains free amino acids (Lucendo et al., 2015). Macronutrients in these formulas require minimal digestion so that they can be completely absorbed and hydrolyzed to different degrees enzymatically (Chen & Peterson, 2009). Macronutrients in these formulas require minimal digestion so that they can be completely absorbed and hydrolyzed to different degrees enzymatically. While the elemental diet provides a great improvement compared to other diet therapies, there are also disadvantages such as not being sustainable, removing all foods from the diet, bad taste, social and psychological negativities caused by the diet, and the formula being expensive (Lucendo et al., 2015). In a systematic meta-analysis, it was stated that amino acid-based elemental diet was the most effective treatment in patients diagnosed with EGE, and showed a recovery rate of over 75%. However, it has been observed that less than a quarter of the patients undergo re-biopsy to evaluate the effectiveness of the elemental diet. While histological remission was reported at a rate of 83% in the biopsy group, it remains unclear whether histological improvement was achieved in all patients.

In a retrospective study, 55 patients were diagnosed with EGE, 8 patients with eosinophilic gastritis, and 3 patients with eosinophilic enteritis (Zalewski et al., 2018). It was observed that 89% of the patients had atopic and 53% self-reported food allergies. Afterwards, 48% of them applied DPT and it was stated that 72% were positive for food allergens and their serum IgE levels were 80%. This group of patients was given SFED, elemental diet and medical treatment. Patients underwent endoscopy and biopsy after treatment. Diet therapy was applied to 30% of the patients (65% SFED, 35% elemental diet). Histological remission was observed 38% in the SFED group and 100% in the elemental diet group. In another case report, it was reported that a 2-month-old child was diagnosed with milk-sensitive EGE (Costa et al., 2015). This patient first started with cow's milk restriction and continued to feed with semi-elemental formula on the eighth day. Twenty days after the symptoms appeared, when the patient lost serious weight, an elemental diet was initiated to help the patient gain weight and reduce his symptoms. With the elemental diet, the patient started to gain weight again. In the subsequent follow-up, solid foods were introduced one by one and no problem was observed. A pediatric case of cerebral palsy fed with PEG (percutaneous endoscopic gastrostomy) has been described very recently (Eren et al., 2020). After the patient was diagnosed with EGE, specific IgE tests and DPT were performed, but no allergen that aggravated the disease was found. Clinical and histological remission has been reported after the patient's enteral product was replaced with a less allergen-causing protein with a hydrolyzed product.

6.1.3. Empiric Elimination Diet

It is a type of diet that eliminates common allergen foods from the patient's diet without applying suspicious allergy tests and without the need to feed the patient with a special formula (Kagalwalla et al., 2006). It has the advantages of making diet therapy more palatable and contributing to social-psychological harmony, and not being deprived of table meals by allowing solid foods**.**

6.1.3.1. The 6-Food Elimination Diet (SFED)

SFED, which completely restricts the 6 food groups known to be most associated with allergies (wheat, milk, egg, oilseeds, soy, and seafood) and biopsies to evaluate the effectiveness of diet treatment and then reintroduce foods one by one, SFED is the most used diet treatment for patients with EGE (Lucendo et al., 2015). In a systematic examination, 34 patients with EGE or colitis were treated with SFED and clinical remission was observed in 85.3% of the patients, but evidence of histological examinations is lacking. In a published retrospective study, it was stated that a patient with a shellfish allergy and mild mucosal layer involvement was successfully treated clinically and histologically with an elimination diet, and that the patient was in good health for more than three years, but the drugs were not discontinued during diet treatment (Chen et al., 2003). A case study on SFED and food reintroducing has been published (Kakiuchi et al., 2020). In this case, it was stated that a 13-year-old boy had complaints of recurrent vomiting and abdominal pain for three months. After the patient was diagnosed with EGE and the pharmacological treatment was discontinued, SFED was applied to the patient for a short time. In three days, abdominal pain completely disappeared, and foods were added back to the diet within five days. When symptoms such as abdominal pain and diarrhea appeared six hours after giving milk and peanuts, it was understood that milk and peanuts were the active food and were excluded from the diet. After the milk and peanuts were completely eliminated, the symptoms were brought under control and resolved within 24 hours. The patient achieved remission with only SFED without medication. Seven months after removing milk and peanuts from his diet, the patient did not show symptoms that may be caused by food allergens such as epigastric pain, urticaria, and anaphylaxis. Pathological consequences, the eosinophilic inflammations in the esophagus, stomach, and duodenum are greatly reduced. Although there is partial remission in histological sense, the complete recovery of clinical symptoms and the absence of recurrence prove the effectiveness of elimination diet treatment in EGE once again. A study was published between 2011-2019, which examined the clinical characteristics and treatment results of patients with EGE (Okimoto et al., 2021). In this study, it was observed that most of the patients responded to glucocorticoid therapy, but in some patients, symptoms reappear as the dose is reduced. Remission of gastrointestinal symptoms of 13 EGE patients was observed with AGED. Also, it has been reported that foods that cause allergies were detected in approximately 70% of this patient group, and recovery continued in approximately 80% of them without glucocorticoid treatment. It is stated in SFED that the foods that cause the most allergies are soy and dairy products. Blood-specific IgE antibody levels were not associated with allergy-causing foods in patients. This is proof that the allergy test-based elimination diet should not be trusted.

6.3.1.2. The 2-Food Elimination Diet

In comparison to SFED, the 2-food elimination diet removes fewer nutrients from the diet, it can increase patients' compliance with the diet, prevent unnecessary endoscopy and contribute to the detection of the food that causes symptoms in a shorter time (Chen & Kao, 2017). For that matter, the 2-food elimination diet may be preferred as the first choice instead of SFED, but it is stated that there is no common opinion due to the lack of studies. An eight-year-old male case diagnosed with EGE has also been described in the literature (Doi et al., 2020). It was stated that the patient had chronic diarrhea that lasted for four years, and considering that soy and wheat intake were the causative foods, a two-food elimination diet was applied. Pharmacological treatment and elimination diet was started at the same time and it was observed that the diarrhea was resolved. After four weeks of treatment, wheat was added back to the diet. One week later, diarrhea started again, and when it was clearly understood that wheat was the active food, it was completely excluded from the diet. Endoscopy performed after 12 weeks has also been proven to provide histological remission. After the patient's diarrhea disappeared, it was found that his symptoms did not recur and he gained weight. According to this study, the elimination diet is effective for EGE and that the two-food elimination diet may also be valid.

6.3.1.3. The Multiple-Food Elimination Diet

According to the studies, multiple food elimination diet is considered to be a promising treatment for EGE, largely due to its clinical and histological improvement, its easy application compared to ED, and its lack of obvious side effects during the follow-up period (Yamada et al., 2014). An adult female patient with EGE, treated with multiple food elimination, has recently been described (Okimoto, et al. 2018). It has been reported that the drug is discontinued while applying diet treatment, and the patient provides clinical and histological remission by removing the egg and milk that cause allergies in the patient. Only 29% of physicians in America stated that they would primarily apply diet treatment (Spergel et al., 2011). Lack of data in adult patients and family preference in pediatric patients were stated as the most common reasons that made it difficult to follow the diet. It has been observed that patients who do not want to try diet treatment primarily have problems such as compliance and management problems. In a published systematic meta-analysis, the author's evaluated studies conducted up to 2014 and reported that they did not accept diet treatment because of unclear histopathological results, and that they could not rely on diet treatment due to the lack of high-quality studies (Lucendo et al., 2015). The effectiveness of diet treatment could not be clearly elucidated in studies conducted until 2014. However, in recently published studies, it has been proven in various case series that EGE patients give positive results to diet treatment, especially in pediatric cases, clinical and histological remission was observed (Costa et al., 2015; Sasaki et al., 2019; Doi et al., 2020; Eren et al., 2020; Kakiuchi et al., 2020). It has been reported in adult cases as well as pediatric patients (Chen et al., 2003; Lamendola et al., 2012; Lucendo et al., 2015; Okimoto et al., 2018; Zalewski et al. 2018).

6.2. Pharmacological Treatment

If diet treatment is not possible and does not work for patients with EGE, pharmacological treatment should be started (Zhang & Li, 2017).

6.2.1. Corticosteroid

The most suitable therapeutic medicines used in the treatment of EGE patients are corticosteroids (Sunkara et al., 2019). It reduces inflammation by suppressing various cytokines (IL-3, IL-4, IL-5) and GM-CSF involved in the pathogenesis of EGE. It is debated how much steroid treatment will be applied. Symptoms usually recur after the initiation of steroid treatment, so long-term use is believed to be necessary (Zhang & Li, 2017; Sunkara et al., 2019). Long-term steroid use has serious side effects in children such as growth retardation, suppression of the adrenal cortex, cushing, hyperglycemia, fluid, and electrolyte disorders. On the other hand, there is a danger of developing resistance with overdose steroid use.

6.2.1.1. Prednisolone

It was observed that prednisolone was preferred as the first choice for patients with a diagnosis of EGE, it recovered most of them, and the group that responded best to prednisolone was patients with serosal involvement (Zhang & Li, 2017). It has been suggested that it generally improves within two weeks with a dose of 0.5-1 mg / kg, and then it is reduced gradually over a period of 6 to 8 weeks (Prussin, 2014). While most of the patients recover with this treatment, symptoms may reappear in some patients. Patients with this condition are treated with low-dose steroids (1-10 mg / day) or budesonide with fewer side effects may be preferred instead of prednisolone (Sunkara et al., 2019). In order to avoid the side effects of long-term steroid treatment, it is important to try alternative medicines for the sustainability of the treatment. Short-term use of systemic steroids has been found to be more beneficial in the treatment of patients (Prussin, 2014).

6.2.1.2. Budesonide

Budesonide, a topical steroid, is often used in patients with Crohn's and ulcerative colitis (Sunkara et al., 2019). Its most important feature is that it is a controlled ileal release capsule preparation (Prussin, 2014). While providing the most optimal transmission to the ileum, gastric transmission is less. Since

EGE patients are known to often show symptoms in the stomach and duodenum, it is preferred to reduce the systemic effect, thus causing less side effects. Patients normally achieve clinical remission at 9 mg/day, but with prolonged use the dose may be reduced to 3 mg/day. It is safer for long-term use compared to other steroid drugs. Its use in pediatric patients is controversial.

6.2.1.3. Immunomodulators

It is preferred as an alternative agent in steroid-dependent or non-responsive cases (Sunkara et al., 2019). Medicines that suppress the bone marrow such as azathioprine and 6-mercaptopurine are used. These medicines inhibit the proliferation of T and B lymphocytes. It has been reported that the appropriate dose for EGE patients is 2-2.5 mg/kg and it will not be beneficial at lower doses (Rached & Haji, 2016).

6.2.2. Leukotriene Receptor Antagonists

Montelukast sodium, which suppresses the inflammatory response accompanied by leukotrienes involved in the pathogenesis of EGE. It is a selective and potent leukotriene (LTD4) inhibitor (Rached & Haji, 2016). While it is frequently used for asthma, it has also been found to be effective for eosinophilic gastrointestinal disorders. A meta-analysis has been published in which studies conducted until 2015 on the use of montelukast sodium in the treatment of EGE were evaluated. According to this meta- analysis, it has been observed that positive results are generally obtained when used alone or in combination with steroids to maintain recovery in steroid-dependent or resistant patients.

6.2.3. Mast Cell Stabilizers

Oral cromolyn sodium is an agent that prevents the release of leukotriene, histamine and other mediators from mast cells, which are known to be involved in the pathogenesis of EGE (Rached & Haji, 2016). In the literature most EGE reports have remission. The normal dose is accepted as 200 mg three or four times a day. It has been stated that in some cases the steroid may reduce its effect (Sheikh et al., 2009). The H1 antihistamine and ketotifen, which is also a mast cell stabilizer, must be used as 1-2 mg twice a day (Rached, & Haji 2016). It has been found that ketotifen provides clinical and histological remission in some patients with EGE, and in one case it has been found to be unsuccessful. In addition, it is used in combination with steroid and montelukast to maintain remission in patients with EGE who do not respond to treatment (Tien et al., 2011).

6.2.4. Biological Agents

According to available sources EGE is known to be associated with IgE and associated with allergies (Talley et al., 1990; Rothenberg, 2004; Khan, 2005; Reed et al., 2015). In a published study, it was expressed that anti- IgE monoclonal antibody (omalizumab) inhibits free IgE and IgE-dependent basophil responses, and even if it decreases peripheral blood eosinophilia after a sixteen-week trial, tissue eosinophilia and clinical symptoms are partially affected (Foroughi et al., 2007). Monoclonal antibodies act by blocking the activation of IL-5, which is involved in the inflammatory response of EGE (Spergel et al., 2012). It has been reported that reslizumab which is anti-IL-5, reduces blood eosinophil values but does not provide a complete histological remission, and clinical symptoms are similar to the control group. Infliximab, an anti- TNF, has been reported to be effective in maintaining recovery in patients with EGE who do not respond to the treatment, but there are controversies about its use, and the development of resistance (Turner et al., 2013).

6.2.5. Intravenous Immunoglobulin

It has been reported that positive results were obtained with intravenous immunoglobulin treatment in a patient diagnosed with EGE with systemic lupus erythematosus and who was steroid resistant (Ciccia et al., 2011).

6.3. Fecal Microbiota Transplantation

A study on performing fecal microbiota transplantation (FMT) in a patient with severe diarrhea and intestinal obstruction has been published (Dai et al., 2014). In this study, prednisone and FMT were used in combination during treatment. In addition to this, it was found that the frequency of diarrhea was greatly reduced even before prednisone was added to the treatment. It has been stated that FMT is effective in patients with chronic diarrhea with a diagnosis of EGE, but there are hesitations in maintaining the same effect when prednisone is not included in the treatment.

6.4. Surgical Treatment

It has been stated that if there are no serious conditions such as perforation, obstruction or intussusception, it is necessary to abstain from the operation (Sunkara et al., 2019). It has been stated that it can be applied in patients who do not respond to diet and medicine treatment and that 40% of the patients may need surgery, however, recurrence can be observed in half of the patients even after surgery (Naylor, 1990).

7. PROGNOSIS OF EOSINOPHILIC GASTROENTERITIS

A study conducted in France, 43 adult patients were examined over 13 years (Pineton de Chambrun et al., 2011). A single attack was observed in 42% of the patients, multiple and renewed attacks in 37%, and continuous attacks in 21%. Another study on the natural history of the disease, 11 patients diagnosed with EGE were followed for more than a year, and recurrence was observed in 5 patients (Chen et al., 2003). More than half of the patients with relapse were found to be under the age of 20. It is thought that young age has an effective role in the recurrence of the disease. Growth differences have emerged in children and adolescents (Sunkara et al., 2019). It has been observed that if the disease is diagnosed in babyhood and a certain nutrient sensitivity is observed, the recovery rate is higher in late childhood. It is known to have a good prognosis. It has an increasing and decreasing frequency, it is a harmless disease. Mild and occasional symptoms can be controlled with various treatments. Mortality rates are rare and have been shown not to be associated with malignancy. Avoiding surgical treatment as much as possible, using different agents instead of steroids alone to reduce side effects, and giving priority to dietary approaches are one of the options that will increase the patient's quality of life.

8. CONCLUSION

In this review, the concept of EGE, its epidemiology, risk factors, diagnosis and treatment methods used, the relationship of the disease with foods and the effectiveness of diet treatments were investigated. There is no gold standard for the treatment of this disease, which occurs with nonspecific symptoms, is very rare, and its diagnosis and detection are quite complex. Lack of a common treatment algorithm in the management of EGE makes the disease even more complicated. According to studies, it is thought that obesity and vitamin D deficiency may be a risk factor in the development of EGE. Most of the patients diagnosed with EGE also have food allergies**.** Hence, it is aimed to improve the patient's quality of life without the need for medication or surgery by trying different diet treatment. Additionally, it has been determined that the most effective diet treatment clinically and histologically is elemental diet. Empirical elimination diets are preferred more often because the elemental diet process has disadvantages such as difficulty in social adaptation, being deprived of table food, having to be fed with a special formula and bad taste. It is observed that empirical elimination diets lead to symptomatic remission, whereas histological recuperation is limited. Nevertheless, the therapeutic effect of this approach, which reduces clinical symptoms without applying any invasive procedure and using medicines, is an undeniable fact. Elimination diets based on allergy testing are not safe due to the possibility of incorrect results of the tests and are not recommended for use in EGE treatment. Studies show that the number of patients responding to

pharmacological treatment is higher than the number of patients responding to diet treatment. Patients generally respond to steroids, but the use of different agents instead of steroids or combined therapy is on the agenda because of the recurrence with dose reduction during the use of the drug and the side effects of long-term use. Surgical treatment, which will adversely affect the quality of life of patients, is considered at the last stage. Because of this confusion, it is extremely important to establish a common treatment protocol for EGE and to prove the effectiveness of dietary treatments with prospective randomized controlled, high-quality studies. In the management of EGE, which is very difficult to diagnose and treat, it is necessary to work with a multidisciplinary team. A dietician must take part in this team. A dietician has responsibilities such as following long-term dietary treatments, evaluating the nutritional status of the patient before, during, and after the diet, providing sufficient energy and protein, and preventing cross-contamination with foods that are considered allergenic for the patient. Vitamin and mineral deficiencies may occur when 6 foods known to cause allergies (wheat, milk, soy, eggs, oilseeds, and seafood) are excluded from the diet for a certain period of time together with the elimination diet used to treat the disease. In fact, most patients have symptoms such as iron deficiency anemia, malabsorption, and deficiency of fat-soluble vitamins before starting diet treatment. Also, vitamin D deficiency is known to be a risk factor for the development of EGE. For all these reasons, it is very important to add alternatives to foods that are eliminated and to prevent deficiency of vitamins and minerals with supplementation if this necessity cannot be met with foods. Patients having sufficient vitamins may contribute to EGE treatment by strengthening the immune response. Although the body mass indexes of the patients were not compared much in the studies, it is thought that obesity may be a risk factor for the development of EGE. Therefore, doing weight control, avoiding allergenic foods, preferring foods that will strengthen the health of the digestive system can contribute to the quality of life of the patient by reducing the symptoms, although it does not eliminate the disease completely. Also, most patients are known to use steroids. Following general healthy eating principles such as avoiding salt and sugar, consuming calcium-containing foods to prevent bone and muscle losses, taking adequate-protein, using healthy fats, choosing carbohydrates with a low glycemic index, restricting smoking, alcohol, and caffeine can help reduce the side effects of steroid use.

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