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Association between Eosinophilic Esophagitis and Food Protein-Induced Enterocolitis Syndrome in Children

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ACCEPTANCE

This thesis, ASSOCIATION BETWEEN EOSINOPHILIC ESOPHAGITIS AND FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME IN CHILDREN, by Ashley Gerken was prepared under the direction of the Master's Thesis Advisory Committee. It is accepted by the committee members in partial fulfillment of the requirements for the degree Master of Science in the Byrdine F. Lewis College of Nursing and Health Professions, Georgia State University. The Master's Thesis Advisory Committee, as representatives of the faculty, certify that this thesis has met all standards of excellence and scholarship as determined by the faculty.

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ABSTRACT

ASSOCIATION BETWEEN EOSINOPHILIC ESOPHAGITIS AND FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME IN CHILDREN

by

Ashley Gerken

Background: The prevalence of food allergy in the pediatric population is increasing. Classic IgE-mediated allergies have been well studied. However, less is known about non-IgE-mediated allergies. Eosinophilic Esophagitis (EoE), a mixed IgE and non-IgE-mediated allergy, and Food Protein-Induced Enterocolitis Syndrome (FPIES), a non-IgE-mediated allergy, have similar symptoms but different ages of presentation (any age vs. <1 year of age; respectively). The purpose of this study is to determine the odds of developing EoE in children previously diagnosed with FPIES or who exhibited symptoms characteristic of FPIES.

Methods: Analysis of retrospectively reviewed medical record data included demographic, clinical, and nutrition characteristics as well as history of gastrointestinal symptoms, diagnosis of EoE, and diagnosis or symptoms of FPIES (history of vomiting) in a large cohort of children receiving care at an urban pediatric gastroenterology clinic. Nutrition characteristics included infant feeding regimen (breast fed vs. formula fed) and age of complementary food introduction. The population sample was provided by the GI Care for Kids Clinical Dietitian. Medical records were reviewed for all patients diagnosed with FPIES between March 1, 2016 and May 30, 2018 and an equivalent number of patients diagnosed with EoE in the same time frame.

Results: The majority of the population (N=148) was male (57.4%) and Caucasian (97.7%). The odds of developing EoE (mean age 9.3 $\pm$ 5.4 years) by prior diagnosis of FPIES (median age 0.83 [Interquartile range; 0.6, 1.2]) or symptoms of FPIES was 0 and 0.25 (95% Confidence Interval; 0.109, -0.575), respectively. Logistic regression analysis revealed that gender, previous history of food allergy and intolerance, and history of vomiting explain 23% to 31% of the variation in EoE diagnosis.

Conclusions: A history of symptoms characteristic of FPIES reported in the first year of life were observed to be protective for the development of EoE during childhood. The treatment for FPIES or its symptoms includes the elimination of common food allergens. Additional studies are needed to evaluate the effect of early infant diet on the future development of EoE.

ASSOCIATION BETWEEN EOSINOPHILIC ESOPHAGITIS AND FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME IN CHILDREN

by
Ashley Gerken

A Thesis

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TABLE OF CONTENTS

LIST OF TABLES

Table Page

ABBREVIATIONS

AAP	American Academy of Pediatrics
AND	Academy of Nutrition and Dietetics
APTs	Atopy Patch Tests
EoE	Eosinophilic Esophagitis
FPIES	Food-protein Induced Enterocolitis Syndrome
OFC	Oral Food Challenge
sIgE	food-specific IgE antibodies
SPTs	Skin Prick Tests
WHO	World Health Organization

CHAPTER I

ASSOCIATION BETWEEN EOSINOPHILIC ESOPHAGITIS AND FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME IN CHILDREN

INTRODUCTION

Food allergies have been part of clinical diagnoses since the early twentieth century; however, their prevalence has grown significantly over the past two decades.[1] With this increase in food allergy prevalence comes an increased need for knowledge about food allergies and the wide variety of etiologies and presenting symptoms and pathologies. In general, a food allergy is any adverse health effect that results from an immune response that can be reproduced when exposed to a given food.[2] It is helpful to understand that an allergy is the result of the body's reaction to a food allergen, which is a specific component of the food, not the entire food item itself.[2] Food allergies can be divided into three main categories: IgE-mediated, non-IgE-mediated and mixed IgE- and non-IgE-mediated. IgE-mediated allergies are the type commonly recognized as a food allergy because these result in an anaphylactic episode. Non-IgE-mediated reactions are less easily identified because they do not incite an anaphylactic response, instead they usually result in gastrointestinal symptoms, such as vomiting and diarrhea. Some food allergies can be IgE- and non-IgE-mediated; these fall in the category of mixed IgE- and non-IgE mediated food allergies.

Eosinophilic Esophagitis (EoE) is considered to be a mixed IgE- and non-IgE-mediated allergy while Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated allergy. Despite the differences between the etiologies of these two

allergies, their clinical presentation and trigger foods appear to overlap. The period of possible presentation also helps distinguish these two conditions. FPIES tends to present within the first year of life[3] while EoE can develop as late as adulthood.[4-6] The relationship between EoE and FPIES, specifically if FPIES predisposes a child for EoE, is unknown.

GI Care for Kids[7] is the largest practice in the Southeast U.S. with 14 locations that specialize in gastrointestinal care for children. The practice treats children with a variety of conditions that affect the esophagus, stomach, intestines, liver, and pancreas including but not limited to inflammatory bowel disease, gastroesophageal reflux disease, Celiac Disease, EoE, and feeding difficulties. The purpose of this study is to examine the potential association between FPIES and EoE in the GI Care for Kids patient population by determining the odds of developing EoE in children previously diagnosed with FPIES or who exhibited symptoms characteristic of FPIES.

Specific Aim 1: To determine if children with symptoms characteristic of FPIES have an increased risk of developing EoE later in life.

Research Hypothesis 1: Individuals with symptoms characteristic of FPIES will have higher odds of developing EoE than those who do not have these symptoms.

Null Hypothesis 1: There will be no difference in the odds of developing EoE between individuals with or without symptoms characteristic of FPIES.

Specific Aim 2: To identify if a diagnosis of FPIES in infancy increases the odds of developing EoE diagnosis later in life.

Research Hypothesis 2: Individuals who have been diagnosed with FPIES will have higher odds of developing EoE later in life.

Null Hypothesis 2: There will be no difference in the odds of developing EoE by previous diagnosis of FPIES.

CHAPTER II

LITERATURE REVIEW

Allergies

A food allergy is any adverse health effect that results from an immune response that is reproduced when exposed to a given food.[2] A variety of food allergies exist and are divided into three categories, IgE-mediated, non-IgE-mediated, and mixed IgE- and non-IgE-mediated allergies. IgE-mediated allergies are characterized by allergic sensitization and the presence of certain symptoms. Allergic sensitization refers to the production of food-specific IgE (sIgE) antibodies, which are produced from allergen-specific B lymphocytes that bind to the surface of mast cells and basophils. Upon ingestion of an allergen, in individuals who have an allergic sensitization, these sIgE antibodies bind to the specific allergen antigens now present in the body and trigger the symptoms characteristic of food allergy-induced anaphylaxis. These symptoms include skin irritation, gastrointestinal distress, and inflammation of the respiratory tract. The following types of food allergies are considered to be IgE-mediated: acute/urticarial/angioedema, contact urticarial, anaphylaxis, food-associated exercise-induced anaphylaxis, oral allergy syndrome, and immediate gastrointestinal hypersensitivity.[8]

Non-IgE-mediated food allergies are generally the result of a cell-mediated response rather than the result of an antigen-antibody interaction. In non-IgE-mediated food allergies the allergic response is triggered by cellular contact with the food protein and not a specific antibody-antigen interaction.[9] The types of non-IgE-mediated food

allergies include: Celiac disease, food protein-induced enterocolitis syndrome, food protein-induced allergic proctocolitis, allergic contact dermatitis, and Heiner syndrome.[8] These food allergies present differently than IgE-mediated food allergies because symptoms generally involve the gastrointestinal tract. FPIES symptoms usually include vomiting, diarrhea, abdominal cramps, blood in stool, failure to thrive, and poor weight gain. While some other non-IgE allergies differ; for example, in food protein-induced allergic proctocolitis the primary indicator is blood and mucus present in the stool whereas in Celiac disease recurrent abdominal pain and malabsorptive diarrhea are common symptoms. A small group of food mediated hypersensitivity conditions are considered mixed IgE- and non-IgE- mediated, meaning reactions can result from either an antibody-antigen interaction or a cell-mediated response.[10] These mixed allergies include: EoE, atopic dermatitis, and eosinophilic gastroenteritis.[8]

The increase in food allergy prevalence in the past two decades has prompted researchers to study food allergies to determine the cause. Genetics and the gut microbiome have been recent areas of interest. While genetic links have been found in IgE mediated allergies, there could also be other explanations. The role of the environment is under investigation and researchers acknowledge the importance of environmental changes as part of this increase. More research would be helpful to expand our understanding of how the role of diet, method of birth delivery, exposure to household pets, and birth order could play a role in developing a food allergy due to their effect on the microbiome.[1]

Overview of Feeding Recommendations in Infants and Young Children

Feeding Recommendations

The American Academy of Pediatrics (AAP), Academy of Nutrition and Dietetics (AND), and World Health Organization (WHO) recommend exclusive breastfeeding for the first 6 months of life. Complementary foods should be added at 6 months while continuing to breastfeed until at least 12 months of age.[11-13] The recommendation to breastfeed exclusively is due to the benefits of human milk shown throughout clinical trials, such as decreased morbidity and mortality, protection against childhood infections and certain acute and chronic diseases, such as acute otitis media, non-specific gastroenteritis, lower respiratory tract diseases, obesity, diabetes mellitus, heart disease, hypertension, and childhood leukemia.[11,12]

Risk for lower respiratory tract infections have been shown to be 72% lower in the first year of life for infants who were breastfed exclusively for 4 months.[11,12] Breastfeeding has also been shown to reduce incidence of otitis media by 23-77%, depending on exclusivity and duration.[11,12] Exclusive breastfeeding for 6 months showed reduced incidence of colds, ear and throat infections. Incidence of non-specific gastrointestinal tract infections was reduced by 64% by any amount of breastfeeding.[12]

In addition, children who were breastfed appear to have reduced risk for many chronic diseases such as obesity, type 1 and 2 diabetes, and heart disease.[11] The relationship between obesity and breastfeeding is complex; however, research shows that each month of breastfeeding results in a 4% risk reduction of becoming overweight.[12] Breastfeeding for 3 months has shown to reduce type 1 diabetes occurrence by 30% and any amount of breastfeeding has shown to reduce development of type 2 diabetes by

40%.[12] Heart disease risk later in life appears to be lower in breastfed individuals due to its effect on lowering cholesterol long term; however, more evidence supporting this is needed.[11]

The benefits particularly related to allergy and gastrointestinal disorders in exclusively breastfed infants include enhanced immunity, reduced risk for nonspecific gastroenteritis, asthma, and protection from allergies.[11] Some evidence shows that children fed with formula are at higher risk for developing asthma and atopic conditions, such as atopic dermatitis and allergic rhinitis. Evidence supports breastfeeding exclusively for 3 to 4 months as a protective measure against upper respiratory infections and wheezing in the first 4 years of life.[14] Studies have shown that breastfeeding results in a 27% reduction in prevalence of asthma, atopic dermatitis, and eczema in individuals with no family history of an allergic disease and a 42% reduction in those with a family history of allergic disease.[12] Inflammatory bowel disease has also shown to be reduced by 31% in breastfed infants and a 52% reduction in risk of Celiac disease has been shown in children who were breastfeeding when first encountering wheat products.[12]

While the benefits of breastfeeding are clear, it is important to introduce complementary foods at an appropriate age. The current recommendation is to introduce complementary foods between 4 and 6 months of age.[13-16] There is currently no evidence to support waiting longer than six months to introduce allergenic foods to reduce allergenic reactions.[12] However, studies have shown varying results related to food allergens, primarily cow's milk, eggs, and cereal, and the development of atopic diseases among infants that had delayed introduction of complementary foods past six months of age.[12] One study found delayed introduction to have no effect on incidence of atopic

dermatitis at a five year follow up.[17] However, a different study showed higher incidence of atopic dermatitis in children introduced to solids before 4 months of age but no difference in asthma prevalence between groups.[18] Another study showed no difference in asthma or atopic dermatitis prevalence based on timing, but did see an increase in atopic dermatitis in children who had delayed egg exposure.[16]

Overall, the literature shows that the protective effect of exclusive breastfeeding may only be seen in those who are predisposed for developing an atopic condition, such as atopic dermatitis. Results are similar for studies regarding food allergy development because atopic diseases and food allergies are so closely related. Outcomes from asthma studies also saw different results based on family history of asthma; however, the controversy is perpetuated by some studies that have shown an increase in asthma prevalence from breastfeeding if the child has a family history. Based on this data it cannot be concluded whether or not breastfeeding is protective for asthma.[16]

Timing of Allergenic Food Introduction

Recommendations for when to introduce the 8 common food allergens, cow's milk, soy, wheat, eggs, peanuts, tree nuts, fish, shellfish, into the infant diet have recently been revised. Before 2012, the WHO recommended waiting until at least 6 months of age, now the AAP and the American Academy of Allergy, Asthma & Immunology recommend introducing solids foods including allergenic items between 4 and 6 months, with 4 days in between each new addition to the diet.[13-16] One study conducted from 2009 to 2012 compared the development of a food allergy in children based on introducing possible allergens at 3 months or 6 months of age.[1] Two groups were tested, the early

intervention group which was exposed to the allergen at 3 months of age, and the standard introduction group which received the allergen no earlier than 6 months of age. Controlling for level of adherence to protocols, no peanut allergies occurred in the early intervention group, while 13 cases arose in the standard introduction group. Egg allergy also showed a significant difference between groups, with a 5.5% allergy rate in the standard group versus a 1.4% allergy rate in the early exposure group.[1]

Eosinophilic Esophagitis

Eosinophilic Esophagitis (EoE) is a relatively new diagnosis, with its earliest reported diagnosis occurring in 1993.[6] A recent position paper from *the Italian Society of Gastroenterology and Gastrointestinal Endoscopy* defines EoE as a "chronic immune-mediated disease of the esophagus characterized by symptoms related to esophageal dysfunction, as well as significant esophageal eosinophilia."[19] This condition is considered to be an atopic disease that is driven by antigen interactions caused by food allergies and aeroallergies.[2] However, in some cases it may be the result of cell-mediated reactions, which is why this is considered a mixed IgE- and non-IgE-mediated allergy.[8] It is the allergic response that causes eosinophils to enter the mucosa of the esophagus.[20] The presence of eosinophils are required for the diagnosis of EoE.[2]

There are four types of Eosinophilic Gastrointestinal Disease. These are EoE, eosinophilic gastroenteritis, eosinophilic gastritis, and eosinophilic colitis, each of which is characterized by inflammation in a specific part of the GI tract. EoE specifically, is characterized by localized inflammation in the esophagus only.[4,5] Ninety percent of individuals diagnosed with EoE have at least one other atopic disease, these are

conditions that are likely caused by genetic tendency to develop an allergic disease.[4] Risk factors associated with EoE are gender, race, and existence of other atopic conditions. Other atopic diseases often seen with EoE are other food allergies, asthma and allergic rhinitis.[6] For example, 10-20% of children with EoE also have an additional IgE-mediated food allergy.[4] Overall, this condition is three times more likely to affect males than females[6] and Caucasians appear to be more likely to develop this condition.[4,5] Overall, there is an estimated prevalence of 0.5-1.0 cases of EoE per every 1000 children and adults in the U.S.[1]

Etiology

EoE is considered a chronic primarily antigen-driven disease that can result from food or aeroallergens. The foods that trigger this disease are typically one of the eight common food allergens. However, the environmental factors, such as aeroallergens, have not been well defined. One systematic review assessed the relationship between various allergens and EoE. In this review, the following factors were evaluated: aeroallergens and pollen, insects, climate, urban vs. rural populations, season, and early-life exposures. Overall, results from this review did not show a definite relationship between EoE and any of these allergens. However, some interesting relationships were seen; such as EoE being more prominent in low population density areas and a cross reaction between some environmental allergens and food allergens.[20]

Diagnosis of Eosinophilic Esophagitis

Symptoms indicating possible diagnosis of EoE vary depending on the age of the patient. Infants and toddlers typically present with symptoms such as gagging, inability to progress to solid foods, and failure to thrive. Older children generally present with abdominal pain and vomiting. Those diagnosed in their teens or into adulthood tend to show symptoms such as dysphagia and food impaction.[4,5]

Eosinophilic Esophagitis is diagnosed via endoscopy and biopsy. There are currently no biomarkers to use as a diagnostic tool for EoE and no single test to diagnose EoE.[1,4] It is important to note that tests typically used for IgE-mediated allergies like Skin Prick Tests (SPTs), sIgE tests, and Atopy Patch Tests (APTs) cannot be used to diagnose EoE but they can be helpful in identifying trigger foods.[2] In their review of EoE, Kahwash and Prasad (2015) recommend that two to four biopsies from at least two different locations when testing for EoE.[5] An eosinophil count of greater than 15 eosinophils per high-powered field is the criteria for diagnosis. In addition, the biopsies must be taken after 8 weeks of proton pump inhibitor treatment to rule out GERD or proton pump responsive esophageal eosinophilia as the etiology.[4,5] Other potential causes of the presence of esophageal eosinophilia must be ruled out before diagnosing EoE. LeLeiko et al. (2017) lists several differential diagnoses, such as eosinophilic gastroenteritis, drug allergy, achalasia, infections, immune-related diseases, celiac disease, immunodeficiencies, Crohn's disease, allergic vasculitis, parasitic infection, eosinophilic leiomyomatosis, graft-versus-host disease, and systemic eosinophilia.[1]

Symptom Management

Treatment of EoE consists mostly of symptom management. This is usually done by corticosteroids or through dietary changes, with dietary changes being the preferred method due to negative outcomes that can arise with prolonged use of corticosteroids, such as impaired growth and osteopenia. While corticosteroids can be effective in the short term, upon cessation of these medications the symptoms will once again arise. Symptom management through dietary changes can be more effective in the long term, and can be done in a few ways.[4,5]

The most successful method is by changing the patient's diet to try a solely elemental formula diet with amino acids. This has almost a 100% success rate with symptom management; however, compliance long term is difficult.[4] Most patients will opt to do an elimination diet, which can be either a targeted elimination diet or an empirically based elimination diet. The targeted elimination diet utilizes information from an allergy test to determine allergenic foods on an individual level. However, this method has only shown 45.3% effectiveness.[1] The empirical elimination diet is usually done as a six-foods or four-foods elimination diet, in which either the six or four most common food allergens are removed from the diet and added back one at a time to see if there is some reaction. If the patient shows no signs of a flare up, then the food is accepted as non-allergenic for that patient. The six main foods eliminated are cow's milk protein, soy, eggs, wheat, nuts, and seafood as these have been clinically proven as the top allergens; and for the four foods elimination choice only the first four are eliminated. [1,4,5] The six and four foods elimination diet has been shown to have greater efficacy than the targeted elimination diet, with 72.1% and 68.2% efficacy respectively.[1]

Food Protein-Induced Enterocolitis Syndrome

Food Protein-Induced Enterocolitis Syndrome is a non-IgE mediated food allergy that typically presents in infants within the first year of life and is characteristic of vomiting within 1-4 hours after ingestion of allergenic food. This condition is distinguished from an IgE-mediated food allergy as it lacks the anaphylactic symptoms affecting the skin and respiratory system. FPIES was first defined during the 1970s but it was not until 2015 that a FPIES diagnostic code was introduced.[3] Due to the lack of diagnostic criteria until recently, determining the prevalence of FPIES is difficult. However, a few studies have quantified prevalence within their study populations. One prospective study in Israel found a prevalence of 0.34%,[21] while another, albeit smaller, population in Italy showed a prevalence of 19%.[22] Understanding the prevalence of FPIES is something further research should address.

The common allergenic foods associated with FPIES vary depending on the age of the individual. Infants younger than 6 months primarily react to cow's milk formula or soy formula;[10] infants with onset between 4 and 7 months is likely due to solid foods, commonly grains, poultry, egg, and certain legumes (peanuts, green pea) and vegetables (sweet potato, squash).[23,24] The most common food allergens shown to cause FPIES in infants are cow's milk and soy[22] and the most common solid foods appear to be rice and oats.[3] In children with FPIES triggered by cow's milk or soy infant formula, the condition appeared to resolve by the age of two. However, FPIES triggered by solid foods took longer to resolve likely due to its later introduction into the diet.[22] It is important to note that geography appears to have an effect on trigger food prominence. In cohorts from the United States. cow's milk and soy appear to be most common, while Australian, Italian,

and Spanish cohorts showed fish as a prominent allergen. Sopo et al. (2012) suggests that this discrepancy might be due to the existence of multiple phenotypes.[22]

Diagnosis of Food Protein-Induced Enterocolitis Syndrome

Diagnosis of FPIES is often very difficult due to its lack of definite identifiable symptoms and lack of a validated test. Because it is a non-IgE-mediated allergy, IgE-mediated allergy skin prick tests and patch tests cannot be used, instead an Oral Food Challenge (OFC) is considered the gold standard for identifying FPIES.[3,25,26] One study protocol required two previous episodes of a FPIES reaction to diagnose without an OFC.[22] According to the *Guidelines for the diagnosis and management of Food Allergy in the United States* a detailed history along with elimination of symptoms when the allergen is removed from the diet is enough to diagnose in the case of a child who has shown hypotensive reactions to the allergen previously. The purpose of this is to avoid the risks an OFC would present. [2] It is important to remember that over time 4-30% of children diagnosed with FPIES will develop IgE-mediated food allergies to the foods causing their FPIES. [26] Unfortunately, no biomarkers nor specific symptoms have been shown to occur in all cases of FPIES, which increases the difficulty of identifying and diagnosing this condition. [25]

The *International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome* has defined two major diagnostic criteria and multiple minor diagnostic criteria; it recommends that a patient meet both the major and at least three minor criteria before being diagnosed with acute FPIES. The major criterion is “vomiting in the 1- to 4-h period after ingestion of the suspect food and

absence of classic IgE-mediated allergic skin or respiratory symptoms."[3] The minor criteria are as follows: 1) more episodes of repetitive vomiting after eating the same suspect food, 2) repetitive vomiting 1-4 hours after eating a different food, 3) extreme lethargy, 4) pallor, 5) emergency department visit from a suspected reaction, 6) intravenous fluids needed due to a suspected reaction, 7) diarrhea within 24 hours, 8) hypotension, 9) hypothermia.[3]

Diagnosis of chronic FPIES is more difficult because it is not as well defined as acute FPIES. In order to diagnose chronic FPIES all differential diagnoses must be ruled out.[25] In the *2017 Consensus Guidelines for the Diagnosis and Management of FPIES*, Nowak-Wegrzyn et al. (2017) developed a few criteria. The main criterion being that the symptoms resolve within days after eliminating the allergen from the child's diet, and then the occurrence of an episode of acute FPIES when that allergen is reintroduced to the diet.[3]

The *2017 Consensus Guidelines for the Diagnosis and Management of FPIES* identified a delineation between mild-moderate and severe FPIES. Mild-moderate FPIES is characterized by the typical symptoms of vomiting, decreased activity, pallor and dehydration that can be resolved with home fluids. Laboratory indicators of mild-moderate include increased white blood cell count with neutrophilia, thrombocytosis, and presence of leukocytes, eosinophils, or increased carbohydrates in stool. However, in severe FPIES vomiting presents as projectile and repetitive, decreased activity level worsens to lethargy, pallor continues, and severity of dehydration requires intravenous fluids. Laboratory indicators of severe FPIES include the same as mild-moderate with the addition of metabolic acidosis and methemoglobinemia.[3]

Differential Diagnosis

There is a significant problem with misdiagnosis of FPIES due to the vague characterization of this condition. Sepsis is the most common misdiagnosis in individuals with acute FPIES; however, it is important to note that with FPIES there is no fever. This qualifier can be used to differentiate between sepsis and FPIES.[25] Acute dehydration from gastroenteritis is another common misdiagnosis. Metabolic disorders, immunodeficiencies, neurologic disorders, and other non-IgE mediated food allergies have also been seen as misdiagnoses in the case of chronic FPIES.[23] In neonates, necrotizing enterocolitis is often diagnosed in place of FPIES.[25]

Symptom Management

Short-term treatment of an acute FPIES reaction is to replace fluids lost through vomiting and diarrhea and long term treatment requires removal of the offending food from the diet. For chronic FPIES, removal of the trigger food, replacement fluids, and initiation of a hypoallergenic fluid usually results in cessation of symptoms within 3 to 10 days.[23]

Typically FPIES does not persist into adulthood; however, the average age of resolution is inconsistent across the literature. Some studies have shown the average age of resolution to be between 2-5 years of age,[26] while another study reported the median age to be 13 years old.[25] There also appears to be inconsistent resolution across the different allergens. For example, grain tolerance is reported to resolve at an average age of 35 months, where as other solid foods do not resolve until an average 42 months. Soy appears to have a wide range of resolution as early as 6 months and as late as 22 years of

age. The average age for resolution of cow's milk allergy appeared to be 6.7 in a US based case series.[3] However, in other studies the average resolution was by the age of two.[22]

Association Between EoE and FPIES

Though the etiology of EoE and FPIES differ, some similarities persist throughout the literature between EoE and FPIES. Both present with the possibility of vomiting and in severe cases failure to thrive. They both tend to affect children more frequently; however, cases have been noted in adult populations for both conditions. In both conditions elimination diets appear to be the main method of symptom management, while a "cure" has not yet been found. In addition, FPIES can sometimes be accompanied by an IgE-mediated food allergy, this situation is considered atypical FPIES. In fact, in a study by Sopo et al. (2012) they found 2 of 66 cases of FPIES that showed some reaction to a skin prick test, indicating the possible presence of an IgE-mediated allergy.[22] This may indicate some link between non-IgE- and IgE-mediated food allergies.

CHAPTER III

METHODS

Study Population

The study population will consist of children between birth and 18 years of age who are currently receiving care at the GI Care for Kids clinic and who have been diagnosed with EoE. Only children with an ICD-9 code of 530.13 or an ICD-10 of K20.0 will be included in the sample.

Study Design

The design of this proposed study will be a retrospective cohort study. Data will be extracted from the EPIC electronic medical record system utilized by the GI Care for Kids clinic. These data will include: demographic characteristics (gender, race), clinical characteristics (gestational age, age at diagnosis of EoE, other diagnoses, weight and length/height at the time of diagnosis of EoE, unexplained vomiting, unexplained diarrhea), nutrition intake (length of time breastfed, length of time fed infant formula, type of infant formula, age first complementary food introduced, and first complementary food). Patient data will be de-identified and each participant will be assigned a random identification number to maintain confidentiality.

Clinical Characteristics

Gestational age and age at diagnosis of EoE will be recorded in months. Weight will be recorded in kilograms, and length or height will be recorded in centimeters. The

following variables will be recorded as “yes” or “no”: diagnosis of FPIES, unexplained vomiting, and unexplained diarrhea. Finally, presence of other diagnoses will be documented and coded.

Nutrition Intake

All durations and time points will be recorded in months, this includes: length of breastfeeding, age of first complementary food started, and length of time fed infant formula. The type of formula will be noted as either intact cow’s milk, hydrolyzed cow’s milk protein, soy protein, hydrolyzed protein, or amino-acid based. The first complementary food will be recorded as either infant cereal, fruit, vegetable or can be entered as free text for other options.

Aeroallergens

The presence of pets and smokers in the household will be recorded as “yes” or “no”.

Statistical Analysis

Frequency statistics will be used to describe the demographic and clinical characteristics of the population. The Odds Ratio statistic will be used to determine the odds of developing EoE by FPIES status (diagnosis and symptoms) for the total population and after subdivision by breastfed versus formula fed and early introduction of complementary foods (before 6 months) versus late introduction of complementary foods (6 months or later). Logistic regression analysis will be conducted to determine the

impact of demographic, clinical, and nutritional characteristics on the development of EoE. All statistical analysis will be conducted using SPSS (version 25.0, SPSS Inc. Chicago, IL). A P-value of <0.05 will be considered significant.

CHAPTER IV

RESULTS

Demographic, Anthropometric, and Nutritional Characteristics

Our study population included 148 participants (57% male), the vast majority of which were Caucasian (98%) and non-Hispanic (97%). All of the study participants were receiving health care at the GI Care for Kids clinic and the median gestational age of the study population was 39 weeks (Table 1). The anthropometric and nutritional characteristics of the study population are shown in Table 2. The mean weight and height z-scores for participants with EoE and FPIES were calculated using age- and gender-appropriate growth curves. These z-scores revealed that participants diagnosed with EoE had average weight and height z-scores equivalent to the 42nd and 41st percentiles, respectively, while those diagnosed with FPIES had average weight and height z-scores equivalent to the 44th and 42nd percentiles, respectively

Table 1. Demographic Characteristics of the GI Care for Kids EoE and FPIES Sample Population

Characteristic	N	Sample
Gender; n (%)		
Male	148	85 (57.4)
Female		63 (42.6)
Race; n (%)		
Caucasian	148	118 (97.7)
African American		17 (11.5)
Asian		6 (4.1)
Other		1 (0.7)
Ethnicity; n (%)		
Hispanic	148	5 (3.4)
Non-Hispanic		143 (96.6)
Gestational Age (Weeks)*	108	39 (38, 39)
Household Pets; n (%)		
Yes	116	68 (45.9)
No		48 (32.4)

EoE – eosinophilic esophagitis, FPIES – food protein-induced enterocolitis syndrome
*Median (Interquartile range; 25%, 75%)

Table 2. Anthropometric and Nutritional Characteristics of the GI Care for Kids Sample Population

Characteristic	N	Sample
EoE Diagnosis Weight Z-score*	59	-0.20 ± 1.50
EoE Diagnosis Height Z-score*	59	-0.24 ± 1.22
FPIES Diagnosis Weight Z-score*	63	-0.15 ± 1.11
FPIES Diagnosis Height Z-score*	63	-0.21 ± 1.17
Length Any breastfeeding (Months)**	52	10 (2.75, 12)
Length Formula Fed (Months)**	52	4 (0, 20.5)
Age Complementary Food Introduced (Months)**	22	5 (4, 6)

EoE – eosinophilic esophagitis, FPIES – food protein-induced enterocolitis syndrome
*Mean ± Standard Deviation
**Median (Interquartile range; 25%, 75%)

Diagnosis and Symptom Characteristics

Half of the population (n=148) was diagnosed with EoE and the average age of diagnosis was 9.26 ± 5.40 years. The remaining participants (n=148) were diagnosed with FPIES at a median age of 0.82 (Interquartile Range [IQR]; 0.58, 1.17) years. Other common diagnoses included food allergy (n=38, 25.7%), food intolerance (n=19, 12.8%), and atopic conditions (n=29, 19.6%). The majority of the population had a history of vomiting (n=104, 70.3%), while fewer participants had a history of diarrhea (n=46, 31.1%) (Table 3).

Table 3. Diagnosis and Symptom Characteristics of the GI Care for Kids Sample Population

Characteristics	N	Sample
EoE Diagnosis; n (%) Yes No	148	 74 (50) 74 (50)
EoE Diagnosis Age (Years)*	68	9.26 ± 5.40
FPIES Diagnosis; n (%) Yes No	148	 74 (50) 74 (50)
FPIES Diagnosis Age (Years)**	71	0.83 (0.58, 1.17)
Food Allergy Diagnosis; n (%) Yes No	148	 38 (25.7) 110 (74.3)
Food Intolerance Diagnosis; n (%) Yes No	148	 19 (12.8) 129 (87.2)
Atopic Condition Diagnosis; n (%) Yes No	149	 29 (19.6) 119 (80.4)
Vomiting History; n (%) Yes No	139	 104 (70.3) 35 (23.6)
Vomit Time (Hours)**	24	2 (2, 4)
Diarrhea History; n (%) Yes No	138	 46 (31.1) 92 (62.2)
Diarrhea Time (Hours)**	8	2.5 (1, 3.8)

EoE – eosinophilic esophagitis, FPIES – food protein-induced enterocolitis syndrome
*Mean ± Standard Deviation
**Median (Interquartile range; 25%, 75%)

Odds Ratios and Logistic Regression Relating EoE and FPIES

The odds ratio statistic revealed zero odds of developing EoE based on FPIES diagnosis (Table 4) and decreased odds of developing EoE (0.25 [95% confidence interval 0.109 – 0.575]) (Table 5) with a history of vomiting. The odds of developing EoE based on FPIES diagnosis did not change after subdividing the population by feeding practices. The odds of developing EoE by FPIES diagnosis remained zero when the population was subdivided into breastfed versus formula fed participants and early versus late complementary food introduction. Univariate chi-square analysis revealed a significant relationship between the diagnosis of EoE and gender ($P<0.05$), previous diagnosis of food allergy ($P<0.01$) and previous diagnosis of food intolerance ($P<0.001$) (Table 6). Multivariate logistic regression analysis indicated that these variables in addition to a history of vomiting explain 23% to 31% of the variation in EoE diagnosis (Table 7). The odds of developing EoE increase with a positive previous history of food allergy, food intolerance, and vomiting while males have lower odds of developing EoE after controlling for the other independent variables.

Table 4. Odds Ratio Table for EoE by FPIES in the GI Care for Kids Sample Population

	EoE + n=74	**EoE –** n=74
FPIES +	0	0
FPIES -	74	74

EoE – eosinophilic esophagitis, FPIES – food protein-induced enterocolitis syndrome
Odds Ratio = 0

Table 5. Odds Ratio Table for EoE by History of Vomiting in the GI Care for Kids Sample Population

	EoE + N=65	**EoE –** N=74
Vomiting History +	40	64
Vomiting History -	25	10

EoE – eosinophilic esophagitis
Odds Ratio (95% Confidence Interval) = 0.25 (0.109 – 0.575)

Table 6. Chi-Square Analysis for Variables Associated with Diagnosis of EoE in the GI Care for Kids Sample Population

	EoE Diagnosis +	EoE Diagnosis -	P-Value
Gender (%)			
Male	33.8	23.6	0.013
Female	16.2	26.4	
Food Allergy (%)			
Yes	7.4	18.2	0.003
No	42.6	31.8	
Food Intolerance (%)	1.4	11.5	0.000
Yes	48.6	38.5	
No			

Table 7. Summary of Logistic Regression Analysis for Variables Predicting Diagnosis of EoE in the GI Care for Kids Sample Population

								95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Gender (Male)	1.023	.397	6.639	1	.010	2.782	1.277	6.057
	FoodAllergyDiag (Yes)	.922	.465	3.932	1	.047	2.515	1.011	6.258
	FoodIntolDiag (Yes)	2.374	.829	8.200	1	.004	10.743	2.115	54.565
	VomitHist (Yes)	1.373	.475	8.345	1	.004	3.946	1.555	10.014
	Constant	-.769	.492	2.445	1	.118	.463		

a. Variable(s) entered on step 1: Gender, FoodAllergyDiag, FoodIntolDiag, VomitHist.

EoE – eosinophilic esophagitis

CHAPTER V

DISCUSSION AND CONCLUSIONS

No association between a diagnosis of FPIES and a diagnosis of EoE was observed in the study population. Therefore, we reject our null hypothesis that there will be no difference in the odds of developing EoE by previous diagnosis of FPIES. However, a relationship was observed between a history of vomiting and EoE, which indicated that a history of vomiting is protective against developing EoE. As a result, we fail to reject our null hypothesis that there will be no difference in the odds of developing EoE between individuals with or without characteristics of FPIES. The relationship between FPIES and EoE was not affected by infant feeding practices (breastfed versus formula fed and early versus late complementary food introduction).

The WHO, AAP, and AND recommend exclusive breastfeeding for the first 6 months of life and the introduction of complementary foods at 6 months of age, while continuing to breastfeed until 12 months of age.[11-13] Fifty-two participants reported some breast feeding in the first year of life. Of those participants, 71% (n=37) were breastfed for at least 6 months, which is similar to the national average of 57.6% according to the 2018 Breastfeeding Report Card.[27] Twenty-seven percent of our study population was introduced to complementary foods at 6 months of age and 36.5% continued to breastfeed for 12 months. Previous research suggests breastfeeding has a protective affect against allergies;[11] however, we observed no difference on EoE development by breastfeeding status. In addition, we observed no difference in age of complementary food introduction and EoE development as was reported in the literature.[1]

Many demographic and symptom characteristics reported by our participant population were consistent with the literature. The average age of diagnosis of EoE (9.26 years) and FPIES (0.83 years) in the study population were consistent with the literature. Previous studies found that EoE is most commonly diagnosed in children between the ages of 5 and 10, while FPIES appears to be commonly diagnosed at about 7 months of age.[6,9] Our study population had a higher percentage of males diagnosed with EoE than females, 33.8% of males and only 16.2% of females. This is consistent with previous estimates of a male to female ratio of 3:1 in those diagnosed with EoE.[4,5] Despite the higher prevalence of a diagnosis of EoE in males, logistic regression analysis of our population data showed that males have decreased odds of developing EoE compared to females when controlling for previous diagnosis of food allergy, food intolerance, or history of vomiting. Cianferoni et al. (2015) found that 90% of patients with EoE had at least one other atopic disease.[4] However, only 19.6% of our study population were diagnosed with another atopic condition. According to Kahwash et al. (2015), 10-20% of children with EoE have a food allergy,[5] which is similar to our observation of 25.7% diagnosed with a food allergy. Some of these variations could be due to the inclusion of patients with EoE and patients with FPIES in our sample population, whereas these previous studies only included patients with EoE. When dividing the population based on diagnosis, the prevalence of another atopic condition was slightly higher at 23%. The FPIES literature reports that symptoms of vomiting usually occur within 1-4 hours after ingestion of the allergen[3,23] and our data support this conclusion with, on average, vomiting occurring 2 hours after allergen ingestion in our study population. Diarrhea

(31%) was not as common as vomiting (70%) in our sample which is also consistent with the literature.[21]

This study has a few limitations, including a moderately small study population (n=148), short follow-up period, and retrospective data collection method. The data were collected through a retrospective chart review of patients seen over a two-year period. This short time frame limited the number of times that patients were seen by the clinicians and could affect the number of FPIES and EoE diagnoses observed in the population. In addition, because this was a retrospective study the information on each participant was limited to the information recorded in the charts. This resulted in missing information for some of the data points we collected, such as weight and height z-scores, age at diagnosis of FPIES or EoE, and information on feeding history. Had this been a prospective study, data collection could have been more complete for each participant and bias in reporting could have been reduced. Specifically, bias is likely present due to the inconsistency of reports of vomit history within the charts. For example, some participants had specific information documented in their medical record, such as the timing of vomiting after eating and the period of time over which the vomiting occurred, while others simply had a statement that the participant had a history of vomiting. There is also room for error due to the inconsistency of reporting from the parent or caretaker as the perception of vomiting may differ. In a prospective study, clarification regarding the severity of vomiting could have been obtained.

In conclusion, no relationship exists between the diagnosis of FPIES and EoE diagnosis in the study population. However, a history of vomiting was observed to have a preventative effect on the development of EoE. In addition, the diagnosis of a food

allergy, food intolerance, or a history of vomiting resulted in increased odds of developing EoE. These findings suggest that screening for signs of EoE may be beneficial for individuals diagnosed with food allergy, food intolerance, or who present with a history of vomiting. The relationship between a history of vomiting and the development of EoE could be due to the increased likelihood of individuals with a history of vomiting seeking treatment earlier. Since treatment of FPIES often includes eliminating allergenic foods, this could prevent EoE developing later on in life. Clinicians speculate that introduction of a wider variety of food items earlier in life due to FPIES allergy could be another explanation for the preventative nature of a history of vomiting associated with FPIES. This usually occurs with FPIES treatment because the common allergens for FPIES are cow's milk and infant cereals. Therefore, to meet energy needs patients often require the introduction of a wider variety of food. Additional studies are needed to evaluate the effect of early infant diet on the future development of EoE.

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