Kaileen Rohr: FPIAP IRB protocol

TITLE: A characterization of patients with prolonged food-protein induced allergic proctocolitis

STUDY PURPOSE AND RATIONALE:

Food allergic-reactions including IgE-mediated , non-IgE mediated, and mixed reactions. While IgE-mediated reactions are commonly associated with potentially life-threatening, anaphylactic reactions, non-IgE mediated food allergies are characterized by delayed onset and chronic symptoms including recurring gastrointestinal symptoms ranging from bloody stools and vomiting to malabsorption and FTT [1,2].

One common non-IgE mediated food allergy in infants is food protein induced allergic proctocolitis (FPIAP). FPIAP is the most common cause of rectal bleeding in infants, and is generally considered to be a benign self-limited allergic disease. The allergens most commonly implicated in the disorder are cow's milk and soy, although a small subset of patients may be reactive to egg, corn, chicken, wheat and other foods[3,4, 5]. Only one large FPIAP prevalence study exists, in which 13,019 infants in Israel were followed prospectively from birth. This study found an overall prevalence of FPIAP of 0.16% [6]. FPIAP most commonly has an onset within one to four weeks of age, and a disproportionate number (approximately 50% of cases) occur in exclusively breastfed infants [4, 7]. FPIAP is a clinical diagnosis based upon the symptom of blood-streaked mucoid stools in an otherwise well appearing and thriving infant. Additional symptoms of vomiting, profuse watery diarrhea, or failure to thrive are typically not seen and if present are suggestive of an alternative diagnosis such as food protein induced enterocolitis or necrotizing enterocolitis[3, 8]. Though not necessary for diagnosis, associated laboratory findings include mild anemia and hypoalbuminemia, as well as peripheral eosinophilia [3, 8]. On colonic mucosal biopsy, a variety of studies have demonstrated eosinophilic infiltrate with surrounding lymphoid nodular hyperplasia [9,10, 11]. Food specific IgE and skin prick tests, if done, are typically negative[3]. Importantly, diagnostic confirmation of FPIAP is obtained following resolution of symptoms within 72 to 96 hours following elimination of the allergen from the infant's diet. In breastfed infants, a maternal elimination of CM and soy is typically successful in resolving symptoms [7, 12, 13]. Utilization of a partially hydrolyzed or an amino acid based formula may be required if the breastfed infant has persistent symptoms despite a maternal elimination diet or if infant is formula fed [14,15]. According to a recent meta-analysis, a majority of infants, 78.8%, were able to tolerate their triggering antigen at 1 year of age[4], and therefore reintroduction of the trigger antigen is typically recommended 1 year of age [7,16].

The exact pathophysiology of the disorder is unknown, however one possible mechanism is delayed development of tolerance in the infant immune system [3,15]. One small study found a relative increase in immunoregulatory Treg cells and a Th2 polarization in infants with FPIAP as compared to healthy controls [15]. The mechanistic reason for delayed tolerance of CM and soy proteins in these infants has not been established

although one theory is that reduced intestinal bacterial colonization may lead to allergen sensitization [17, 18]. The delayed tolerance in affected infants is thought to result in a T cell hypersensitivity reaction to the ingested allergen with resultant eosinophilic infiltration of the colon [19]. Theoretically, development of tolerance with age permits reintroduction of the offending food into the infant's diet without further signs or symptoms. Rates of eczema among infants with FPIAP have been shown to be similar to the general population - 22% reported in FPIAP [3] as compared to 18.6-21% in the general population[20, 21]. No long term risk of inflammatory bowel disease has been observed in children followed prospectively for 10 years[7].

Despite the fact that the majority of patients with FPIAP will experience resolution by 1 year of age, it is has been shown that a subset of FPIAP patients can develop concomitant IgE-mediated sensitivity to the food allergen(s), suggesting more persistent sensitivity. More recently, we have observed that some FPIAP patients, even without evidence for allergen specific IgE, fail to become tolerant to the trigger allergen within the first year life with continued gastrointestinal symptoms as well as symptoms of food intolerance.

Assessing the clinical features of these FPIAP patients who do not outgrow their allergy may help to further characterize this group of FPIAP patients. We hypothesize this particular group may have a higher likelihood of other atopic disease and/or a family history of atopy, allergic proctocolitis or IBD. If our hypothesis is correct, these results may potentially suggesting that the delayed development of tolerance resulting in allergic proctocolitis may be suggestive of more persistent or inherited defects in immunologic tolerance, and therefore a unique subset of higher risk patients who require closer allergy and gastrointestinal follow-up.

STUDY DESIGN

We aim to describe and compare the demographic and clinical characteristics of patients with self-resolving and prolonged FPIAP. The study is designed as a retrospective case control study, in which a control is defined as an infant diagnosed with FPIAP who subsequently tolerated inciting food by age of 1 year, while cases are defined as patients diagnosed with FPIAP who were unable to tolerate inciting food by age of 1 year. We anticipate approximately 20 cases and 40 controls for this small study.

STATISTICAL ANALYSIS

We will conduct a standard descriptive analysis, including frequencies and proportions for categorical data and means (with standard deviation) and medians (with interquartile ranges) for continuous data. If differences are observed between the cases and controls, a Chi-square test of proportions will be used to determine significance for categorical variables, and an unpaired t test will be used for continuous variables (with significance level of $p<0.05$).

STUDY LOCATION
NYP – Columbia Medical Center, Division of Allergy and Immunology.

STUDY SUBJECTS:
The data will be obtained from CROWN EMR through a search of patients who presented to the Columbia- NYP Allergy department during the years of 2010-2016 with a diagnosis of allergic proctocolitis.

Inclusion criteria:
(1) a history of bloody stools in child which began prior to 1 year of age
(2) a clinical diagnosis of FPIAP
(3) resolution of symptoms in response to an elimination diet
(4) an oral food challenge at the age of approximately 1 year

Exclusion criteria:
(1) persistence of bloody stools following a maternal elimination diet or after switching to a soy, partially hydrolyzed, or amino acid formula
(2) diagnosis of failure to thrive during the period of inquiry
(3) history of necrotizing enterocolitis or abdominal surgery
(4) a positive stool culture.

STUDY PROCEDURES:

Retrospective chart review of all pediatric patients diagnosed with FPIAP who meet the above inclusion and exclusion criteria who were seen between January 1, 2010 to July 1, 2016 at NYP Columbia Medical Center.

Demographic data to be obtained:
- Patient age at time of diagnosis
- Patient age at time of OFC
- Gender

Clinical data to be obtained
- Gestational age at birth
- Birth weight
- Delivery type(NSVD, C-section)
- Perinatal complications (including NICU stay)
- Past medical history
- Past surgical history
- Family history of allergic disease (including allergic proctocolitis), IBD
- Medications
- Feeding history (BM – Y/N and if Y duration, Formula- Y/N and if Y duration, Combination)
- BM vs. Formula (and type) when developed symptoms
- Allergen attributed to symptoms, feeding history (breastmilk, type of formula)

- Symptoms at presentation (vomiting, diarrhea, colic, abdominal pain)
- Type of elimination diet required to resolve symptoms (maternal elimination diet vs. partially hydrolyzed formula vs. amino acid formula)
- Additional laboratory work when available: CBC, HFP, IgE levels, allergen-specific skin testing.

RECRUITMENT
There will be no recruitment as this is a retrospective chart review.

CONFIDENTIALITY OF STUDY DATA
The individual patient demographic and clinic information will be kept confidential and will be collected and all information will be kept on a password protected, encrypted computer and stored at the NYP – Columbia Medical Center Allergy Department. Only the study staff will have access to the link between the children's medical record number. Individual patient demographic and clinical information will be kept confidential and stored on password-encrypted computers in locked offices. This information will not be shared with anyone or any organization outside the study team except as mandated by the IRB. Collection of sensitive information about subjects will be limited to the amount necessary to achieve the aims of the research, so that no extraneous information is collected at any point. Once the chart review is completed, the data used will be de-identified. Information that includes patient identifiers will not be stored after the chart review is completed and data has been collected

POTENTIAL RISKS
There is a potential risk of loss of confidentiality, which will be minimized by restricting access of any personal information to the study team and keeping any personal information in a secure location.

POTENTIAL BENEFITS
No direct benefit will be obtained by any of the subjects studied in this research. However, future patients diagnosed with FPIAP may benefit from knowledge regarding prognosis, specifically risk factors for sustained symptoms and potentially future allergic disease.

DATA AND SAFETY MONITORING:
All data will be available upon request by the Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board (IRB), and/or the Office of Human Research Protections (OHRP).

STUDY QUESTIONNAIRE
No study questionnaire will be used in this study.

ALTERNATIVE THERAPIES
No alternative therapies will be used in this study.

COMPENSATION TO SUBJECTS

No compensation will be provided to subjects.

COST TO SUBJECTS

There is no cost to subjects in this study.

RADIATION AND RADIOACTIVE SUBSTANCES

No radioactive substances will be used in this study.

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