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FOOD REINTRODUCTION IN FPIES

INTRODUCTION

Food Protein Induced Enterocolitis Syndrome (FPIES) lies within the spectrum of non-IgE-mediated food allergies. It is a clinical diagnosis based on a suggestive and reproducible history. T-cells are the likely mediators for FPIES; a neuro-endocrine mechanism is also suspected, but there is still considerable need for further understanding of the pathophysiology of FPIES. Classic FPIES is a delayed onset gastrointestinal reaction, usually 1-4 hours post ingestion and can vary in duration and symptom severity. Symptoms can include anyone, or a combination of, projectile emesis, diarrhoea, abdominal pain, lethargy, ashen appearance, hypotension, and even hypothermia. Urticarial and respiratory complaints are not characteristic. Any food can be a trigger and any age can be affected though it is more common in children. Clinicians should suspect FPIES in any patient with a consistent reproducible history to a specific food. Due to lack of provider familiarity with the condition, it may go misdiagnosed especially in the adult population; misdiagnosing FPIES for food poisoning with seafood for instance. Unlike IgE-mediated allergies, in the paediatric population, FPIES usually resolves sooner with an average age of about three. Excellent resources exist differentiating the spectrum of food allergies—in particular the non-IgE spectrum.[1-4]

The majority of patients with FPIES (65-80%) will be fairly clear when there is a single trigger. It is more difficult in polysensitized individuals or when the food allergen is consumed on a regular basis leading to chronic FPIES. Foods that are empirically most likely to trigger a patient vary based on geography and age, but FPIES often involves foods that are often overlooked as common allergens. Milk is by far the most common and best documented within the literature. There is no objective diagnostic tool to confirm FPIES except for a food challenge in the clinical setting. Acute events may show serological evidence of neutrophilia, thrombocytosis, methemoglobinemia, or acidemia and IgE may be present through serum specific or skin prick testing. It is important to note that though IgE may be present, FPIES is not IgE-mediated. None of these are useful tools to confirm or predict FPIES. The only treatment for FPIES is avoidance, there is no other established therapeutic algorithm.

Chronic FPIES can be more insidious and often overlooked. It may present with changes to stool consistency; frequency of bowel movements and constipation can be present especially after a diarrhoeal event; reflux potentially requiring medication for its management; gastrointestinal pain which can lead to frequent nocturnal awakenings. There is also the potential concern that enteropathies may impact a child's growth; if a child was to show growth curves falling significantly, it may be due to malnourishment secondary to a cellular food allergy. FPIES can have a very

low threshold required for a reaction. Though not common, a maternal diet involving the consumption of the culprit food in an exclusively breastfed infant can be enough to lead to reactions in the most sensitive infants.[6] Advanced cases of chronic FPIES can lead to more significant symptoms and laboratory changes such as leukocytosis, eosinophilia, and even failure to thrive. These situations pose difficulty in distinguishing FPIES from eosinophilic enteropathies and food protein induced enteropathies. These other conditions will not be addressed but they may in fact lie along a continuum or spectrum of non-IgE-mediated food allergies.

The aim of this article is to inform practitioners on a safe and reliable strategy for introduction of the food in the context of FPIES. This approach can be utilised to confirm the diagnosis in a suspected patient or to confirm the persistence of FPIES. A confirmational challenge is recommended to establish a diagnosis and avoid the unnecessary burden of avoiding a food that is not responsible.[2] Ultimately, it is a shared decision between the patient/family and clinician to perform a challenge especially if the original reaction was severe. Unlike IgE-mediated allergies, a challenge in FPIES should never be converted to a therapeutic protocol; oral immunotherapy is not applicable to FPIES. IgE-mediated allergies can be treated with oral immunotherapy (OIT). If a food challenge were to induce a reaction, clinicians might consider switching over to OIT to treat the allergy. FPIES can present with or without symptoms. If a challenge or reintroduction fails in FPIES, clinicians can discontinue and attempt it again later.

FOOD REINTRODUCTION

It may be preferable to use the term 'reintroduction' rather than 'challenge' in the setting of FPIES as it should be a slower process. Below, four important elements involved with food reintroduction are introduced. Baseline quiescence of symptoms for a patient should be clearly established prior to any reintroduction. If chronic FPIES is suspected it is recommended to postpone reintroduction; the best treatment for FPIES remains avoidance and/or elimination of the culprit food(s) from the diet. Clinicians should consider that chronic FPIES may lead to further problems if the chronic inflammation acts a nidus for further sensitisations or can act to delay spontaneous resolution.

1) LOCATION: Physician-supervised challenges are typical, and the severity of the original reaction may certainly warrant such an approach in a supervised setting. However, recent changes in how to deliver healthcare in a pandemic setting have made virtual challenges more common and permissible. These can be performed safely if families/patients are properly informed of the risks and benefits and if the initial reaction is not severe.[5]

For FPIES, a home-based reintroduction may be more appropriate given that:

a) Time constraints make dosing intervals in the office impractical as symptoms may take hours to develop between doses. There is no consensus as to how long patients should wait between doses, as this varies based on patient history.

b) Patients may feel most comfortable at home if a reaction were to occur. Protracted emesis or diarrhoea may last hours. A busy office with an unfamiliar washroom is not the ideal setting for a patient to weather these symptoms.

c) Reactions can be disconcerting to other patients and staff. Contact with bodily fluids also may pose a risk to others, including cleaning staff.

d) To date, there has never been a documented case of death in the literature from FPIES.

e) The majority of reactions will have occurred in the home setting. As there is no standardised treatment for FPIES, and the original reactions used for the clinical diagnosis will invariably have resolved spontaneously on their own, it should be reasonably safe to assume home reintroduction is safe.

2) TIMING: After clear avoidance of the suspect food, a reintroduction can be attempted usually every 6-18 months. As the timing of spontaneous resolution varies, there is no steadfast rule to predict when this will occur.

a) The risk of accidental ingestion may preclude the need for a scheduled reintroduction. Accidental ingestions for peanut average 12.4% per annum based on a large Canadian cohort.[7] Peanut ingestion is a good benchmark due to the awareness surrounding this allergen. Common foods like soy or milk may be even more common to ingest accidentally and can be used as an advantage to ensure follow-ups are booked every 6-12 months in the paediatric population knowing that many will have had an exposure.

b) Temper a reintroduction with the need for a particular food within a diet. Shrimp is not a necessary requirement in any diet and an adult may not wish to schedule any exposure. Nutritional and fiscal constraints on a family should be considered for the timing of reintroduction since avoidance can be onerous on a family, with alternatives being expensive.

c) Reintroductions should be timed around daycare, school, or work schedules in the event of symptoms.

3) PRODUCT CHOICE:

a) Some proteins are denaturable especially those within the liquid FPIES spectrum. The UK Milk Ladder and Egg Ladder are very useful and easily accessed resources based on denaturable proteins. Each step along the ladder would be one reintroduction.

b) If the patients has more than one trigger, start with the least reactive food based on the patient's history. A successful reintroduction of a milder allergen may also act as a predictor of gradual tolerance.

c) A successful reintroduction of a food into the diet allows the patient/family to expand the diet but also provides a sense of achievement and positive reinforcement. It is important to avoid starting with a food reintroduction failure.

d) If possible, a single product should be used for reintroduction such as cheese instead of pizza or soy milk rather than chicken nuggets.

e) It is also important to use a product that is typical in a diet (i.e. peanut butter rather than peanut protein). While the reaction will be due to the protein, isolating the protein is not critical for reintroduction. The modification of proteins can change reactivity as indicated by the dairy ladder.

f) In rare cases if the allergen can trigger symptoms through lactation, it is fully permissible to conduct the reintroduction first through the maternal diet. This situation may be the exception in terms of scheduling a reintroduction much earlier to avoid cessation of breast feeding and/or restricting the maternal diet.

4) PROTOCOL: There is a paucity of literature demonstrating the optimal method to challenge or reintroduce non-IgE-mediated food allergy. One protocol for FPIES recommends a target weight-based dose of 0.06–0.6 g/kg of body weight.[3,5] The target dose is divided into three equal measures with consumption over 30-45 minutes, generally not to exceed a total of 3 g of protein or 10 g of total food (100 mL of liquid). It should be noted that lower challenge doses are used for patients with a history of severe reactions. In addition, this protocol recommends having IV access and a baseline CBC prior to challenge.

a) Start with sub-threshold levels (lowest dose at which no observed reaction). This minimizes the severity of reactions but also indicates to the patient/family what levels are permissible in the diet.

b) The actual starting dose should be as small as possible and may depend on the concentration of protein. Tofu compared to soy milk will be different. For tofu even a touch to the tongue could be enough to elicit symptoms. Generally, 2mg of protein is a good starting point.

c) Doses can be doubled or quintupled each interval. This can be done by weight or volume depending on the product. A pre-printed hand out to give to patients/families can be useful for home reintroductions.

d) Trials can be done over days simply with a single dose each day. The history may dictate onset of symptoms

after perhaps an hour; milder symptoms may manifest and result in onset later at lower doses.

e) If a quicker protocol is desired, the dosing interval should be double that of the historical timing for the patient. In other words, if on history the onset was 1 hour post ingestion, dose every 2 hours.

f) Home reintroductions require open lines of communication with the physician. Families and patients need to be instructed to contact the physician's office if and when symptoms develop. Milder symptoms may be overlooked that are otherwise identifiable to the physician. The patient's lowest observed eliciting level may not be as overt as the previous reaction(s). A specific list of symptoms to monitor for can be provided to the patient/family prior to the reintroduction.

SUMMARY

FPIES is a fascinating entity within the spectrum of food allergies. It generally has a very clear history and reproducibility. The reintroduction of suspect foods can be done to confirm the diagnosis or persistence of FPIES, but a pragmatic and cautious approach is recommended. The decision to proceed with a reintroduction should be mutually agreed to by the physician and the patient/family and there should be a clear rationale for the utility of a food reintroduction. The risks associated with reintroduction can be mitigated with careful consideration of the timing, location, and pace of the reintroduction.

References:

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