

THE MOTHER OF ALL FOOD ALLERGIES

Anaphylaxis from peanuts. Buzzing lips from apple. Vomiting and diarrhea producing shock from oat. Steatorrhea from wheat. Bloody stools from breast milk. These phenomena are examples from the range of manifestations of immune reactions to foods in common pediatric experience—immediate hypersensitivity and oral allergy syndrome, food protein-induced enterocolitis syndrome, gluten-sensitive enteropathy (celiac disease), and allergic colitis.

But, what about constipation from milk, eczema from eggs, dysphagia from chicken, or sleep disturbance from everything? Are they immune-mediated? Or, are they phantom associations? Certainly, every three-year-old drama queen who hasn't voluntarily opened her anal sphincter since being introduced to the porcelain monster isn't allergic to milk. Right? Right. Nevertheless, it is becoming increasingly clear that immunologic reactions to multiple foods can present in more subtle fashion than previously recognized and must be included in the broader differential diagnosis for a variety of symptoms.

The outstanding article by Latcham et al in this edition of *The Journal* describes 121 children in Great Britain with multiple food allergies.¹ The retrospective analysis has drawn together clinical, histologic, and immunologic parameters to describe and distinguish subtypes on the basis of presentation. Immediate responders are compared with those whose reactions are delayed. The groups are not pure, however, because the vast majority (93%) of the immediate reactors also have delayed reactions.

Immediate responders characteristically have "traditional" allergic reactions with urticaria, vomiting, or anaphylaxis associated with elevated serum IgE, and positive skin prick and radioallergosorbent test (RAST) to the offending foods. They often pose little difficulty in diagnosis from history, although the dramatic immediate reactions of food protein-induced enterocolitis syndrome may confuse the casual listener, as victims are typically skin test-negative to the offending protein because the process is cell-mediated. An excellent analysis and description of food protein-induced enterocolitis syndrome has been published recently and is essential reading for pediatricians.²

Delayed reactions to food proteins are more complicated to diagnose. Commonly available allergy testing with skin prick or RAST will most likely fail to identify the culprit. In

the current series, only 27% of the delayed responders had positive skin tests. However, clinical suspicion that an immunologic reaction might underlie the symptom is increased by the frequent association (68%) with other atopic symptoms such as eczema, asthma, and hay fever. It is clear that the perception that "if your skin tests are negative then you're not allergic to it" needs either to be abandoned or the terminology changed.

Symptoms may point generally to food, but determining which food(s) is difficult when only delayed reactions occur and standard skin prick testing is negative. Skin patch testing—prolonged application of food to the skin surface—has recently been suggested as an additional means of detecting responses to foods in patients with allergic eosinophilic esophagitis, another recently described disorder that sometimes develops as a consequence of delayed reactions to food.^{3,4}

In the absence of perfect testing, double-blind placebo-controlled food challenges (DBPCFC) are necessary for confirmation of a relationship between the symptom and ingestion of the food. For delayed reactions, DBPCFC are reliable when clearly positive or negative, but when the symptoms are non-specific (sleep disturbance in a toddler, for example) they are fraught with the vagaries of the subjectivity beast. Because they are time-consuming and produce illness when a reaction develops, the challenge for us is to develop accurate, reproducible, noninvasive means for identifying the offending foods.

At the same time, identifying the immune defect that permits the development of hypersensitivity to food antigens is essential. In the current study, careful examination of other immune markers including IgG subclass levels and quantitation of lymphocyte subpopulations revealed subtle deviation from normal.

Although neither causal nor diagnostic in and of themselves, these findings lend further credence to the notion that these children have underlying immune dysregulation. Failed induction of oral tolerance leading to sensitization against multiple food antigens and the repeated or prolonged infections reported in nearly one

See related article, p 40.

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DBPCFC Double-blind placebo-controlled food challenges

third of these children may be sequelae of a common pathophysiologic process. Until we understand oral tolerance and can induce it at will with probiotics or other provocative signaling at the appropriate time in immune development, these children will continue to mount inappropriate responses to otherwise harmless dietary components.⁵ The question as to why there seems to be an increasing population of children who fail to develop oral tolerance remains unanswered.

It should be of particular concern to gastroenterologists and pathologists alike that mild enteropathy resulting from immune reactions to food was only discovered on morphometric analysis of duodenal biopsies, many after a provisional diagnosis of "normal" had been entertained. Mildly altered crypt:villous ratio and patchy infiltration of the lamina propria with lymphocytes or eosinophils are subject to considerable subjective interpretation and debate under the best of circumstances, as endoscopic biopsies are small and difficult to orient precisely for cross-sectional analysis. In addition, the definition of normal is a moving target, as our understanding and threshold for recognizing the histologic impact of the mucosal immune response to dietary antigens change. The patchy nature of the inflammatory process demands that multiple biopsy specimens be taken to assure adequate representation.

The need to include an immunologic reaction to food in the differential diagnosis of common symptoms, irrespective of severity, is ever more important. Many of the children in the study developed symptoms and presented in infancy, but referral for definitive diagnosis was not made until years later in some. The frustration of families in those situations should not be underestimated. Months and years of delay, denial, and barking up the wrong tree take an enormous emotional toll on the family while perpetuating the damage to the baby. It might be easy to see how a parent insistent on additional testing for fairly nonspecific symptoms might eventually be accused of Munchausen's syndrome by proxy, but the fact that 5 of 77 families in this cohort were so reproached despite other objective and suggestive findings in their children is shameful.

At the same time, it is not surprising that these families fail to successfully navigate the subspecialty labyrinth. The gastroenterologist did the endoscopy and didn't see much, the biopsy results were underwhelming to the pathologist, and the allergist said the child wasn't allergic because the skin tests were negative. Random elimination of foods didn't help. The child is still sick. Now what? Of course, there is no simple solution. When all indications point to food allergy, an elemental diet trial becomes both diagnostic and therapeutic when successfully completed, which is no small task after infancy.

For the purposes of the current study, multiple food allergy was diagnosed if the child was hypersensitive to two or more foods. At the severe end of the spectrum, 10 children required prolonged exclusive use of an amino acid-based formula. These children are perceived as "allergic to everything." Although they have not been challenged with literally "everything," they have reacted to everything they have tried. Continuing food challenges in the face of repeated failure is emotionally taxing and, if not carefully done, commits the child

to perpetual illness during the failed search for something to eat. It is essential to recognize these cases and suspend food challenges until such time as optimal health is restored, and until the child and parent are ready to give it another go.

Parents uniformly want to know the natural history. Will my child "outgrow" this? Will my child ever be able to eat? From the article it is clear that many young children will develop oral tolerance, but it is equally clear that some do not, and that we currently do not have the ability to identify and classify those persons except in retrospect.

For children who fail to develop significant oral tolerance, school age is particularly difficult. Food as nutrition, party fare, treat, snack, prize, reward, or commercial advertisement is everywhere. For the child whose backpack contains an infusion pump and formula instead of books, food outside the parents' observation represents a challenge, potential threat, or opportunity to cheat. The presence of food in the classroom magnifies the difference between the hypersensitive child and those who eat, and increases the psychologic impact of the disorder.

Elemental formulas whose protein fraction is free amino acids offer legitimate therapy for children with multiple food allergies. However, there seems to be substantial inertia in the pediatric community to go beyond protein hydrolysate (ie, polypeptide-based) formulas. Confirming prior observations, nearly one third of the children in the current study, including many breast-fed infants, did not tolerate hydrolysate formulas.⁶ The use of hydrolysates, although they are less costly and more easily available, must be abandoned as quickly as cow's milk-based formula if symptoms aren't promptly controlled.

The impact and implications of prolonged use of amino acid-based formula on the children and families was beyond the scope of the manuscript, but deserves attention. Exclusive use of formula from infancy forestalls normal acquisition of oromotor skills, such that when food trials are proposed, the child may be developmentally unprepared to accept the new food, irrespective of its immunologic importance. Gagging, vomiting, and overt refusal confound the interpretation of immune tolerance. In addition, with prolonged use, many children simply refuse to drink enough formula to meet their nutritional requirements and thus require tube feeding.

The cost of elemental formulas is prohibitive for most families. The constant battle to obtain insurance compensation over insipid arguments posed by companies prepared only to preserve their fiscal security has forced families to engage media attention or legal representation, and has pushed many state legislatures to compel coverage. As evidence for the increasing problem of food protein hypersensitivity is published, perhaps the mainstream insurance community will withdraw its head from its bottom (line), formally recognize the importance of these conditions, and remove the barriers to immediate coverage.

On a final note, the term "multiple food allergies" seems somehow inadequate to describe all the affected patients along the spectrum of the disorder. It is intellectual impotence to name things for what they are not (eg, "non-IgE mediated food allergies"), but until the true nature of the defect is

understood, it may have to do. In keeping with current times, perhaps we could just call it “the Mother of All Food Allergies” until then.

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PRECOCIOUS PUBERTY: MCCUNE-ALBRIGHT SYNDROME AND BEYOND

As a rule, the first signs of puberty appear in girls between the ages of 8 and 11 years and in boys between 9 and 12. If signs of puberty appear at an earlier age, the pediatrician should consider the possibility of precocious puberty, should seek information about family history, and should consider referring the patient to a pediatric endocrinologist.^{1,2}

The age at menarche has not changed over the last several decades and is pegged at 12.6 years in white girls and 12.0 years in African American girls.¹ These long held views on the definition of puberty were called into question in a 1997 report by the Pediatric Research in Office Settings program in which 17,077 girls, 3 to 12 years of age, were evaluated for the age of onset of secondary sexual development. The authors concluded that girls “across the US are developing pubertal characteristics at a younger age than currently used norms.” The study focused on premature thelarche and premature adrenarche, both characterized by only one sign of puberty.³ On the basis of that single report, which was marred by ascertainment bias because the girls were self-referred, the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society stated, perhaps prematurely: “In most cases, evaluation of girls with early breast and/or pubic hair development to look for a pathologic etiology of precocious puberty need not be performed for white girls older than 7 years and African American girls older than 6 years of age”.⁴ Several endocrinologists warned that liberation of the definition of “normal” carries with it the risk of overlooking pathologic features,⁵ and the topic even made it onto the front page of *The New York Times*.⁶

In a very thorough recent study, Midyett et al asked the simple question: Are pubertal changes in girls before eight benign?⁷ They found that of 1570 6- to 8-year-old girls seen at their clinic in Kansas City during a 5-year period, 223 were

referred solely for signs of puberty. Indeed, 47.1% had true precocious puberty and 12.3% overall also had diagnoses of other treatable conditions, including congenital adrenal hyperplasia, growth hormone deficiency, hypothyroidism, hyperinsulinism, pituitary adenoma, neurofibromatosis and, yes, two girls had McCune-Albright syndrome. In 35% of the girls with precocious puberty, they found a bone age advancement of >3 SD, clearly indicating a markedly diminished growth potential for these girls had they gone untreated. Obesity was not a mitigating factor and equal attention should therefore be paid to obese and nonobese girls with signs of early pubertal development.

The inescapable conclusion of these findings is that signs of puberty in 6- to 8-year-old girls should not be considered normal or benign (16/25 patients with McCune-Albright syndrome in the study by Eugster et al were <8 years⁸). These children should be seen by a pediatric endocrinologist and have, at a minimum observation of statural growth, a physical examination and a bone age evaluation. True precocious puberty (characterized by breast and pubic hair development in girls, or testicular enlargement in boys) occurs in approximately 1 in 5000 children and is five to six times more common in girls than boys. In most affected girls (80–90%), but in only half of the affected boys, precocious puberty is gonadotropin-dependent and idiopathic in nature. Central nervous system tumors or lesions are much more common in boys. These CNS lesions may be hamartomas, pineal, dysgerminomas, and neurofibromatosis. Less commonly precocious puberty is gonadotropin independent and may include testotoxicosis (male limited with premature Leydig and germ

See related article, p 61.

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LHRH Luteinizing hormone-releasing hormone
