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Nutritional problems related to food allergy in childhood

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Food allergy is becoming an increasing problem worldwide with an estimated 6–8% of children affected at some point in their childhood. The perceived prevalence of food allergy is even higher with an estimated 20% of children adhering to some form of elimination diet. Against this background, accurate diagnosis is essential to prevent the imposition of unnecessarily restrictive diets on young children. Raising clinical awareness amongst health professionals as to the clinical characteristics, epidemiology, investigation, and management of food allergic disorders is key to tackling this growing problem. In this article, three separate cases of children with poor nutrition and secondary morbidity are presented, highlighting the varying scenarios in which these conditions can be encountered. In the first child, the features clinically displayed were hypocalcemic seizures and rickets due to prolonged breast feeding, poor weaning, and inadequate dietary supplementation. The second case reveals the dangers of complementary diagnostic allergy testing leading to poor nutrition as a consequence of an unsupervised elimination diet. The last report describes a child with multiple food allergies, failure to thrive, and protein losing enteropathy to highlight the diversity of nutritional problems faced by allergists and to underline the importance of specialist dietetic input in the management of a child with food allergy.

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Food allergy is becoming an increasing problem worldwide with an estimated 6–8% of children affected at some point in their childhood. The perceived prevalence of food allergy is even higher with an estimated 20% of children adhering to some form of elimination diet (1). The importance of good dietary intervention in children with single or multiple food allergies remains an essential part of their holistic care and should be seen as an integral part of the allergy consultation. To this end, the inclusion of a pediatric dietician readily available in clinic as part of the allergy team (2) to review both new and old patients remains crucial to the welfare of all children on elimination diets.

Case 1

A 10-month-old Asian boy was admitted to the wards with self-limiting generalized tonic-clonic seizures. He had been a full term delivery without complications and was entirely breast-fed from birth on an unrestricted maternal diet. He had suffered no prodromal illness and was developing normally. There was a history of him reacting to cow's milk formula at 4 months and yoghurt at 6 months with vomiting, urticaria, and facial swelling. His mother was advised to try goat's milk formula which provoked a similar reaction. While awaiting referral to a specialist allergy clinic his mother continued breast feeding and

restricted his intake of weaning foods to a limited number of fruits and vegetables only.

On examination his vital signs were normal. He measured on the 50th centile for height and head circumference, 25th centile for weight. He had mild atopic eczema affecting the face and extensor aspects of the limbs and slight thickening of his wrists. Examination of his abdomen revealed no distension or buttock wasting. His tone, power and reflexes were all within normal limits.

His full blood count on admission was as follows: hemoglobin 6 g/dl, mean cell volume 66 (fl), white cell count $6 \times 10^9/l$, and platelets $400 \times 10^9/l$. The bone biochemistry markers were revealing with a decreased corrected calcium of 1.2 (normal 2.25–2.6 mmol/l), phosphate 0.9 (normal 1.2–2.2 mmol/l), and an elevated alkaline phosphatase 2560 (normal 250–800 U/l). Serum electrolytes as well as other renal bloods and tubular markers along with glucose were all within normal range thus excluding possible hypoglycemia and making a diagnosis of Fanconi's anemia unlikely. The serum parathormone level was elevated and the vitamin D levels were diminished.

A diagnosis of seizures secondary to hypocalcemia was made with a concurrent diagnosis of clinical rickets and iron-deficiency anemia in a child with immediate hypersensitivity to cow's milk. The symptoms were directly attributable to the infant's nutritionally deficient and restricted diet, imposed as a consequence of maternal fears regarding the risk of further allergic reactions to weaning foods. The child's medical condition was treated with vitamin D, calcium, and iron supplementation with a good clinical response. Allergy testing confirmed his immediate hypersensitivity to cow's milk but revealed no new allergens. The family was seen by a pediatric dietitian and a nutritionally adequate weaning diet was started, which was adjusted as the child matured. As an alternative to breast and cow's milk, soya products were introduced. At the age of 3 yrs, he passed a hospital-based challenge test to cow's milk, which has since been included in his diet.

Discussion

The presentation of children with a clinical diagnosis of rickets is becoming increasingly common in the 21st century even in developed countries (3, 4) despite its pathophysiology being well understood (5) and prevention mechanisms being in place (6). Hypocalcemic seizures, although a less common presentation of dietary

deficiency, has been recorded in patients with nutritional vitamin D deficiency (7) and should be borne in mind when working up the causes of seizure activity, since it is easily rectified. This is especially important in the age group of the case presented since rickets is a disorder with a peak age of 3–18 months (8) and is more common in countries with limited sunshine, and in children with darkly pigmented skin. In exclusively breast-fed babies born to dark skinned mothers, the wearing of traditional modest dress may compound the lack of exposure to sunshine and is thus another potential risk factor for vitamin D deficiency.

Both vitamin D deficient rickets and calcium deficient rickets are well described separate entities and have been widely reported in the literature especially in children with cow's milk allergy, who are not receiving adequate supplementation (9–11). Rickets occurs in growing children and is due to failure to mineralize cartilage matrix known as osteoid (12). In older infants and toddlers it is thought to be primarily secondary to vitamin D deficiency. Vitamin D levels in breast milk vary between 20 and 60 IU/l (13) which is well below the recommended intake of 200 IU/l for all breast-fed and bottle fed infants (14). In-fact higher quantities of vitamin D might be required in those infants with darker skins due to the poor formation of vitamin D by the skin in this group. In the above case history, the failure to wean the child on to a follow-on formula at the age of 6 months and the poor variety of weaning solids led to the development of rickets and hypocalcemia.

Two studies have highlighted the importance of dietary calcium intake in the prevention of rickets in infants. DeLucia et al. showed in a series of 43 children in the United States that poor calcium intake was equally and in some case more consequential for the development of rickets than failure to ingest adequate quantities of vitamin D (15). Thacher et al. found that breast milk contained less calcium than matched-age controls in Nigerian children with nutritional rickets.

There is a strong correlation between anemia and vitamin D deficiency (16) and therefore if one is present lack of the other should be investigated and confirmed. It has also been shown that treatment with iron alone leads to rising levels of vitamin D suggesting that iron deficiency might be a factor in deficiency of vitamin D (12, 17).

In the management of an infant with cows milk allergy, breast feeding should ideally continue if tolerated, for as long as possible, under

the supervision of a dietitian to ensure nutritional adequacy with supplementation and weaning onto other solids from 6 months of age [World Health Organisation recommendation (18)]. Where breast-feeding is no longer an option, a number of alternatives exist.

Extensively hydrolyzed hypoallergenic formulae (eHF) are designed to be tolerated by 90% of infants with cows milk allergy due to the breakdown or hydrolysis of their nitrogen components into free amino acids and peptides < 1500 kD. These formulae, which can be either casein or whey based, are recommended as the first line choice of formula for most infants with cow's milk allergy. A number of those commonly used are listed in Table 1. For the small proportion of children who react to these eHF, an elemental formula comprising of pure synthetic amino acids can be utilized. This has been shown to be both safe and well tolerated in children with both immunoglobulin E (IgE) and non-IgE mediated cow's milk protein allergy (19–21) ensuring adequate growth.

An alternative to hypoallergenic formulae in infants over 6 months of age with immediate hypersensitivity to cows milk are the soya-based formulae. These are well tolerated by most children with IgE mediated cows milk allergy (86–92%) (23, 24) but are poorly tolerated by infants with non-IgE mediated cows milk allergy (up to 60%) (23). Recent studies have highlighted concerns surrounding a potential link between infant soya formulae and peanut allergy (25). Additional concerns surround the phyto-estrogen content of soya and its potential to induce Leydig cell failure in male marmosets (26, 27). Current UK Department of Health guidelines advise against the use of soya milk in infants under 6 months of age or in those infants not yet established on a weaning diet, with alternative sources of protein.

Other plant-based formulas, such as rice and oat milk exist, but the calorie and protein content in both are poor (rice milk 0.4 g/100 ml and oat milk 1.0 g/100 ml) compared with cow's milk-based infant formulae (1.9 g/100 ml) and there-

fore cannot be recommended for an infant solely on formula (28). Rice and oat milk may however be used as a suitable alternative to cows milk in older children with adequate growth on diets which are otherwise nutritionally sound.

Numerous mammalian milks including goat, mare, buffalo, and ewe are available, the majority of which cross-react with cow's milk protein (29, 30) and hence are not suitable for children with cow's milk protein allergy. However, camel's milk has been suggested as a possible substitute (in areas where supply is not an issue) as the milk protein is significantly different to that of cow's milk (29, 31). Importantly, it is also rich in minerals including iron, manganese, and selenium (32).

Case 2

A 5-yr-old girl is referred to the allergy clinic because of concerns regarding her highly restricted diet and poor weight gain. She had a past history of mild atopic eczema and was known to have reacted to eggs at 2 yr of age with rapid onset urticaria and vomiting. Most other foods including cow's milk, wheat, fish, and peanuts were previously tolerated. She currently had mild intermittent asthma. Six months previously, after undergoing allergy tests by an alternative practitioner (IgG testing and electrodermal (VEGA) testing), she was advised to exclude a wide variety of foods including dairy, eggs, gluten, beef, chicken, fish, citrus, tomatoes, and strawberries. She was advised to adhere to a rotational diet of permitted foods to minimize 'overloading her immune system.'

Although her mother felt that there may have been some initial improvement in her daughter's asthma, this was later thought to be less likely. Her daughter had found the diet difficult to adhere to and was now losing weight. She had not been referred or assessed by a pediatric dietitian.

Allergy testing showed detectable Specific IgE antibody (UniCAP System FEIA; Phadia, Inc., Uppsala, Sweden) to egg 0.8 KIU/l and house dust mite 10.6 KIU/l. There was no detectable IgE to cow's milk, wheat, peanut, tree nuts, soya, fish, shellfish, beef, sesame, grass pollen, moulds, cat, and dog. A hospital-based open food challenge test to cooked egg was negative.

All foods were reintroduced into her diet over the course of several weeks under dietician supervision with consequent regain in weight and general improvement in health. She was provided with a clear written asthma management plan detailing the use of inhaled β_2 agonist

Table 1. Alternative hypoallergenic formulas for those children with CMPA

Formula	Protein base	Type	Molecular weight (kD)	Recommended for CMPA
Nutramigen	Casein	eHF	<1200	Yes
Preigestimil	Casein	eHF	<1200	Yes
Pepti-Junior	Whey	eHF	<1500	Yes
Pepti	Whey	eHF	<1500	Yes
Neocate	Amino acids	Elemental	—	Yes

eHF, extensively hydrolyzed formula; CMPA, cow's milk protein allergy.

therapy and advice regarding house dust mite avoidance measures. She was later discharged from specialist follow-up.

Discussion

The use of alternative diagnostic allergy tests is widespread despite there being a lack of evidence to support the validity of these tests when evaluated within blinded randomized trials (Table 2) (33, 34). The institution of dietary restrictions as a consequence of these tests can impact on growth and nutrient intake as well as possibly endangering patients by misdiagnosis (35). Food allergy is widely misconceived by the general public as 20% alter their diet because of a perceived adverse reaction to food (36). When food allergy is defined as 'any immune response to food proteins' (37), it occurs in approximately 6–8% of young children and up to 4% of adults in developed countries (38). In a study by Senna et al. (39) looking at the accuracy of alternative diagnostic allergy tests compared with double blind placebo controlled food challenge (DBPCFC), only 1/87 patients had an agreement between the alternative test and DBPCFC. 79/87 patients did not have any food allergy as judged by skin prick test (SPT), and the remaining eight patients had proven food allergy that differed from those diagnosed by the alternative techniques. Sixty-six percent of patients referred with a suspicion of food allergy in their cohort had previously had at least one type of alternative/complementary allergy test. This high

percentage is unsurprising and would be similarly expected in the United Kingdom due to the paucity of allergy services available on the National Health Service (38).

Elimination diets are potentially hazardous in children, with cases of rickets, kwashiorkor, vitamin, and mineral deficiency being reported in the literature (35, 40). Children with two or more food allergies have been shown to be shorter and to consume less calcium and vitamins than those with one food allergy or age-matched controls (41). This effect was lessened if the child received dietetic support. It is essential therefore that an accurate diagnosis of food allergy is made by a physician with appropriate training, prior to the institution of a diet which eliminates proven allergens. The involvement of a registered dietitian should be mandatory to ensure that all the nutritional needs of a growing child are met.

Case 3

A 5-month-old male infant with severe atopic eczema from the age of 3 wk presented to the emergency department with a 2-wk history of worsening diarrhea and weight loss. He was established on both breast feeds and an extensively hydrolyzed formula but was failing to thrive. His mother described him as being irritable with constant back arching, crying, itching, and disturbed sleep. His development was normal. The family history was positive for atopy in both parents.

Table 2. Alternative/complementary techniques in diagnosing food allergy (39, 40)

Alternative diagnostic test	Explanation
Specific IgG antibodies	The measurement of IgG subclasses and their ratios as a diagnostic tool in evaluating the presence of allergy
Hair analysis	Analysis of hair sample to determine presence or absence of allergy and provide individualized treatment advice
Cytotoxic test	Numerous variations exist, but essentially involves the application of a blood sample to panels of food antigens which is reviewed under a microscope for changes in the morphology of leukocytes
Electrodermal test (VEGA)	A negative electrode is held by the patient, and the positive electrode is applied to various acupuncture points. The allergen is placed in a glass vial and placed in the circuit. A drop in skin conductance as measured by a galvanometer indicates allergy
Applied kinesiology	The arms are held out perpendicular to the body, one hand contains the allergen in a glass vial; light pressure is placed on the contralateral arm. Any weakness indicates allergy
Iridology	Specific changes in the iris are meant to reflect pathologic processes in the different systems of the body
Provocation-neutralization	Sublingual or intradermal provocation with an allergen monitored for 10 min for a wheal or any effect on the body. If a response occurs a different dose of antigen is given to neutralize the allergen
Pulse test	Additional to provocation-neutralization or used alone, a change in the pulse by 16 beats per minute indicates allergy. Delayed reactions are monitored by waiting 2–3 h after the provocation to see if the pulse changes

On examination his weight was below the 0.4th centile, height 25th centile, and head circumference 25–50th centile. His vital signs were within normal limits but he appeared wasted, miserable, itchy, and lethargic and was clinically 5% dehydrated. He had marked periorbital and peripherical edema with generalized lymphadenopathy. He had widespread, severe eczematous inflammation of the skin. There was no abdominal distension, visceromegaly, or ascites and the perianal margins were normal.

Investigations revealed: Na 125 mmol/l, K 5.0 mmol/l, chloride 113 (normal 96–110 mmol/l), urea 8 (normal 2.5–6.5 mmol/l), creatinine 101 (normal 20–65 µmol/l), glucose 0.2 (normal 2.6–5.0 mmol/l), albumin 26 (normal 35–55 g/l), total protein 48 g/l, alkaline phosphatase 129 U/l, C-reactive protein 20, Hb 14.1 g/dl, WCC $33 \times 10^9/l$, Neuts $30 \times 10^9/l$, and platelets $407 \times 10^9/l$. All cultures (blood, urine, stool and cerebrospinal fluid) were negative although *Staphylococcus aureus* was isolated from a skin swab. An allergy screen showed detectable Specific IgE to: cows milk 45.3 KIu/l, egg white 41.4 KIu/l, soya 4.23 KIu/l, cod 5.26 KIu/l, wheat 9.37 KIu/l, peanut 50 KIu/l, and sesame 31.4 KIu/l.

The infant was hospitalized and rehydrated with saline, 4.5% albumin, and glucose and started on broad spectrum intravenous antibiotics. Treatment of the eczema was optimized with emollient therapy, a moderately potent topical steroid and antihistamines. A diagnosis of severe eczema in association with multiple food allergy and protein losing enteropathy was made. Once stabilized, feeding with an amino acid formula (Neocate®, Nutricia UK, White Horse Business PK, trow bridge, Wilts BA140XQ) was commenced. His mother was carefully counseled regarding the option of continuing to breast feed while eliminating suspected allergens from her nursing diet and supplementing her diet with calcium.

Over the next few days, he improved with resolution of edema, improvement in weight gain, a reduction in stool frequency and gradual clearance of the eczema. Breast feeding was discontinued after the first week as his mother found the elimination diet too difficult to adhere too. Under the supervision of a pediatric dietitian, a nutritionally balanced weaning diet was commenced at 6 months with the exclusion of all suspected allergens and inclusion of vegetables, fruits, wheat-free grains, and meats. A hospital-based open oral food challenge test to wheat at 15 months produced an immediate reaction with urticaria and angioedema. He tolerated fish

during a challenge 2 wk later and fish is now an additional protein source within his restricted diet. He remains under close follow-up by the pediatric allergy team and further oral food provocation tests are planned. He continues to thrive with a normal stool pattern and is free of eczema.

Discussion

The presentation of children with possible multiple food allergies always presents a diagnostic challenge and consequent difficulty in ensuring that a nutritionally adequate diet is followed. This is exacerbated where the presenting pathology is a mixture of IgE mediated and non-IgE mediated disease especially in young children where the consequences of poor nutrition can be life long (42).

In children with atopic eczema, food proteins are capable of producing both immediate (IgE mediated) and delayed (non-IgE mediated) responses. Studies utilizing the DBPCFC test have shown that IgE mediated food allergy affects 35–56% of children with moderate to severe eczema leading to reactions in the skin, gut, and respiratory tract (41, 43–46), and that there is a positive correlation with disease severity and young age (47). There is remarkable consistency amongst studies as to the foods most commonly implicated with the majority citing cow's milk, hen's egg, and peanut as causing IgE mediated reactions most frequently. In a series of studies by Sampson et al. 90% of immediate reactions were due to eight foods (cows milk, hens egg, peanut, tree nuts, wheat, soya, fish, and shellfish) (41, 43). In recent years, allergy to kiwi and sesame are becoming increasingly recognized both in the UK and USA (48). In studies looking at delayed responses to foods in children with eczema, up to one half developed delayed reactions in the skin and gut following on from the immediate response during challenge testing (49–51). Isolated delayed responses occurred in only 12% of challenge tests (49, 50).

In infancy, food proteins may be encountered directly through oral consumption or indirectly via either transmission in breast milk or through inhalational or epicutaneous skin contact (52, 53). In the recent EPAAC study, (Early Prevention of Asthma and Allergy in Childhood) 46% of infants aged 1–2 yr with eczema had detectable specific IgE to milk, egg, or peanut. Differentiating those infants who are sensitized but tolerant from those infants who are sensitized and allergic presents an important clinical challenge. There does however appear to be a direct

correlation between the level of food specific IgE (serum IgE concentration or SPT wheal size) and the probability of a clinical reaction to that food if ingested with previously defined threshold values for reactivity to certain foods in individual populations (54, 55).

The gastrointestinal manifestations of food allergy are varied with well described clinical entities being recognized (Table 3) (56). Protein losing enteropathy is a feature of both non-IgE mediated allergic enteropathy disorders as well as of the eosinophilic gastroenteritis disorders (mixed IgE and non-IgE). In food protein induced enteropathy, the infant usually presents with protracted diarrhea in the first 9 months with up to half suffering vomiting and failure to thrive. Blood loss in the stools is typically absent. Iron deficiency anemia is common and hypoproteinemia occurs in 35–50% (56). Serum specific IgE is rarely detected and response to an elimination diet is usually good with resolution within 2–3 yr. In eosinophilic gastroenteritis predominant symptoms include vomiting, diarrhea, blood loss in stools, growth retardation, protein losing enteropathy, and growth failure. Serum specific IgE is present in approximately 50% (57). Response to an elimination diet is variable. The diagnosis is confirmed histologically following endoscopy and biopsy.

This patient presents with a mixed picture having eczema, detectable specific IgE to multiple foods, protein losing enteropathy, growth failure, diarrhea without blood loss, vomiting, and iron deficiency anemia. In addition, he was edematous secondary to hypoalbuminemia. He responded well to elimination of the offending dietary proteins and thus never went on to have a histologic diagnosis. Subsequently, he reacted in a typical IgE mediated hypersensitivity fashion to wheat. The spectrum of multiple food allergy, severe eczema, irritability, vomiting, and failure to thrive has previously been termed 'Multiple Food Protein Intolerance' by some authors (58). One of the cardinal features of this spectrum is a failure to tolerate extensively hydrolyzed formula

or soya-based formula. These infants may react to a wide range of foods including transmitted proteins within breast milk and other foods normally considered of 'low allergenic potential.' Most infants tolerate the subsequent introduction of foods over the next few years but may retain IgE hypersensitivity to certain foods such as nuts, sesame or fish.

The case highlights the need to consider both IgE and non-IgE mediated hypersensitivity reactions to individual food proteins within the same patient. It also illustrates the overlap between eosinophilic gastroenteritis disorders and the dietary protein induced syndromes as a continuum of eosinophil associated disorders that might be closely related with similar underlying immunopathogenic mechanisms (57).

Removal of the causal proteins remains the mainstay of treatment. This should be carried out under close dietetic supervision. An amino acid formula is the formula of choice as up to 10% of these infants will react to the extensively hydrolyzed casein or whey formulae with persistence of symptoms (19–22). Alteration of the maternal diet of breast-fed infants may lead to clinical improvement in some but not all infants but may impact on both maternal and hence infant nutrition and growth. Resolution of clinical symptoms should occur within 1–3 wk. Failure to do so should prompt urgent referral for endoscopy and biopsy.

A clear strategy regarding allergy re-assessment, testing, and challenge needs to be implemented with close follow-up and dietary supervision. The dietary recommendations need to be tailored to the individual child taking into account the overall nutritional requirements, the risk of reaction on re-exposure and natural history of the specific food allergy in question as regards the likelihood of persistence vs. outgrowing. The timing of challenges will depend on the clinical history, type of food allergen, and demonstration of declining specific IgE tests.

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Table 3. IgE-mediated and non-IgE mediated allergic diseases

	Ig-E Mediated	Non-IgE Mediated
Skin	Urticaria	Atopic eczema dermatitis syndrome
Gastrointestinal	Gut anaphylaxis	Enteropathy
	Oral Allergy syndrome	Enterocolitis syndrome (FPIES)
	Eosinophilic gastroenteritis	Allergic Proctocolitis
		Eosinophilic gastroenteritis
Respiratory	Asthma	Heiner syndrome
	Rhinitis	

FPIES, food protein induced enterocolitis syndrome.

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