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REVIEW ARTICLE

Food Allergy in Children: An Overview

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Abstract The estimated prevalence of food allergy amongst children in the west is around 6–8% but there is paucity of data in the Indian population. There is a complex interplay of environmental influences and genetic factors in the immunopathogenesis and manifestations of food allergy. A reliable thorough clinical history, combined with positive skin prick tests or food-specific IgE, is essential for a more precise diagnosis of food allergy. Currently there is no cure for food allergy. The management of food allergy usually includes strict avoidance, patient education and provision of emergency medication (adrenaline-autoinjectors). Emerging therapies based on evolving research are focused on a more active approach to management which includes early introduction of potentially allergenic foods, anticipatory testing and desensitisation to food allergens. Lack of food labelling policy and non availability of adrenaline auto-injectors is a huge limiting factor for effective management of food allergy among children in India. The present review focuses on IgE mediated food allergy.

Keywords Food allergy · Children · Diet · Anaphylaxis · Food labelling · Adrenaline auto-injectors

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'What is Food Allergy?'

The term 'food allergy' refers to 'a specific immune response that occurs reproducibly on exposure to a given food'. These immune responses can be IgE mediated (type 1 hypersensitivity), non-IgE mediated (cell mediated reactions) or a combination of both [1].

Food intolerances are non-immune reactions. These may occur in response to exposure to metabolic substances (lactose intolerance), toxins (microbial contamination or scombroid fish poisoning), pharmacologically active components (caffeine, tyramine in aged cheese triggering migraine) *via* undefined mechanisms. Non-IgE mediated food allergy is commonly misinterpreted as food intolerance [1].

Prevalence in Asia / India

The prevalence of food allergy in Asia is perceived to be low. However, there is a paucity of data regarding the prevalence of food allergy in the Indian population, particularly in children. Current studies have tended to utilise patient or parent-reported questionnaires and are likely to overestimate prevalence [2]. The recent EuroPrevall-INCO study estimated the prevalence of food allergy among adults in southern India at 1.2 % with cow's milk accounting for 0.5% and apple 0.5%. Data on the prevalence of food allergies in children from this study is awaited [3]. Similar studies have found the prevalence of food allergy in children at 4-5% in Singapore, 10.9% in Korea, 4.98% in north-east China and as high as 12.6% in Japan [4–7]. In China, food allergy prevalence has increased significantly in the 10 y period from 3.5% in 1999 to 7.75% in 2009 [8]. It is expected that with further increasing urbanisation, development and affluence, the prevalence of food allergy in Asia, including India will increase similar to the

observed rise in asthma prevalence, mirroring that of the western world [9–12].

Prevalence in the West

The estimated prevalence of food allergy amongst children in UK, Canada and US is around 6–8% [13–17]. In Australia, challenge proven IgE-mediated food allergy affects up to 10% of 1-y-old children [18]. Overall, current studies estimate a prevalence for food allergy of 5% adults and 8% children [1]. A three-fold increase in the prevalence of peanut and tree nut allergy was observed in UK and US between 1997 and 2008, whilst Australia has seen a 10-fold increase in specialist referrals for food allergy and five-fold increase in hospital referrals for food-related anaphylaxis [19].

'Major Allergens'

Any food protein can potentially trigger an allergic reaction. 'Major allergens' most commonly responsible for significant reactions include milk, egg, peanut, tree nuts, shellfish, fish, wheat and soya [20]. In India, chickpea (Cicerarietinum) is a common allergen as it is consumed in various forms including boiled, roasted and flour [21]. Anaphylaxis to chickpea has been reported [22].

Risk Factors

Food allergy is more common among males in childhood. There is recent evidence of ethnic variations in skin and respiratory allergy and that patterns of sensitisation to foods differ among ethnic groups within the same geographic population, with such sensitisation being more common in non-white minorities in the United States. However, there is also evidence that food allergy in North America is more prevalent in white than non-white groups. But the increase in food allergies over a 10 y period (based on hospital discharge diagnosis) was three-fold higher in non-white groups [23–26].

Vitamin D insufficiency, dietary factors such as reduced consumption of omega-3-polyunsaturated fatty acids, antioxidants and obesity (inflammatory state) have also been associated with an increased risk of food allergy. Use of antacids reduces digestion of allergens resulting in exposure to more intact protein. Co-existent atopy (atopic dermatitis, asthma), increased hygiene and reduced exposure to infections may increase risk of food allergy [20, 27–30].

Breakdown of skin barrier integrity as in atopic dermatitis and delay in introduction of potentially allergenic food in infants allows for exposure of food and environmental allergens through the cutaneous route which may increase topical sensitisation, thus evading oral tolerance. Earlier onset and greater severity of eczema in infants, increases the risk of food allergy [31]. In addition, skin barrier impairment (as measured by transepidermal water loss) in the neonatal period predicts food allergy at 2 y of age [32]. This clearly illustrates that the route of sensitisation in IgE mediated food allergy is cutaneous, while early-life ingestion of foods like peanut can be protective [33]. These risk factors provide possible avenues for food allergy prevention.

Environment

The changing natural history and disease profile of allergic disease in children may be partly due to a complex gene-environment interaction whereby allergenic propensity may be modified or amplified across generations through epigenetic effects which can induce heritable changes in gene expression. Epigenetics may be thought of as the 'bridge' between genotype and phenotype due to an event that changes the final outcome of a locus or chromosome without altering the underlying DNA sequence [19].

Epithelial barrier dysfunction due to filaggrin (FLG) loss-of-function mutations are associated with peanut allergy where skin exposure may be the sensitising route. Cigarette smoke and increased exposure to inhaled pollutants due to a rise in traffic and urbanisation are associated with increase in allergenic propensity [19].

Immuno-Pathogenesis and Oral Tolerance Induction

The gastrointestinal tract is comprised of single layer of columnar epithelial cells and separates the internal sterile environment from the external world [20]. 'The gastrointestinal mucosal barrier' consists of physiological and immunological components. The immunological component consists of innate (neutrophils, macrophages, natural killer cells, epithelial cells and toll like receptors) and adaptive (intra-epithelial lymphocytes, peyers patches, secretary IgA and cytokines) responses. Developmental immaturity of the gut barrier and immune system in infants and young children may have a role in the increased prevalence of allergy seen in the first few years of life [20, 34]. The mucosal immune system encounters enormous quantities of antigen and must supress immune reactivity to food proteins in order to develop tolerance [19]. The antigen presenting cells (intestinal epithelial cells and dendritic cells) and T regulatory cells (through the production of TGF-beta and IL-10) play a vital role in the development of oral tolerance [34].

The IgE mediated hypersensitivity response occurs due to a TH2 biased immune response. Intestinal epithelial cells and gut dendritic cells process the luminal antigen and present it to

T cells on a MHC class II complex. TH2 cells produce IL-4, IL-5 and IL-13 which then stimulate B cells to produce specific IgE to the food protein. This binds to mast cells to cause sensitisation initially. Subsequent exposure may trigger clinical symptoms as food protein cross links the specific IgE on the mast cells, releasing specific mediators [20].

Oral Allergy Syndrome (OAS)/Pollen-Food Allergy Syndrome (PFAS)

Respiratory sensitisation to Bet V1 in birch pollen may lead to oral pruritus when eating raw apples amongst numerous other foods due to cross reactivity to homologous apple protein mal d 1. This represents an example of how oral tolerance is bypassed due to sensitisation *via* the respiratory route. Primary IgE mediated food allergy have symptoms usually in early infancy whilst OAS develops later [20, 35].

Natural History - Do Children Grow Out of Food Allergy?

Allergy to cow's milk, egg, wheat and soya typically resolves during childhood. However, there is recent evidence to suggest that resolution rates have slowed. In contrast, allergy to peanut, tree nuts, fish, shell fish and sesame tend to persist lifelong and rarely resolve [1, 36]. Prognosis is influenced by the disorder, for example, non-IgE mediated cow's milk allergy has a better outcome than IgE mediated disease. Higher food-specific IgE levels at diagnosis also appear to indicate likely persistence and a decrease in their values over time may signal resolution, indicating future tolerance [1, 37]. Additional studies combing clinical and laboratory information may provide long term prognostic information to guide clinicians in the future [1]. Although the proportion of children that outgrow food allergy to specific foods varies between studies, around 50–60% of children with milk and egg allergy demonstrate tolerance by school age [1, 38].

Diagnosis of Food Allergy

Initial evaluation requires a thorough allergy focused history. This should determine probable causal foods (raw or cooked), time course of reaction including symptoms, consistency of the reaction, quantity ingested, and other factors (exercise, medications and intercurrent illness) [20]. IgE mediated food allergy are of acute onset (within 2 h of exposure) and the presenting symptoms are often skin, respiratory and gastrointestinal, whereas non-IgE mediated food allergy has a delayed onset (usually 1 to 24 h) of symptoms. This will help to determine the likely immunological mechanism (IgE mediated/

non-IgE mediated), estimate the probability of allergic reaction to the specific food and guide targeted allergy testing [skin prick tests (SPT) or food-specific IgE]. In cases where there is diagnostic uncertainty, oral food challenge remains the gold standard [usually open but double blind placebo controlled food challenge (DBPCFC) is preferred] [36]. A reliable history in combination with positive SPT or specific IgE is required for diagnosis of IgE mediated food allergy. These tests in isolation without a supporting clinical history cannot be used for definitive diagnosis of food allergy [36]. A positive allergy test (SPT or food-specific IgE) alone signifies sensitisation and not allergy. Increasing SPT wheal size or concentration of food-specific IgE levels correlate with increased likelihood of IgE mediated clinical allergy but generally do not correlate well with reaction severity. There is no role for SPT or food-specific IgE levels in the diagnosis of non IgE mediated food allergy [20, 39, 40].

Recent development and introduction of component resolved diagnostics involves measurement of specific IgE levels to individual component proteins that make up the allergenic food. These tests may more reliably differentiate between sensitisation without clinical allergy and clinically relevant food allergy, effectively reducing the need for food challenges. The most convincing data for these techniques is from peanut components, although more studies are needed to confirm this [36].

Use of total serum IgE measurements, intradermal tests, patch tests and basophil activation tests are not recommended. Use of unproven tests such as serum allergen specific IgG4 measurements, hair analysis, iridology, applied kinesiology and electrodermal vega testing should be discouraged.

Management

Currently there is no cure for food allergy. Traditionally, the approach includes strict avoidance of the offending food, patient and family education (including recognition of an allergic reaction) and provision of families with patient specific emergency medications (adrenaline auto-injectors) and management plans in the event of an allergic reaction [36]. Careful attention to food label reading, care when obtaining food from restaurants, avoidance of cross-contact of allergenic foods during meal preparation (shared cutting boards, slicers, mixers) is necessary [20].

The lack of a comprehensive food labelling policy for at least the most common allergens within packaged foods and non-availability of adrenaline auto-injectors is a huge limiting factor in India. Increased awareness about food allergy among healthcare professionals, schools and the community is a priority in order to provide effective management of food allergy in India.

Adoption of a 'more active approach' in the management of food allergy is an emerging concept which is based upon evolving research [36]. This includes: a) Early dietary introduction of potentially allergenic foods; b) Active anticipatory testing for related allergens once a specific food allergy is identified; and c) Newer strategies.

Early Dietary Food Introduction

Early dietary introduction of potentially allergenic foods may prevent the development of food allergy. This is supported by various recent studies which have shown that early exposure to cow's milk, egg and peanuts may be protective against the development of IgE mediated allergy to these foods [33, 36, 41–44].

Most recent systematic review and meta-analysis [including the results of interventional studies such as LEAP (Learning Early About Peanuts) and EAT (Enquiring About Tolerence) in the United Kingdom] by Lerodiakonou et al. found moderate-certainty evidence that early introduction of egg (from 4 to 6 mo) or peanut (from 4 to 11 mo) to infants was associated with reduced risk of egg and peanut allergy respectively, which will help provide more definitive guidance on early introduction of potentially allergenic foods in infants [45]. Advice around early introduction of peanut in high risk children has already been issued in the United States.

Active Anticipatory Testing

In addition to testing for the suspected allergen, recent guidelines recommend testing for co-allergens (allergen commonly found to be present in association with the suspected allergen). For *example*, in children with peanut allergy, testing for tree nuts and sesame is recommended as the estimated rate of co-allergy is 30–40% and 25% respectively [36, 41, 46, 47]. This anticipatory approach has the potential advantages of avoiding unnecessary restrictions in the diet of children, avoiding allergic reactions in the community and preventing development of allergy to co-allergens by facilitating early introduction [36].

Newer Strategies

Newer strategies that are aimed to help develop tolerance to allergenic foods more quickly have emerged recently. These include:

1) Early introduction of baked forms of milk and egg if tolerated in children with cow's milk and egg allergies.
2) Desensitisation to food allergens.
3) Use of probiotics in infants with cow's milk allergy.

Early Introduction of Baked Milk/Egg

There is evidence now in the literature that 70–75% of children with cow's milk and egg allergies can tolerate them when extensively heated. This could potentially make dietary restrictions easier and hasten the development of tolerance, although it remains difficult to predict which children will tolerate baked allergens [36, 48–50].

Desensitisation - Oral Immunotherapy (OIT)

Food OIT (concentrated on cow's milk, egg and peanut) is an area of intensive research and represents an exciting and potentially disease modifying treatment which is expected to evolve in the future [36]. Food OIT involves administration of small but increasing doses of allergenic food to children who are allergic to that particular food in an effort to increase their clinical tolerance [36]. It is not yet recommended for routine clinical use and should not be attempted outside specialist allergy units [36].

Probiotics

Another emerging area of interest has been the potential role of probiotics in management of cow's milk allergy. Supplementation of extensively hydrolysed casein formula with Lactobacillus GG has been shown to accelerate the development of tolerance in infants with cow's milk allergy. Further prospective trials are currently in progress [36, 51, 52].

Conclusions

There is a paucity of data on food allergy in Indian children. A reliable thorough clinical history, combined with targeted allergy testing (SPT or food-specific IgE) is essential for diagnosis of IgE mediated food allergy in children. In cases of diagnostic uncertainty oral food challenge (DBPCFC) is the gold standard investigation. An active approach to the management of food allergies has advantages to the families and children with food allergy including the possibility of inducing tolerance and significant improvement in the quality of life. Food immunotherapy is an emerging area of considerable interest and research and is expected to evolve soon. Lack of food labelling policy and non-availability of adrenaline auto-injectors is a huge limiting factor for effective management of food allergies among children in India.

Compliance with Ethical Standards

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