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THE DIAGNOSIS AND MANAGEMENT OF FOOD ALLERGY IN CHILDHOOD

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Food allergy has reached epidemic proportions in developed countries over the past few decades for reasons not well understood. With the growing disease burden and the need to improve food allergy diagnosis, better diagnostics tools such as component resolved diagnostics (CRD) have been introduced for clinical use. Still, oral food challenges remain the gold standard tool for establishing food allergy diagnosis. Current food allergy management strategies rely on avoidance of the culprit allergen. Inspired by the success of specific immunotherapy in inhalant allergy, the past decade has been marked by increasing international effort to find curative treatments. The results from several clinical trials, examining success of allergen-specific immunotherapy in food allergy, have recently become available and are discussed within this review article. **Conclusion** – The results from these clinical trials promise new curative therapies for food allergy sufferers in the near future. Moreover, several ongoing interventional studies looking into early- life introduction of allergenic foods could provide us with specific answers on future primary prevention strategies.

Key words: Food allergy ▪ Childhood ▪ Diagnosis ▪ Treatment ▪ Allergen-specific immunotherapy.

Introduction

The prevalence of both self-reported and clinically diagnosed food allergy has increased in developed countries over the short period of time (1, 2). Food allergy has reached epidemic proportions in developed parts of the world (1) with up to 20 million European citizens suffering from food allergy (3) and reports of increasing prevalence in developing countries (4).

Following the International Study of Asthma and Allergy Survey (ISAAC) which recorded a global increase in prevalence of asthma, rhinitis and eczema some 2 decades ago (5), a "second wave" of allergy epidemic in the form of increasing prevalence of food allergy has been noted (6). The reasons for such an increase are not very well understood.

Definition

Food allergy is characterised by reproducible immunological response on repeated exposure to offending allergen. Depending on the immunological mechanism involved, it can be divided into either IgE mediated or non-IgE mediated food allergy (1). The current review will only focus on IgE mediated food allergy in childhood.

IgE mediated food allergic reaction is defined as an acute onset of symptoms usually within minutes to up to 2 hours following ingestion of offending food (1). The primary mechanism of reaction is through synthesis of food specific IgE antibodies that bind to FcεRI surface receptors found on mast cells and basophils. The re-exposure to the food leads to antigen-antibody cross linking on the surface of mast cell or basophils (1). This triggers a cascade of intracellular events, resulting in release of pre-formed mediators, such as histamine and proteases (tryptase) and formation of the new mediators (cytokines and eicosanoids). The distribution of the mast cells in the tissue such as skin and mucosal surfaces is one of the main reasons that symptoms of allergic reaction to food predominantly involve skin, gastrointestinal and respiratory systems.

Epidemiology

The estimated worldwide prevalence of food allergy varies according to age with 3-8% reported prevalence among children and 1-3% among the adults (7). Unsurprisingly, food allergy is a leading cause of anaphylaxis seen in emergency departments across the USA and UK (8, 9) and is the most common reason for anaphylaxis in the paediatric age group (10).

Several factors such as geographical region, the age of children studied, the level of evidence used to establish food allergy diagnosis, have influence on the reported prevalence figures (2). The global survey on prevalence of food allergy conducted among 89 countries in 2012 by the World Allergy Organisation highlighted the issue of lack of comparative data on food allergy prevalence between different countries, with 51 countries missing data of any kind (2). The data provided in this survey was categorised into three categories depending on the level of evidence that was provided; the highest level of evidence was based on oral food challenge (OFC) confirmed food allergy in an unselected population, the second best level of evidence was based on suggestive clinical history, with positive result to culprit allergen on skin prick test (SPT) or food-specific IgE (sIgE). The lowest level evidence was considered if the food allergy prevalence was based on parental self-report (questionnaire) (2). There was a great variation in food allergy prevalence between regions with highest prevalence noted in North America and Western Europe compared to the rest of the world. Using the OFC as a most stringent criterion for diagnosing food allergy, the prevalence of food allergy in pre-school children (< 5 years) was higher in developed countries such as Australia, Norway, UK, and Denmark, (10%, 6.8%, 4% and 3.8%, respectively) (2). Interestingly, most recent data from industrialised part of China show that rates of OFC confirmed food allergy among pre-schoolers are similar to those reported for developed countries (2). Although in this survey food allergy was confirmed to be less common among school-age children (>5 years) than among pre-schoolers (<5 years), still significantly more school-age children in the UK have had OFC proven food allergy than e.g. school-aged children in Turkey (2.5% vs. 0.16%, respectively) (2).

In countries like Australia food allergy has reached epidemic proportions with up to 10% of less than 5 year old children having confirmed food allergy (2). Allergy to cow's milk, hen's egg, peanut, tree nuts, wheat, soybean, fish and shellfish account for the majority of food allergic reactions seen during the childhood. Worldwide the most common food allergens during childhood are cow's milk and hen's egg, and in countries like the UK, USA and Australia peanut and tree nut allergy are frequent (1). Allergy to cow's milk

and hen's egg tend to be outgrown during early childhood, unlike allergy to peanuts or tree nuts (1).

Symptoms and diagnosis

Symptoms

In general, symptoms and severity of food allergy can vary between subjects and between episodes depending on several factors such as age, route of exposure to allergen, the amount of allergen consumed, food processing methods used during preparation of food, presence of other allergic disease, concomitant infection, or presence of factors which increase gastrointestinal absorption of the food (exercise, intake of non-steroidal inflammatory drugs) (1).

The most common symptoms of food allergy involve skin (urticaria, angioedema, itching, morbiliform rash, erythema), gastrointestinal (nausea, vomiting, abdominal pain, diarrhoea) and respiratory system (acute rhinoconjunctivitis, wheezing, coughing, stridor) with the most severe presentation in the form of anaphylaxis (1). In young children food allergy can present as a food aversion due to underlying symptoms of lip tingling, abdominal pain or nausea, which non-verbal child cannot express. In very young children severe reactions can present as paleness and floppiness due to underlying cardiovascular compromise (11). Depending on the child's age, irritability, reduced activity or sudden change in behaviour, can be one of the first manifestations of developing a reaction and therefore detailed history taking during assessment and, in acute circumstances, careful observation is paramount.

Diagnosis

Diagnosis of food allergy is based on the detailed history of allergic reaction and its relatedness to the consumption of suspected food (1). The findings on the physical examination depend on its proximity to the allergic reaction. In the majority of cases physical examination will be completely normal, as children will usually present to the paediatrician or paediatric allergist after the resolution of acute symptoms. The exceptions are children who suffer with other atopic comorbidities, such as eczema or asthma.

The correct diagnosis is usually made on basis of combination of clinical history and presence of allergen-specific IgE antibodies by either SPT or detection of serum allergen-specific IgE (sIgE) antibodies by immunoassay (eg. ImmunoCAP, Phadia, ThermoFisher Scientific, Sweden). Although the presence of positive skin prick test response or detection of serum sIgE antibodies does not always accurately predict if the child has an allergy, generally the likelihood of clinical allergy correlates with the size of the SPT weal and the level of sIgE (11-13). If indicated, as in cases where there is no clear history of allergic reaction on exposure to suspect food, OFC are considered a gold standard for diagnosing food allergy(1, 12). However, in some children performing OFC is associated with a higher risk of causing anaphylaxis and in these cases OFC is best avoided. Under such circumstances, using 95% positive predictive value (95% PPV) thresholds for SPT or sIgE to offending allergen can be used to predict whether a child has a clinical allergy(14).

The reported PPV values for both SPT and sIgE vary between studies due to differences in age of children studied, PPV significance value, challenge method and prevalence of food allergy to specified allergen among study population(11). In a population-based HealthNuts study of several thousand one year-old children in Australia, researchers assessed children with positive SPT and sIgE results to four common food allergens and compared it to the outcome of their OFC (14). Children and their parents

were approached to undergo SPTs and give a blood sample for measurement of sIgEs to egg, peanut, sesame seed and cow's milk or shrimp during their routine immunisation in primary care. Children who had positive results on either SPT or sIgE underwent OFC to suspect allergen and the results were compared to calculate the accuracy of each test in predicting clinical allergy by determining 95% PPV thresholds for each food allergen. For SPT results the 95% PPV threshold for egg was 4 mm, peanut 8 mm, and sesame 8 mm. For baked egg challenges 82% PPV was determined as 11 mm. Similarly, 95% PPV for sIgE to peanut was 34 kU_A/L and for egg 1.7 kU_A/L. For other allergens the 95% PPV could not be determined. The HealthNuts study is ongoing and it will be interesting to observe any change in these values, as children may be outgrowing their food allergy by the age 6 years follow up.

In the instance of confirmed childhood food allergy to hen's egg, baseline sIgE can be a good predictor of resolution of clinical allergy (15). Of 512 infants recruited into a multicentre study in USA diagnosed with hen's egg allergy and/or atopic eczema with positive SPT to egg, absence of systemic symptoms and having egg sIgE <10 kU_A/L at presentation were the greatest predictors of resolution of egg allergy by the age of 6 years (15).

However, the results of SPT or sIgE always need to be interpreted in the light of clinical history as many children with detectable sIgE levels are tolerant to a food in question(16). The false positive results can occur because sIgE reagents, based on crude allergen extracts, contain non-allergenic molecules that are homologous with inhalant allergens and can cross react with food allergen extracts. Recent advancements in molecular allergy have enabled better understanding of the relationship between allergen sensitisation patterns and clinical presentations. In our landmark study set within MAAS birth-cohort (Manchester Asthma and Allergy Study), we have previously shown that the level of sIgE to crude peanut extract is a poor predictor of peanut allergy, as almost 80% of 8-10 year old children who tested positive to peanut sIgE (sIgE ≥ 0.2 IgE kU_A/l) were confirmed peanut tolerant on oral peanut challenge(16). Using component resolved diagnostics tool we have shown that sensitisation to *Ara h 2 (Arachis hypogaea)* peanut component was the best indicator of peanut allergy, correctly discriminating between peanut allergy vs peanut tolerance in 92.6% of cases. The discriminative power of *Ara h 2* was not improved with the use of additional clinical information such as gender, personal and familial history of atopic disease.

The components are increasingly used for assessment of a patient's risk in terms of exposure to food allergen. For instance, major peanut components *Ara h 1, 2 and 3 are* associated with peanut allergy (16), whilst *Ara h 8* and *Ara h 9* components indicate primary sensitisation to pollen allergens. Components have also been useful in predicting a risk of clinical reactivity among hazelnut sensitised subjects, with those sensitised to *Cor a 9* (*Corylus avellana*) and *Cor a 14* hazelnut components, having a higher risk of systemic reactions than those sensitised to *Cor a 1* and *Cor a 8* (17).

Likewise, sensitisation to an egg white allergen ovomucoid -*Gal d 1(Gallus domesticus)* is associated with reactivity to baked egg and higher risk of persistence of egg allergy (18). This is thought to be related to the presence of disulfide bonds that stabilise ovomucoid and increase its heat resistance (18). Moreover, serial decline in *Gal d 1* levels recorded over the period of time can be a useful guide on whether to assess the development of tolerance by performing an oral food challenge. On the contrary, sensitisation to a major egg white allergen ovalbumin (*Gal d 2*) is associated with tolerance to baked egg due to

its heat-induced loss of IgE- binding epitopes(18).

Children who are sensitised to *Gal d 1* and reactive to both boiled and raw egg, are more likely to be sensitised to multiple other foods (e.g. cow's milk) and inhalant allergens (e.g grass pollen), compared to children who are not sensitised to *Gal d 1,* as demonstrated in one study of 68 children (1-11 years old, median age 4.1 years) with a history of egg allergy, who underwent detailed assessment of their allergic status with SPT, sIgE measurements and oral challenge to boiled and raw egg (19). Given the heterogeneity of the age group studied, it could be argued that the likelihood of multiple sensitisations is age dependent, with persistent egg allergy being an indicator of atopic tendency (11).

In multisensitised children with several atopic co-morbidities the clinician may request many tests to determine the individual sensitisation pattern. With recent advancements in molecular allergy, both single assay and multiplex component resolved diagnostics (CRD) are available (20). Microarray multiplex CRD platform called ImmunoCAP ISAC® (Immuno Solid-phase Allergen Chip, Phadia, TermoFisher Scientific, Sweden) enables screening for 112 allergen components from 51 different common allergen sources (20). Some of the potential advantages of multiplex platform are requirement for significantly less serum (110 μg/single vs 30 μg for ISAC®) and a better overview of true sensitisation pattern in patients with complex multiple sensitisation. However, the essential difference between established standard single CRD assay and ISAC® chip is that, unlike single assays, ISAC® is a semiquantitative test using arbitrary ISAC Standard Units (ISU) making direct comparisons less possible (20). Therefore, before ISAC® can be recommended for standard clinical use, there is a need for studies comparing the results obtained from both laboratory assays.

Oral Food Challenges

Oral food challenge is a gold standard tool for diagnosing food allergy, as neither positive SPT nor the presence of allergen sIgE in serum are sufficiently sensitive to predict clinical reactivity (14, 16).

In MAAS unselected birth-cohort study of over a thousand 8-year old children, of 110 children who were found to be peanut-sensitised, only 19 had clinical peanut allergy confirmed by either a strongly suggestive clinical history and SPT or sIgE to peanut ≥ 95% PPV (n=12), or positive peanut oral challenge (n=7) (16). Therefore, conducting an OFC not only aids diagnosis of clinical peanut allergy, but can prevent unnecessary dietary avoidance among those who are sensitised but tolerant to peanut. Moreover, as demonstrated in a study conducted among 143 egg-allergic children (median age 3.8 years), about two thirds of children with egg allergy are tolerant to extensively heated egg (e.g. biscuits, cakes) (21) and availability of such information has great implications on the extent of a child's dietary avoidance advised by health care professionals.

Importantly, OFC is a useful tool for assessing if the child has acquired tolerance to foods such as milk or egg, as many children develop tolerance to milk and egg before they start primary school (14) and, because of concern that long-term avoidance of allergenic food can have a negative impact on child's nutritional intake (13).

The OFC procedure involves giving small, increasing doses of suspected allergen over 20-30 minute intervals until an adequate amount of allergen for the child's age has been consumed uneventfully. A detailed description of adequate portion sizes for various allergens has been described in the expert group report published elsewhere (13). The principal indications for conducting a food challenge in children are; a) to establish a correct diagnosis of food allergy, b) to monitor resolution of

food allergy, c) to establish if the food allergen is associated with atopic eczema, d) to assess the tolerance to cross-reactive foods, e) to assess tolerance to heat processed allergens and f) to expand the diet in children who are on multiple dietary restrictions because of subjective symptoms or alternative diagnosis (13).

OFC have been used in clinical practice for the past 40 years with open, single-blind, and double-blind placebo-controlled food challenges (DBPCFC) being the most frequently used types. The choice of OFC type depends on several factors like the patient's clinical history, allergen involved, availability of challenge material, time involved and availability of appropriately trained staff to perform challenges (12, 13). In children, open challenges are often preferred due to a shorter duration of the challenge procedure and because of anticipation that children will react with objective signs e.g. urticaria or wheezing. However, the decision on the type of challenge to be used has to be made for each individual patient, as occasionally older children may report subjective symptoms only (e.g. itching, throat tightness, abdominal pain, dyspnoea) which during an open OFC may render results inconclusive. Also, children who have eczema and have been on an avoidance diet for suspected allergen may be challenged to establish if they have clinical allergy. In these cases preferably DBPCFC should be performed as it will provide more conclusive results, minimising bias that can occur with subjective symptoms during an open challenge (12, 22). Unfortunately, DBPCFC test is not available in every specialist centre due to a requirement for standardised, appropriately blinded challenge meals.

The largest retrospective analysis of children (n=740) who have undergone DBPCFC in single centre in Germany has demonstrated that DBPCFC are safe and particularly useful in distinguishing clinical reactivity in children who also have atopic eczema (22). Younger children with atopic eczema were more likely to be classified as placebo-reactors, i.e. more likely to have delayed-onset symptoms after placebo day, which was attributed to their underlying eczema rather than genuine clinical allergy.

Another emerging indication for using OFCs is to determine a child's individual threshold of reactivity for the allergen in question, which could enable health care professionals to provide better risk management advice. A recent study has examined allergen threshold levels for 5 common food allergens among 2-18 year old children, which helped researchers predict the dose of allergen that can elicit allergic reaction among 5% of allergic population (23).

In summary, OFC have many clinical uses but there is need for its wider applications, as well as for the standardisation of protocols and challenge materials used.

Management

Emergency treatment

Emergency treatment of acute allergic reaction should be done following the recommendations outlined in the international guidelines for treating Anaphylaxis published by World Allergy Organisation (10). The initial treatment of acute allergic reaction should follow the Airway, Breathing, Circulation, Disability, Exposure approach for managing of acute illness.

The mainstay of the treatment for 'a serious acute, severe and life-threatening systemic hypersensitivity reaction'-anaphylaxis, is an intramuscular injection of 0.01mg/kg of 1:1000 (1mg/1ml) undiluted adrenaline given at a maximum dose of 0.3 mg for a child and 0.5 mg for an adult into anterolateral aspect of the thigh (1, 10). The intravenous adrenaline injections are not recommended as it can cause cardiac arrhythmias and is best avoided. In case of symptoms and signs of drop in the blood pressure such as floppiness

(younger child), dizziness, light-headedness, the child should be laid flat with lower extremities elevated to improve cerebral blood perfusion. Milder allergic reactions comprising of urticaria and/or angioedema or gastrointestinal symptoms only, can be treated with oral antihistamines. Lower respiratory symptoms should be adequately treated with inhaled salbutamol and a short course of oral corticosteroids can be given as a second-line treatment for children who have had lower respiratory or cardiovascular symptoms.

Long –term management

Long-term management of food allergy relies on accurate identification of culprit allergen causing index allergic reaction. Currently, the mainstay of treatment for food allergy is strict avoidance of offending foods and administration of emergency treatment medication in case of accidental allergic reaction. An exclusion of a major nutrient, such as milk, in early childhood can predispose the child to an unbalanced dietary intake and growth faltering, especially in cases where children have been avoiding multiple foods (24). In order to ensure balanced nutrition and for detailed avoidance advice, each newly diagnosed child should be seen by dietician.

Parents and the child should be educated by the physician on how to recognise symptoms and signs of allergic reaction and provided with clear written instructions on how to manage accidental reactions. Strict avoidance of the offending food requires significant adjustment in patients' lifestyles (3). This includes patient education on reading the food labels and recognising allergens in manufactured and processed foods (1). As a result, a lifelong avoidance of offending foods is a burden that has a significant negative effect on the quality of life of food allergic subjects and their families (25).

It is estimated that about 10-18% of allergic reactions to food occur in schools and the European Academy of Allergy and Clinical Immunology (EAACI) 'Task Force on the Allergic Child at School' emphasises the need for clear communication about a child's allergy between parents and school staff, including provision of written emergency management plans provided by child's allergist (7). In addition, the task force has recognised a number of areas for improvement within school environment that would facilitate better management of risk posed to the food allergic child, including teacher and staff training on how to recognise and manage allergic reaction. Recently, the EAACI has launched food allergy public awareness campaign, with more detailed information found on their website (http://infoallergy.com/Tools-Extras/foodallergycampaign/). Another excellent source of information is the UK- based Anaphylaxis Campaign charity's website, which provides lots of free information about food allergy (http://www.anaphylaxis.org.uk/).

Avoidance of food allergens is not easy to maintain and accidental ingestions frequently occur (1). Avoidance of allergens by food allergic subjects can be extremely difficult in situations when food is prepared and eaten away from home, such as in restaurants, take away or at a friend's house, with about 40 -100% of fatal food-related anaphylactic reactions occurring in this setting(1). Evidence suggests that it is often the lack of clear communication and understanding of allergen and allergic reactions in 'outside from home' settings that underlies these fatal episodes (26). In order to protect allergic consumers from allergen containing food products, consumer safety laws in the European Union and other developed countries require food manufacturers to declare common allergens on the food packaging. However, food safety and food labelling legislations do not cover precautionary 'may contain' labelling, often used by manufacturers to indicate possible contamination with the allergens during food handling and production (27). Although

precautionary labelling was intended to aid consumers, a great variation and existence of alternative wordings creates a significant problem for allergic consumers when choosing what to eat (27). Variation in wording of precautionary labels, although not intended to convey different degrees of risk, can be perceived as such by patients and their families. Up to 8% of accidental reactions have been attributed to precautionary labelling being ignored by patients and their families (28), mainly because of the absence of an allergic reaction to a product with similar labelling in the past. Patients and families living with food allergy dislike precautionary labelling because they are uncertain about the basis for its use; it reduces their food choices considerably and has a negative impact on health related quality of life and psychological well-being.

Recently, there has been a joint international effort between clinicians, scientists and the food industry to develop reference allergen dose levels for common food allergens, in order to rationalise and facilitate decision making when it comes to the precautionary food labelling by food manufacturers (29). In return, provision of such information on food packaging will aid parents and children in assessing their risk of accidental exposure to food allergens. However for such information to be useful in practice, parents and the child would need to be informed on the amount of allergen, i.e. threshold dose triggering reaction in the child. To establish the threshold allergen dose triggering reaction, a child would need to undergo a low threshold DBPCFC to the culprit allergen. However, in practice this may be reserved for the allergens less likely to be outgrown during the childhood and for children with multiple food allergies and limited dietary choices.

Oral immunotherapy

With the growing food allergy burden and only symptomatic treatment options available, in recent years there has been an exponential increase in the number of studies investigating curative alternatives for treating food allergy. Inspired by success of allergen-specific immunotherapy for inhalant allergens, allergists in many centres across Europe and United States have explored the option of food allergen-specific immunotherapy for desensitisation and induction of oral tolerance.

Several studies have explored oral immunotherapy (OIT) for treating cow's milk allergy, however, there is a great variation in protocols including duration, type and amount of allergen given during up-dosing and maintenance phase, as well as selection of the allergen dose that confers successful desensitisation (30). A study conducted among 81 cow's milk allergic children assessed the safety of cow's milk OIT during 25 months follow up, showing that 75% of children were able to tolerate immunotherapy well, having only minor symptoms (31). Desensitisation was more likely to fail in those who had cow's milk sIgE > 50 kU_A /L, SPT mean wheal size ≥ 9 mm or who at initial DBPCFC challenge reacted with more than just skin symptoms. However, many children who underwent successful desensitisation had frequent allergic reactions reported during the OIT and needed dose adjustments if they had more severe post-OIT reactions, or if the concomitant factors known to aggravate allergic reactions were implicated, e.g. infectious disease.

A similar desensitisation success rate was noted for 5-11 year old children who took part in a randomised placebo controlled trial for desensitisation to egg (32). Of 34 children who successfully completed egg OIT, 30 were desensitised at 22 months. However, just 2 months after the stopping of OIT only 11 children retained their tolerance to the egg on the open challenge. Of note is that children who were desensitised to egg at 22 months were advised to avoid eating eggs for the following 4-6 weeks before the open chal-

lenge. This suggests that many children lost their unresponsiveness due to a lack of regular exposure to the egg allergen.

It is important to understand what regulates sustained effectiveness of the OIT. A separate study looking into immunological parameters of egg-allergic children, who were successfully desensitised, found that there was a marked increase in a number of effector regulatory T cells (T_{reg}) (33). Effector T_{reg} cells are essential in controlling the balance between different subsets of T cells and are able to suppress T helper type-2 (Th2) activity.

A pilot clinical trial of OIT to peanut, conducted among 1 to 16 year old children, examined the rate of tolerance vs desensitisation achievement after 3 years of peanut OIT (34). Of 39 children who initially enrolled to receive peanut OIT, 6 discontinued treatment due to side effects and 9 for other reasons. Of 24 children who completed their OIT, based on DBPCFC to peanut conducted a month after stopping the OIT, half of the children achieved tolerance and the other half were desensitised. Interestingly, during the course of the study all children had a steady decline in their peanut sIgE and increase in blocking peanut $sIgG_4$ antibodies.

What seems to differentiate success and failure in immunotherapy is a significant increase in blocking $sIgG_4$ antibodies that bind to the same allergen epitopes as IgE. A competition assay performed among children who underwent OIT with cow's milk, showed that children who successfully completed OIT had a greater overlap between sIgE and $sIgG_4$ for epitope binding unlike the children who discontinued OIT due to the side effects (35).

The timing of the OIT could be an important factor influencing the outcome of the OIT as younger children may respond better to immunotherapy. Of 54 children who took part in an 18 month long randomised double-blind trial of epicutanous specific immunotherapy to peanut, using pharmaceutical patches containing peanut protein, 25 children (up to 17 years of age) were randomised to receive active treatment. Based on the primary outcome of achieving at least a 10-fold increase in cumulative reactive dose at the end of study challenge, the younger children (5-11 years) were more likely to be successfully desensitised (36). This increase was paralleled by increase in peanut $sIgG_4$.

Another randomised controlled, cross-over trial of peanut OIT, conducted among 7-16 year old children examined the rate of children who would pass DBPCFC to peanut after 6 months of daily ingestion of 800 mg peanut protein (3.2 g whole peanut)(37). After 6 months 62% of children (24 of 39) were able to pass DBPCFC with 1400 mg of peanut protein, compared to 0% among children in the control group (0 of 46 children). In the second phase of the study, children who were in control group underwent OIT and 54% of them passed peanut DBPCFC after 6 months. What is more important, 84% of children in the first phase and 91% of children in the second phase were able to tolerate daily ingestion of 800 mg of peanut protein with only mild, mainly skin side effects.

Considering the recent increase in the number of studies examining the effects of the allergen-specific immunotherapy, this seems to be a promising curative treatment for food allergy. However, the application of immunotherapy is still not ready for routine clinical use as there is a need for better data on safety and the long term effectiveness of the treatment, as well as a wider consensus and standardisation of immunotherapy protocols.

Towards primary prevention

There has been a recent debate as to whether delayed introduction of solids into infants diet has contributed to the rise in prevalence of food allergy observed in developed countries (38, 39). A so called "window of opportunity" for development of oral tolerance

may be missed for those children who are introduced to solids beyond 6 months of age. There are mixed reports on whether introduction at 6 months of age versus at 4 months or before, increases the risk for the subsequent development of food allergy (38). However, the effect of timing of the introduction of solids is hard to interpret, as a number of confounding factors such as duration of follow up, socioeconomic status, family history of atopic disease and history of eczema make the conclusion much more difficult (39).

The first year of life is characterised by rapid developmental changes, including loss of gag reflex, development of chewing and swallowing, increase in gastric acid secretion which can determine an infant's readiness to move on from liquids to solid foods. With the introduction of solids, the pattern of gut colonisation by commensal bacteria changes significantly from predominantly gram positive bacteria to mainly anaerobic bacteria and *lactobacilli* species. An interaction between changing intestinal microbiota and the developing immune system may determine immune system homeostasis, i.e. tolerance induction versus failure in oral tolerance, resulting in atopic immune response towards food antigens (38).

Another hypothesis is that a change in diet, such as eating more processed and less fresh and home prepared foods, has contributed to an increase in food allergies. A case-control study examining dietary habits of food allergic infants and their age matched controls during their first year of life, found that children who were diagnosed with food allergy by the age of 2 years were less likely to eat fresh fruits and vegetables and home prepared foods compared to controls (40).

A number of primary prevention studies targeting either pregnant or breastfeeding mothers or infants using various intervention strategies, have been examined for the overall evidence in their preventative role for the development of food allergy (39). None of the antenatal strategies, such as antenatal exclusion of common food allergens, intake of probiotic supplements or that modification of diet of breastfeeding mother have been proven to prevent food allergy in the offspring. The evidence on the effect of primary prevention strategies among infants is mixed and generally there is no unique recommendation for the prevention. However, several intervention studies (LEAP, EAT, HEAP), designed to compare the effect of early vs late introduction of allergenic solid foods such as eggs or peanuts, are still ongoing and will be interesting to find out their results (38).

Overall, there is no conclusive evidence to support any of the primary prevention strategies including earlier introduction of solid foods than currently recommended (39), however this may become available in the near future with interventional studies expected to be completed within next year.

Conclusion

Oral food challenge remains a gold standard tool for diagnosing food allergy. However, new molecular allergy diagnostic tools have become available over the past several years greatly improving the clinical decision making in food allergy. A recent surge in studies looking into the food allergen-specific immunotherapy promises a better outlook for food allergy sufferers and a chance for curative treatment. In addition, interventional studies looking into early- life introduction of allergenic foods that are currently underway will provide us with specific answers on future primary prevention strategies within the next couple of years.

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