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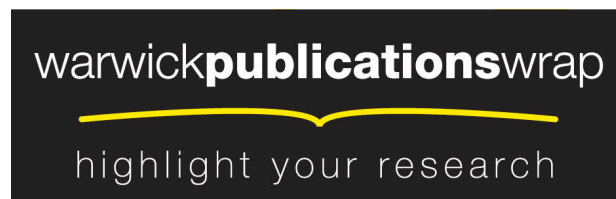
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Title Page.

Diagnosing and Managing Food Allergy in Children

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Diagnosing and managing food allergy in children

Key Words: food allergy, hypersensitivity, IgE mediated, Non-IgE mediated, skin prick tests

Practice Points:

1. Children often present with apparently complicated food allergy stories.
2. The history should be aimed at diagnosing if a child has food allergy and, for each allergen, define the nature of what is being reported into one of 4 clear categories
3. Investigations such as skin prick testing and specific IgE are helpful only if an IgE mediated process is suspected. They must be carefully targeted and linked to history as their positive predictive value is only 50 to 65%.
4. The mainstay of management is avoidance.
5. There are currently no good tests for non-IgE mediated allergy and non allergic hypersensitivity.

Abstract: Food allergy has increased in developed countries over the past 20 to 30 years and is a common reason for referral of children to Paediatric services.

Diagnosing and managing food allergy in children is dependant on a thorough and well targeted history with questions focused at differentiating the nature of the reaction for each suspected allergen. Along with skin prick testing or specific IgE blood testing, it should be possible to classify reactions into 4 groups: IgE mediated food allergy, Non IgE mediated food allergy, Non allergic food hypersensitivity and symptoms falsely assumed to be due to foods. This is helpful as there are significant differences in the risk profile, dietary approach and management between each group.

Introduction

Children are often brought to clinics with concerns about food allergy. Estimates of true incidence are quoted as between 2 and 8% of children. The prevalence of diseases associated with atopy has increased in many parts of the world over the past 20 to 30 years [1]. Nobody has a single answer as to why but the most popular theory is the hygiene hypothesis where excessive hygiene measures can switch the nature of T cell responses in potentially atopic individuals [2].

Presentations range from mild and infrequent reactions, with investigations often unnecessary, to complex and severe reactions. Many doctors feel uneasy about the consultation, due to parental anxiety and this is compounded by the lack of confidence many feel in diagnosing and managing allergy [3]. This need not be the case.

Although the pathogenesis and epidemiology of many hypersensitivity processes remain poorly studied, the majority of food allergies have distinct patterns, each with a clear logic of investigation and management. By identifying these patterns, the clinician can often help families understand how to feed their child even if they have complex or multiple allergies.

Understanding Allergy

Box 1

Hypersensitivity

An umbrella term where objectively, reproducible symptoms or signs are initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. The definition specifically excludes infection, autoimmunity and toxic reaction.

Allergy

Hypersensitivity initiated by an immunological mechanism.

This can be IgE mediated or non IgE mediated

Johansson et al [4]

Both professionals and the general public use a confusing range of terms to describe allergic responses. Box 2 lists terms in common usage and it is notable that many are poorly defined, or used interchangeably by some and subject to strict definitions by others.

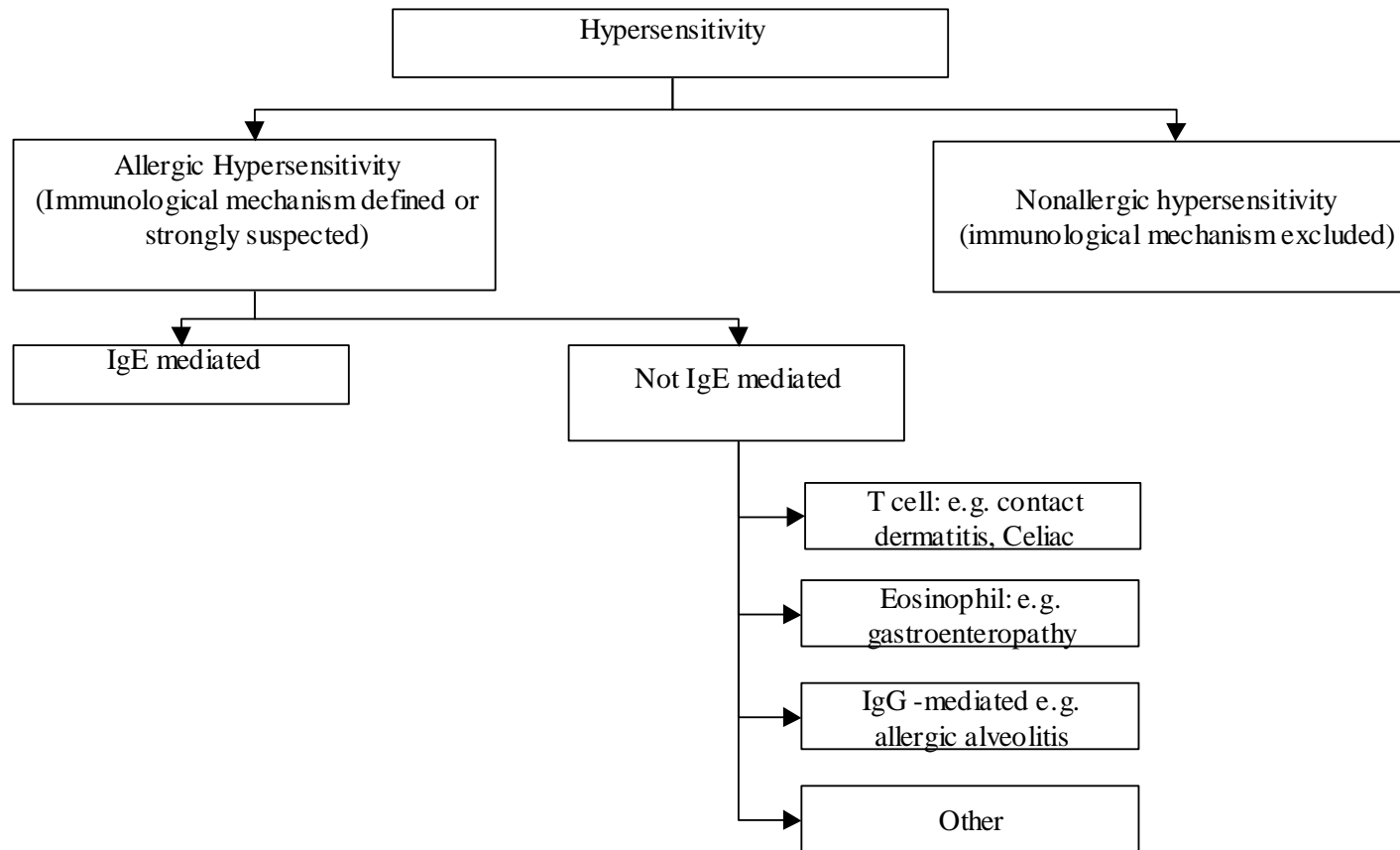
There are 4 major patterns with different implications for the family

1. IgE mediated food allergy
2. Non IgE mediated food allergy
3. Non allergic food hypersensitivity
4. Symptoms falsely assumed to be due to foods.

The true hypersensitivities are summarised in Figure 1.

Box 2
Sensitivity
Hypersensitivity
Allergy
Atopy
'True' allergy
IgE mediated allergy
Rapid hypersensitivity
Immediate hypersensitivity
IgE mediated rapid hypersensitivity
Type 1 hypersensitivity
Atopic or anaphylactic hypersensitivity
Delayed allergy
Non IgE mediated allergy
Type IV hypersensitivity
Slow type allergy
Intolerance
Pseudoallergy

Figure 1 adapted from Johansson et al [4]



Approach to the consultation

The history is the most helpful to identify the suspected food trigger and define the type of reaction. A detailed history is necessary for each possible trigger (box 3) to differentiate the type of reaction (table 1) remembering that one individual may have different types of reaction to different foods (e.g. they could have eczema made worse by milk and also a non allergic response to wheat) and that even if all reactions are the same type, they may be of different severity. Also, a single food can cause examples of each type of hypersensitivity. For example, cow's milk can cause:

1. IgE mediated allergy causing urticaria
2. Non IgE mediated allergy causing cows milk protein sensitive enteropathy, usually diarrhoea
3. Non allergic hypersensitivity causing lactose intolerance, usually diarrhoea

Box 3

1. Who and what were present?
2. Where were you?
3. How much did you eat? Did you swallow it?
4. Who gave it to you?
5. Did you eat anything else?
6. What happened?
7. What were you doing at the time?
8. What action did you take? Did it help?
9. How often does this happen?
10. What do you know already?

For example, a child has a severe reaction at a party. Did they eat nuts, inhale pollen, blow up a balloon, cuddle a cat, or get stung by a bee?

Table 1

	IgE mediated allergic hypersensitivity	Non-IgE mediated allergic hypersensitivity	Non allergic hypersensitivity
Timing of onset of reaction	Typically rapid-seconds to 30 minutes. Reproducible	Slow- up to a couple of days	Slow- hours to days
Mechanism	IgE mediated with mast cell degranulation	Diverse- includes T cell, eosinophil and IgG mediated responses	Multiple
Classic clinical features	Wide spectrum- wheeze, urticaria, vomiting, angioedema anaphylaxis [5]	failure to thrive, chronic diarrhoea, eczema, rhinitis, rectal bleeding [1]	Variable. Abdominal pain, diarrhoea, flushing etc.
Common examples	Peanut, tree nut, egg, cows milk,	Food sensitive eczema	Lactose, caffeine and wheat

	fish, soya, wheat, shellfish [6]	Cows milk protein intolerance, Coeliac disease	intolerance
Systems involved	Respiratory, gastrointestinal, skin	Respiratory, gastrointestinal, skin	Any
Relationship of dose to reaction	Can have severe response to minimal exposure	Dose response relationship	Dose response relationship
Investigations	Skin Prick testing, Specific IgE	Dietary exclusion and reintroduction under guidance of dietician.	Dietary exclusion and reintroduction under guidance of dietician

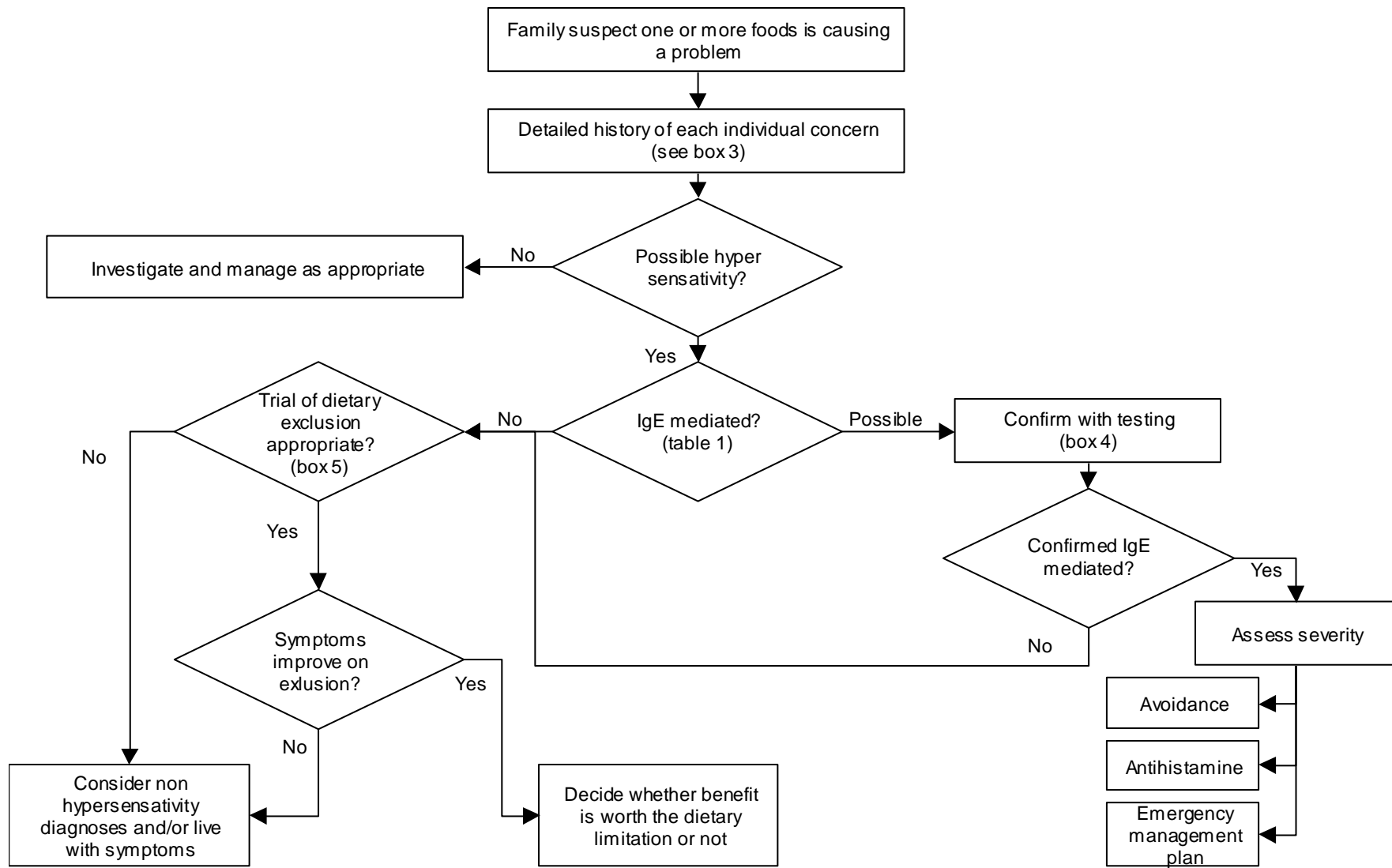


Figure 2 shows the sequence of considering each concern. We will discuss each type of hypersensitivity in some detail but it is notable that the key decisions are whether the process is IgE mediated or not and, if not, whether a trial of exclusion is appropriate and, if undertaken, successful.

Investigation and Management

IgE mediated allergy

Overview

IgE mediated reactions are usually the most straightforward to diagnose but can be the most anxiety provoking. There is usually a clear temporal relationship between food ingested and reaction and there are useful investigations.

Clinical History

Reactions usually come on rapidly although the peak of severe reactions can be after some hours [5] and the reaction can be biphasic.

Gastrointestinal

There may be itching of the mouth and throat and/or swelling of the lips and tongue and this is often the first site of reaction. Later symptoms may be stomach cramping, nausea, vomiting and diarrhoea.

Skin

Rapid urticaria and angioedema are classical.

Respiratory

There can be aggravation of respiratory symptoms including sneezing, rhinorrhoea, nasal obstruction, chest tightness, wheezing, cough and tightness in the throat [5].

Severe reactions

IgE mediated food allergy is the most common cause of anaphylaxis seen in Emergency Departments, accounting for 90% [7]. Presentations include severe facial oedema, respiratory distress and/or hypotension mostly in children who also have asthma [8].

Examination

Examination in the absence of an acute event may add little but attention needs to be paid to the skin, respiratory tract and gastrointestinal tract, ear, nose and throat. and the nutritional status of the child [9]. Signs of under treated asthma are a marker of potential severity.

Investigation

The most relevant investigations are IgE sensitivity tests either in vivo (by skin prick testing) or in vitro by measuring allergen specific IgE levels (box 4)

Box 4

Skin Prick Testing

Skin prick tests require specific training but can be performed in a clinic setting and the results of the investigation explained immediately. The overall positive predictive value of skin prick testing is reported as only 50-65% [9] although if a wheal is greater than 7 or 8 mm depending on the food, this can approach near certainty [10]. A negative test carries approaching a 100% negative predictive value [9].

Unfortunately, the relationship between the size of wheal and degree of reactivity is

weak. Antihistamines should be avoided for at least 2 days prior and sufficient clear skin is required.

Specific IgE

Quantitative measurements of serum food-specific IgE provide information similar to skin prick testing, but with similar limitations in interpretation. A negative test has an excellent negative predictive value [9] but a positive doesn't prove clinical reactivity. Caution is necessary in children with severe eczema especially with a baseline total IgE > 1000kU/l. because of high false positives.

There is a larger range of allergens available to test against, over 200 foods compared to a much smaller range for skin prick testing. Tests can be taken whilst on antihistamines. However, a blood sample is required and the family need to return for another appointment to discuss results.

Mast cell tryptase

This can be helpful to confirm IgE mediated anaphylaxis if taken within an hour or two of a suspected reaction [11].

Food Challenges

A) Open challenge

This confirms a food is safe to eat and is useful when there is a convincing history but skin prick testing is negative or if a child is thought to have grown out of their allergy. Foods are introduced in increasing doses up to the amount likely to be consumed by accident, e.g. in peanut allergy, 4-8 peanuts. A clear emergency protocol and appropriate staff training is mandatory.

B) Double-blind placebo controlled food challenge (DBPCFC)

Although often defined as the gold standard for research and advocated by some as an 'office procedure' [6], few find it practical not least because it is very difficult to disguise foods.

Management

Each child needs an individual management plan to be explained to parents in the clinic and shared with nursery/school.

Avoidance

The main treatment of food allergy is the avoidance of the food and this can be difficult to achieve. The availability of a dietician in the clinic is highly desirable and is helpful to develop a menu that eliminates the food and still remains nutritious. Avoidance can be challenging especially with complex food labelling (Picture 1)

Medication

- **Antihistamines** An antihistamine such as Cetirizine should be given immediately for mild reactions and then regularly for 2 to 3 days depending on the response.
- **Epinephrine** (Adrenaline). In the event of a severe reaction, the immediate treatment is epinephrine intramuscularly [12].
An epinephrine auto injector should be provided for patients who are at risk of having a life-threatening episode. Deciding who is most at risk is a significant challenge [3] and is fully discussed elsewhere [13] and a new consensus statement has been published recently [14]. Training is essential.

- **Steroids** Patients who have respiratory involvement should be given prednisolone 1mg/kg (maximum 40mg) immediately and once daily for 4-5 days.
- **Asthma management** There is good evidence that asthma has a significant association with severe reactions. It is less clear whether optimal management of asthma changes a child's risk profile although it seems advisable [8].
- **Immunotherapy** There are not currently immunotherapy regimes available for de-sensitisation because of the risk of anaphylaxis during up-dosing.

Egg allergy and MMR

Many doctors are still under the impression that MMR is contraindicated or risky in those with egg allergy. This is not the case as most reactions are due to other components such as gelatine. Most egg allergic children should get MMR in the normal way with only those who have had a previous severe reaction to egg considered for immunisation in hospital [15].

Oral Allergy Syndrome

This is a form of contact IgE mediated allergy primarily occurring in the oropharynx. Symptoms include the rapid onset of itching of the lips, tongue, palate and throat. Other sites are rarely affected. The antigens are usually from fresh fruits and vegetables for example, the birch pollen syndrome with linked sensitivity to apple mugwort and celery

There is commonly a history of allergic rhinitis due to pollens. The diagnosis is confirmed by clinical history and skin prick testing may be helpful. Management is with antihistamines and observation to ensure that these are not initial symptoms of a systemic reaction.

Non IgE mediated allergy

Overview

Non-IgE mediated allergic reactions have a slower onset of action and so may not be so easy to link to food ingestion. Symptoms can be vague and variable and include failure to thrive, chronic diarrhoea due to enteropathy or colitis, eczema, rhinitis or rectal bleeding.[1]. Despite the disparate nature of this group, they share clear common features: as well as being slower in onset of action, they are not acutely life threatening, show a dose response (such that some sufferers can tolerate a certain amount of the trigger), and lack confirmatory tests. Presentations linked to asthma and eczema are more obviously allergic with some of the gut presentations being more easily missed as they may appear clinically indistinguishably from, for example, gastro oesophageal reflux.

Eczema/Atopic dermatitis

Food responses contribute to eczema in some children mainly in infancy [1]. This results in a dose responsive worsening of their skin if certain foods are in the diet. Diagnosis is challenging as there are no useful tests. Eczema management should be optimised and, if this is unsuccessful, or there is good reason to suspect an aggravating food, a trial of exclusion should be considered [16] focusing on a suspected food or, rarely, blindly to milk or egg. (box 5)

Food protein-induced enterocolitis

This is most commonly due to cow's milk or soya milk but can also occur in exclusively breast-fed infant, triggered by milk protein in the mother's diet It usually

occurs in young infants below the age of 3 months and presents with vomiting and diarrhoea and stools containing streaks of blood. Skin prick tests are negative but useful to eliminate an IgE component [1].

Food protein enteropathy

This presents in the first several months of life with vomiting, diarrhoea, abdominal pain following feeding and malabsorption and if unrecognised can cause failure to thrive. It is most often caused by cows milk (Cows Milk Sensitive Enteropathy, CMSE) or by soya resulting in lymphocyte and eosinophil infiltration of the mucosa of the gastrointestinal tract [1] and is associated with other atopic diseases There may be associated eosinophilia and iron-deficiency anaemia.

Allergic dysmotility

Dietary antigens (usually cow's milk, soy or wheat) can induce gastroesophageal reflux or constipation. Careful consideration of children with delayed food allergic responses frequently uncovers a history of infant colic, gastroesophageal reflux and chronic abdominal pain

Infantile Colic

Usual features include intense paroxysms of crying, drawing up of the legs and excessive gas. It generally develops in the first 4 weeks of life and persists through to the fourth month. Aetiology is multi factorial but food hypersensitivity, often to cows milk [1], is a significant factor [17]. If allergy is a suspected cause, a trial of hypoallergenic formula e.g. hydrolysed or amino acid formula should resolve symptoms

Eosinophilic esophagitis and eosinophilic enteropathy

These are emerging as clinical entities, which overlap with non-IgE mediated food allergy, but which may also occur without food responses. Eosinophilic oesophagitis is associated with infant gastroesophageal reflux disease and abdominal pain, dysphagia or vomiting, sometimes with loose stools in older children. Investigations to confirm diagnosis include endoscopy with biopsy. Some propose a combination of skin prick and patch testing but there is no agreed diagnostic pathway. Management is with dietary exclusion in infants [1] this is almost always withdrawing cows milk in the first instance.

Respiratory symptoms

It is unclear whether asthma, like eczema, can be generally exacerbated by foods in the diet in addition to IgE mediated bronchospasm. Additionally, it is possible that apparently food related asthma might actually be respiratory symptoms from antigen induced reflux [1] There is currently too little evidence for strong recommendations. If there is sufficient clinical suspicion, a trial of exclusion may be relevant.

Coeliac disease

This a non-IgE mediated allergy to the gliadin component of gluten found in wheat, oat, rye and barley causing enteropathy and malabsorption. The result is villous atrophy in the mucosa of the small bowel. Patients also have characteristic serology. Symptoms include diarrhoea, abdominal distension, flatulence and weight loss. The availability of screening and confirmatory tests are in contrast to the other causes of non-IgE mediated allergy.

Investigation

The only useful tests currently available are screening and testing for coeliac disease and trials of food exclusion (see box 5)

Box 5

Trial of food exclusion

Where non IgE mediated allergy or non allergic hypersensitivity is suspected consider a trial of exclusion and re-introduction. This is usually done over 16 to 24 weeks with 6 to 8 weeks exclusion, 6 to 8 weeks re-introduction and, some would suggest, a further period of exclusion.

Advantages are that a clear diagnosis can aid treatment and showing that a food is not the cause of symptoms definitively can allow a return to a normal diet.

Disadvantages are the potential huge disruption to the diet of a child and their family as well as the dependence on reporting to judge outcome. Dietetic oversight is vital.

There are no clear cut rules but a trial of exclusion should be considered where:

1. The symptoms are severe such that the family would continue to exclude the food if shown to be relevant
2. There is a single or very limited number of target foods
3. The exclusion can be managed to minimise dietary impact
4. Where the family are accepting of the effort required

Management

Food exclusion will give an indication of how large an improvement is possible. The family can compare this against the challenge of the diet. There is often a dose response, so the diet can be relaxed with time. The obvious exception is with coeliac disease where tight control avoids long term sequelae. It is not clear whether this is true of other gut enteropathies.

Nonallergic hypersensitivity

Overview

The history and examination will identify some children as needing investigation for other diagnoses. In addition, some will have a vague history with a concern that symptoms are due to food.

There are a number of well described non-allergic mechanisms by which food can cause symptoms. This includes food and drink causing pharmacological and irritant effects, effects dependant on differences in an individual's ability to metabolise and eliminate certain compounds, for example, slow acetylators having a more marked response to caffeine exposure and withdrawal. [18] and enzyme defects such as lactose intolerance secondary to lactase deficiency and abdominal symptoms due to fructose deficiency.

Unfortunately, the situation is complicated by a current Zeitgeist of blaming many problems, particularly behavioural, on foods. A full discussion is beyond the scope of this paper. What is clear is that with such a variety of potential mechanisms and limited work in this area it is as foolish to dismiss such claims as it is to believe them unquestioningly.

Investigations

Immune investigations are not relevant. Where there is a clear malabsorption history, stool infection screen, reducing substances and tests for primary causes such as Cystic Fibrosis should be done. Where the history is unclear, consider a trial of exclusion and reintroduction (see box 5)

Management

Management of any proven non-allergic food hypersensitivity is avoidance with appropriate dietetic support.

Non hypersensitivity

Of the children presenting with suspected allergy, there are symptoms reported that are not due to a food or other precipitant. This is a challenging group. In some, another diagnosis may be made but this is not always possible. It is tempting to view this as a diagnosis of exclusion but as has been noted, it is only usually possible to exclude IgE mediated allergy to specific foods as there are currently no tests that exclude the other types of reaction.

Where a trial of food exclusion is appropriate (box 5), this can assist although where parental beliefs are strong, interpretation of the outcome can be difficult. As with the non allergic hypersensitivity group, it is unhelpful to dismiss concerns as this can polarise parental views. Where possible, a clear and non-judgemental exploration of the concerns and honesty about the limitations of current understanding can help families to accept a pragmatic approach to their child's diet that allows for relaxed meal times and appropriate nutrition.

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