Who should manage infants and young children with food induced symptoms?

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A proposal for a unified, interdisciplinary approach

In recent years, many developed countries have experienced a rapid increase in real and perceived food allergic disorders.^{1,2} This phenomenon has caused a dramatic rise in the need for clinical allergy services, and waiting lists have in many centres become unmanageable. The costs to the NHS for managing allergic disorders in the UK currently exceeds £1 billion per annum.³ Health services have been generally slow to adapt to the increased need for allergy services, and access to specialised paediatric allergy services has remained particularly limited.³ This may potentially lead to adverse clinical outcomes due to unacceptable diagnostic delay or suboptimal management.⁴ The small number of paediatric subspecialists in tertiary centres is currently unable to assess children with allergies in a timely fashion. As a result, there is an urgent need for re-training of paediatricians in the management of food allergic disorders, including IgE mediated food allergy, gastrointestinal allergic manifestations, and food protein induced infantile atopic eczema.⁵⁻⁸

The overall prevalence of food allergy is about 8% in children under 3 years of age, and 4% in the general American population.⁹ Prevalence figures from

published data on food induced symptoms seem to be influenced by the recruitment method and the clinical setting in which patients were studied—that is, cohorts presenting predominantly with dermatological, gastrointestinal, or IgE mediated clinical manifestations. In a recent German population based study, only 10% of self-reported food induced symptoms were confirmed on subsequent formal assessment, corresponding with a prevalence of 4.2% for proven food induced clinical symptoms.²

STATUS QUO

Medical subspecialists may be influenced by specialty based clinical bias and may fail to identify relevant clinical manifestations of allergic disorders outside their area of interest. A model of the current interactions between the three subspecialties dermatology, allergology, and gastroenterology is shown in fig 1. As IgE mediated food allergy may occur in infants and small children with atopic dermatitis (AD) or gastrointestinal manifestations,^{6,8} the subspecialties of allergology and gastroenterology can be considered as complementary to each other. By contrast, dermatology and gastroenterology seem to have little clinical overlap. The prejudice of the status quo of the different views of the three subspecialties concerning food induced symptoms is presented in table 1.

Paediatric dermatologists predominantly deal with AD and urticaria. Although the close association between AD and food allergy has been shown in several studies,^{8,10,11} many dermatologists (and other specialists) do not include food allergy testing or elimination diets in the management of infants and young

Figure 1 Present prejudice of interaction between dermatology, allergology, and gastroenterology.

Table 1 Current referral patterns to the three professions concerning food related symptoms			
	Dermatologist	Allergologist	Gastroenterologist
Predominant symptoms seen in patients	Atopic eczema Urticaria	IgE mediated reactions Allergic rhinoconjunctivitis Allergic bronchial asthma	Persistent vomiting Persistent diarrhoea Failure to thrive
Suspected underlying pathomechanism	Immediate or delayed type hypersensitivity	IgE mediated hypersensitivity	Non-IgE mediated food hypersensitivity
Preferred investigations	Skin testing	Specific serum IgE antibodies (CAP system FEIA) Skin prick test Atopy patch test Oral food challenges	Growth charts Stool microscopy/culture Endoscopy and biopsies Coeliac serology Serum micronutrient levels
Main therapeutic approaches	Emollients Topical anti-inflammatory agents Empirical diet	Elimination diet Adrenaline autoinjector Pharmacotherapy	Elimination diet Dietary supplementation

children with AD. In older children and adults with AD, food allergy is less likely to be a significant aetiological factor.¹² Treatment of AD by dermatologists is predominantly symptomatic and relies on topical anti-inflammatory agents, as well as wet dressings and skin emollients.¹³

Paediatric allergologists mostly see infants and children with IgE mediated clinical symptoms, including asthma and/or allergic rhinoconjunctivitis. Diagnostic tests and challenge procedures aim to show IgE sensitisation.^{7 14 15} Treatment is primarily based on allergen elimination, and symptomatic or anti-inflammatory pharmacotherapy, as well as the prevention and emergency treatment of food anaphylaxis.

Finally, *paediatric gastroenterologists* treat infants and children with persistent diarrhoea, vomiting, or failure to thrive.¹⁶ Clinical manifestations are usually non-IgE mediated and slowly evolving.¹⁷ The diagnostic work-up includes stool investigations for infection and malabsorption, serological screening for coeliac disease, endoscopic examination, and mucosal biopsies.⁶ Treatment options include hypoallergenic elimination diets and nutritional supplementation.¹⁸ Corticosteroids and novel steroid sparing immune modulating therapies may be required in patients with refractory or relapsing eosinophilic gastrointestinal disorders who failed to respond to elemental diets.^{6 19}

SYNERGISTIC EFFECTS

Clinical improvements of eczema²⁰ and of gastrointestinal symptoms²¹ have been reported in infants and children

with food induced symptoms after commencing a hypoallergenic elimination diet. There may be multiple synergistic effects (fig 2). Successful elimination of a relevant food allergen is likely to induce clinical remission via pathomechanisms from within all three subspecialties: by decreasing skin inflammation, gut inflammation, and systemic inflammation, (a) the overall energy expenditure will decrease, (b) energy absorption from the gut may increase, and (c) generalised catabolic effects may be reduced. All these changes will contribute to increased net energy intake, improved growth velocity, and resolution of allergic food induced symptoms.

UNIFIED APPROACH

In view of the many similarities, common pathomechanisms, and overlapping effects, it may be feasible to ameliorate the differences in the diagnostic and therapeutic approaches to children with food induced symptoms. We propose a unified, interdisciplinary diagnostic approach for infants and young children with food induced clinical symptoms (box 1).

The medical history should include symptoms from within all relevant subspecialties, for example, a history of urticaria, eczema, diarrhoea, vomiting, growth development, sneezing, persistent nasal discharge and itch, wheeze, or other breathing difficulties. Other factors that may lower the threshold for severe systemic reactions, for example, in exercise induced anaphylaxis, should also be explored. The dietary history should include details on early infant feeding, suspected previous intolerance reactions to foods, and the current diet (with

particular reference to macro- and micro-nutrient intake). Current or previous periods of elimination diets and dietary supplementation (for example, iron, calcium) should also be documented.

During the consultation, basic anthropometric measurements (height and weight) should be taken and plotted on centile charts in order to assess the infant's growth velocity. The physical examination should start with the detailed inspection of the skin and examination of the ears, nose, and throat. In children with persistent nasal symptoms, anterior rhinoscopy is helpful to evaluate the nasal mucosa for colour, swelling, and secretions. The auscultation of the chest and palpation of the abdomen for hepatosplenomegaly, ascites, or masses should also always be performed. Further specific clinical tests may be necessary according to the history or clinical presentation.

Basic investigation for suspected food allergies should be similar in all three subspecialties, including screening tests for IgE sensitisation by skin prick test (SPT) or measurement of specific serum IgE concentrations to common food allergens.^{14 15} The history, together with the IgE results may form the basis for a diagnostic elimination diet, which aims to achieve remission of symptoms after elimination of the suspected food from the diet.¹⁸ The duration of this diet depends on the type of reaction, and may range from several days up to several weeks. If symptoms improve during this elimination diet, the aetiological role of the eliminated food should be confirmed by controlled oral food challenges. The need for open versus double blind, placebo controlled food challenges (DBPCFC)²² depends on the type of symptoms. In the majority of infants with suspected food induced symptoms, open challenges will be provide sufficient clinical evidence for food allergies. Older children or patients with more subjective symptoms may require DBPCFC.

In some cases, specific diagnostic tests may be necessary to prove the causal relation between clinical symptoms and the ingestion of certain foods. In patients with AD, the combination of an IgE based test (food specific IgE concentrations or SPT) with the atopy patch test (APT) enhances the diagnostic accuracy.²³ In patients with suspected enteropathies or lactose malabsorption, screening for coeliac disease should include measurement of total serum IgA, antigliadin IgG and IgA, as well as endomysial IgA or tissue transglutaminase IgA.²⁴ Endoscopy and small bowel biopsy are required to make a definitive diagnosis of coeliac disease.^{6 15 24}

Figure 2 Synergistic effects of an elimination diet in food induced symptoms.

Box 1: Unified paediatric diagnostic and therapeutic approach

- (1) Medical history (e.g. symptoms of skin, gastrointestinal tract, and/or respiratory system)
- (2) Dietary history (e.g. early feeding, current dietary intake, previous intolerance reactions, eliminated foods)
- (3) Physical examination (e.g. weight, height, skin, ENT, chest, abdomen)
- (4) IgE screening (e.g. food specific serum IgE antibody levels, skin prick testing)
- (5) Diagnostic elimination diet (e.g. specific elimination, oligo-allergenic diet, maternal elimination diet)
- (6) Oral food challenges (e.g. open versus double blind, placebo controlled challenges)
- (7) Optional: specific diagnostic tests (e.g. small bowel biopsy for suspected enteropathies, atopy patch test in eczema)
- (8) Therapeutic specific elimination diet (under supervision of dietician, energy and micronutrient supplementation)
- (9) Experimental approach: (e.g. specific oral tolerance induction, immune modulating agents, anti-IgE therapy)

After having identified the clinically relevant food items, a therapeutic specific elimination diet will be formulated and implemented. The diet should provide energy, protein, and micronutrients and be supervised by a paediatric dietician.¹⁸ In children with protein energy malnutrition, supplementation will include energy dense macronutrients (carbohydrate and fat), as well as minerals, vitamins, and trace elements. In infants with cows' milk and soy allergy, an extensively hydrolysed formula (whey or casein predominant) should be prescribed.^{25–26} Infants with multiple food protein intolerance (MFPI) will fail to respond to extensively hydrolysed formula and require treatment with amino acid based formula.^{26–28} Due to their complex nutritional requirements, infants with MFPI should be managed by a gastroenterologist or allergologist, in collaboration with a paediatric dietician.¹⁸

Specialist referral to an allergologist should be considered in selected cases, which may benefit from new or experimental treatment options. Severe cases of atopic dermatitis in older children who require systemic treatment with cyclosporine or other immune modulating agents should be referred to a dermatologist or allergologist. In children with allergy to egg or cows' milk, specific oral tolerance induction (SOTI) may offer an alternative to long term strict dietary avoidance.²⁹ SOTI may increase the threshold level and reduce the risk of significant food allergic reactions after inadvertent exposure.^{29–30} In addition, anti-IgE therapy (for example, for life threatening peanut allergy) has recently introduced a novel treatment option.^{5–31}

CONCLUSIONS

Implementation of a unified approach in the diagnostic work-up of infants and

children with suspected food induced disorders is necessary to overcome the intrinsic differences between the three main subspecialties involved in the care of young children with food allergies and intolerances. A unified clinical approach may facilitate early referral of suspected food induced disorders, reduce diagnostic delay, and prevent unnecessary, potentially harmful dietary restrictions.^{32–36} Fragmentation of care may be avoided by setting up regional allergy networks of general paediatricians and subspecialists in order to achieve early referral to screening clinics, and secondary or tertiary specialist assessment of infants and children with complex medical or nutritional requirements.

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IMAGES IN PAEDIATRICS

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Acute haemorrhagic oedema of infancy

A 6 month old clinically well child presented with a rash and peripheral non-pitting oedema following an upper respiratory tract infection (fig 1). He was diagnosed with acute haemorrhagic oedema of infancy.

Also known as Finkelstein's¹ or Seidlmayer's disease,² acute haemorrhagic oedema of infancy is a benign, self-limiting disease, which generally develops in children less than 2 years of age.

Figure 1 Consent was obtained for publication of this figure.

First described in 1913,³ it has been recognised as a condition with a very dramatic and impressive clinical presentation. Children will have a prodromal illness, which is suddenly followed by the onset of red macules or urticarial lesions. Consequently, symmetrically distributed, large, tender, ecchymotic, purpuric lesions (described in a cockade pattern) appear with non-pitting oedema. It mainly affects the face and extremities, sparing the trunk and mucous membranes. Some areas may even become necrotic. Visceral involvement is rare, whereas the kidneys and joints are spared. Spontaneous recovery occurs within 2–3 weeks. Occasional relapses have been reported.⁴ The differential diagnoses include meningococcaemia, forms of small vessel vasculitis, e.g. Henoch–Schönlein purpura, or reactive erythemas, e.g. erythema multiforme and drug eruption. Since there are no diagnostic laboratory examinations, the history and physical examination provide clues to the successful recognition of the disease. Aetiologically acute haemorrhagic oedema of infancy represents a hyper-

sensitivity, or leucocytoclastic vasculitis, characterised by inflammation of the small dermal vessels with fibrinoid necrosis and extravasation of red blood cells.⁴ Treatment with oral corticosteroids has been reported, but this is unnecessary due to its spontaneous recovery.⁵

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