

Paediatric allergy in review

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Abstract

This will provide an overview of allergy to facilitate an understanding of the epidemiology, immuno-pathology, and the early life origins of the allergic diseases, which are increasing in prevalence worldwide. This veritable allergy epidemic poses a significant public health burden in both the developed and the developing worlds and makes optimal allergy care in both primary and tertiary settings a priority. A clear body of literature supports the commonly observed evolution of early food allergies and atopic dermatitis to the later development of the airways allergic diseases, namely allergic rhinitis and asthma. The main hypotheses behind these concepts are described. A typical clinical case is discussed in order to highlight this allergic march in the clinical setting and current and future strategies for allergy prevention are explored.

Keywords allergic march; allergic rhinitis; allergy; asthma; atopy; eczema; food allergy; hypersensitivity; IgE; immediate; sensitization

Introduction

Allergic eczema, asthma, hay fever and food allergy are collectively known as 'atopic diseases'.

Atopy may be defined as a state of IgE hyper-responsiveness to specific allergen exposure – in other words a predisposition to allergic disease. However, not everyone with atopy, or evidence of sensitization to a specific allergen on allergy testing, develops the clinical manifestations of allergy.

The term 'allergy' refers to a hypersensitivity reaction initiated by immunological mechanisms. This is an adaptive immune response which has evolved following a primary exposure to an antigen/allergen which may best be defined as an altered acquired specific capacity to react. Allergy can be antibody or cell-mediated and is a response to a specific protein allergen which may be immediate or delayed. IgE-mediated disease is the most frequent and best understood clinical expression of atopic disease, although other mechanisms may occur in atopic individuals. In food induced enteropathies and allergic eczema and asthma, allergy tests sometimes confirm IgE sensitization. However, non IgE mediated allergy is also recognized – conventional allergy testing is non-diagnostic but there is a clear clinical response to a double blind placebo controlled allergen

challenge. In practice, the majority of diagnoses are made with a combination of a supportive history and positive allergy tests, facilitated more recently, by clearer diagnostic cut-offs for skin prick tests and specific IgE's.

Prevalence

There has been a true increase in the prevalence of allergic diseases over the last few decades.

Cross-sectional studies, such as the International Study of Asthma and Allergies in Children (ISAAC), have confirmed that atopic diseases represent a widespread and major health problem. The prevalence of asthma has increased at about 50% each decade, over the last 30 years, in most if not all developed countries. Similar increases are being seen in prevalence data for other atopic diseases, including recent Centres for Disease Prevention and Control (CDC) data for skin-test sensitization.

See [Figure 1](#) for current rates of atopic symptoms and comorbidities in UK children, aged 12 years.

The rise in prevalence of allergy and its health cost implications are not fully accounted for by improvements in the diagnosis and identification of children with atopic conditions over time. This phenomenon has been noted in both the developed and the developing world, especially in children, for which several hypotheses have been postulated.

Health and economic consequences

According to the Department of Health in 2006, the direct cost to the NHS of managing all allergic diseases has been estimated at over £1 billion per annum in the UK. Estimates for primary care (GP consultations) ranged from £211 million to £311 million and estimates for secondary care (hospital inpatient) ranged from £56 million to £83 million. Primary care prescribing costs represented the most significant proportion of costs at over £0.7 billion. Identifying causal risk factors and addressing them has the potential to significantly reduce the health/economic burden.

Risk factors

Genetic

Allergic diseases tend to cluster in families. This suggests the existence of a genetic predisposition that has been confirmed by family and twin studies. However, there is not a simple Mendelian pattern of inheritance and it is accepted that there are multiple genes involved which have an additive effect and interact with environmental factors to predispose to atopy. Advances in genetics and molecular biology, through linkage studies in chosen family clusters and genome wide association studies (GWAS) in large and diverse populations, facilitate the location of chromosomal regions related with allergic pathology. The genes situated in these regions are considered candidate genes. Identifying the functional consequences of genetic variations has aided understanding of the mechanisms of allergic sensitization and its manifestation as specific allergic disease. It is important to understand that there are independent influences on susceptibility to allergic sensitization which differ from those which affect the risk of allergy manifesting as a specific atopic disease. Thus GWAS have identified genetic polymorphisms associated with specific diseases independent of allergy both in relation to eczema and asthma. For eczema

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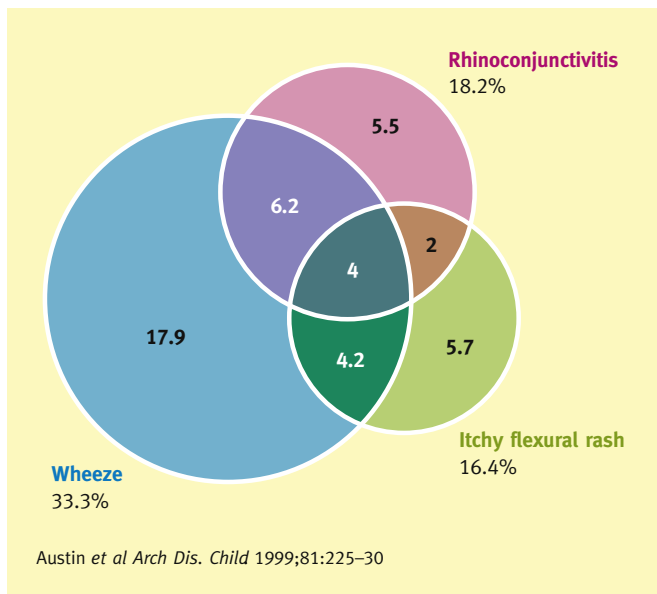


Figure 1 Current atopic symptoms in 12 year olds (ISAAC UK).

polymorphisms in skin barrier function genes such as filaggrin and for asthma airway epithelial function genes such as ADAM 33 (A Disintegrin and metalloprotease 33) affect risk, independent of allergic sensitization.

However, polymorphisms in IL4R and TLR4 are related to allergen-specific IgE. Highly significant associations have also been identified between SPINK5 variants and visible eczema (but not IgE levels) and between IL13 variants and total IgE. A greater understanding of these and other candidate genes may clarify some aspects of allergic diseases and provide therapeutic targets.

Allergen exposure

The development of sensitization to an allergen requires exposure to that allergen. A close association between allergen exposure, and sensitization to that specific allergen has been identified in a number of cross-sectional studies performed in children and adults. However, the relationship is not linear, with both very high and very low levels being associated with a reduced risk of sensitization. Low levels are not sufficient to initiate a response while high levels induce tolerance. This suggests that for the majority of ubiquitous allergens for which complete avoidance is impossible, induction of tolerance by high dose exposure will be a better public health strategy. This has changed concepts considerably over the last 5 years.

Data from a large birth-cohort study, MAS (Multicentre Allergy Study) suggest that while domestic allergen exposure is a strong determinant for early sensitization in childhood, it does not appear to be a primary cause of airway hyper-responsiveness or asthmatic symptoms. This confirms the concept that disease specific genes and independent environmental factors affect the manifestation of allergy.

Infection and endotoxin exposure

The hygiene hypothesis proposes that high rates of exposure to childhood infections are protective against the development of atopy and allergic disease. There is a known lower prevalence of respiratory allergic disease and sensitization to common

allergens in children who grow up in large families with older siblings. In addition, it is thought the increased exposure to endotoxins on farms or in homes with animals could modify immune responses to reduce the prevalence of atopic diseases. This is because endotoxin and other bacterial and viral factors trigger an immune response involving T-helper 1 lymphocytes (Th-1) associated with the generation of Interferon-gamma which suppresses the production of the allergy promoting cytokines, Interleukins (IL-) 4, 5, 9, 13.

Bowel flora

The intestinal microflora is a major source of stimulation of the immune system in early childhood. The intestinal microbiota can enhance Th-1 and T-regulatory cell (T-reg) responses. The latter are associated with the generation of IL-10 and Transforming Growth Factor- β . Different patterns in the intestinal microflora are associated with different levels of atopy, specifically with a likely protective effect of a bifido-bacteria dominant environment. However, intervention studies are needed to demonstrate the relevance of these findings and to examine the effect of adding probiotics to infant formulae. Data hitherto indicate that probiotics (live microorganisms thought to be beneficial to the host) and prebiotics (non-digestible food ingredients that stimulate the growth and/or activity of bacteria in the digestive system) may be of value in allergy prevention. However, more work is required before any recommendations can be made. The intestinal microbiota are complex and we understand little of the ecological balance of the very numerous bacterial species and the way they affect immune activity.

Diet and lifestyle

Diets have changed dramatically over the last few decades and although egg and milk allergies are most common in childhood, there are marked geographical differences in the rates and specific types of food allergies. Several novel food allergies have been noted, such as to kiwi and sesame. Current hypotheses implicate reduced intakes in omega 3 dietary fatty acids (mostly from fish) and anti-oxidants (selenium, vitamin C) in an increased risk of allergic inflammation. Demographic trends in vitamin D insufficiency have mirrored increases in allergic diseases. As this vitamin has receptors on immune active cells and clearly has immune modulatory effects it has been a focus of recent research studies. However, there is insufficient evidence for clear and specific dietary modification having any effects on allergy prevalence at present.

Pollutants

Maternal smoking during pregnancy is significantly associated with recurrent wheezing in infancy and early childhood and the risk of developing IgE responses to food proteins early in life. Interactions with epithelial barrier and antioxidant gene polymorphisms are likely. This is well demonstrated in relation to polymorphisms in anti-oxidant genes such as Glutathione methyl transferases. These are only associated with an increased prevalence of asthma in environments where there are high levels of pollutants. Several excellent reviews exist which summarize and discuss environmental exposures such as smoking, air pollution, diet, microbial exposures and day care, allergens and pet

keeping, moisture and dampness, and chemicals at the workplace that have been related to the new onset of asthma.

The effects of many gene–environment interactions are likely to be the consequence of epigenetic mechanisms. These are the acquired but heritable moderations of gene expression by methylation of DNA which silences genes, or chemical modification of histones in the chromosome backbone which can enhance gene expression. Thus grand-maternal smoking during the embryonic period of the mother increases risk of asthma independent of maternal smoking.

Immunological paradigms of sensitization and disease

Although the production of IgE is known to start in the 11th week of gestation, it is rare for specific sensitization to food or inhalant allergens to be detected in cord blood. After birth, total serum IgE concentrations increase with age. However, it is possible to detect differences in cord blood T-cell responses in those newborns that subsequently develop allergy. The problem of atopy begins antenatally when the nascent immune system develops an aberrant balance between Th1, Th2 and T-regulatory cell immune responses to common antigens to which the mother is exposed. The balance of responses is affected by genetic predisposition and the timing and nature of the allergen exposure.

Antenatally there is normally a bias towards a Th2 response, as part of the protection of the foetus against maternal Th1 activity which might otherwise be directed against foeto-paternal antigens. It is well established that excessive maternal Th1 responses will induce miscarriage or intra-uterine growth retardation in both murine models and humans.

Postnatally, probably through microbial exposure, the Th1 and Th2 balance is restored. However, the allergically prone infant retains a Th2-biased response which leads to progressive increase in IgE. The IgE binds to high affinity receptors on the mast cell and basophils (FCεRI). Subsequent exposure to allergen leads to degranulation of these cells with release of vaso-active mediators inducing the immediate allergic reaction (such as urticaria, angio-oedema, anaphylaxis). There is also release and generation of mediators which induce cell migration of neutrophils and notably eosinophils which results in delayed responses appearing after around 4 h after exposure and lasting for several days. In the airways this will enhance bronchial hyper-responsiveness which can last for several weeks.

The allergic march of childhood

It is well known that atopic eczema (frequently in infancy association with food allergy) predates the development of asthma and allergic rhinitis by several years. An observed pattern of allergic phenotypes which develop in early childhood, and their natural histories, has been called the “The Allergic March”.

See Figure 2 for a graphic representation of the allergic march and its characteristics.

This is characterized by a typical sequence of IgE antibody responses and clinical symptoms that appear early in life, persist over years or decades, though they sometimes remit spontaneously with age.

Although, in practice, there is wide individual variation, the Allergic March paradigm highlights that food allergy and atopic eczema are typically seen first, beginning in the first few months

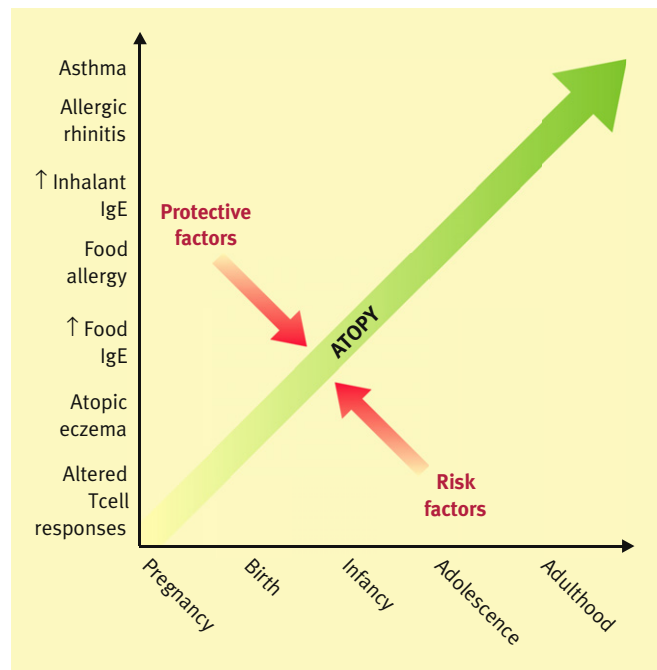


Figure 2 The atopic march.

to a year of life. These conditions can improve and be outgrown in many children during the preschool years. Asthma and allergic rhinitis tend to declare themselves later, becoming increasingly common at around 3–4 years and on into the school-age years.

The IgE responses directed to food proteins may be observed during the first months of life, and are most commonly directed to hen's egg and cow's milk. Even in completely breast-fed infants, specific serum IgE antibodies to these foods can be detected. It is possible that sensitization to food protein allergens could occur via mother's milk but there is increasing evidence that the eczematous child may be sensitized through skin contact to foods for which there has been no oral exposure.

Case study

See Figure 3 of infant with atopic facial eczema.



Figure 3 Atopic eczema.

CJ was first seen as a 6 month old from an atopic family, having developed an intensely itchy facial and flexural rash from the age of 3 months. He had been exclusively breastfed until the age of 4 months. The micro-vesicular erythematous eruption with characteristic distribution was classical of atopic eczema. His mother was a smoker, however he had no respiratory symptoms. At the age of 12 months, CJ developed facial swelling (angio-oedema) following ingestion of a small amount of custard, which contains egg and milk.

Investigations, including, IgE antibodies and food challenge, were undertaken.

Discussion

A useful diagnostic approach advocated by most allergists is to take a strong clinical history focussing on the following questions:

Q1: Is the patient atopic?

CJ's parents are atopic and he has eczema. Both eczema and a family history of allergy are independent risk factors for the development of food allergy.

Q2: Does allergy contribute to the patients' symptoms?

There is a common misconception that breastfed infants cannot have food allergy. However, the allergen load via breast milk is significant and the commonest implicated allergens are cow's milk and egg.

Q3: What are the clinically relevant allergens?

CJ's history was suggestive of atopic IgE mediated eczema and angio-oedema due to cow's milk and/or egg allergy, and this was confirmed on allergy testing.

He was managed with an appropriate avoidance diet. Topical skin therapy is also very important to suppress inflammation (steroids or calcineurin inhibitors) and to build-up the damaged skin barrier (emollients). Anti-histamines will reduce urticarial reactions which are common in infants with eczema.

Prognosis — high risk for asthma and other allergies.

At the age of 24 months, CJ's mother noted a paroxysmal nocturnal cough causing post-tussive vomiting and sleep disturbance for 1 week during a cold. Subsequently, noisy breathing was heard when he was upset and occasionally with a persistent and sleep disturbing cough at night.

Notes: The differential diagnosis for recurrent persistent respiratory disease in childhood includes asthma (which may be classified as multi-trigger wheeze), viral-induced wheeze, milk aspiration, foreign body, cystic fibrosis, primary ciliary dyskinesia. However, family history of asthma and sensitization to indoor allergens, especially house dust mite, are the two strongest risk factors for childhood asthma.

CJ was started on a salbutamol inhaler for management of his cough to good effect. With time, he was started on a low-dose inhaled steroid for effective asthma control. However, at the age of 12 years, he was admitted with an acute episode of stridor and wheezing associated with generalized urticaria, angio-oedema and hypotension. This occurred within 5 min of eating a brazil nut.

Q1: What is CJ's risk of having another anaphylactic event on exposure to the same food?

Worldwide, 0.05–2% of people are estimated to have anaphylaxis at some point in their life. Foods are the commonest causes for anaphylaxis (61%). Surveys have shown that 1 per

1000 adults and 1 in 170 children experience at least one episode of anaphylaxis. One in 12 children suffer a recurrence.

Skin testing was unexpectedly negative to brazil nut. However, he had taken the brazil nut from a packet of mixed nuts. He had a 12 mm weal at the site of the skin test to peanut. Management included avoidance advice from a dietician, and training in the use of rescue treatment for inadvertent exposure including the use of an adrenalin injector.

Prospects for the future: intervention and prevention

Primary prevention

Primary interventions are aimed at preventing the development of allergic disease in an at risk but healthy population. Previous studies, beginning from birth or prior to birth, include supplementing the diet with probiotics and/or prebiotics. These have produced conflicting results but there is a suggestion that this approach will impact on prevalence. Similarly, vitamin D research has yielded variable findings. However, larger studies are required. Supplementation of the maternal diet during pregnancy with fish oils (containing omega-3 fatty acids) has also produced some very modest changes in immune profiles at birth and small differences in early allergic manifestations. Reducing exposure to dust mite allergen and other major indoor allergens, and/or to allergenic foods during pregnancy and/or after delivery has not been shown to be consistently of benefit. The Department of Health advice to avoid nuts in pregnancy was recently withdrawn due to the lack of evidence that it would decrease the development of peanut allergy. Studies are now in progress to establish whether deliberate early exposure to peanuts will reduce the risk of sensitization.

Breastfeeding as a protective factor for the development of atopy remains controversial. Beneficial aspects of breastfeeding, such as evidence of protection against infectious disease, obesity and several chronic illnesses, justify the recommendation for exclusive breastfeeding for at least 4 months, with the WHO currently recommending 6 months. In the ISAAC study, breastfeeding was associated with protection against non-atopic wheeze, which was particularly evident in non-affluent countries. There is no evidence that maternal food allergen avoidance during lactation prevents atopic disease.

There is evidence that atopic eczema may be delayed or prevented by the use of extensively or partially hydrolyzed milk protein formulae, compared with standard cow milk formula, in infancy. However, protection may only be related to the food proteins that were avoided but not for prevention of disease such as atopic eczema or respiratory allergy. There is no convincing evidence for the use of soy-based infant formula for the purpose of allergy prevention.

The extent to which the risk for atopic sensitization and disease manifestation may be decreased by dietary intervention in early infancy is unclear. The majority of studies seem to indicate that the development of allergic disease such as asthma later in childhood will be delayed but not prevented. There is currently a large UK based study EAT study, testing the hypothesis that the introduction of six allergenic foods into the diet of infants from 4 months of age, alongside continued breastfeeding, results in a reduced prevalence of food allergies by 3 years of age.

Currently the only recommendations that can be made for primary prevention during pregnancy and in early infancy are to

abstain from smoking and to eat a sensible balanced diet without avoidance of potential food allergens and to breast feed for at least 4 months.

Secondary prevention

These interventions take place in young at-risk children prior to the establishment of allergic disease. For example, these measures include the WHO recommendations to treat atopic eczema/atopic dermatitis topically, and possibly with systemic pharmacotherapy, to prevent respiratory allergy. The Study of the Atopic March [SAM] work is looking at topical calcineurin inhibitor in young children with new-onset atopic eczema. Reduction in specific allergen exposure is recommended for young children already sensitized to house dust mites, pets or cockroaches to prevent onset of allergic disease. Similarly, there is some data to indicate that treating upper airways disease (e.g. allergic rhinitis) can reduce the risk of development of asthma. This particularly relates to the use of allergen immunotherapy.

The PAT study (pollen allergen immunotherapy in children with allergic rhinitis), which administered pollen immunotherapy for 3 years with standardized allergen extracts of grass and/or birch significantly reduced the development of asthma in children who initially only had seasonal rhinoconjunctivitis. The beneficial effect lasted for several years after stopping the therapy.

Tertiary prevention

Immunotherapy continues to be the only way to successfully modify allergic disease to promote tolerance. Subcutaneous immunotherapy (SCIT) has celebrated its centenary and is known to be effective through promoting the production of IL-10 and reducing the production of Th-2 cytokines. The field continues to hold promise with new modes of administration which are child-friendly and effective, namely sublingual immunotherapy (SLIT).

For the treatment of severe persistent allergic (IgE mediated) asthma, omalizumab (a recombinant DNA-derived humanized IgG1k monoclonal antibody that selectively binds to human IgE) is recommended where conventional pharmacotherapy has failed. NICE guidance states that omalizumab add-on therapy is only recommended in those with severe asthma and IgE mediated allergy to a perennial allergen confirmed by clinical history and allergy skin or blood testing.

Care pathways

The Royal College of Paediatrics and Child Health (RCPCH) has developed care pathway for allergic diseases. These are presented in two parts: an algorithm with the stages of ideal care and a set of competences required to diagnose, treat and optimally manage food allergy. This important document, which is found on the RCPCH website and published on-line by Archives of Disease in Childhood, will assist the development of integrated care networks. By focussing on competence it is hoped, ultimately, that primary care physicians will be able to deliver appropriate management of many atopic children and refer in a timely fashion those who need more specialized care. The pathways also provide source guidelines which have used appropriate evidence-based approaches. These include the NICE food allergy and eczema guidelines, BTS/SIGN asthma management guidelines etc. ◆

FURTHER READING

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Practice points

- Eczema in infants under 6 months is strongly associated with food allergy, most commonly to milk and egg — refer for allergy assessment early
- Eczema and some food allergies (milk, egg, soy) tend to be outgrown or improve with age
- Children with food allergy and eczema are at high risk of allergic rhinitis and asthma
- Allergic rhinitis and other food allergies (nuts, seafood) tend to persist
- Optimization of the prevention, recognition and treatment of further reactions is important to minimize the impact on quality of life
- Growth and nutrition should be monitored
- Early consideration for appropriate immunotherapy is important as there is a chance to modify or prevent further allergic disease, specifically in the treatment of allergic rhinitis to prevent progressing to asthma
- The essence of allergy diagnosis is an appropriately focussed history supplemented by examination and allergy skin or blood tests
- Where doubt exists about specific allergy diagnosis a direct organ challenge may be necessary but should only be performed in specialist centres