Food allergy: Riding the second wave of the allergy epidemic

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Abstract

Food allergy is a substantial and evolving public health issue, recently emerging over the last 10–15 yr as a 'second wave' of the allergy epidemic. It remains unclear why this new phenomenon has lagged decades behind the 'first wave' of asthma, allergic rhinitis and inhalant sensitization. In regions like Australia, which lead the respiratory epidemic, challenge-proven IgE-mediated food allergy now affects up to 10% of infants. Although their parents were among the first generation to experience the large-scale rise in allergic diseases, disorders of oral tolerance were previously uncommon. Of further concern, this new generation appears less likely to outgrow food allergy than their predecessors with long-term implications for disease burden. Allergic disease has been linked to the modern lifestyle including changing dietary patterns, changing intestinal commensal bacteria and vehicular pollution. It is not yet known whether the rise in food allergy is a harbinger of earlier and more severe effects of these progressive environmental changes or whether additional or unrelated lifestyle factors are implicated. New studies suggest environmental factors can produce epigenetic changes in gene expression and disease risk that may be potentially heritable across generations. The rising rates of maternal allergy, a strong direct determinant of allergic risk, could also be amplifying the effect of environmental changes. Preliminary evidence that non-Caucasian populations may be even more susceptible to the adverse effects of 'westernisation' has substantial global implications with progressive urbanization of the more populous regions in the developing world. Unravelling the environmental drivers is critical to curtail a potential tsunami of allergic disease.

While attention has been steadily focused on the well-established surge of respiratory allergic diseases, a second wave of allergy has been slowly building behind it. Food allergy is now looming as a new epidemic with vast and significant implications. In a bizarre and puzzling twist, the very fact that this new epidemic has lagged decades behind the original epidemic of asthma and allergic rhinitis, raises a series of new and intriguing questions.

The 'first wave' of allergic disease asthma and allergic rhinitis began gaining momentum more than 50 yr ago, with evidence that that these conditions may have approached a crest in the most 'Westernised' countries by the 2000s (1–4). Aeroallergen sensitization became so common that almost half of the population in countries like Australia experienced symptoms of allergic rhinitis at some stage of life (5) and nearly a quarter had symptoms of lower airways reactivity (5). Although food allergy was certainly noted, it remained uncommon, little more than a footnote against the scale of the respiratory epidemic. Against this background, the 'second wave' has emerged only very recently, becoming most evident in the last 10 yr (6–8), in the very same countries that lead the respiratory epidemic, including Australia, the UK and the USA.

In developing countries, recent reports show a rise in non-food allergic diseases such as asthma in countries that are adopting a more 'westernised' lifestyle (9–11). This has major implications for these heavily populated regions of the world, because a second wave epidemic of food allergy may also occur in these countries because of as yet undetermined factors associated with the 'modern lifestyle'. If rising rates of allergy, in particular food allergy, mimic findings from the west, there is likely to be a major impact on healthcare provision of specialist allergy services worldwide.

Growing evidence for the second wave

As the rise in food allergy has been relatively recent (12), most regions do not have accurate or current prevalence data, particularly in infants and young children under 3 yr of

age who are most commonly affected. Many estimates are based on parent or self-reported questionnaires or surveys, but very few objectively confirm the prevalence of food allergy through the gold standard of oral food challenge. Even those few studies undertaking food challenges until recently have been hampered by poor challenge participation rates resulting in potential for substantial bias.

Recognizing these limitations, one large-scale US survey documented a greater than threefold rise in the prevalence of peanut and tree nut allergy between 1997 and 2008 (6). This was largely because of the increase in prevalence of allergy in children younger than 18 yr. Similar rates of nut allergy have been also reported in UK (13, 14) and Australian children (8). Data from Australia, a country with one of the highest rates of food allergy in the world, indicate that there has been more than a 10-fold increase in specialist referrals for food allergy, coupled with more than a fivefold increase in the number of hospital referrals for food-related anaphylaxis, the most severe and potentially life-threatening form of IgE-mediated food allergy reaction (8). Again, most of this increasing disease burden was seen in young children, particularly in those of preschool age (8). This dramatic increase in hospital admissions for anaphylaxis in Australia [around twice that described in United Kingdom (7)] was independent of both referral bias and location (8).

Current prevalence of 'challenge positive' IgE-mediated food allergy even higher than anticipated

The only definitive way of accurately assessing the prevalence of clinical IgE-mediated food allergy in young infancy is by systematic testing and food challenges in a large unselected community population. To our knowledge, the only large-scale single-centre, population-based cross-sectional study of food allergy in 12-month-old infants is the Australian 'Healthnuts Study'. This is internationally unique, and its large size (n = 5000), population-based formal sampling frame and high community participation rate (73%) support precise and unbiased estimates. Furthermore, it is also the first entire population-based cohort phenotypically characterized for true food allergy by oral food challenge. Unlike other studies, every participant (regardless of individual or family allergy history) underwent skin-prick testing at 12 months and children with positive tests irrespective of SPT wheal size proceeded to hospital-based food challenge to confirm the clinical food allergy. Another unique feature of this study is that the prevalence was adjusted for participation bias – both at the point of initial population screening and at invitation for food challenge. Participation rates were high (85%), and non-participants were also surveyed to allow for any bias towards allergy. Preliminary analysis of the first 2848 infants assessed indicates very high rates of atopy with 18.0% (95% CI 16.7%, 19.4%) showing food sensitization. Furthermore, challenge-proven IgE-mediated food allergy now affects up to 10% of 12-month-old infants, with 8.9% (95% CI 7.8–10.0) egg allergic and 3.0% (95% CI 2.4–3.8) peanut allergic. Eczema was also common, affecting 26.7% (95% CI 25.0%, 28.4%) of this community population (15). These findings confirm that food allergy rates are now higher than ever previously reported, even after adjusting for participation bias. The findings are consistent with the growing numbers of patients being referred with significant IgE food allergy across Australia and growing burden on paediatric allergy health care services. Similar observations in many regions suggest that data currently being collected from other developed countries are also likely to reflect this.

A new generation, a new disease profile?

Another curious and puzzling observation is that this newest generation of children are presenting with a different profile of disease than their parents, in particular demonstrating an earlier and more dramatic failure of oral tolerance during the first year of life. Although their parents were among the first generation to experience the large-scale rise in allergic diseases, disorders of oral tolerance were uncommon in infants from this past generation who were more likely to present with respiratory allergies (asthma and allergic rhinitis) later in childhood. More concerningly, children from this second generation appear less likely to outgrow food allergy than their predecessors which has obvious long-term consequences for the healthcare system and allergy services in particular. New studies suggest that both egg and milk allergies, which were previously regarded as almost universally transient with resolution in the preschool years, are now commonly persisting into late childhood and adolescence (16, 17). These observations suggest that both the natural history and the disease profile are also changing in the face of presumed environmental pressures. It also raises an important question of how allergic propensity might be amplified or modified across generations through epigenetic effects, as discussed in more detail later.

The usual suspects or new causal pathways?

As the rise in allergic disease has occurred more rapidly than changes to the genome can occur and because allergic disease appears significantly more prevalent in 'Westernised countries', it has been hypothesized that factors associated with progressive lifestyle changes within affected regions are responsible for the changes in prevalence. The current most popular candidate lifestyle factors associated with the allergy epidemic include declining microbial exposure (18), an increased pro-inflammatory modern diet (19) and inhaled pollutants associated with motor vehicles and the rise in traffic. Although clear and progressive changes in these factors have been long implicated in the rise of asthma and inhalant sensitization, they have not yet been proven to be causative possibly because of the multifactorial aspect of lifestyle risk factors.

These hypothesized factors, however, do not explain the temporal differences in susceptibility to inhaled vs. food-related allergic diseases. Specifically, they do not explain the temporal delay in the rise of food allergy and eczema, nor do they explain the changing patterns of allergic disease severity and persistence. Furthermore, food allergy continues to rise

as asthma reaches a plateau and even enters decline in highly westernized regions (1), suggesting that different risk factors are at play.

Mechanisms of environmental influence?

There is now firm evidence from animal studies that environmental exposures during critical stages of development can alter gene expression and disease predisposition through epigenetic mechanisms (20). Although these notions of 'developmental origins' originated in cardiovascular and metabolic medicine, the epidemic rise in allergic and autoimmune diseases (21) faster than genome changes can occur also suggests an associated susceptibility of the immune system to modern environmental changes. Moreover, the clinical expression of allergic disease in very early infancy strongly reinforces that both antenatal events and very early post-natal events are likely to play a critical role. The placenta and the foetus are both vulnerable to exogenous and endogenous maternal influences during this period. Notably, most of the environmental factors implicated in the development of allergic disease (including microbial exposure, dietary factors, cigarette smoke and other pollutants) have also been shown to influence foetal immune function in pregnancy and contribute to an increased risk of subsequent allergic disease (reviewed in Ref. 22). There is now preliminary evidence that each of these has been associated with epigenetic effects (reviewed in Ref. 22), modifying immune programming by epigenetically activating or silencing immune-related genes.

Epigenetics can be described as the bridge between genotype and phenotype – an event that changes the final outcome of a locus or chromosome without altering the underlying DNA sequence (23). For example, a majority of cells in the human body have identical genotype, but there are diverse cell types with different functions. Epigenetic modification acts as a mediator for environmental influences on gene expression and a modulator of disease risk associated with genetic variation (24). As Th1, Th2, Th17 and Treg differentiation is known to regulate epigenetic changes via DNA/histone methylation and/or histone acetylation, there has been growing speculation that environmental changes that modulate these epigenetic control mechanisms may modify the risk of allergic disease by altering gene expression in these pathways during early development (22, 25).

A role for transgenerational epigenetic effects: an amplifying effect of maternal allergy?

Maternal allergy is a stronger determinant of allergic risk and immune neonatal function than paternal allergy (26–28), suggesting effects of direct materno–foetal interactions *in utero* or other maternally imprinted effects. Foreseeably, the rise in maternal allergy may also be amplifying the effect of environmental changes and potentially influencing the age of onset, phenotype and severity of disease in the offspring. In this way 'allergy may beget more allergy'.

There is some evidence that allergic women have modified immune interactions with their foetus in pregnancy, with lower Th1 IFN-γ responses to HLA-DR-mismatched foetal antigens compared with non-allergic women (29). These factors may affect the cytokine milieu at the materno–foetal interface and could be implicated in the attenuated neonatal Th1 responses observed commonly in infants of atopic mothers (30), a recognized risk factor for infant allergic disease (31–33). This suggests that the endogenous effects of the maternal allergic phenotype may compound the increasingly pro-allergic exogenous environment.

Allergic women appear more likely to have infants with food allergy, although there are few published studies on this. Our most recent birth cohort studies show that food allergy (positive food SPT and history of IgE-mediated symptoms) occurs in 13% of 1-yr-old infants of atopic (SPT+) women compared with only 4% of infants of non-atopic (SPT−) women ($p < 0.001$) (S. L. Prescott, unpublished data November 2010). We have also seen that the rates of allergy in offspring may be increasing in this 'high risk' population, as seen in several prospective birth cohorts of allergic women sampled from the same community. Around 9% of allergic women recruited in a 1999 cohort had a child with IgE-mediated food allergy at 1 yr of age (34), compared with 13% infants from a cohort of allergic women recruited after 2005 (unpublished data), suggesting changing environmental effects over this period.

Perhaps more significantly, epigenetic changes induced by environmental changes can be inherited across generations. This allows heritable adaptations to environmental changes, but may also confer an amplified heritable disease risk as a result of adverse environmental exposures in subsequent generations, as seen in animal models of allergic disease (35). We speculate that at least part of the increase in allergic disease could have been mediated by environmental changes that had their initial impact on gene expression in preceding generations, inducing heritable changes in gene expression patterns that confer increased disease risk. This phenomenon could also make it more difficult to identify causal pathways, as relationships between exposures and phenotype within a generation may not reflect any transgenerational temporal lag effects. Finally, the role of changing maternal intestinal microbial milieu and its impact on offspring may be a significant but unmeasured player in the evolving allergy epidemic.

Different processes governing oral tolerance compared with tolerance to inhaled allergens

Oral tolerance is arguably one of the first and most significant challenges that the immune system faces. From the sterile environmental of the womb, the newborn infant is exposed to a vast array of new antigenic proteins in relatively high 'doses'. Most of this foreign antigenic load is derived from colonizing commensal bacteria and food components. To prevent inflammatory responses to these largely harmless antigens, the gastrointestinal-associated lymphoid tissue has evolved complex mechanisms to promote tolerance as a default response (reviewed in Ref. 36). Tolerance has been described to occur in the 'two phases' (36). In the first instance, there is establishment of an immunosuppressive

milieu, which inhibits unwanted *local* inflammation in the gut. This subsequently provides optimal conditions for the development of highly regulated *systemic* immune responses. Dendritic cells (DC) play a central role in both of these processes, producing immunomodulatory cytokines (IL-10 and TGFβ), which suppress local inflammation in an antigen-nonspecific manner. DC also promote differentiation of antigen-specific regulatory T cells (Treg), which are essential for systemic immune surveillance and tolerance.

The development of clinical tolerance to food allergens (even in food allergic children) is typically associated with loss of both lymphoproliferation and Th2 responses to food allergens usually in early childhood (37). Some food-specific cytokine responses appear to persist (IL-10 and IFN-γ) (37, 38), suggesting an active process of suppression rather than deletion of allergen-responsive cells.

These events appear to contrast with the development of tolerance to inhaled allergens, which develops more gradually following exposure to much 'lower doses' of allergens. Lymphoproliferation to inhaled allergens is sustained throughout life and clinical and immunological tolerance maintained by the Th2 suppressive effects of allergen-specific Th1 and Treg clones. The rise in respiratory disease many decades before food allergy could indicate that processes underlying inhalant tolerance are more sensitive to environmental changes or that disruption of tolerogenic environmental influences in the gut has been more recent. The success of oral tolerance appears to depend on a number of oral exposures. Although the best known of these are optimal colonization and breast milk, dietary immunomodulatory factors including prebiotics (soluble fibre), fat soluble vitamins and polyunsaturated fatty acids may also have an important anti-inflammatory role (reviewed in Ref. 39). There is also some evidence to suggest that both the gastric acid milieu (40) and a window of opportunity of optimal allergenic solids introduction between 4 and 6 months of age (41, 42) are potential factors for oral tolerance development. The composite effects of 'cleaner' environments (reviewed in Ref. 43) and more inflammatory 'western' dietary patterns (39) are likely to influence susceptibility to disorders of oral tolerance significantly and are important ongoing areas of research.

The implications for rapidly urbanizing developing regions: anticipating a tsunami?

Lower rates of allergic disease in the most populous regions of the world do not mean that these populations are less susceptible. To the contrary, there is evidence that Asian populations may be more susceptible to allergic disease when living in 'westernised' environments (44, 45). Earlier studies of respiratory disease observed that both allergic symptoms and sensitization were more common in Asian Australians than in non-Asian Australians (44). Rates were also higher in Australian-born Asians than in Asian immigrants, with the prevalence increasing with length of stay in Australia (44). More recent studies have similarly noted that non-white races are more susceptible to food allergy, particularly Asian populations (45), suggesting a strong genetic propensity that is amplified by a western environment. This is consistent with earlier work indicating evolutionary differences in genetic polymorphisms affecting candidate genes (46). Most significantly, this has major global implications, as the heavily populated regions of Asia are becoming rapidly urbanized, westernized and industrialized. Rates of asthma and allergic rhinitis have already risen rapidly (5), and although prevalence rates are still lower than in the 'west', there are already likely to be more asthmatics in China than the rest of the world combined. Eczema prevalence has already increased to significant levels in Asia (47). As urbanization inevitably progresses, we can also anticipate a major rise in food allergy. Recent reports suggest that this is occurring in China (48). A better understanding of the environmental drivers of allergic propensity would ideally provide opportunities to prevent this. As yet this is beyond our grasp.

Food allergens – friends or foe?

Failure of tolerance is highly selective, affecting responses to only a very limited number of antigens/allergens, and suggesting that protein allergenicity is an important determining factor. Thus, while changes in allergen exposure do not seem to explain the rise in allergic disease, allergenicity likely determines the target of the misdirected immune response. There is good evidence that complete allergen avoidance is an unattainable therapeutic goal (49) and early evidence to suggest that it might even be harmful. Evolving evidence suggests that earlier regular exposure may actually be important for promoting tolerance (14, 42). Recently, we have shown that introduction of cooked egg between 4 and 6 months of age decreased the risk of development of egg allergy at age 12 months by fivefold and that this risk was strongest for those from non-allergic families providing supportive evidence that this effect was not confounded by 'reverse causation' because of high-risk families delaying the introduction of allergenic solids beyond the first year of life (42).

This intriguing finding needs to be further confirmed by prospective, randomized controlled trials. Even then, it is likely that the effects of allergen feeding will vary between individuals and populations as a result of phenotypic, genotypic and other environmental variants. In our own efforts to address this, we are performing two double-blind randomized controlled trials to examine whether there is any difference in the development of challenge positive IgE-mediated egg allergy in children who start daily egg powder with other weaning foods (from 4 to 6 months) compared with the placebo group (receiving image-matched rice powder) who do not start egg until 8–10 months. One study is examining children with only a first degree relative with allergy, but no evidence of symptoms themselves, whereas the other study is enrolling infants who are already developing an allergic phenotype (eczema) before 4–6 months. We anticipate that the effect of early feeding could be different in this second group, known to have differences in barrier integrity rendering their skin and gastrointestinal tracts more 'permeable' to allergens (26, 27). As with treatment of most complex, multifactorial conditions, it is likely that prevention of allergy

needs to be 'individualized' and the effect of any intervention will vary with both genetic and environmental factors. This also means that the answer to this question many not be revealed by the results of a single study, but a series of studies examining different populations using different regimes under different conditions.

A final word

Investigating the causes of the rise in food allergy constitutes an enormously exciting challenge that may take many decades to unravel. In the process, we need a more thorough understanding of the developing immune system and the events that lead to oral tolerance. This should ideally include identification of predisposing genes, critical environmental determinants and maternal–foetal interactions which pave pathways to disease. Epigenetic paradigms may hold the keys to understanding early gene environmental interactions, rising rates of disease and potential transgenerational effects. Most excitingly of all is the looming possibility that targeted modulation of early determinants may not only reduce the impact of early allergic disease but also have lasting benefits against chronic adult disease. There have been significant advances in non-food allergy research in only the last 30–40 yr, from a time when very little was known at all. While food allergy research has lagged behind, accelerating technologies give great cause for optimism in this green fields research with enormous possibilities for discovery.

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