How epidemiology has challenged three prevailing concepts about atopic dermatitis

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Abstract

We challenge three prevailing concepts in understanding atopic dermatitis using data from epidemiological studies. First we show that whilst atopy is *associated* with atopic dermatitis to some degree, its aetiological importance is not likely to be a simple cause and effect relationship, especially at a population level. Our epidemiological data do not exclude a *contributory* role for IgE-mediated immunological *processes*, especially in those with existing and severe disease. Second, evidence is presented that does not support a straightforward inverse relationship between infections and atopic dermatitis risk. A link, if present, is likely to be more complex depending critically on the timing and type of infectious exposure. Third, recent evidence suggests that the risk of subsequent childhood asthma is not increased in children with early atopic dermatitis who are not also early wheezers, suggesting a co-manifestation of phenotypes rather than a progressive atopic march. Collectively, these observations underline the importance of epidemiological studies conducted at a population level in order to gain a more balanced understanding of the enigma of atopic dermatitis.

What prevailing concepts?

A number of ideas about atopic dermatitis have developed over the last 40 years, often based on clinician's experiences of people with more severe disease who present themselves for treatment. Some ideas have become firmly embedded into the belief systems of practitioners and researchers simply because the notions have been promulgated many times in textbooks and at allergology and dermatology meetings. Thus, there is a common perception that atopic dermatitis is atopic (by atopy we mean demonstration of IgE sensitization in the serum or by a positive skin prick test).[1] Another popular idea is that the rise in atopic dermatitis is mainly due to lack of infections – the so-called "hygiene hypothesis". Then there is the notion that children with atopic dermatitis progress from skin disease through to asthma as the child becomes older – the "atopic march".

Whilst generating ideas from hospital patients is fine, rigorous epidemiological studies are needed to relate numerators to defined populations in order to test such ideas. The purpose of this short rostrum article is to provide a brief glimpse at what epidemiology has contributed to our understanding of the three themes of (i) how atopic is "atopic" dermatitis? (ii) is atopic dermatitis due to lack of infections? and (iii) do children with atopic dermatitis progress to asthma? Throughout the rest of the article, we shall refer to atopic dermatitis as "eczema" in accordance with the new World Allergy Organisation nomenclature committee's recommendations published in this journal.[1] We have based our material on systematic reviews of the literature where possible, and in the tradition of *Journal of Allergy and Clinical Immunology* rostrum articles, we have allowed ourselves some space for debate and research recommendations in our concluding section.

(i) How atopic is "atopic" eczema?

There is continuing controversy as to whether allergic sensitization, ie skin prick test positivity or elevation of specific IgE levels to common environmental allergens, is an essential feature of childhood eczema. Early studies demonstrated very high levels of total serum IgE in children with eczema, and *in vitro* research has shown skin from affected individuals to be rich in IgE-bearing antigen-presenting dendritic cells - considered instrumental in the capture of environmental allergens.[2] Further studies underlying the importance of sensitization include the observation that inhalation of house dust mite allergen can provoke eczematous skin lesions in predisposed patients, and that IgE receptors can act as mediators in the clinical expression of eczema following skin application of aeroallergens in the atopy patch test.[3] It is not surprising therefore that many regard allergic sensitization as an integral part and important *cause* of childhood eczema. Yet despite detailed knowledge of the underlying immunological *mechanisms* in childhood eczema, the *aetiological* role of sensitization in childhood eczema remains uncertain.

Recent epidemiological research suggests that while sensitization to environmental allergens is clearly *associated* with the disease phenotype that is called eczema, it does not seem to be an important *aetiological* factor.[4] Indeed, the strength of the association between allergic sensitization and childhood eczema varies widely between studies. Up to 50% of eczema sufferers in hospital settings are not sensitized, and an even greater proportion are not sensitized in cases ascertained from community studies as shown in the 12 population-based studies summarised in Table 1.[4,5] A recent systematic review found good evidence to suggest that those with more severe eczema are also more likely to be sensitized, thus partly explaining the higher sensitization rates in hospital versus community studies.[4] The strength of the association between allergic sensitization and eczema phenotype also varies between

developing and industrialized nations. Population-based data collected from 31,000 children aged 8 to 12 years from 22 countries as part of the International Study of Asthma and Allergies in Childhood (ISAAC) using standardised diagnostic criteria that includes physical examinations has shown that the association between allergic sensitization and flexural eczema is weaker in low than in high income countries.[6] The population-attributable risk for allergic sensitization, i.e. the proportion of flexural eczema that is directly attributable to atopy at the population level varies from below 50% in affluent countries to almost zero in a number of non-affluent study centres. [6] Taken together, these findings suggest that allergic sensitization is not a pre-requisite for childhood eczema nor is it a uniform cause of eczema, and that other risk factors linked to western lifestyle must be sought to explain the high prevalence of childhood eczema in industrialized countries. At the same time, these epidemiological data do not exclude a *contributory* role for IgE-mediated immunological processes, especially in those with existing and severe disease.

Having acknowledged that some people with eczema are atopic and some are not, does this mean than eczema can be conveniently divided into two distinct types?: an allergic (extrinsic) and a non-allergic (intrinsic) phenotype?[7] We would caution against such a premature binary classification based on easily-measurable epiphenomena which do not necessarily play an important aetiological role. Perhaps there are five or more types of eczema, the defining patterns of which will become clearer as we learn more about the genetic and environmental causes of what is currently recognised as the common phenotype of eczema.[8] For example, the recent discovery of two independent loss-of-function genetic variants (R510X and 2282del4) in the gene encoding filaggrin (FLG) as very strong predisposing factors for eczema might tempt us to start dividing eczema into a dry (or defective barrier) and non-dry

types.[9] Other important discoveries around the corner may help to explain the variation of eczema phenotype, so it is premature "to put all our eggs into the IgE basket".[10]

Cohort studies of five years duration or more that assemble children with eczema defined by reliable diagnostic criteria[11] in early life and who are also tested for atopy are needed to see whether those with genuine atopic eczema differ from those with non-atopic eczema in terms of incidence of subsequent asthma, eczema persistence, and eczema severity over the following years. Those conducting randomised controlled clinical trials of people with eczema should also consider measuring atopy as a covariate so that exploratory sub-group analysis could be done to see if treatment response is different in those with and without atopy.

(ii) Is atopic dermatitis due to lack of infections?

Epidemiological studies have shown that eczema is commoner among children growing up in smaller families and in those from higher socio-economic status.[12] It seems plausible that reduced exposure to certain viral and bacterial pathogens in early life could lead to an increase in eczema incidence. Deprivation in stimulation of the developing immune system from certain microbial antigens in the gastrointestinal mucosa or other lymphoid tissues may lead to immunological deviations which could increase the risk of sensitization to environmental allergens and eczema.[13] Microbial antigens can act as inducers of regulatory T cell-mediated anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta, and a lack of stimulation from such cytokines could promote skin inflammation as seen in eczema, especially in those with a genetic predisposition.[14]

However, there is currently no clear epidemiological evidence to suggest that exposure to a specific infection *reduces* the risk of childhood eczema. In fact, a recent

systematic review found that some childhood infections such as measles, are associated with an *increased* risk of eczema development as shown in Table 2.[15] In addition, the decreased risk of eczema seen with increased number of siblings appears to persist after adjustment for early childhood infections, suggesting that early postnatal or even pre-natal factors, such as an alteration of the gut microflora, play an important role in eczema development. This may be why frequent antibiotic prescribing in infants increases the risk of eczema development and could also explain why probiotics have been shown to reduce the risk of developing eczema. The protective effect on eczema development seen with day care attendance during infancy, endotoxin exposure, and being brought up with a pet during early life, could all be mediated by non-pathological microbial stimulation of the infant's immune system and warrant further study.[15] Microbial stimulation or lack of it may be important for eczema development, but the association is far from simple. It is important for future work to carefully examine the effect of *timing* and the degree of individual microbial and other infectious exposures on eczema risk. It is also possible that other endemic infections such as gut parasites simply suppress the expression of latent eczema in certain populations where allergic disease rates are very low,[16] and a study is currently underway in Vietnam by the authors to evaluate the effects of wide-scale de-worming programmes on the subsequent expression of allergic disease.

(iii) Do children with atopic dermatitis progress to asthma?

Whilst eczema, asthma and allergic rhinitis tend to cluster in the same individuals and families, the exact relationship between early eczema and subsequent asthma over time is far from clear.[17] The simple notion of the "atopic march" i.e. a child who progresses from eczema to asthma and hay fever as they become older, is a popular one.[18,19] Indeed, the concept formed the very basis of the ETAC study - one of the

largest randomised controlled trials in the field of eczema - a study that failed to show any benefit from the antihistamine cetirizine in preventing subsequent asthma in children with early eczema.[20] In order to evaluate the role of preceding eczema in subsequent asthma development, cohort studies that compare children with early eczema to those who do not have eczema and who are then followed over time to estimate the incidence of subsequent asthma are needed. One recent such study is the Multi-Centre Allergy Study (MAS), a German birth cohort study that followed 1314 children from birth to 7 years.[21] The MAS study showed that early wheeze and a specific sensitization pattern were significant predictors for wheezing at school age, irrespective of early eczema. Early eczema *without these co-factors* did not confer any increased risk of subsequent asthma (adjusted odds ratio 1.11, 95% confidence intervals 0.56-2.20). The idea of a distinct subgroup of children with early eczema and early wheeze is further supported by the observation of a specific sensitization pattern to wheat, cat, mite, soy or birch (a less prevalent sensitization pattern at age 2 years) in that group plus significantly reduced lung function at age 7 years. Such an important finding needs to be confirmed in other studies, but if true, it spells the end of the idea of a simple atopic march from eczema to asthma and instead points to an early co-manifestation of two phenotypes at an early age.[22] The link between eczema and asthma is further challenged by positional cloning studies that suggest a closer relationship between eczema and psoriasis than between eczema and asthma[23]. It has also been noted previously that the epidemiology of eczema seems to be much more aligned to allergic rhinoconjunctivitis than asthma.[24] Perhaps eczema is not that close to asthma after all and that they cluster together simply because they happen to share some causative risk factors. Let the cohort studies begin...

Where does all this epidemiological data leave us?

We have challenged three prevailing concepts in the field of eczema with epidemiological research based on systematic reviews of the literature. It is all very well challenging prevailing concepts with epidemiological evidence, but where does that leave the practising clinician and future research agenda for eczema? In clinical terms, the fact that not all eczema is atopic is important to remember so that the consultation is not dominated by an obsession with allergic factors – indeed non-allergic factors such as *Staph aureus*, physical factors such as low humidity, excessive heat, emotional stress and addressing the defective barrier function may be just as important.[25] Since the relationship between infections and eczema is not a simple one, it is not surprising that therapeutic ramifications such as administration of probiotics for eczema has so far been disappointing, at least for established disease.[26] Children with eczema who do not exhibit early wheezing are probably not at an increased risk of developing significant asthma compared with children who do not have eczema, and such information could be quite useful in the consultation of the family of a young child with eczema.

Future research should adhere to the new WAO nomenclature to assist in scientific communication[1], and where possible children with eczema should be tested for atopy so that the role of atopy in determining prognosis, disease associations, severity and responsiveness to treatment can be determined. Infections probably play some part in regulating the development of eczema, but future studies will need to dissect the timing, magnitude and type of such infectious or macrobiotic stimulation in order to clarify those that are protective, neutral or harmful. With regards to the natural history of disease, we should look to more cohort studies that evaluate the link between early wheezing in the presence of eczema, and also explore some of the ideas suggested by

Bieber on a new possible concept of an “atopic march” from barrier dysfunction, through early sensitization to eventual auto-sensitization from skin antigens.[27]

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