

Two types of eczema—or are there?

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In this issue of the Journal, Kusel et al¹ report on a birth cohort study of 263 children born to atopic parents from Western Australia. In addition to providing useful data on the early onset and persistence of eczema and its relationship to other atopic diseases, the main novelty of this article is the finding that risk factors for those who had atopic eczema—that is, the phenotype of eczema plus specific IgE sensitivity—were different from those who had nonatopic eczema (or the previously so-called *intrinsic type*). The authors suggested that male sex; onset of rash in first year; prolonged breast-feeding; and a history of food allergies, allergic rhinitis, and asthma were associated with the atopic type of eczema, whereas the nonatopic form of eczema was more common in girls and in those who had attended daycare centers early in life. To what extent are these findings true and what do they mean for current clinical practice and future research?

Strengths of the study by Kusel et al¹ include the prospective study design, clear definition of disease and atopy, and good follow-up rates. Nevertheless, there are some dangers in taking the suggestion by Kusel et al¹ that there are 2 distinct types of eczema with different risk factors at face value.

The first danger is the role of chance. Although the authors state that the nonatopic form of eczema was associated with female sex and childcare in the first year, those associations were not statistically significant at the conventional level, as shown in Table VI of their report. Also, 21 risk factors were explored across 2 disease subgroups, and it is possible that some of the positive associations found at the 5% significance level simply arose by chance. Perhaps a more stringent level of statistical significance was needed for so many exploratory analyses.^{2,3}

Problems of interpretation in relation to chance are also possible. For example, the authors state in their conclusion that the nonatopic form of eczema has no relationship with asthma and hay fever. Although it is true that there did not appear to be a statistically significant association between doctor diagnosis of asthma and nonatopic eczema in their report, the risk was increased for such children with an odds ratio of 1.8 and upper 95% CI of 4.6. In other words, the results are still compatible with an increased risk of asthma of up to 4.6 for nonatopic eczema children. The wide CIs indicate that the study had insufficient power to exclude even quite large associations within this smaller group of patients with nonatopic eczema. Put simply, no evidence of an association is not the same as evidence of no association.

A more subtle issue relating to the role of chance affecting interpretation of this study is the fact that the 2 subgroups of atopic versus nonatopic forms of eczema were unbalanced in their power to reveal underlying associations. There were twice as many cases of atopic eczema as the nonatopic form in the study by Kusel et al,¹ so in one sense, it is not surprising that the larger group revealed more statistically significant associations than the smaller one (5 risk factors reached the 5% level of statistical significance for the atopic form of eczema, compared with none for the nonatopic form). The effects of lower power for the nonatopic form can readily be seen in the wide CIs for effect estimates in Table VI of their report. There is thus a risk of claiming associations for one group but not another simply because one group had more power to detect such associations. Such a problem is likely to recur in other cohort studies, because nonatopic cases usually form a minority. Care therefore needs to be taken in interpreting the influence of study power on study conclusions by examining CIs or by ensuring that each atopic or nonatopic subgroup has the same power to detect possible associations.

Confounding by disease severity may be another important issue. A previous systematic review of the relationship between atopy and eczema showed that 7 out of 8 relevant studies found eczema severity positively associated with positive skin prick test responses or IgE antibody levels.⁴ IgE sensitization may therefore be more of a predictor (or even an epiphenomenon) of eczema severity. It thus follows that associations claimed to be unique for atopic eczema may in fact be risk factors for eczema severity. Future studies should consider

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TABLE I. Recommendations for future epidemiologic studies of atopic and nonatopic forms of eczema

- (1) There should be a clear definition of the eczema phenotype—for instance, the United Kingdom modification of the diagnostic criteria by Hanifin and Rajka.⁷
- (2) There should be a clear definition of what constitutes atopy—that is, positive skin prick or IgE antibody test results.⁸
- (3) Ideally, classification of patients with eczema as atopic or not atopic should be performed at more than 1 time point to avoid misclassification bias.
- (4) Cohort studies should be encouraged because they offer the strongest design to explore the temporal sequence between atopy and eczema.
- (5) Possible risk factors of atopic versus nonatopic eczema should be specified *a priori*.
- (6) Ideally, studies should have similar power for evaluating risk factors in both forms of eczema.
- (7) Given the possibility that IgE sensitization may be a surrogate for eczema severity, associations for atopic versus nonatopic eczema should be stratified by disease severity.

performing sensitivity analyses by adjusting risk factor analyses by disease severity when comparing atopic versus nonatopic forms of eczema.

What is the significance for clinical practice? Although it is exciting to speculate that there may indeed be 2 or more variants of eczema with a different prognosis, disease associations, and modifiable risk factors, it is too premature to interpret the current study's interesting findings as proving that such subtypes exist until they are replicated in other studies. A previous systematic review on the relationship between IgE sensitization and eczema found some evidence to support the notion that IgE sensitization is associated with more persistent eczema and more allergic airway disease in later life.⁴

What are the implications for future research? We strongly endorse the commitment of Kusel et al¹ to exploring the possibility that there might be at least 2 variants of eczema, and we encourage others conducting epidemiological, genetic, and clinical studies of eczema to collect data on atopy and to plan an appropriate subgroup analysis so that a better picture of the 2 possible types can be built up. Indeed, failure to consider different disease subgroups within the eczema phenotype might be one reason why some hitherto undescribed risk factors for eczema have not been discovered. For example, if the same factors (such as season of birth) have opposing risk effects in the 2 possible different types of eczema, then simply examining all eczema cases lumped together as 1 homogenous group runs the risk of missing important associations, because the opposing risk factor associations could cancel each other out. The study by Kusel et al¹ also provides a useful starting point for generating hypotheses: that there may be a different set of risk factors for atopic and nonatopic eczema that can now be explored in other birth cohorts such as the German Multicenter Allergy Study.⁵

The current study by Kusel et al¹ also illustrates how the proportion of atopic patients among patients with eczema

can change and increase over time, with different individuals expressing atopy at different time points in the follow-up. The corollary is that studies such as those with a cross-sectional design that define atopic state on the basis of just 1 test at 1 point in time may be especially prone to misclassification bias. We agree with the authors' strategy for defining nonatopic cases as those who were never classified as atopic at any stage to avoid temporal misclassification.

Future epidemiology studies should also give careful consideration to the appropriate control group for making comparisons with the atopic and nonatopic forms of eczema. In calculating the risk estimates for atopic eczema, for instance, should cases with eczema and atopy be compared against all others in the cohort (including nonatopic eczema cases, nonatopic noncases, and atopic noncases)? Or should they be compared just against all noncases (which will diminish the ability to evaluate associations with atopy since some controls will also be atopic) or just against nonatopic noncases? It is unclear what constituted the control group in the study by Kusel et al,¹ but we would recommend that control groups include all noncases to maximize power and to avoid a study that inadvertently identifies risk factors for just atopy if all atopic noncases are excluded from controls. Constructive suggestions for future epidemiologic studies of atopic versus nonatopic eczema are shown in Table I.

There might well be at least 2 forms of eczema, but until further studies demonstrate a consistent pattern of different risk factors or prognosis or response to treatment, we urge a degree of skepticism. One previous study that conducted skin prick tests and aeroallergen tests on people with eczema proposed that there were 4 subtypes of eczema based on their responses.⁶ Although this could be true, there is danger that the number of types of eczema will grow in a multiplicative fashion depending on the number of tests that are available, and many of those tests may not be related to underlying disease genesis. We should take stock and gather more evidence before we chop up eczema into lots of little bits. If, on the other hand, it emerges from several studies that there is a consistent constellation of associations with different types of eczema in a way that increases our predictive ability—for instance, modifiable risk factors for disease preventions, prognosis, association with asthma, or response to treatments—then it would make sense to change the nosology of what we now consider just 1 disease. Until such studies emerge, it is recommended that researchers persist in studying the visible disease phenotype of eczema as a primary analysis while conducting planned subgroup analysis among patients classified as atopic and nonatopic.

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