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Expression Patterns of Atopic Eczema and Respiratory Illnesses in a High Risk Birth Cohort

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Capsule Summary

Increased severity of respiratory illnesses, RSV wheezing and early allergic sensitization were significant risk factors for atopic eczema disease persistence. These children represent a distinct phenotype of AE.

Keywords

atopic dermatitis; atopic march; wheezing; birth cohort; eczema; atopic eczema

To the Editor

Atopic eczema (AE) is the most common chronic inflammatory skin condition in childhood. 1 The natural course is variable and difficult to predict. Some patients completely “outgrow” their disease, while others develop more significant and persistent disease. 2 In addition, AE in early childhood has been linked to an increased risk of allergic rhinoconjunctivitis and asthma. Patterns of expression and identification of factors associated with the persistence of AE may lead to improved primary and secondary prevention strategies to halt the progression of the atopic march, as well as improved prognostication of the clinical course of AE. We examined the natural history of AE in children enrolled in the Childhood Origin of ASThma (COAST) study, a high-risk birth cohort comprised of children with parental histories of asthma and/or allergies, to define early risk factors for the persistent expression of disease.

The COAST study enrolled 287 high-risk children before birth who participate in annual study visits. Children were followed to age 6 and were classified as having AE if: (1) AE was diagnosed by a physician at a study visit or (2) the Eczema Area and Severity Index³ score completed by the study team was ≥ 1 , or (3) a parent reported physician-diagnosed AE. Over 99% of the yearly AE diagnoses were made using criteria 1 or 2. Physician-diagnosed wheezing respiratory illness and asthma were defined as previously published.⁴

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Using latent class modeling analysis, children fit into one of three AE phenotypes. The majority of these children never had AE or had a transient course ($n = 167$, 62%). Fourteen percent of children ($n=38$) had little or no disease in the first three years of life, and then developed AE in years 4–6 (late-onset AE). Sixty-six children (24%) had early/recurrent AE, with early and persistent skin manifestations throughout the period of observation. There were no significant differences in gender, ethnicity, birth weight, gestational age or parental atopic history between the groups.

A novel finding in our study was that children with early/recurrent AE had more moderate-to-severe viral respiratory illnesses in the first year of life compared to the healthy/transient group ($p=0.02$, Table I). Additionally, wheezing illnesses in year 1 continuing through age 4 were significantly associated with early/recurrent AE (Figure 1). When viral pathogenesis was investigated, RSV-associated wheezing in the first year of life was most closely associated with early/recurrent AE (Table I and Figure 1). A positive relationship between moderate-severe respiratory illnesses in infancy and AE provides evidence contrary to the original hygiene hypothesis. There are limited data examining the relationship between viral respiratory illnesses in early life and the natural history of AE. One large longitudinal study prospectively asked mothers about respiratory illnesses and AE by telephone, and reported a positive correlation.⁵ Our study extends these findings by identifying a relationship between proven viral illnesses, severity of illness and the specific phenotype of early/recurrent AE.

The relationship between respiratory tract illnesses and AE suggests that these disorders are linked by a common underlying susceptibility factor, possibly related to immune regulation, epithelial barrier function, or both. Early sensitization may indicate a greater degree of immune dysregulation (e.g. defective T regulatory cells), which could contribute to persistent AE and progression through the atopic march. Alternatively, it has been proposed that the defective skin barrier in AE promotes sensitization after cutaneous contact with allergens.⁶

During the first year of life, children with early/recurrent AE were more likely to develop allergic sensitization (to food and/or aeroallergen) compared to the healthy/transient and late onset AE phenotypes (Table I). Following the cohort longitudinally, children with early/recurrent AE continued to have significantly higher rates of allergen-specific IgE at age 2, 5 and 6 years (Figure 1), while total serum IgE levels did not significantly vary between the defined AE groups until age 6 years. At age 6, children with none/transient AE had a higher total IgE (Supplementary Material).

Interestingly, dog in the home at the time of birth was less common in the early/recurrent group (10%) compared to the healthy/transient (43%) and late onset (50%) groups (Table I). Exclusive breastfeeding for the first six months of life was associated with late onset disease vs early/recurrent disease ($p=0.05$, Table I). Other factors, including daycare attendance, older siblings, and environmental tobacco smoke exposure were not different. Early/recurrent AE was more closely associated with atopic biomarkers and other atopic diseases throughout early childhood (Supplementary Material).

The increasing prevalence of AE has led to the search for environmental factors that modify the risk or natural history of AE. In our study, lack of exposure to dogs, but not cats, was associated with early/recurrent AE. This finding is consistent with other reports that exposure to dogs, particularly near the time of birth, has been associated with distinct changes in immune development in early childhood, and lower rates of wheezing by age 3 yr.⁷ In contrast to the factors discussed above, breastfeeding was associated with late onset atopic eczema. It is possible that exclusive breastfeeding delays the onset of AE in children who might otherwise have developed it in infancy. Similarly, our data suggest that breastfeeding may have differential effects depending on the specific phenotype of AE. Published studies have had

varied results with respect to effects of breastfeeding on AE, and findings may differ depending on the atopic history of the parents or the failure to consider different phenotypes of AE.^{5,8,9}

In conclusion, children in this high-risk cohort can be grouped into one of three distinct AE phenotypes: healthy/transient, late onset and early/recurrent AE. Our data suggest that frequent significant respiratory viral illnesses, early onset of allergic sensitization and wheezing are associated with early/recurrent AE, while exposure to dogs may have beneficial effects. Further studies to define the underlying mechanisms linking AE to respiratory illnesses and other potentially modifiable factors are warranted to identify new therapeutic targets and strategies for prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AE	atopic eczema
COAST	Childhood Origins of ASThma
FEIA	Fluoroenzyme immunoassays
EASI	eczema area and severity index
RSV	respiratory syncytial virus
RV	rhinoviruses
ETS	environmental tobacco smoke
LCA	latent class analysis

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Figure 1.

Longitudinal assessment of wheezing and allergic sensitization. For the three AE groups, separate graphs depict the prevalence of wheezing illnesses (A), RSV-specific wheezing illnesses (B), and age-specific changes in any positive FEIA (C, ≥ 0.35 kU/L for food or aeroallergen,) annually from birth to age 6 years. * $p < 0.05$ healthy/transient vs. early recurrent, $^{\dagger}p < 0.05$ early/recurrent vs. late onset.

Table 1

Risk factors for persistent atopic eczema at year 1

Year 1 risk factor	Group			P-value	
	None/Transient (62%)	Early/recurrent (24%)	Late Onset (14%)	None/transient vs Late Onset	Late Onset vs Early/recurrent
MSI	1.9 ± 1.7	2.5 ± 1.7	2.0 ± 1.7	0.75	0.02*
RV MSI	1.1 ± 1.3	1.2 ± 1.2	0.7 ± 1.0	0.12	0.58
RSV MSI	0.3 ± 0.5	0.5 ± 0.5	0.3 ± 0.5	0.77	0.02*
Wheezing Illness	23%	45%	29%	0.46	0.003*
RV wheezing Illness	15%	24%	15%	0.91	0.12
RSV Wheezing Illness [†]	13%	36%	17%	0.52	0.0003*
Exclusive breastfeeding 1 st 6 mos	31%	26%	46%	0.10	0.51
ETS exposure	21%	29%	33%	0.14	0.19
Older siblings	53%	63%	53%	0.98	0.19
Day care	45%	53%	44%	0.92	0.33
Cat at birth	29%	29%	34%	0.58	0.92
Dog at birth [†]	43%	10%	50%	0.38	<0.0001*
Any + Food FEIA [†]	18%	48%	11%	0.29	<0.0001*
Any + Aero FEIA	9%	23%	10%	0.81	0.007*
Any + FEIA	21%	53%	16%	0.49	<0.0001*
Total IgE (kU/L)	13 [5, 32]	16 [9, 29]	12 [5, 26]	0.56	0.09
Food allergy	2%	15%	2%	0.98	0.001*
					0.07

Abbreviations: RV, rhinovirus; RSV, respiratory syncytial virus; MSI, moderate-to-severe respiratory illness determined by symptoms scores (mean with ± SD);³ ETS, environmental tobacco smoke exposure; FEIA, fluorezyme immunoassay;

[†] included in latent class model.