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Duration of neonatal intensive care unit exposure associated with decreased risk of atopic dermatitis

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Abstract

Background/Objectives: Premature infants have lower rates of atopic dermatitis (AD) compared with full-term infants, though little is known about the factors contributing to this association. We explored the infant and environmental factors that may contribute to the association between prematurity and atopic dermatitis, including mode of delivery, birthweight, gestation, and duration of stay in the neonatal intensive care unit (NICU).

Methods: This was a single-center retrospective study. Independent samples t tests or chi-square tests were used to compare groups on continuous and categorical variables, respectively. Logistic regression then examined the association of the predictor variables with AD.

Results: Four thousand sixteen mother-infant dyads were included. Infants had a higher risk of developing AD if they were delivered vaginally ($P = .013$), did not stay in the NICU ($P < .001$), had a longer gestation ($P = .001$), or had a higher birthweight ($P = .002$). In modeling atopic dermatitis with the predictor variables, only NICU length of stay remained significantly associated with a lower risk of AD ($P = .004$).

Conclusion: Infants had a lower risk of developing AD if they had a longer stay in the NICU.

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CONFLICTS OF INTERESTS

Dr Schoch serves on the medical advisory board for Janssen Biotech, Inc. The other authors have no relevant conflicts of interest to disclose.

INSTITUTIONAL REVIEW BOARD APPROVAL

The Institutional Review Board at the University of Florida approved this study.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Keywords

atopic dermatitis; neonatal intensive care unit; prematurity; preterm

1 | INTRODUCTION

Infantile AD is the first step in the proposed "atopic march," followed by food allergies, asthma, and allergic rhinitis.[1] In infants with AD, a compromised skin barrier exposes cutaneous immune cells to antigens and allergens, allowing for sensitization. This early sensitization places infants at risk for future allergic diseases, leading to the "atopic march."[2] Recent breakthroughs in AD have focused primarily on treatment,[3] while there has been less focus on the prevention of AD. A multi-site randomized controlled trial demonstrated that consistent emollient use in infancy reduces the occurrence of AD by up to half,[4] indicating that the neonatal period is a crucial, modifiable period in the pathogenesis of AD. The protective effect of emollient use may be due to repair of this barrier defect, which blocks antigen exposure.

Perhaps counterintuitively, preterm infants develop AD less often than full-term infants.[5–14] Though some investigators have not found a significant relationship between prematurity and eczema,[5,15–19] a recent meta-analysis supports the proposed link in extremely preterm infants.[20] Many of the studies included a predominantly Caucasian population, limiting the generalizability of the results.[6,7,9–13,15–19] A confounder in this relationship, lower birthweight has also been linked to a lower risk of atopic dermatitis.[21] Other possible confounders, including mode of delivery, do not appear to be related to subsequent development of atopic dermatitis.[19] These descriptive population-based studies do not offer insight into the causative mechanisms behind this association. Further research is needed to better understand the specific infant, maternal, and environmental factors contributing to this association.

Herein, we explore the infant and environmental factors that may contribute to the association between prematurity and atopic dermatitis, including mode of delivery, birthweight, gestation, and duration of stay in the neonatal intensive care unit (NICU). A better understanding of the mechanisms behind the lower rate of atopic dermatitis in preterm infants may provide a key clue in AD prevention. Identifying a modifiable cause of AD may also prevent the atopic march, thereby also reducing the incidence of food allergy, asthma, and allergic rhinitis.

2 | METHODS

The University of Florida Institutional Review Board approved this study. All infants born at the University of Florida Shands Hospital (UF Health) from June 1, 2011, to April 30, 2017, were included in the study. Utilizing electronic health records (EHR), we then identified a sub-group who received primary care within our system past the initial birth visit. Children were included in the study sample if they had at least two well child visits, including one well child visit at or after 300 days of life. Retrospective review of the EHR included demographic, birth, maternal, and clinic data. A child was classified as having

atopic dermatitis if ICD codes for atopic dermatitis were recorded in the EHR, including ICD-9 (691.8) and ICD-10 (L20.83, L20.84, L20.89, L20.9, L30.8, L30.9) codes.

Data were inspected for implausible values, missingness, and distributional form. Summary statistics (ie, means, standard deviations (SD), and frequencies) were computed for study variables. Exact 95% confidence intervals (CI) were calculated for the incidence of atopic dermatitis. Independent samples t tests or chi-square tests were used to compare groups with/without atopic dermatitis on continuous variables and categorical variables, respectively. We used logistic regression to simultaneously examine the association of the predictor variables of sex, delivery mode, gestational age, birthweight in grams, and length of stay in the NICU, with atopic dermatitis. The level of significance was set at 0.05, and all hypothesis testing was two-sided. SAS version 9.4 was used for all analyses.

3 | RESULTS

In total, 4016 mother-infant dyads met criteria for inclusion in the study (Figure S1). Approximately 49% of the infants were female; 39.2% were black, 7.6% were Hispanic, 38.5% were white, and 14.7% were of other race/ethnicity. Sixty-five percent of deliveries were vaginal (see Table 1 for sample demographics).

Atopic dermatitis was diagnosed in 26.6% of the sample (95% CI = [25.2%, 27.9%]). In bivariate analyses, delivery mode ($P = .013$), NICU stay ($P < .001$), gestational age ($P = .001$), and birthweight ($P = .002$) were significantly associated with incidence of atopic dermatitis. Infants had a higher risk of developing atopic dermatitis if they were delivered vaginally, did not stay in the NICU, had a longer gestation, or had a higher birthweight (Table 2). Extremely preterm (less than 28 weeks) and very preterm (28 to less than 32 weeks gestation) infants had the lowest rates of atopic dermatitis at 10.9% and 19.0%, respectively.

In modeling atopic dermatitis with the predictor variables of delivery mode, gestational age, birthweight in grams, and length of stay in the NICU, we found that only length of stay in the NICU was related to the development of atopic dermatitis after adjusting for other variables in the model. Infants who spent more time in the NICU had a lower risk of developing atopic dermatitis ($P = .004$). Logistic regression coefficients and standard errors are reported in Table 3.

Maternal age was significantly associated with atopic dermatitis, with a mean maternal age of 27.4 years in infants with atopic dermatitis and a mean age of 28.0 years in infants without atopic dermatitis. This age difference, however, was not felt to be clinically significant. Maternal age was included in the original logistic regression model, however did not significantly change the model, and was excluded from the final model.

4 | DISCUSSION

The lower rate of atopic dermatitis among premature infants is associated with duration of exposure to the neonatal intensive care unit. This highlights the importance of early life exposures, as this effect may be due to interactions between the microbiome,

developing cutaneous immunity, and the evolving skin barrier of the preterm infant. The skin microbiome of premature infants differs from that of full-term infants, with more predominance of *Staphylococcus* species in the premature infant cutaneous microbiome.[22] The early presence of *Staphylococcus* in the skin microbiome may confer protection. Kennedy et al[23] found that early colonization with *Staphylococcus* was associated with a lower risk of atopic dermatitis at one year of age. It is possible that time spent in the NICU may be associated with increased likelihood of colonization with *Staphylococcus* in a dose-dependent manner; further studies are needed. This influence of the NICU environment on the establishment of the neonatal intestinal microbiome has been previously described.[24] However, little is known about the influence of the NICU on the skin microbiome.

In the infant's rapidly developing immune system, there is a delicate balance between the acquisition of tolerance and the development of antigen sensitization. It is possible that the timing of antigen exposure plays a role. Scharschmidt et al[25] demonstrated that lack of cutaneous bacterial antigen exposure in murine infancy leads to subsequent inflammatory responses upon re-exposure. Tolerance develops when regulatory T cells rapidly migrate to the pups' skin during the second week of life, in response to the cutaneous organisms. Exposure outside of this "critical window" does not lead to tolerance, but rather inflammation.[26] Such a critical window of cutaneous immune tolerance may exist in humans, but the antigens of interest and timing of such a window are unknown.

Other aspects of exposure to the NICU environment may influence subsequent development of atopic dermatitis. Exposure to humidified isolettes in the NICU may influence skin barrier development, and thus the development of atopic dermatitis. Early infections and stimulation of the immune system may also play a role, which warrant a rigorous prospective study. Premature infants also have increased early exposure to antibiotics, and further research is needed to examine the association between timing of antibiotic exposure and atopic dermatitis.

While a critical window of immune tolerance and increased *Staphylococcus* exposure in the NICU may explain the lower rates of atopic dermatitis among preterm infants, this theory does not explain the higher rates of atopic dermatitis found in post-term[12] and high birthweight[21,27] infants. This result was not duplicated in the present study, as no significant difference was found in atopic dermatitis rates between the late preterm, early-term, full-term, and post-term groups. Larger multicenter studies are needed.

This study is strengthened by the racial diversity within the present cohort. The majority of studies examining the relationship between prematurity and eczema, including a recent systematic review and meta-analysis, did not comment on race.[20] The linkage of maternal and infant medical records, which allowed us to examine both maternal and infant variables in their contribution to the development of infantile atopic dermatitis, was an additional asset.

This study was performed at a single tertiary medical center, and multicenter studies are needed to explore the relationship between prematurity and the subsequent development of eczema. Limitations of this study include the use of retrospective data in the reporting

of patient outcomes (particularly diagnostic codes) and missing data (Tables 1 and 2). The limitations of electronic health records in research have been previously outlined.[28] Of particular concern to this study is the limitation of diagnostic accuracy. While most pediatricians and pediatric subspecialists are comfortable with the diagnosis of atopic dermatitis, it may be difficult to discern atopic dermatitis from other common neonatal rashes, such as seborrheic dermatitis. Additionally, family history of atopy is not readily available in the EHR, but may contribute to the risk of AD.

This is the first study to identify an independent association between duration of NICU stay and a lower risk of atopic dermatitis. Knowledge gaps exist in our understanding of skin microbiome acquisition in the first weeks of life. A better understanding of host-microbe interactions of neonatal skin will lead to novel strategies for protection from atopic disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Demographic data[a]

Feature	N (%) or Mean (SD)
Sex	
Female	1954 (48.8%)
Male	2052 (51.2%)
Race	
Black	1574 (39.2%)
White, non-Hispanic	1543 (38.5%)
Hispanic	286 (7.1%)
Asian	213 (5.3%)
Multiracial	135 (3.4%)
Other	262 (6.5%)
Payer	
Medicaid	2079 (51.9%)
Private insurance	1310 (32.7%)
Managed care	485 (12.1%)
Self-pay	62 (1.6%)
Medicare	39 (1%)
Other	31 (<1%)
Delivery mode	
Vaginal	2425 (65.0%)
Cesarean section	1309 (35.1%)
Mean Maternal age at delivery (y)	27.8 (5.8)
NICU stay	
No	3457 (86.1%)
Yes	559 (13.9%)
Mean NICU length of stay (d)	3.9 (18.1)
Mean Gestational age (wk)	38.1 (3.3)
Gestational age	
Early preterm (<28 wk)	119 (3.1%)
Very preterm (28 to <32 wk)	121 (3.2%)
Moderate to late preterm (32 to <37 wk)	448 (11.7%)
Early term (37 to <39 wk)	1089 (28.3%)
Full term (39 to <41 wk)	1765 (46.0%)
Late/post-term (41 wk or greater)	301 (7.8%)
Mean Birthweight (g)	3036.0 (757.5)
Birthweight (g)	
Extremely low birthweight (<1000 g)	131 (3.3%)
Very low birthweight (1000 to <1500 g)	102 (2.5%)
Low birthweight (1500 to <2500 g)	451 (11.2%)
Normal birthweight (2500 to <4000 g)	3124 (77.8%)

Feature	N (%) or Mean (SD)
Macrosomia (>4000 g)	208 (5.2%)

Note: Demographic data including sex, race, and payer of the cohort, as well as maternal factors (age) and infant factors (delivery mode, gestational age, birthweight) are summarized.

[a] Categorical responses may not sum to total sample size of 4016 due to missing data.

TABLE 2

Relationship of infant factors with atopic dermatitis[a]

Feature	Rate of atopic dermatitis N (%) or Mean (SD)	*P*-value
Sex		
Female	512 (26.2%)	.617
Male	552 (26.9%)	
Delivery mode		
Cesarean section	315 (24.1%)	.013
Vaginal	675 (27.8%)	
Maternal age (y)		
No atopic dermatitis	28.0 (5.8)	.007
Atopic dermatitis	27.4 (6.0)	
NICU stay		
No	960 (27.8%)	<.001
Yes	105 (18.8%)	
NICU length of stay (d)		
No atopic dermatitis	4.6 (20.0)	<.001
Atopic dermatitis	2.0 (10.9)	
Gestational age (wk)		
Early preterm (<28 wk)	13 (10.9%)	.001
Very preterm (28 to <32 wk)	23 (19.0%)	
Moderate to late preterm (32 to <37 wk)	129 (28.8%)	
Early term (37 to < 39 wk)	295 (27.1%)	
Full term (39 to < 41 wk)	486 (27.5%)	
Late/post-term (41 wk or greater)	72 (23.9%)	
Birthweight (g)		
Extremely low birthweight (<1000 g)	19 (14.5%)	.002
Very low birthweight (1000 to <1500 g)	22 (21.6%)	
Low birthweight (1500 to <2500 g)	104 (23.1%)	
Normal birthweight (2500 to <4000 g)	869 (27.8%)	
Macrosomia (>4000 g)	51 (24.5%)	

Note: Independent samples *t* tests or chi-square tests were used to compare groups with/without atopic dermatitis on continuous variables and categorical variables, respectively.

[a]Categorical responses may not sum to total sample size of 4016 due to missing data.

TABLE 3

Modeling of atopic dermatitis with predictor variables

	Atopic dermatitis		
Logistic model parameter	**Logistic Regression Coefficient Estimate**	**Standard Error**	***P*-value**
Intercept	−0.4826	0.7785	.535
Sex			
Female	−0.0370	0.0771	.631
Male [ref]			
Delivery mode			
Cesarean section	−0.1488	0.0828	.072
Vaginal [ref]			
NICU length of stay	−0.0116	0.00400	.004
Birthweight (g)	0.000086	0.000090	.336
Gestational age	−0.0183	0.0247	.459

Note: Logistic regression was used to simultaneously examine the association of the predictor variables of sex, delivery mode, gestational age, birthweight in grams, and length of stay in the NICU, with atopic dermatitis.