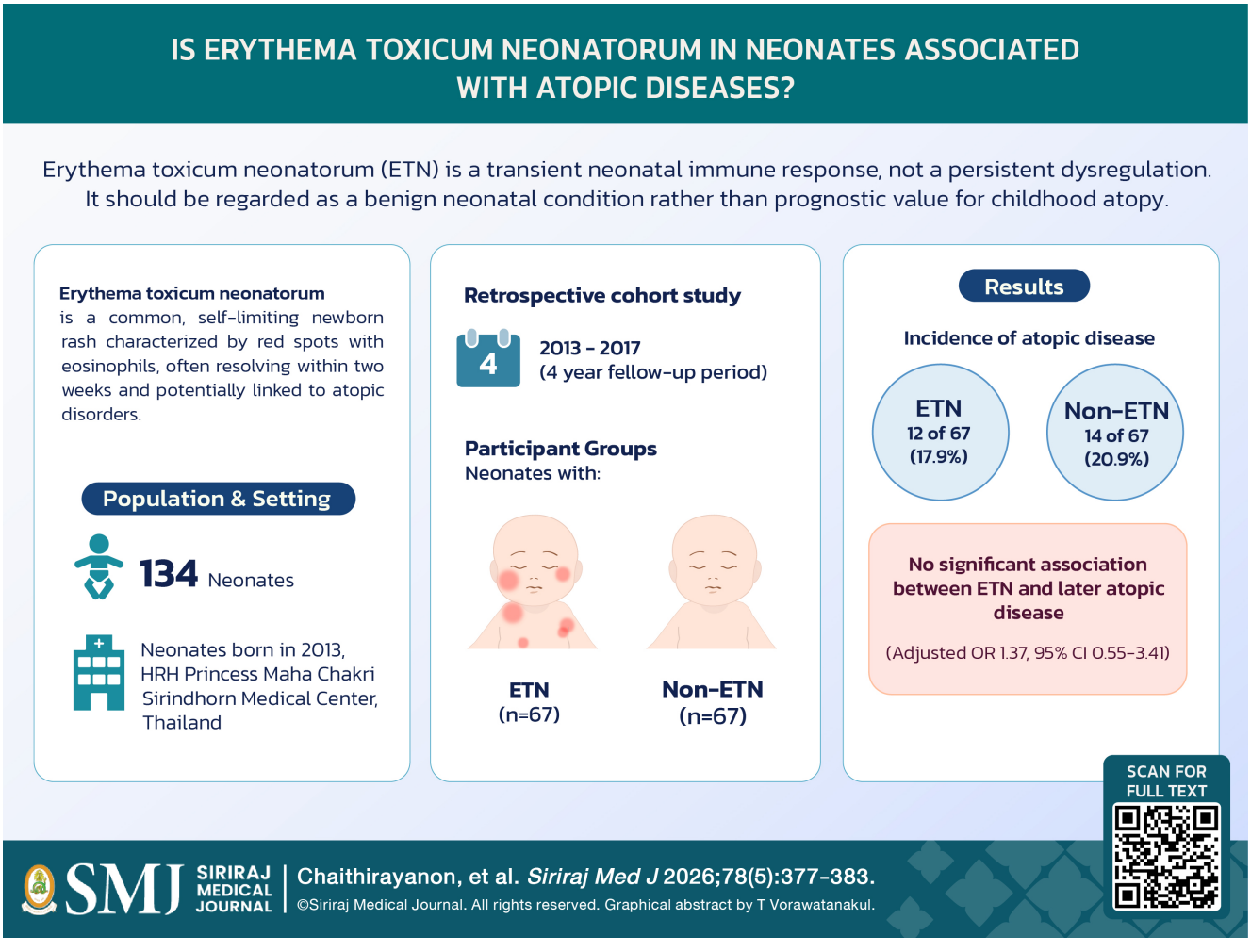
Is Erythema Toxicum Neonatorum in Neonates Associated with Atopic Diseases?

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ABSTRACT

Objective: Erythema toxicum neonatorum (ETN) is a benign rash commonly observed in newborns, typically resolving spontaneously within one to two weeks. The lesions are characterized by multiple erythematous macules containing eosinophils and are known to be associated with peripheral eosinophilia, a condition commonly seen in atopic diseases. Therefore, the presence of ETN may be associated with the subsequent development of atopic diseases. This study aimed to determine the prevalence of atopic diseases in newborns with and without ETN and to evaluate the association between the presence of ETN and the manifestation of atopic diseases during childhood.

Materials and Methods: This retrospective cohort study utilized electronic medical records and telephone interviews of subjects born at HRH Princess Maha Chakri Sirindhorn Medical Center in 2013. Participants were divided into two groups: newborns with ETN and those without ETN. The follow-up period for diagnosing atopic diseases extended to four years after birth (2017).

Results: A total of 134 newborns were included in the study (67 with ETN and 67 without ETN). During the follow-up period, 12 of 67 newborns with ETN and 14 of 67 newborns without ETN developed atopic diseases. Statistical analysis revealed that the presence of ETN was not associated with an increased risk of developing atopic diseases (adjusted odds ratio (OR) 1.37; 95% CI 0.55-3.41). However, a significant association was found between a family history of atopic diseases and the development of atopic conditions in the children.

Conclusions: The presence of ETN does not increase the risk of developing atopic diseases during childhood.

Keywords: Atopic diseases; erythema toxicum neonatorum; newborn; rash (Siriraj Med J 2026;78(5):377-383)

INTRODUCTION

Erythema toxicum neonatorum (ETN) is a benign, self-limited skin condition seen in newborns. ETN is a relatively common skin lesion, affecting approximately 16% to 30% of neonates.[1,2]

It typically presents as erythematous macules, often accompanied by small, white-yellow papules or pustules measuring approximately 1–3 mm in diameter. These lesions are commonly distributed over the trunk, thighs, and buttocks, while the palms and soles are rarely affected. ETN usually appears within the first 2 to 4 days of life and resolves spontaneously within one week without leaving any residual marks.[2]

The reported incidence of ETN ranges from 21% to 41% across studies. The wide variation in incidence is likely due to differences in the timing of neonatal skin assessments among studies.[3] Diagnosis of ETN is primarily clinical, based on its characteristic presentation. In certain cases, the microscopic examination of ETN with Wright stain can be performed, which reveals eosinophils in the superficial layers of the skin[4], particularly near the entrances of subcutaneous ducts. This observation may help explain the absence of lesions on the palms and soles. Additionally, peripheral eosinophilia may be detected in approximately 15% of affected neonates.[3]

To date, the precise etiology of ETN remains unclear. Several hypotheses have been proposed, including allergic reactions, a graft-versus-host-like response, and mechanisms involving the innate antimicrobial barrier.[5] Nonetheless, various studies have examined risk factors associated with ETN. These include increased gestational age at birth, vaginal delivery, higher birth weight, and male sex.[6]

Atopic diseases refer to a group of hereditary allergic disorders characterized by an exaggerated immune response to typically harmless environmental antigens. These diseases are of significant clinical importance due to their high prevalence and substantial impact on quality of life.[7] The prevalence of atopic diseases in children is estimated to range from approximately 10% to 30%, depending on the specific condition.[8,9] This hypersensitivity is mediated through immunoglobulin E (IgE). All atopic diseases fall under the category of Type I hypersensitivity reactions, which occur when an antigen binds to IgE receptors on mast cells, triggering the release of inflammatory mediators such as histamine, proteases, and leukotrienes. These mediators contribute to the characteristic allergic inflammation. The most common atopic diseases consist of asthma, atopic conjunctivitis, allergic rhinitis, atopic dermatitis, and food allergy. The presence of one atopic condition increases the risk of developing additional atopic diseases. Interestingly, recent studies have demonstrated an association between eosinophils and three major atopic diseases: atopic dermatitis, allergic rhinitis, and asthma.[10]

There is currently no clear association between ETN and atopic diseases. While some studies have suggested a link between ETN and an increased risk of developing

atopic conditions later in life, others have found no such association. This study aimed to determine whether ETN in newborns is associated with the development of atopic diseases in childhood.

MATERIALS AND METHODS

Participants

This study was reviewed and approved by the Institutional Review Board for Clinical Research in Humans of Srinakharinwirot University with CoA SWUEC/E/M-024/2566E. Informed consent was obtained from the parents and/or legal guardians of subjects by means of a voluntary written agreement form. The calculation of the sample size for this research was based on a study by Odelram et al.[11] exploring the relationship between eosinophils and atopic disease manifestation. Thus, a total of 134 neonates at HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) of Srinakharinwirot University, Ongkharak, Thailand from 2013 to 2017 were recruited. These were healthy individuals not admitted to neonatal intensive care unit (NICU), and whose mothers had previously received care at the MSMC antenatal clinic (ANC).

Research design

This study was designed as a retrospective cohort study by analyzing data previously collected from 2013 to 2017, categorizing neonates into either of the two categories – ETN and non-ETN. Children with a history of ETN were identified from the hospital medical database during the aforementioned period, whereas the control group without a history of ETN was randomly selected from infants born at MSMC within the same period. Details of data collection included gender of neonate, date of birth, gestational age, birthweight, mode of delivery, family history of atopy, and smoking in household.

Data collection

Neonates were evaluated by pediatricians or pediatrics residents at MSMC. The data collection form was reviewed by a pediatric dermatologist and a pediatric allergist before being implemented for patient data collection to ensure that all essential information was adequately obtained. Non-invasive full body examinations were carried out and the presence of rash, or the lack thereof, was documented accordingly using the form previously drafted which classified skin manifestations into different categories; Mongolian spot; salmon patch; hemangioma; port wine stain; cytomegalovirus (CMV) rash; Café au lait macule; sebaceous hyperplasia; erythema toxicum neonatorum; milia; desquamation; miliaria; collodion membrane; Epstein pearls; subcutaneous fat necrosis; cutis marmorata; bullous diseases; angel kiss. Neonates were allowed more than one category if presented with several skin manifestations. In addition to the type of rash, other information was noted namely gestational age, date of birth, birth body weight, mode of delivery and maternal underlying diseases. In addition, diagnosis of atopic diseases was performed by experienced pediatricians at MSMC based on clinical manifestations and investigations.

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22. Frequency data were expressed as percentages (%). For univariate analysis, Chi-square tests were used to compare birth body weight, gender, family history of atopy, and household smoking. For multivariate analysis, adjusted odds ratios (ORs) were calculated from crude odds ratios using the Hosmer-Lemeshow method, accounting for other variables. A p-value < 0.05 was considered statistically significant.

RESULTS

There were 134 participants, of whom 69 (51.5%) were male. Most participants (98.5%) were term newborns. In the ETN group, 35 participants were female (52.2%) and 32 were male (47.8%). Twelve participants with ETN were diagnosed with atopic disease in childhood, in which 7 of them had allergic rhinitis, 8 had atopic dermatitis, 1 had asthma, and none had food allergy. It should also be noted that some individuals may present with multiple atopic diseases. There were 5 participants with a family history of atopic diseases and 6 lived in households with smoking.

In the non-ETN group, there were 30 female participants (44.77%) and 37 male participants (55.22%). Fourteen of the participants without ETN had atopy, with 9 of them had allergic rhinitis, 2 had atopic dermatitis, 4 had asthma and 2 had food allergy. Three participants revealed family history of atopic diseases, and 2 of total non-ETN participants' households had smoking. All information was presented in Tables 1 & 2.

A chi-square test of independence was performed to examine the association between ETN and the development of atopic diseases later in life, as shown in Table 3. Multivariate analysis results are presented in Table 4. In this study, the presence of atopic diseases was the outcome variable, while the exposures included ETN in newborns, gender, household smoking, and family history of atopy. Our results showed that only 17.9% of newborns with ETN developed atopic diseases later in

TABLE 1. Demographic and clinical information between ETN and Non-ETN groups.

Clinical information	ETN (n = 67)	Non-ETN (n = 67)
Gender		
Female	35	30
Male	32	37
Atopic diseases		
Presence	12	14
Absence	55	53
Family history of atopy		
Presence	5	3
Absence	62	64
History of smoking in the family		
Presence	6	2
Absence	61	65

TABLE 2. Type of atopic diseases between ETN and non-ETN group.

Type of atopic diseases	ETN (n = 12)	Non-ETN (n =14)
Allergic rhinitis	7*	9
Atopic dermatitis	8	2
Asthma	1	4
Food allergy	-	2

*Within the data, two participants presented with allergic rhinitis as well as asthma and 4 participants presented with allergic rhinitis as well as atopic dermatitis.

TABLE 3. Chi-square test for factors associated with atopic disease.

Clinical Parameters	Presence of atopic disease				X^2 (df)	p-value
	Presence		Absence			
	N	(%)	N	(%)		
Presence of ETN					0.191 (1)	.662
Yes	12	17.9	55	82.1		
No	14	20.9	53	79.1		
Gender					0.072 (1)	.789
Female	12	18.5	53	81.5		
Male	14	20.3	55	79.7		
Family history of atopic diseases					10.105 (1)	.001
Yes	5	62.5	3	37.5		
No	21	16.7	105	83.3		
Smoking in the household					1.782 (1)	.182
Yes	3	37.5	5	62.5		
No	23	18.3	103	81.7		

TABLE 4. Crude and adjusted odds ratios for the multivariate analysis.

Covariates	Unadjusted Model			Adjusted Model	
	OR	95% CI	p-value	OR	95% CI
Presence of ETN					
ETN	0.83	0.35-1.95	.662	1.37	0.55-3.41
Non-ETN	1.00	-		1.00	-
Gender					
Female	0.89	0.38-2.01	.789	1.11	0.45-2.73
Male	1.00	-		1.00	-
Family history of atopic diseases					
Yes	8.33	1.85-37.58	.001	0.13	0.03-0.63
No	1.00	-		1.00	-
Smoking in the household					
Yes	2.69	0.60-12.06	.182	0.73	0.12-4.53
No	1.00	-		1.00	-

life (Table 3), with an adjusted OR for newborns with ETN was 1.37 (95% CI 0.55-3.41) (Table 4). However, this finding also did not reach statistical significance. Therefore, no significant association was found between the presence of ETN in newborns and the subsequent development of atopic diseases.

The proportion of participants with atopic diseases did not differ significantly by gender or household smoking. However, a significant association was found between a family history of atopy and the development of atopic diseases. Among those with a positive family history, 62.5% developed atopic diseases (Table 3). In the multivariate analysis, a family history of atopy was significantly associated with the development of atopic diseases. The crude odds ratio (OR) was 8.33 (95% CI 1.85–37.58), whereas the adjusted OR was 0.126 (95% CI 0.03–0.63) (Table 4).

DISCUSSION

This study explored the relationship between the presence of ETN at birth and the development of atopic diseases during childhood. Other factors, such as gender, household smoking, and family history of atopy, were also examined. No significant association was found between ETN and atopic diseases. In contrast, participants with a family history of atopy were approximately eight times more likely to develop atopic diseases based on crude OR. The association between family history of atopy and the development of atopic diseases was statistically significant in the current study.

The association between ETN and atopic diseases has been hypothesized based on the presence of eosinophils in ETN skin lesions, as well as the occurrence of eosinophilia in individuals with atopic diseases. Previous studies have shown that blood eosinophil levels are associated with the severity of atopic dermatitis. Specifically, individuals with atopic dermatitis who also have a family history of respiratory atopic diseases were found to have higher peripheral eosinophil counts compared to those without such a family history.[12] Moreover, research has indicated that neonates with elevated eosinophil counts or total IgE levels in cord blood have an increased risk of developing atopic diseases.[13] Another study by Witmer and colleagues reported that neonates with ETN have an increased risk of developing eosinophilic esophagitis, with an odds ratio of 3.52.[14]

Based on these findings, elevated eosinophil levels appear to be associated with the development of atopic diseases such as allergic rhinitis, asthma, and atopic dermatitis. Given that ETN is also characterized by the presence of eosinophils in skin lesions, these observations form the basis of the present research hypothesis: that ETN in infancy may be associated with an increased risk of developing atopic diseases later in life. However, our results from univariate analysis did not reveal that ETN was associated with an increased risk of atopic diseases. On the contrary, it suggested that the presence of ETN rash at birth might be a protective factor against atopic diseases (OR=0.826), compared to the control group (neonates without ETN). Compared with the prospective

study by Gonzalez Echeverría[4] in 1997 in which the most common atopic manifestation with ETN as a possible risk factor was atopic dermatitis, the results of this study were similar as atopic dermatitis was the most common in the ETN sample group. However, this information could not be reliably concluded due to the insignificant *p*-values, which could be a result of a small sample size, and unadjusted confounding factors. This warrants the need to include a larger sample size to further study the relationships.

With regard to gender, females were 20% less likely to develop atopic diseases than males (p=.889), but there was no statistical significance. In other studies, male was three times more likely to develop asthma than female pre-puberty. However, there were no difference in the prevalence and severity of allergic dermatitis and allergic rhinitis in both genders.[15,16] With respect to smoking exposure, neonates exposed to household smoke exhibited a higher likelihood of developing atopic diseases compared with unexposed neonates; however, this association did not reach statistical significance. This finding is partly consistent with the systematic review and meta-analysis by Kantor et al., which demonstrated that both passive and active smoking are associated with an increased prevalence of allergic dermatitis.[17]

Due to the insignificant results in this study, there is no definite conclusion on the relationships between the development of atopic diseases from both factors, sex and smoking in household. The only statistically significant factor associated with the development of atopic diseases in this study was a family history of atopy. However, a discrepancy was observed between the crude and adjusted odds ratios. Specifically, the crude OR indicated that neonates with a family history of atopy were more likely to develop atopic diseases (OR 8.33, 95% CI 1.85–37.58), whereas the adjusted OR suggested an inverse association (OR 0.126, 95% CI 0.03–0.63), representing a reversal in the direction of effect. The authors postulate that this inconsistency may be attributable to the small sample size, which can introduce unmeasured confounding and lead to model instability during multivariate adjustment. In addition, when considering the existing literature, most studies consistently demonstrate that a family history of atopy is a significant risk factor for the development of atopic diseases. Previous studies have identified family history of atopy as one of the most important predisposing factors for atopy in childhood, with one atopic parent conferring approximately a 25% risk, and two atopic parents increasing the risk to around 50%.[18,19] Therefore, based on the crude OR and clinical plausibility, a family history of atopy is more likely to be a risk factor for the development of atopic diseases rather than a protective factor, as suggested by the adjusted OR.

The clinical implication of this study is that physicians may reassure parents about ETN in the neonatal period is unlikely to be associated with the subsequent development of atopic diseases. Nevertheless, obtaining a family history of atopy remains important for guiding anticipatory counseling and early preventive strategies in infant care to reduce the risk of atopic diseases in childhood.

Limitation

The main limitation of this study is the low statistical power. The sample size was 67 participants per group, which is considered rather small and could make it difficult to detect true effects or relationships of ETN and the development of atopy. Apart from this, due to the nature of this study being a retrospective cohort study, there is potential for recall bias and inaccurate data collection. However, this bias was minimized by double-checking the electronic medical records of each participant.

CONCLUSION

In conclusion, the relationship between ETN rash at birth and the development of atopy in childhood is inconclusive. The only statistically significant predisposing factor in this study is family history of atopy. This is largely due to inadequate sample size. Further study is needed to include larger and more representative sample size for meaningful and trustworthy scientific contribution.

Data Availability Statement

Data will be made available on request.

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DECLARATIONS

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Conflict of Interest

All authors declare no conflicts of interest.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, S.C.1 and A.T.; Data collection, N.C., N.S., S.S., S.C.2, and A.N.; Formal analysis, N.C., N.S., S.S., S.C.2, and A.N.; Manuscript writing (first draft), N.C., N.S., S.S., S.C.2, and A.N.; Writing – review and editing, S.C.1, A.T., and V.S.; Supervision, V.S.; All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

ChatGPT (OpenAI) was used solely for language editing of complex sentences. All AI-assisted content was carefully reviewed, validated, and approved by the authors to ensure accuracy and adherence to academic and ethical standards.

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