

Support for 2 variants of eczema

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Background: Studies investigating the natural history and risk factors for eczema have historically considered eczema as a single entity, without regard for the individual's atopic status. The association between atopy and eczema is complex, and as many as 2/3 of patients with eczema are not atopic.

Objective: To investigate the risk factors for eczema in relation to the child's atopic status in a cohort of high-risk children.

Methods: A prospective birth cohort of 263 children was followed for 5 years and closely examined for eczema.

Antenatal and postnatal data on environmental exposures were collected by interview. Skin prick test to define atopic status was performed at 6 months and 2 and 5 years of age.

Results: Of the subjects, 66.1% had eczema in the first 5 years, and the majority (85.5%) reported onset of rash in the first year. A third of those with eczema were not atopic (nonatopic/intrinsic eczema). Children with atopic eczema (extrinsic eczema) were more likely to be male, to have been breast-fed longer, and to have a history of food allergies, allergic rhinitis, and current wheeze. Nonatopic eczema was more common in girls, and an association was found with early daycare attendance.

Conclusion: This study supports the presence of 2 variants of eczema: atopic eczema occurring early in childhood and nonatopic eczema with early daycare attendance. It is likely that environmental factors have a different effect on these 2 variants of eczema, and future studies should thus consider eczema as 2 variants in determining the effect of attributable risks. (*J Allergy Clin Immunol* 2005;116:1067-72.)

Key words: Eczema, atopic/extrinsic, nonatopic/intrinsic, risk factors

Although the prevalence of eczema, a chronic, relapsing skin condition, has increased in Westernized countries,¹⁻⁵ it is unknown which aspects of the Western lifestyle play a critical role in disease expression. Higher disease concordance rates in monozygotic compared with dizygotic twins (85% vs 21%)⁶ suggest a genetic basis. The natural history

Abbreviations used

ETS: Environmental tobacco smoke

OR: Odds ratio

SPT: Skin prick test

of eczema is also not known, and although >50% of patients develop symptoms in infancy, and >60% are clear of symptoms during adolescence, little is known about the complex pathophysiological mechanisms. Because the majority of cases of eczema present in early childhood, intrauterine and early life factors could play a pivotal role in disease expression. Maternal atopy,⁷ increased maternal age,⁸ higher birth weight,^{9,10} and ethnicity—black/Asian race¹⁰ have been reported to be associated with increased risk of eczema. Findings of sex differences have been inconsistent, with some showing higher incidence in girls^{2,5} and others no sex differences.¹⁰⁻¹⁴

Children from small families of higher socioeconomic status have a higher prevalence of allergic sensitization and clinical atopic diseases.^{8-9,13} Environmental risk factors such as house dust mites, pet exposure, tobacco smoke, air pollution, low humidity, and excessive use of soap and other skin irritants have also been implicated in the onset or exacerbation of eczema.¹⁵⁻¹⁷ The protective role of breast-feeding is controversial, with some studies showing benefit^{5,18} and others showing no effect.^{9,19} Food allergens have also been reported to cause exacerbations of eczema.^{16,17}

The majority of these studies have considered eczema only as a single entity,^{1-3,7,10} without considering the atopic status of the individual. It is recognized that, like asthma, there are different variants of eczema: the atopic form, which is associated with environmental allergen-specific IgE, and the nonatopic form, which has the typical appearances of eczema but without elevated antigen specific IgE.^{20,21} Recent studies have reported that 45% to 64% of patients with eczema are not atopic, and children with nonatopic eczema have a lower risk of developing asthma than those children with atopic eczema.²²⁻²⁵ It is likely that the risk factors and natural history for these 2 variants of eczema are different, and clear disease definitions are necessary to assess the gene-environmental effect of these exposures on disease expression. In the current study, we investigate the risk factors of atopic and nonatopic eczema in early childhood.

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TABLE I. Characteristics of the cohort

Characteristic	Number (%)
Male	111 (56.1)
No. of older siblings	
0	103 (52.0)
1	55 (27.8)
2	31 (15.7)
3 or more	9 (4.5)
Pet ownership	112 (56.6)
Childcare attendance in first year of life	
Nil	139 (70.2)
First 6 mo of age	20 (10.0)
7-12 mo of age	39 (19.8)
Antenatal smoking	8 (4.0)
Environmental tobacco smoke exposure	25 (12.6)
Maternal history	
Asthma	97 (49.0)
Hay fever	131 (66.2)
Eczema	61 (30.8)
Atopy	157 (79.3)
Paternal history	
Asthma	62 (31.3)
Hay fever	93 (47.0)
Eczema	22 (11.1)
Atopy	159 (80.3)
Biparental atopy	124 (62.6)
Duration of breast-feeding	
0-6 wk	11 (5.5)
7-12 wk	16 (8.0)
13-20 wk	11 (5.5)
21-26 wk	11 (5.5)
>26 wk	149 (75.5)
Atopic eczema	87 (43.9)
Nonatopic eczema	44 (22.2)
Atopic, no eczema	31 (15.7)
Nonatopic, no eczema	36 (18.2)

METHODS

A total of 263 children at high risk of developing atopic disease (at least 1 parent with a doctor-diagnosed history of asthma, hay fever, or eczema) were recruited prenatally between July 1996 and June 1998 into a prospective birth cohort study. The children, all born at full term, underwent medical examination by the study doctor at 6 weeks, 6 months, and 12 months of age, and then annually, with specific attention for the presence of eczema. The diagnosis was based on the criteria set out by Hanifin and Rajka²⁶ with a positive diagnosis made if ≥ 3 of the primary features were present.

The children underwent skin prick tests (SPTs) at 6 months, 2 and 5 years of age to a panel of 7 allergens (fresh cow's milk, egg white, rye grass, *Alternaria*, *Aspergillus*, house dust mite, and cat dander). Histamine was used as the positive control and normal saline as the negative control. Similar concentrations of allergens were used at all 3 time points. The wheal size was read after 15 minutes, with a wheal size ≥ 2 mm considered a positive reaction at 6 months and 2 years and a wheal size ≥ 3 mm at 5 years. Antihistamines, if taken, were withheld for at least 96 hours before the SPT.

Children were considered to be atopic if they had a positive SPT reaction to at least 1 allergen at any test time (ie, 6 months or 2 or 5 years).

Skin prick tests were also performed on all of the parents with the same panel of allergens, and a wheal size ≥ 3 mm was considered

TABLE II. Age of onset and type of eczema in cohort

Onset of eczema	No. (% of patients with eczema)
0-6 mo	94 (71.8)
7-12 mo	18 (13.7)
1-2 y	9 (6.9)
2-3 y	4 (3.0)
3-5 y	6 (4.6)
Type of eczema	
Current eczema	46 (35.1)
Transient	31 (23.7)
Intermittent	39 (29.8)
Persistent	61 (46.6)

positive. Parental history of doctor-diagnosed eczema, hay fever, and asthma was obtained by face-to-face questionnaire interview.

Definitions

Transient eczema was eczema present only in the first year of life.

Intermittent eczema was eczema presenting intermittently but for less than 3 years.

Persistent eczema was eczema present for at least 3 of the 5 years of the study.

Atopic eczema was eczema and positive SPT on at least 1 occasion at 6 months or 2 or 5 years.

Nonatopic eczema was eczema present, but not ever having a positive SPT reaction.

Data were analyzed with the Statistical Package for Social Sciences, version 11.0 (SPSS Inc, Chicago, Ill), with significant levels and their 95% CIs calculated by using standard χ^2 test and Cochran + Mantel-Haenszel statistics. Statistical significance was defined at the $P < .05$ level.

Approval for the study was obtained from the relevant local ethics committees.

RESULTS

Characteristics of the cohort

A total of 198 children (75.3%) were followed up for the full 5 years of the study. The majority of the children who were excluded or withdrew from the study did so within the first 12 months of the study, with the most common reason for withdrawal being move/transfer away from Western Australia. There was no significant difference in the prevalence of eczema in the first year or atopic status (SPT performed at 6 months) in these children who withdrew from the study.

There was a male preponderance, with boys accounting for 56% of the cohort. The majority of the children were first born (52.0%) and lived in a household with a pet (56.6%), most commonly a dog (29.7%). They were unlikely to attend daycare in the first year of life, only 12.6% were exposed to environmental tobacco smoke, and more than 75% breast-fed for more than 6 months (Table I). This is a cohort at high risk of atopy, with 79.3% of mothers and 80.3% of fathers being atopic and more than half (62.6%) with biparental atopy.

Of the cohort, 66.1% had eczema (43.9% atopic and 22.2% nonatopic), 15.7% were atopic but did not have

TABLE III. Relationship between atopy and type of eczema

Type of eczema at age 5 y	SPT positive at				
	6 mo (N = 42)	2 y (N = 82)	5 y (N = 67)	Any visit (N = 118)	All 3 visits (N = 22)
Transient (N = 31)	13	12	11	20	6
Intermittent (N = 39)	6	18	14	25	4
Persistent (N = 61)	18	32	28	42	11
No eczema (N = 67)	5	20	14	31	1

TABLE IV. Relationship between type of eczema and other atopic conditions

Type of eczema	Doctor-diagnosed asthma OR (95% CI; P value)	Allergic rhinitis OR (95% CI; P value)	Current wheeze OR (95% CI; P value)	Current asthma OR (95% CI; P value)
Transient	1.0 (0.4-2.4; P = .9)	0.6 (0.3-1.4; P = .2)	0.3 (0.1-0.9; P = .04)	0.6 (0.2-1.8; P = .4)
Intermittent	1.2 (0.6-2.5; P = .6)	1.8 (0.8-3.9; P = .1)	1.8 (0.9-3.8; P = .08)	1.5 (0.7-3.5; P = .3)
Persistent	2.2 (1.2-4.2; P = .02)	2.8 (1.5-5.3; P = .001)	1.8 (1.1-3.5; P = .05)	1.8 (0.9-3.8; P = .1)

Bold text indicates significant results.

TABLE V. SPT positive to food and inhalant allergens in children with atopic eczema

Type of allergen	SPT positive at		
	6 months (N = 37) No. (% of atopic eczema)	2 years (N = 62) No. (% of atopic eczema)	5 years (N = 53) No. (% of atopic eczema)
Food allergen	32 (36.8)	34 (39.1)	13 (18.3)
Inhalant allergen	16 (18.4)	55 (63.2)	55 (66.6)

eczema, and 18.2% were not atopic and did not have eczema (Table I).

Prevalence and age of onset of eczema. Of the 66.1% with eczema in the first 5 years, the majority (71.8%) reported onset of rash in the first 6 months of life, 13.7% between 7 and 12 months of age, 6.9% between 1 and 2 years, and 7.6% between 3 and 5 years of age (Table II). At 5 years, 35.1% of the cohort had current eczema (ie, eczema within the last 12 months). Of the children with eczema, 23.7% were found to have the rash only in the first year of life (transient eczema), 46.6% had persistent eczema, and the remainder (29.8%) had intermittent eczema (Table II).

Relationship among eczema, positive SPT, and other atopic conditions. There was close association between eczema and atopy, with 87 of the 118 (73.7%) children who were atopic having eczema. Children with persistent eczema were more likely to be atopic when tested at 6 months, 2 years, and 5 years (odds ratio [OR], 2.3; 95% CI, 1.3 - 4.1; P < .006; Table III). Positive SPT to ingested allergens at 6 months was not found to be a significant risk factor for transient eczema, with only 15 of the 36 children who were SPT-positive to egg white or cow's milk at 6 months of age developing eczema in the first year of life.

Of the 22 children who were very atopic (positive SPT at 6 months, 2 years, and 5 years), 21 had eczema, and 11 had persistent eczema (Table III). All of these children had onset of rash in the first year of life.

Children with persistent eczema were more likely, at 5 years of age, to have doctor diagnosis of asthma (OR, 2.2; 95% CI, 1.2-4.2; P = .02), allergic rhinitis (OR, 2.8; 95% CI, 1.5-5.3; P = .001), and current wheeze (OR, 1.8; 95% CI, 1.1-3.5; P = .05; Table IV).

A third of the children (33.6%) with eczema were not atopic at any time, and these children were considered to have nonatopic eczema. However, the majority (66.4%) of the patients with eczema were found to be atopic (atopic eczema). Children with atopic eczema were twice as likely to be atopic to food allergens at 6 months than inhalant allergens (36.8% vs 18.4%; Table V). However, at the 2- and 5-year SPTs, they were more likely to react to inhalant allergens (Table V).

Significant differences were found between these 2 variants of eczema. Atopic eczema was significantly more likely to start in the first 6 months of life (OR, 9.3; 95% CI, 3.7-23.1; P < .005) and to be significantly associated with other atopic conditions, including food allergies, hay fever, asthma, and current wheezing (Table VI). These relationships remained after adjusting for confounding factors such as sex, season of birth, breast-feeding, daycare attendance, pet ownership, and environmental tobacco smoke exposure.

Risk factors for eczema. Children with a maternal history of asthma were 3 times more likely to have eczema (OR, 3.5; 95% CI, 2.0-7.0; P < .0005), whereas paternal asthma was associated only with transient eczema (OR, 2.4; 95% CI, 1.1-5.2; P = .03; Table VII). Maternal asthma and eczema were found to be risk factors for persistent eczema (Table VII), although the relationship with maternal eczema failed to reach statistical significance. No relationship was found between maternal history of hay fever or paternal history of hay fever or eczema.

Differences were found in the risk factors for the atopic and nonatopic variants of eczema.

Atopic eczema was significantly more common in boys (OR, 2.0; 95% CI, 1.1-3.5; P < .05; Table VI), with onset usually in the first 6 months of life (OR, 9.3; 95% CI,

TABLE VI. Differences between atopic and nonatopic eczema

	Atopic eczema (N = 87) OR	P value	Nonatopic eczema (N = 44) OR	P value
Male	2.0 (1.1-3.5)	.02	0.5 (0.2-1.1)	.07
Pet	0.8 (0.4-1.5)	.5	1.0 (0.5-2.1)	.96
Childcare in first year	1.7 (0.8-3.5)	.17	2.2 (0.9-5.1)	.07
Older siblings	1.2 (0.6-2.2)	.7	1.7 (0.8-3.7)	.16
ETS exposure	0.5 (0.2-1.5)	.2	0.6 (0.2-2.2)	.5
Onset in first 6 mo	9.3 (3.7-23.1)	<.005	2.1 (0.9-4.2)	.06
Month of birth				
January to April	1		1	
May to September	1.7 (0.8-4.0)	.19	0.7 (0.3-1.7)	.39
October to December	1.5 (0.7-3.2)	.35	0.6 (0.2-1.4)	.21
Other atopic conditions				
Doctor diagnosis of asthma	3.2 (1.5-6.9)	.003	1.8 (0.7-4.6)	.21
Food allergies	4.2 (1.7-10.4)	.001	2.1 (0.7-6.2)	.17
Allergic rhinitis	3.5 (1.7-7.1)	<.0005	1.1 (0.5-2.7)	.8
Current wheeze	2.6 (1.1-6.3)	.03	1.1 (0.4-3.5)	.8
Maternal history				
Asthma	2.0 (1.1-3.5)	.01	1.9 (0.9-3.8)	.06
Hay fever	0.9 (0.5-1.6)	.64	0.7 (0.3-1.5)	.3
Eczema	1.7 (0.9-3.0)	.11	1.5 (0.7-3.6)	.3
Atopy	1.2 (0.5-3.0)	.6	1.1 (0.4-3.1)	.87
Paternal history				
Asthma	1.1 (0.6-2.0)	.82	0.6 (0.3-1.4)	.2
Hay fever	0.7 (0.4-1.2)	.16	1.0 (0.5-2.1)	.9
Eczema	1.3 (0.6-3.2)	.5	1.2 (0.4-4.4)	.7
Atopy	1.6 (0.4-5.8)	.63	1.2 (0.5-3.5)	.57

Bold text indicates significant results.

TABLE VII. Relationship between parental atopic disease and type of eczema

Type of eczema	Hay fever OR (95% CI; P value)	Asthma OR (95% CI; P value)	Eczema OR (95% CI; P value)
Maternal			
Eczema ever	0.7 (0.4-1.3; P = .2)	3.7 (2.0-7.0; P < .005)	1.9 (1.0-3.7; P = .06)
Transient	0.7 (0.4-1.7; P = .53)	1.8 (0.8-3.9; P = .14)	0.9 (0.4-2.1; P = .82)
Intermittent	0.9 (0.5-2.0; P = .96)	1.4 (0.7-.9; P = .3)	1.6 (0.8-3.3; P = .2)
Persistent	0.81 (0.4-1.5; P = .5)	2.0 (1.1-3.7; P = .03)	1.4 (0.7-2.6; P = .34)
Paternal			
Eczema ever	0.8 (0.4-1.4; P = .4)	0.8 (0.4-1.5; P = .5)	1.4 (0.5-3.8; P = .5)
Transient	0.7 (0.3-1.5; P = .32)	2.4 (1.1-5.2; P = .03)	1.2 (0.4-3.9; P = .73)
Intermittent	0.9 (0.4-1.7; P = .7)	0.7 (0.3-1.4; P = .3)	2.5 (1.0-6.4; P = .06)
Persistent	1.1 (0.6-2.1; P = .7)	0.6 (0.3-1.2; P = .13)	0.5 (0.16-1.5; P = .2)

Bold text indicates significant results.

3.7-23.1; $P < .0005$; Table VI), whereas nonatopic eczema was more common in girls, with onset later in childhood. There was a trend for daycare attendance to be a risk factor for nonatopic eczema (OR, 2.2; 95% CI, 0.9-5.1; $P = .07$). This association, however, failed to reach statistical significance after controlling for confounding factors such as number of older siblings (Table VI).

Children with atopic eczema were found to have been breast-fed for longer than children with nonatopic eczema (see Fig E1 in the Online Repository in the online version of this article at www.jacionline.org). This association did not reach statistical significance after adjusting for confounders such as socioeconomic status and daycare attendance.

No significant associations were found between perinatal factors such as birth weight, birth length, head circumference, mode of delivery, pet ownership, birth order, or socioeconomic status and the 2 variants of eczema.

DISCUSSION

Prevalence and age of onset of eczema

Compared with other studies,^{2,4} the higher prevalence of eczema in the current study of high-risk children is not surprising and is comparable to a previous Australian high-risk cohort.²⁷ Comparison between studies is difficult with different data collection methods,^{2,3} outcome

measures dependent on parental recall,⁴ or older study populations in a condition well documented to present in infancy and early childhood.⁴ Disease definitions have been unclear, and the term *atopic dermatitis* has been used without SPT or IgE measurements to verify atopic status.^{1-4,13} We found that the majority of eczema (71.8%) developed in the first 6 months of life, a finding similar to that of other studies.^{28,29}

Relationship among eczema, positive SPT, and other atopic conditions

Children who were atopic were twice as likely to have eczema, and the children who were more atopic (positive SPT at 6 months and 2 and 5 years) were 4 times more likely to have eczema. These findings have been reported in other studies^{29,30} and confirm the important role played by atopy in the pathogenesis of eczema.

However, 33.6% of the eczema in the current study was the nonatopic variant. Normal IgE levels or negative SPT has been reported in 20% to 40%^{29,31} and 45% to 64%²³⁻²⁵ of patients with eczema. In the current study, the cohort has been followed to 5 years of age. It is possible that a percentage of the nonatopic children may later become sensitized, and for a subgroup of the nonatopic patients with eczema, this may represent a transient stage occurring in early childhood.

Distinct differences in clinical pattern and risk factors were found between atopic and nonatopic eczema. Atopic eczema was more common in male patients, with onset of the rash occurring within the first 6 months of life. Significant associations were found between atopic eczema and other atopic conditions such as food allergies, allergic rhinitis, and current wheezing. Studies showing sex differences have been inconsistent, with some showing male preponderance,³²⁻³⁶ others no associations,³⁷ or female preponderance.^{8,12,34,38} These studies investigated older children and did not differentiate atopics from nonatopics.

Risk factors for eczema

Children with atopic eczema were more likely to have mothers with asthma. Studies have shown the risk of atopic disease to be between 50% and 88% depending on whether 1 or both parents are affected.^{39,40} The lack of a relationship between eczema and biparental eczema in the current study is surprising. Because eczema is a condition that waxes and wanes, recall bias may have accounted for the low parental prevalence rates for eczema.

Onset of rash in atopic eczema occurred earlier in life compared with nonatopic eczema. Daycare attendance was associated with nonatopic eczema, and although this association was not found to be significant because of the small number of children attending daycare in early infancy, it is worth further investigation. *Staphylococcus aureus* expresses a variety of superantigens that have been implicated in flare-ups and exacerbations of eczema.⁴¹ Children attending daycare have been reported to have more respiratory illnesses,⁴²⁻⁴⁴ and it is plausible that daycare attendance similarly renders children at increased

risk of staphylococcal skin colonization. This exposure may set off inflammatory skin responses resulting in the immunological cascade seen in eczema. Daycare attendance is also associated with other cofactors (eg, exposure to gastrointestinal and dermatological viruses, different food intake) that may also exert an effect on eczema.

Children with atopic eczema were breast-fed longer. Because the onset of atopic eczema occurred early in life, it is possible the mothers prolonged breast-feeding; this practice is currently viewed as being protective against atopic conditions. However, it is also possible that prolonged breast-feeding may in itself be a risk factor for atopic eczema. The protective role of breast-feeding on the development of atopic disease is controversial, with several investigators showing protective effects^{18,45,46} and others no significant association.^{19,47} More recent studies suggest that breast-fed infants may be at increased risk of asthma and recurrent wheezing at 6 years (in atopic children of mothers with asthma).^{48,49} Ongoing transfer of immunologic data from mother to infant through breast-feeding may prolong the close immunologic interaction of the fetal-maternal unit, thus influencing the development of the child's immune system. Considerable differences found in the individual composition of immunologic fatty acids and polyamines in human milk may well account for the differences seen in studies reporting the role of breast-feeding and allergic sensitization.

Exposure to environmental tobacco smoke (ETS) and pet exposure in the home were not found to have an effect on the development of eczema in this cohort. The small percentage of children exposed to ETS might have made it difficult to detect any small associations.

CONCLUSION

The genetic basis of eczema is unclear, and the interaction of genetic and environmental factors in disease expression is far from being elucidated. Epidemiological research into this complex condition, which has a wide range of symptomatology and a fluctuating course, has been difficult with a lack of suitable diagnostic criteria. Previous studies have considered eczema as a single disease entity, even though more recent studies have found that 10% to 64% of patients with eczema are not atopic.

This study supports the delineation of eczema into atopic and nonatopic variants. Atopic eczema is more common, presents early in infancy, has a male preponderance, and is associated with sensitization to environmental allergens. The more atopic the child, the more likely the child is to have persistence of eczema into the preschool years. Because this form presents early in infancy, factors operating *in utero* and early life may thus be critical in its development. Nonatopic eczema presents later in childhood and has no relationship with the classical atopic triad of asthma, hay fever, and eczema. Early daycare attendance has been associated with this form of eczema. Several studies have linked eczema with socioeconomic advantage, suggesting a strong environmental influence

on this disease. It is likely that these environmental factors have different effect on the pathogenesis of these 2 variants of eczema, and it is thus important for future studies to consider eczema as 2 different variants in the determination of the effect of attributable risks.

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