Predicting eczema severity beyond childhood

Kam Lun Hon, Yin-Ching K. Tsang, Terence Chuen W. Poon, Nga Hin Pong, Matthew Kwan, Shirley Lau, Yuen-Chun Chiu, Hin-Hei Wong, Ting-Fan Leung

Hong Kong, China

Background: **We evaluated factors associated with eczema severity in adolescence.**

Methods: **Nottingham Eczema Severity Score (NESS), family and personal history of atopy, skin prick test for common food and aeroallergens, highest serum IgE level and eosinophil count were evaluated. Patients with paired NESSs (childhood-NESS is NESS performed at <10 years of age; adolescence-NESS is NESS performed at age >10 years) were further analyzed.**

Results: **Adolescence-NESS (*n*=383 patients) was associated with eczema onset in infancy, dust mite and food allergen sensitization, dietary avoidance, use of wet wrap, traditional Chinese medicine, immunomodulant (azathioprine or cyclosporine), high IgE level, eosinophil count, but not with family/personal history of atopy. Eighty-two patients had both childhood-NESS and adolescence-NESS (mean follow-up of 6.8 years) showing that adolescence-NESS was associated with childhood-NESS severity grades (*P*=0.034). Of these patients, 48% remained in the same severity grades, whereas 39% improved, and 13% deteriorated from childhood to adolescence.**

Conclusions: **It is not possible to assure parents that their child can outgrow eczema. In eczema prognosis research, long-term follow-up is warranted.**

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Author Affiliations: Department of Pediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong (Hon KL, Tsang YCK, Poon TCW, Pong NH, Leung TF); Faculty of Medicine, The Chinese University of Hong Kong (Kwan M, Lau S, Chiu YC, Wong HH)

Corresponding Author: Kam Lun Hon, MD, Department of Pediatrics, The Chinese University of Hong Kong, 6/F, Clinical Science Building, Prince of Wales Hospital, Shatin, Hong Kong (Tel: 852 2632 2859; Fax: 852 2636 0020; Email: ehon@hotmail.com, ehon@cuhk.edu.hk)

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Introduction

Childhood eczema is a chronic distressing disease.[1-7] Disease onset is usually before 5 years of age in the majority of patients.[2,6,8] The prevalence of atopic diseases among these individuals and their family members are high and include eczema, asthma or allergic rhinitis. Atopy is also evidenced in laboratory tests (such as positive skin prick reaction to common food and aeroallergens or elevated serum IgE levels above laboratory reference range for age).[4,6,7,9,10] Parents are often assured that eczema is characterized by periods of exacerbation and remission with a natural tendency to improve or resolve eventually when their child reaches adolescence. However, there are only few long-term studies to provide evidence for this notion. Risk factors of persistent diseases include severe disease and early food allergy.[11-15] We evaluated factors associated with eczema severity in adolescence.

Methods

The clinical data of consecutive patients with atopic eczema (AE) followed up at the pediatric dermatology clinic of our university hospital were reviewed. Eczema was diagnosed according to UK Working Party's Diagnostic Criteria for Atopic Dermatitis.[16] Disease severity was assessed by Nottingham Eczema Severity Score (NESS). NESS is a self-administered questionnaire with a validated Chinese version which evaluated a patient's eczema severity over the preceding 12 months.[17-19] NESS is routinely recorded in the first visit, and randomly scored in subsequent visits. NESS further categorized AE severity into three groups: mild, moderate or severe. Family and personal history of atopy, use of wet wrapping, dietary avoidance, traditional Chinese medicine, immunomodulants (azathioprine or cyclosporine), skin prick test for common food and aeroallergens (house dust mite *D. pteronysissnus* and *D. farinae*), highest serum total IgE level and eosinophil count were analyzed. In case of missing data, hard copy, electronic medical records and the investigator's own database were accessed. In a subset of patients whose first visits were prior to 10 years of age, paired NESS (childhood-NESS at <10

Table 1. Association of different factors with eczema severity by adolescence-NESS

Factors	Mild (*n*=111)	Moderate (*n*=134)	Severe (*n*=138)	*P* value
	+ *vs.* – (%)	+ *vs.* – (%)	+ *vs.* – (%)	
Onset age ≤1 y (*n*=301)	39 *vs.* 40 (49.4)	56 *vs.* 50 (52.8)	75 *vs.* 41 (64.7)	0.028
Males (%)	54 *vs.* 57 (48.6)	73 *vs.* 61 (54.5)	82 *vs.* 56 (59.4)	0.237
Paternal atopy (*n*=334)	39 *vs.* 55 (41.5)	51 *vs.* 64 (44.3)	55 *vs.* 70 (44.0)	0.728
Maternal atopy (*n*=337)	37 *vs.* 58 (38.9)	41 *vs.* 74 (35.7)	49 *vs.* 78 (38.6)	0.993
Siblings atopy (*n*=338)	47 *vs.* 47 (50.0)	58 *vs.* 58 (50.0)	66 *vs.* 62 (51.6)	0.808
Personal AR (*n*=323)	73 *vs.* 20 (78.5)	84 *vs.* 30 (73.7)	86 *vs.* 30 (74.1)	0.489
Personal asthma (*n*=309)	44 *vs.* 44 (50.0)	48 *vs.* 60 (44.4)	53 *vs.* 60 (46.9)	0.698
Food avoidance ever (*n*=319)	44 *vs.* 44 (50.0)	72 *vs.* 34 (67.9)	96 *vs.* 29 (76.8)	<0.0005
Wet wrap ever (*n*=295)	17 *vs.* 66 (20.5)	42 *vs.* 59 (41.6)	61 *vs.* 50 (55.0)	<0.0005
TCM ever (*n*=320)	29 *vs.* 60 (32.6)	73 *vs.* 40 (64.6)	65 *vs.* 53 (55.1)	0.004
Immunomodulant ever* (*n*=310)	3 *vs.* 82 (3.5)	18 *vs.* 91 (16.5)	22 *vs.* 94 (19.0)	0.003
Dust mites (*n*=297)	68 *vs.* 9 (88.3)	102 *vs.* 3 (97.1)	113 *vs.* 2 (98.3)	0.006†
Food allergens (*n*=294)	47 *vs.* 29 (61.8)	70 *vs.* 33 (68.0)	88 *vs.* 27 (76.5)	0.028
	n Median (IQR)	*n* Median (IQR)	*n* Median (IQR)	
Highest IgE (*n*=265)	66 649 (1636)	93 1778 (4068)	106 4414 (9577)	<0.0005
	n Mean±SD	*n* Mean±SD	*n* Mean±SD	
Highest eosinophils (*n*=311)	80 7.5%±5.5%	107 9.3%±7.0%	124 12.4%±6.9%	<0.0005

NESS: Nottingham Eczema Severity Score; TCM: traditional Chinese medicine; AR: allergic rhinitis; IQR: interquartile range. "+": presence of the studied factor; "–": absence of the studied factor. *: Immunomodulant ever refers to the use of azathioprine cyclosporine; †: Fisher's exact test.

years of age and adolescence-NESS at age of >10 years by January 2014) were further analyzed. These patients were then divided into three groups, namely better, same, and worse according to changes in disease severity, and possible prognostic factors analyzed for any significant difference. Data were expressed as mean and standard deviation, and analysis of variance was used to compare means unless otherwise stated. All comparisons were made two-tailed, and *P* values less than 0.05 were considered to be statistically significant.

Results

All NESSs

In total, 902 NESSs of 674 eczema patients (386 males, 57.3%) who had been followed up at the pediatric dermatology clinic between 2002 and 2014 were reviewed. Data of the patients were assessed in June 2014. There were wide variability and only a statistically significant small decrease in the mean NESS between different age groups among the 902 NESSs (*P*=0.020; Fig.). NESS was performed on patients over 1 year of age. Patients were often referred after infancy and they were followed up at our tertiary center till late adolescence before they were referred to adult dermatology service. Hence, the number of NESSs performed in children after 10 years of age was 2 times more than that in young children.

Adolescence-NESS

In June 2014, the data of 383 patients who were above 10 years of age with adolescence-NESS were analyzed (Table 1). Patients with onset of eczema in infancy (≤1 year of age) had more severe eczema in adolescents (*P*=0.028). There was no significant association between the severity of eczema in adolescence and personal allergic rhinitis (*P*=0.489), asthma (*P*=0.698), history of atopy in father (*P*=0.728), mother (*P*=0.993) or sibling (*P*=0.808). The use of immunomodulant (azathioprine or cyclosporin, *P*=0.003), traditional Chinese medicine (*P*=0.004), wet wrap, and dietary

Table 2. Association between childhood and adolescent eczema severity by NESS (*n*=82)

		Eczema severity after 10 y old		
		Mild	Moderate	Severe
Eczema severity before 10 years old	Mild	7	4	3
	Moderate	6	8	4
	Severe	7	19	24

P=0.034 by Fisher's exact test. Spearman's correlation coefficient=0.333, *P*=0.002.

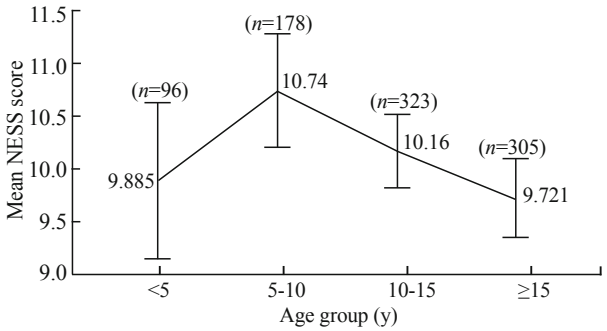

Fig. Mean Nottingham Eczema Severity Score (NESS) score of different age groups (*n*=902). *P*=0.020 by Welch's ANOVA, Mean NESS score of age group 5-10 y is significantly higher than that of ≥15 y (*P*=0.013).

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Table 3. Eczema severity change is generally independent of clinical parameters (*n*=82)

Factors	Eczema severity change at adolescence						*P* value
	Better (*n*=31)		Same (*n*=39)		Worse (*n*=11)		
	+ *vs.* – (%)		+ *vs.* – (%)		+ *vs.* – (%)		
Onset age ≤1 y (*n*=81)	22 *vs.* 9 (71.0)		31 *vs.* 8 (79.5)		6 *vs.* 5 (54.5)		0.248
Males (%)	19 *vs.* 13 (59.4)		18 *vs.* 21 (46.2)		6 *vs.* 5 (54.5)		0.534
Paternal atopy (*n*=80)	19 *vs.* 12 (61.3)		19 *vs.* 20 (48.7)		6 *vs.* 4 (60.0)		0.544
Maternal atopy (*n*=80)	12 *vs.* 19 (38.7)		19 *vs.* 20 (48.7)		3 *vs.* 7 (30.0)		0.487
Any siblings atopy (*n*=80)	20 *vs.* 11 (64.5)		17 *vs.* 22 (43.6)		4 *vs.* 6 (40.0)		0.080
Personal AR (*n*=82)	21 *vs.* 11 (65.6)		30 *vs.* 9 (76.9)		9 *vs.* 2 (81.8)		0.218
Personal asthma (*n*=82)	13 *vs.* 19 (40.6)		20 *vs* 19 (51.3)		5 *vs.* 6 (45.5)		0.574
House dust mites (*n*=76)	28 *vs.* 1 (96.6)		36 *vs.* 1 (97.3)		10 *vs.* 0 (100)		>0.999†
Food allergens (*n*=76)	22 *vs.* 7 (75.9)		24 *vs.* 13 (64.9)		8 *vs.* 2 (80.0)		0.496
Wet wrap ever (*n*=82)	18 *vs.* 14 (56.2)		16 *vs.* 23 (41.0)		3 *vs.* 8 (27.3)		0.072
Food avoidance ever (*n*=78)	25 *vs.* 5 (83.3)		26 *vs.* 11 (70.3)		9 *vs.* 2 (81.8)		0.414
TCM ever (*n*=82)	18 *vs.* 14 (56.2)		20 *vs.* 19 (51.3)		8 *vs.* 3 (72.7)		0.449
Immunomodulant ever* (*n*=82)	7 *vs.* 25 (21.9)		1 *vs.* 38 (2.6)		2 *vs.* 9 (18.2)		0.024†
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	
Highest IgE (*n*=59)	25	2150 (5656)	29	2754 (6765)	5	3290 (11380)	0.950
	n	Mean±SD	*n*	Mean±SD	*n*	Mean±SD	
Highest eosinophils (*n*=70)	28	10.6%±5.4%	34	11.0%±6.9%	8	10.9%±4.0%	0.947

NESS: Nottingham Eczema Severity Score; TCM: traditional Chinese medicine; AR: allergic rhinitis; IQR: interquartile range. "+": presence of the studied factor; "–": absence of the studied factor. *: Immunomodulant ever refers to the use of azathioprine cyclosporine; †: Fisher's exact test.

avoidance, were strongly associated with more severe disease at adolescence (reverse casuality, $P<0.0005$). House dust mite (*D. pteronysissnus* and *D. farinae*) sensitization was positive in 88.3%, 97.1% and 98.3% of mild, moderate and severe patients, respectively (*n*=297 patients, $P=0.006$). There was also a significant association of food sensitization with adolescence-NESS ($P=0.028$). The highest eosinophil counts in patients with mild, moderate and severe eczema at adolescence were 7.5±5.5%, 9.3±7.0% and 12.4±6.9%, respectively ($P<0.0005$). The median serum highest IgE levels in patients with mild, moderate and severe eczema were 649 (1636), 1778 (4068) and 4414 (9577) IU/mL, respectively ($P<0.0005$) (Table 3).

Childhood-NESS and adolescence-NESS

Of the 674 patients, 82 had both childhood-NESS and adolescence-NESS (mean follow-up 6.8±2.6 years), showing that adolescence-NESS was associated with child-NESS severity grades (Table 2, $P=0.034$), but none of the other clinical parameters might predict who would improve or deteriorate (Table 3). Of these patients, 48% remained in the same severity grades, whereas 39% improved, and 13% deteriorated from childhood to adolescence.

Discussion

Childhood eczema is a common chronic relapsing disease.[1,2,6,20] Physicians often assure parents that most patients tend to improve with age, and their children may outgrow their eczema some years later. However, parental expectations are quite different in that most anxious parents seek for disease cure. Sampson and colleagues[11] reported that patients with persistent disease are not as severely affected as they were in infancy. Nevertheless, the more severe and long lasting the AE, the more likely that it will continue into adult life.[12] The natural course of AE may be divided into subgroups that display different clinical features but AE in adolescence and adulthood is a broadly heterogeneous disease.[21]

Roth and colleagues[12] reported 50 years ago that AE persisted into adult life in approximately 70% of patients with severe AE and 60% of those with milder AE. A family history of atopy was found in 66% of AE patients but prognosis concerning the severity of the disease cannot be based on the family history.[12] Furthermore, personal history of asthma, hay fever, urticaria, migraine headache, and rhinitis were found in 55% of AE patients. They also demonstrated that determination of eosinophil count in blood is not a useful tool in predicting the severity or course of AE.[12] On the other hand, Rystedt et al[13] showed that severe disease in childhood, family history of AE and atopy, and female sex are risk factors influencing eventual prognosis. Using both tabular and stepwise logistic regression analyses, they further demonstrated that the prognostically unfavorable factors were, in order of importance, severe (widespread) dermatitis in childhood, family history of AE, associated allergic rhinitis, and/or bronchial asthma (with allergic rhinitis as the dominant of these two factors), female sex and early age at onset.[14] Another group of researchers[15] followed up 121 children with infantile eczema and

found persistence into adult life occurred in 63% of AE patients, with 32 % having a chronic continuous course. Prognostically unfavorable factors were delineated as early onset severe disease within the first 6 months of age and very high serum IgE levels. Our study of 383 adolescent patients confirmed that severe disease in adolescence was associated with onset in infancy, aeroallergen sensitization, high IgE level, eosinophil count, but not with family or personal atopy status.[21]

Patients with a history of dietary avoidance, wet wrap, TCM or immunomodulant usage had more severe disease in adolescence (reverse causality). Interestingly, use of TCM ever was associated with severe disease in adolescence. In many Asian cities, herbal medicine is extensively sought by many parents and patients in preference to western medicine.[22] It is not known if history of TCM usage is associated with severe disease or if patients with more severe disease tend to use TCM. Many Asian patients would think that western medicine cannot offer a cure, and that topical steroids and associated treatment have significant side effects.[22] Complementary and alternative medicine practices may be an important factor of non-adherence and treatment failure in pediatric skin disease management.

The theory of "Atopic March" favors the consideration of eczema as a systemic disease, and indicates that many children with AE go on to develop asthma and allergic rhinitis as their eczema improves with time.[2,5,6,23] In the subset of patients who had been followed up from childhood to adolescence (Table 2, *n*=82), 48% of the patients remained in the same severity grades. 50% of these patients with mild childhood eczema progressed to moderate-to-severe disease in adolescence, whereas only 14% of patients with moderate-to-severe disease in childhood improved to have mild disease in adolescence. Furthermore, none of the clinical parameters might predict who would improve or deteriorate (Table 3). Hence, it is not possible to assure parents and patients of the expectation that they can outgrow their eczema during adolescence. Diligent follow-up and ongoing supports for these families are therefore advocated.

The limitations of this study were that only clinical factors and some basic atopy tests were used for the prognosis study. Many advances in basic and genetic research are not available for analysis.[10,24-26] The interpretation of clinical factors and atopy tests are more complicated than one might have thought. We used NESS instead of other common scores for the determination of disease severity over a 12-month period.[17-19] Many severity scores such as SCORAD or SASSAD are less appropriate because they merely assess disease severity over a 1-2 week period during which eczema severity may wax and wane dramatically with weather changes, psychosocial issues and superimposed *S. aureus* infection.[27-29] The age of assessment may be problematic. Ideally disease severity should be assessed at time on onset and serially to document progress. Unfortunately, many patients were referred at older age and childhood-NESS is not available. Many of the young patients are still young and have not reached adolescence for the adolescence-NESS to be evaluated. Therefore, it is difficult to obtain paired NESS unless patients are recruited early and followed up for a long period. Clinical status such as family or personal history of atopy may also be difficult to determine. We generally accept doctor-diagnosed asthma, allergic rhinitis or eczema. Family atopy status may also be limited if patients are adopted, have no siblings or siblings of young age. Personal history is limited, particularly in young children, if their respiratory atopy has not yet manifested. Patient characteristics, lifestyle, socioeconomic status and co-morbidities may also be confounding factors. Furthermore, some parents do not consent the full spectrum of laboratory evaluations to be performed, especially in the young patients with milder disease. Finally there might be investigation bias in assessing outcome, as investigators were not blinded to the patients' status during assessment. This study assumes that each age group represents the population at large. In a tertiary hospital setting, the population of patients that we encounter and follow up are likely to be biased towards more severe disease.[20] Hence, the conclusions may not be generalized and a larger sample size with more young children with mild disease may be needed.

The strength of the study is that the data were collected over 10 years. Many patients had been diligently followed up until they reached 18 years before they were referred to the adult dermatology service.[30] As the pediatric dermatology service is a public service, children can obtain consultations and medications at very low costs. Hence, bias due to drop outs/loss to follow up are relatively not significant. This is also evidenced from the fact that the number of adolescence-NESS far exceeds childhood-NESS in our study (Fig.). The use of NESS for measurement of eczema severity has some limitations.[31,32] However, neither SCORAD or EASI would have been a more adequate outcome measure because both assess the acute symptomatology of eczema in time (up to one week). Eczema is awaxing and waning disease and a score for chronicity such as NESS that measures disease severity over a 12-month interval may be more appropriate. Importantly, many important covariates such as patient and parent factors have been assessed. The use of topical therapy would be an interesting variable but would vary from weeks to weeks and is virtually impossible to quantify in this study.

In conclusion, severe childhood disease, allergen sensitization, high IgE level, eosinophil count, dietary avoidance, use of wet wrap, TCM and immunomodulant are associated with more severe disease in adolescence (reverse causality). Although eczema may improve in adolescence, it is not possible to assure parents that their child can outgrow it. In eczema prognostication research, patients should be followed up till adolescence.

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