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Are lifetime prevalence of impetigo, molluscum and herpes infection really increased in children having atopic dermatitis?

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ABSTRACT

Background: Cutaneous infections such as impetigo contagiosum (IC), molluscum contagiosum (MC) and herpes virus infection (HI) appear to be associated with atopic dermatitis (AD), but there are no reports of concrete epidemiological evidence.

Objective: We evaluated the association of childhood AD with these infections by conducting a population-based cross-sectional study.

Methods: Enrolled in this study were 1117 children aged 0–6 years old attending nursery schools in Ishigaki City, Okinawa Prefecture, Japan. Physical examination was performed by dermatologists, and a questionnaire was completed on each child's history of allergic diseases including AD, asthma, allergic rhinitis and egg allergy, and that of skin infections including IC, MC and HI, as well as familial history of AD.

Results: In 913 children (AD; 132), a history of IC, MC or HI was observed in 45.1%, 19.7%, and 2.5%, respectively. Multiple logistic regression analysis revealed that the odds of having a history of IC were 1.8 times higher in AD children than in non-AD children. Meanwhile, a history of MC was significantly correlated to the male gender, but not to a personal history of AD. As for HI, we found no correlated factors in this study.

Conclusions: The lifetime prevalence of IC was indeed higher in young children with a history of AD.

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1. Introduction

Atopic dermatitis (AD) is a common, chronic or chronically relapsing, severely pruritic, multifactorial eczematous skin disease, predisposing the patient to bacterial and viral infections attributable to abnormalities in both the innate and acquired immune system [1]. Epidermal barrier dysfunction, such as decreased ceramide production, decreased filaggrin production due to genetic mutation and/or atopic inflammation, defective secretion of antimicrobial peptides, and mechanical stress induced by the itch-scratch cycle, appear to be fundamentally involved in the predisposition to bacterial and viral infections in AD [1–5].

Impetigo contagiosum (IC) and molluscum contagiosum (MC) are two of the most common cutaneous infectious disorders that

occur during childhood. Epidemiologic data on pediatric dermatology from Switzerland [6] and Turkey [7] suggest that IC and MC are among the ten most common diseases in children aged 3–5 years old. IC is caused by the direct inoculation of *Staphylococcus aureus* (*S. aureus*) or group A streptococci into superficial abrasions/traumas frequently associated with insect bites, eczema or burns. Lesions are highly contagious and can spread rapidly by direct contact with family and nursery school classmates [8]. The condition is reported to be more common in children with AD living in tropical climates [9], and in conditions of overcrowding and poor hygiene [10]. Meanwhile, MC is more common in children who attend swimming pools, who bathe together, and who are immunosuppressed. It is also reported that MC lesions are common and/or spread more extensively in patients with AD, and that the presence of concomitant AD is an important risk factor associated with treatment failure of MC [11]. On the other hand, the most commonly reported viral complication in subjects with AD is eczema herpeticum or Kaposi's varicelliform eruption, which

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is caused by extensive cutaneous infection with herpes virus type 1 or 2. Eczema herpeticum can be complicated by keratoconjunctivitis, viremia and sometimes multiple organ involvement with meningitis and encephalitis [12]. In contrast to IC and MC, this severe type of herpes virus infection (HI) occurs most frequently in the second and third decade of life [13]. Among the various skin infections, IC, MC and HI are empirically and clinically considered to be the three major disorders associated with AD. However, we found no previous reports on the actual association of these skin infections with childhood AD using population-based epidemiological examinations.

In 2001, we initiated an annual cross-sectional study on children aged 0–6 years old in Ishigaki City, Okinawa, Japan. We visited several nursery schools and conducted skin examinations and a questionnaire survey. This population-based study is named the Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). Using the KIDS data, we have already published our findings on several important issues such as AD prevalence, serum immunoglobulin (Ig)E and thymus- and activation-regulated chemokine levels, spontaneous regression ratio and risk factors for AD among the KIDS children [14–17]. In the present study, we investigated the lifetime prevalence of IC, MC and HI among the KIDS children examined in 2006 and 2007. We then evaluated the association between a history of IC, MC and HI and a history of AD using multivariate analysis.

2. Methods

2.1. Study design

The study design has been previously reported [15]. Briefly, we contacted all nursery schools (i.e., 14 schools) in Ishigaki City, Okinawa Prefecture, Japan requesting the children's participation in the study. After obtaining written informed consent from the children's parents or guardians, we visited the 14 nursery schools during the summer and performed skin examinations on children aged 0–6 years old. In 2006 and 2007, medical skin examinations were performed on 1117 children who were enrolled in KIDS. Of these 1117 children, 913 (81.7%) returned their questionnaires, which were used for analysis in the present study. Approval for the study was obtained from the Ethics Committee of Kyushu University Hospital as well as from the directors and classroom teachers of the schools.

2.2. Questionnaire

A structured questionnaire was filled out by the children's parents or guardians, and included questions concerning data on age, gender, birth, personal history of AD, asthma, allergic rhinitis (AR) and egg allergy (EA), and familial (parents and siblings) history of AD. An additional question on the child's history of contracting infectious skin diseases (IC, MC and HI) was included in the questionnaires administered in 2006 and 2007.

2.3. Definitions

The medical skin examination of the children was performed by dermatologists from the Department of Dermatology, Kyushu University Hospital. AD was diagnosed according to the Japanese Dermatological Association criteria [18]. Children who had been diagnosed with AD as a result of the physical examination or from answers on the questionnaire were considered as AD children in this study in order to include present and cured AD. Definitions of asthma, AR and EA were assessed by questionnaire if a parent or guardian reported that a doctor had diagnosed the child as having these diseases. Furthermore, children who were reported in the

questionnaire to have displayed adverse effects after eating eggs were diagnosed as having EA. The diagnosis of IC, MC and HI was made if a parent or guardian answered "yes" to the question "Has your child ever been diagnosed with IC (or MC or HI) by a doctor?"

2.4. Statistical analysis

Univariate analysis for the difference in factors between boys and girls was appropriately performed using the chi-square test for comparison between the two groups. The association between history of infectious skin diseases and gender, personal history of allergic disorders or familial history of AD was assessed using the chi-square test or Fisher's exact test. Then we examined the actual correlation between a history of skin diseases and a history of AD using multiple logistic regression analysis. Results were expressed as odds ratios with the respective 95% confidence interval (CI). To confirm the validity of the logistic regression model, we determined the post-estimation goodness-of-fit parameter for the logistic regression model using the Hosmer–Lemeshow goodness-of-fit test, and found the model to be valid ($P > 0.05$). In the multiple logistic regression analysis, the effects of age were controlled by including variables that showed significant correlation in univariate analysis as independent variables in the model. We calculated Pearson's correlation coefficients in the study variables, and found that all of the correlation coefficients ranged between -0.8 and 0.25 , which implied that there was no risk of multicollinearity in the multiple logistic regression model since the risk increases when the correlation coefficients approach 1, such as $r = 0.8$ or greater (Table S1). A P value of < 0.05 was considered statistically significant. All analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population

Table 1 shows basic characteristics of the 913 participating children. Among these children, 759 (83.1% of our study population) who had no missing answers on the questionnaire were included in the multivariate analysis (Fig. 1). The mean ($\pm$ standard deviation) age of the enrolled children was $2.9 (\pm 1.4)$ years, and 55.1% were boys. The age distribution between boys and girls was not significantly different (Table 1). The proportion of children with a history of AD and AR was 14.7% and 2.8%, respectively, and showed a similar rate in both boys and girls, whereas asthma and EA were more common among boys than girls (Table 1). As for infectious skin diseases, a history of IC was the most common in all children (45.1%), and showed a similar rate in both boys and girls. However, MC and HI were more prevalent in boys than in girls (Table 1). In addition, the prevalence of any familial history of AD in boys and girls was not significantly different (Table 1).

3.2. History of IC, MC and HI in AD and non-AD children

Since a history of IC, MC and HI was assumed to show a gradual and cumulative increase with age in children, we next analyzed the age distribution of a history of IC, MC or HI. None of the children under 1 year old had a history of MC or HI (Table 2). The incidence of IC and MC gradually increased with age. Among a total of 334 children aged 4–6 years old, 177 (51.5%) and 107 (31.1%) children had a history of IC or MC, respectively. The incidence of HI was less than 5% in each age stratum (Table 2). We then evaluated the age distribution of IC, MC and HI among AD or non-AD children. A history of IC in AD children tended to overwhelm that in non-AD children in any age stratum, but a history of MC appeared to be similar in frequency between AD and non-AD subjects. The

Table 1
Characteristics of participating children.

	Number (%)		P-value ^a	
	All (n = 913)	Gender categories		
		Females (n = 410)		Males (n = 503)
Age (year)				
0	12 (1.3)	5 (1.2)	7 (1.4)	0.095
1	171 (18.7)	93 (22.7)	78 (15.5)	
2	193 (21.1)	80 (19.5)	113 (22.5)	
3	203 (22.2)	85 (20.7)	118 (23.5)	
4	205 (22.5)	84 (20.5)	121 (24.1)	
5	109 (11.9)	55 (13.4)	54 (10.7)	
6	20 (2.2)	8 (2.0)	12 (2.4)	
History of allergic diseases				
AD ^b	132 (14.7)	58 (14.4)	74 (15.0)	0.803
Asthma ^c	150 (16.9)	52 (13.1)	98 (20.0)	0.006
AR ^d	25 (2.8)	10 (2.5)	15 (3.1)	0.632
EA ^e	37 (4.1)	10 (2.5)	27 (5.4)	0.028
History of infectious skin diseases				
IC	412 (45.1)	175 (42.7)	237 (47.1)	0.180
MC	180 (19.7)	60 (14.6)	120 (23.9)	<0.001
HI	23 (2.5)	5 (1.2)	18 (3.6)	0.024
Familial history of AD				
Paternal ^f	37 (4.1)	16 (4.0)	21 (4.3)	0.807
Maternal ^g	64 (7.1)	30 (7.4)	34 (6.8)	0.737
Sibling ^h	77 (9.3)	34 (9.0)	43 (9.5)	0.831

AD, atopic dermatitis; AR, allergic rhinitis; EA, egg allergy; IC, impetigo contagiosum; MC, molluscum contagiosum; HI, herpes virus infection. Significant values ($P < 0.05$) are indicated in bold.

^a Difference between females and males using the chi-square distribution.

There are missing values with respect to these variables due to incomplete answers on the questionnaires. The respective numbers for "all", "females" and "males" are as follows: ^b899, 404, 495, ^c889, 398, 491, ^d886, 396, 490, ^e905, 404, 501, ^f896, 405, 491, ^g905, 406, 499, ^h832, 377, 455.

frequency of a history of HI was very low in both AD and non-AD children (Table 2).

3.3. History of IC was significantly associated with history of AD

Next, we examined the factors associated with a history of IC, MC or HI using univariate analysis. The proportion of children with

a history of AD among the children without a history of IC, MC or HI was 53/498 (10.6%), 95/721 (13.2%) and 127/877 (14.5%), respectively (Table 3). In contrast, the proportion of children with a history of AD among the children with a history of IC, MC or HI was 79/401 (19.7%), 37/178 (20.8%) and 5/22 (22.7%), respectively (Table 3). We found a higher prevalence of both a personal and familial AD history in children with IC compared with children without IC. As for MC, male gender and a history of AD and EA were more frequent among children with a history of MC than their counterparts. The factor associated with a history of HI was male gender (Table 3).

Next, to identify the actual factors correlated with a history of IC, MC or HI, we conducted a multiple logistic regression analysis including the variables that showed a significant correlation by univariate analysis shown in Table 3, adjusted for the effects of age (Table 4). The results revealed that age was a significant predictor of a history of IC and MC (Table 4). The odds of a history of IC were 1.8 times higher in AD children than in non-AD children (Table 4). Furthermore, there was a significant association between a paternal family history of AD and a history of IC (Table 4). However, AD did not show significant association with a history of MC or HI. Other allergic diseases were not associated with a history of IC, MC or HI, whereas the odds of a history of MC were 1.59 times higher in boys than in girls (Table 4).

4. Discussion

AD appears to be associated with or to aggravate skin infections, including such major types as IC, MC and HI. However, since IC and MC are common skin diseases in children, it would be necessary to perform a population-based epidemiological study to reveal any actual association. Our population-based cross-sectional study demonstrated that the odds of a history of IC were 1.8 times higher in AD children than in non-AD children. IC is a highly contagious infection that is usually transmitted by direct contact, although the exact mechanism of *S. aureus* colonization in the skin is not known. In IC, bacteria do not infect intact skin, but instead enter through sites of minor trauma. Most AD patients are colonized with *S. aureus*, which may be cultured from skin lesions and, to a lesser

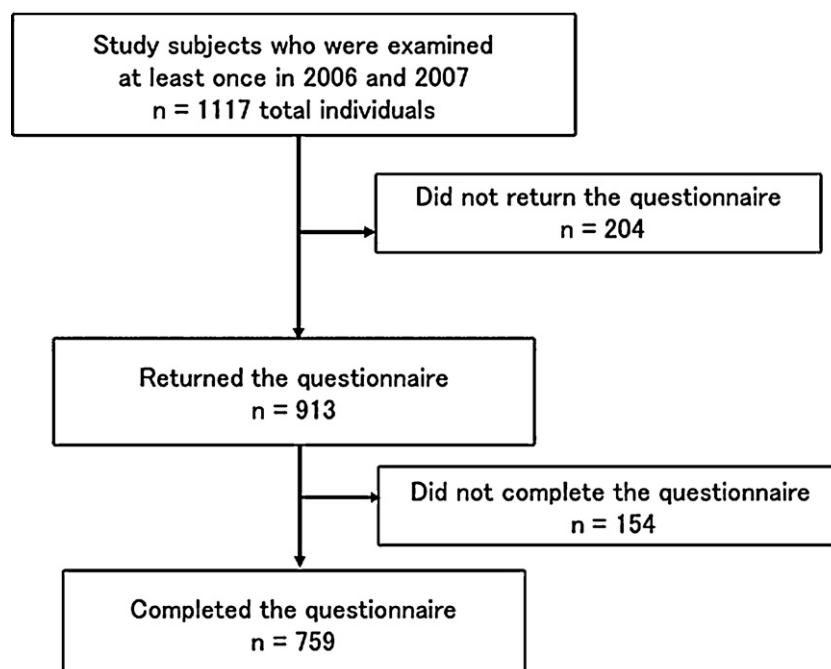


Fig. 1. Flow chart of study.

Table 2

Rate of lifetime prevalence of IC, MC and HI among AD and non-AD children.

Age (year)	All				AD categories ^a							
	n	IC (%)	MC (%)	HI (%)	Non-AD children				AD children			
					n	IC (%)	MC (%)	HI (%)	n	IC (%)	MC (%)	HI (%)
0	12	1 (8.3)	0 (0.0)	0 (0.0)	10	1 (10.0)	0 (0.0)	0 (0.0)	2	0 (0.0)	0 (0.0)	0 (0.0)
1	171	61 (35.7)	11 (6.4)	7 (4.1)	156	53 (34.0)	7 (4.5)	6 (3.9)	14	7 (50.0)	4 (28.6)	1 (7.1)
2	193	86 (44.6)	23 (11.9)	2 (1.0)	160	65 (40.7)	18 (11.3)	2 (1.3)	31	20 (64.5)	5 (16.1)	0 (0.0)
3	203	87 (42.9)	39 (19.2)	3 (1.5)	165	65 (39.4)	30 (18.2)	1 (0.6)	34	18 (52.9)	9 (26.5)	1 (2.9)
4	205	103 (50.2)	63 (30.7)	6 (2.9)	166	78 (47.0)	49 (29.5)	4 (2.4)	37	23 (62.2)	14 (37.8)	2 (5.4)
5	109	66 (60.6)	38 (34.9)	4 (3.7)	94	54 (57.5)	33 (35.1)	3 (3.2)	11	9 (81.8)	4 (36.4)	1 (9.1)
6	20	8 (40.0)	6 (30.0)	1 (5.0)	16	6 (37.5)	4 (25.0)	1 (6.3)	3	2 (66.7)	1 (33.3)	0 (0.0)

AD, atopic dermatitis; IC, impetigo contagiosum; MC, molluscum contagiosum; HI, herpes virus infection.

^a There are missing values due to incomplete answers on the questionnaire concerning the history of AD.**Table 3**

Factors associated with history of skin infections; univariate analysis.

Variables	History of IC			History of MC			History of HI		
	IC+	IC–	P	MC+	MC–	P	HI+	HI–	P
Male gender	237/412 (57.5)	266/501 (53.1)	0.180	120/180 (66.7)	383/733 (52.3)	<0.001	18/23 (78.3)	485/890 (54.5)	0.024
History of AD	79/401 (19.7)	53/498 (10.6)	<0.001	37/178 (20.8)	95/721 (13.2)	0.010	5/22 (22.7)	127/877 (14.5)	0.211 [*]
History of asthma	73/401 (18.2)	77/488 (15.8)	0.337	38/175 (21.7)	112/714 (15.7)	0.056	5/21 (23.8)	145/868 (16.7)	0.272 [*]
History of AR	13/399 (3.3)	12/487 (2.5)	0.478	5/174 (2.9)	20/712 (2.8)	0.564 [*]	0/22 (0.0)	25/864 (2.9)	0.529 [*]
History of EA	18/409 (4.4)	19/496 (3.8)	0.666	14/180 (7.8)	23/725 (3.2)	0.005	2/23 (8.7)	35/882 (4.0)	0.241 [*]
Paternal history of AD	24/403 (6.0)	13/493 (2.6)	0.013	8/179 (4.5)	29/717 (4.0)	0.798	2/22 (9.1)	35/874 (4.0)	0.229 [*]
Maternal history of AD	35/409 (8.6)	29/496 (5.8)	0.113	10/177 (5.6)	54/728 (7.4)	0.411	1/23 (4.3)	63/882 (7.1)	0.507 [*]
Sibling history of AD	46/371 (12.4)	31/461 (6.7)	0.005	20/170 (11.8)	57/662 (8.6)	0.206	2/20 (10.0)	75/812 (9.2)	0.567 [*]

Data is represented as n/N (%). AD, atopic dermatitis; AR, allergic rhinitis; EA, egg allergy; IC, impetigo contagiosum; MC, molluscum contagiosum; HI, herpes virus infection. P values were determined by chi-square test.

^{*} P values were determined by Fisher's exact test.

Significant values (P < 0.05) are indicated in bold.

degree, from nonlesional skin. Mechanical trauma caused by scratching due to itching is believed to result in barrier dysfunction leading to skin surface infection in AD. Furthermore, antimicrobial peptides such as human β -defensin-2 and LL-37 have an innate protective effect against skin infection, but the concentration of these peptides in AD patients is too low to effectively eradicate *S. aureus* [19]. Interleukin (IL)-4 and IL-13 produced from lesional Th2 cells and genetic predisposition appear to affect the defective synthesis of antimicrobial peptides in AD [20]. Dysfunction of the skin barrier, small traumas caused by scratching, colonization of bacteria on the skin surface and decreased levels of antimicrobial peptides in the skin might be responsible for the high lifetime prevalence of IC in AD.

We obtained the result that 20.8% of the children who had a history of MC also had a history of AD, which was similar to the results of previous hospital-based studies [21,22]. However, multiple logistic regression analysis showed no significant difference in the history of MC between AD and non-AD children. This similar association of MC between AD and non-AD individuals,

of course, does not rule out the possibility that MC is exacerbated by concomitant AD, although we could not address this point in the present study protocol. MC lesions take several months to years to resolve spontaneously [11,23,24], but the presence of concomitant AD is the most significant factor associated with relapse and the risk of treatment failure of MC [11,25,26]. Children with AD and MC may visit clinics more frequently due to the easily spread or persistent tendency of the lesions, which may cause a referral bias in a hospital-based study. In addition, a history of MC was more prevalent in boys than in girls in our study, as reported previously [27,28]. The association of MC with bathing and attendance at swimming pools has been reported, and Postlethwaite et al. [28] suggested that the higher male susceptibility to MC might be due to boys going swimming more frequently than girls. We could not evaluate this possibility in this study.

Previous studies showed that the incidence of IC was 29.4 per 1000 person years (1–4 year olds) in the Netherlands [29], whereas that of MC was 18.1 per 1000 person years (1–4 year olds) in the Netherlands [29] and 1268 per 10,000 person years (0–14 year

Table 4

Factors associated with a history of IC, MC and HI: multiple logistic regression analysis.

Variable	OR (95% CI)		
	History of IC	History of MC	History of HI
Age	1.23 (1.10–1.37)^c	1.53 (1.33–1.76)^c	1.11 (0.78–1.58)
Male gender	–	1.59 (1.09–2.32)^a	2.71 (0.88–8.39)
History of AD	1.80 (1.16–2.81)^b	1.64 (1.00–2.68)	–
History of EA	–	2.08 (0.92–4.68)	–
Paternal history of AD	2.44 (1.07–5.56)^a	–	–
Sibling history of AD	1.53 (0.90–2.60)	–	–
Hosmer–Lemeshow test	$\chi^2 = 7.96$, $P = 0.24$	$\chi^2 = 10.12$, $P = 0.26$	$\chi^2 = 13.26$, $P = 0.10$

This analysis covers 759 children who had no missing answers on their questionnaires. AD, atopic dermatitis; AR, allergic rhinitis; EA, egg allergy; IC, impetigo contagiosum; MC, molluscum contagiosum; HI, herpes virus infection; OR, odds ratio; CI, confidence interval.

^a $P < 0.05$ (significant values are indicated in bold).^b $P < 0.01$ (significant values are indicated in bold).^c $P < 0.001$ (significant values are indicated in bold).

olds) in the UK [30]. In Fiji, the prevalence of IC was 25.6% (5–15 year olds) [9], and in Japan, that of MC was 5.6% (4–5 year olds) [27]. However, it is difficult to compare the results considering the difference in study area and participant age. Our children were likely to have a high frequency of lifetime episodes of IC (45.1%) and MC (19.7%). One reason for this is that the other studies showed the prevalence or incidence, but not the lifetime prevalence. In accordance with this notion, Steer et al. demonstrated that the cumulative incidence of IC among school children 5–15 years old in Fiji was 47.5% [9]. In general population of the Netherlands, the cumulative incidence of MC in children under 15 years old was 17% [31]. Another possible factor is the climate of Ishigaki City which is located in a subtropical area with high temperature and humidity, since IC and MC are more common in tropical climates [9,32].

As for HI, we found no significant difference in the history of HI between AD and non-AD children. As described previously, HI is not common in children 0–6 years old [29], as was also the case in the present study. It might be difficult to confirm the actual association between HI and AD due to the low prevalence of HI in young children. It should be emphasized that large-scale epidemiological studies on HI and AD using adult subjects indicated that HI is actually exacerbated by concomitant AD, and vice versa. In adult AD patients, it is well known that the most clearly delineated risk factor for the severe form of HI (eczema herpeticum) is disruption of the epidermal barrier [33]. Previous reports have shown that a high serum IgE level and early onset of AD are both risk factors for eczema herpeticum [34]. Peng et al. [13] also found that skin lesion area and total IgE levels were significantly higher in AD patients than in those not suffering from eczema herpeticum. Moreover, a recent report by Beck et al. [12] demonstrated that, compared to AD patients without eczema herpeticum, AD subjects with eczema herpeticum had more severe skin scores, more body surface area affected, and higher biomarkers such as thymus- and activation-regulated chemokine levels.

We also investigated whether a history of IC, MC and HI was correlated with a history of other allergic diseases including asthma, AR and EA, which are commonly associated with AD [35–37]. However, we found no significant correlation of these infections with either asthma, AR or EA, suggesting that a local skin condition was a major factor for the preponderant association of IC with AD. The fact that this study is based on a general population is a strong point, but it should be emphasized that there are possible limitations in interpreting the results. Information on the personal history of asthma, AR, EA, IC, MC and HI was based on the questionnaire results, and AD was determined by the physical examination and questionnaire results in order to include present and cured AD, because the resolution/remission rate of AD is around 80% in children aged 0–6 years old [15]. There might be a recall bias in the parents' reports of prior allergic diseases and skin infections. Questionnaire-based prevalence studies could overestimate the data. Another limitation is that the present study was a cross-sectional investigation and hence the results must be interpreted with caution regarding the time sequence, because this study does not assess "present" IC and AD. In conclusion, we consider this to be the first demonstration that the lifetime prevalence of IC, but not that of MC or HI, did indeed increase in AD children compared with their non-AD counterparts. Our findings may support the presence of defective cutaneous innate immunity in AD.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jdermsci.2010.09.003.

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Supplemental Table I. Correlation of variables

	1	2	3	4	5	6	7	8	9
<i>Independent variables</i>									
1. Age	—								
2. Male gender	.04	—							
3. History of AD	.04	.01	—						
4. History of asthma	.08 ^a	.09 ^b	.15 ^c	—					
5. History of AR	.11 ^b	.02	.07 ^a	.18 ^c	—				
6. History of EA	.03	.07 ^a	.23 ^c	.09 ^b	.11 ^b	—			
7. Paternal history of AD	−.02	.01	.19 ^c	.05	.07 ^a	.16 ^c	—		
8. Maternal history of AD	−.08 ^a	−.01	.07 ^a	−.06	.01	.01	.03	—	
9. Sibling history of AD	.03	.01	.23 ^c	.11 ^b	.03	.02	.13 ^c	.10 ^b	—

<i>Dependent variables</i>									
10. History of IC	.14 ^c	.04	.13 ^c	.03	.02	.01	.08 ^a	.05	.10 ^b
11. History of MC	.25 ^c	.12 ^c	.09 ^a	.06	.00	.09 ^b	.01	−.03	.04
12. History of HI	.02	.07 ^a	.04	.03	−.03	.04	.04	−.02	.00

Data represents Pearson's product-moment correlation coefficient.

AD, atopic dermatitis; AR, allergic rhinitis; EA, egg allergy; IC, impetigo contagiosum; MC, molluscum contagiosum;

HI, herpes virus infection.

^a $P < 0.05$, ^b $P < 0.01$, ^c $P < 0.001$.