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Role of parental atopy in cow's milk allergy: a population-based study

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ABSTRACT

Background: A family history of atopy has been considered an independent risk factor for atopic diseases in children.

Objective: To relate the risk of an infant developing IgE-mediated cow's milk allergy (IgE-CMA) to the atopic status of parents.

Methods: Assessment of the parental atopic status of children with IgE-CMA (n = 66) previously identified in a large-scale prospective study was compared with the parental atopic status of a control group of healthy infants (n = 156). The atopic status was identified both by self-reporting and skin prick tests (SPTs).

Results: Analysis for the risk for infants to develop IgE-CMA depended on the assessment method used. No significant differences were noted in self-reported parental atopic status between the IgE-CMA patients and the control group. However, among the subgroup of infants with persistent IgE-CMA (n = 25), maternal but not paternal self-reporting for atopy was more likely compared with parents of the control group (P = .04). In contrast, when analyzed by SPT, in both this persistent subgroup and the total allergic cohort, no significant differences were noted whether analyzed by single parent or both parents and whether the parent tested singly or multiply positive on the SPT.

Conclusion: In families with children with persistent IgE-CMA, self-reporting of atopy by parents may be biased. Furthermore, the demonstration of IgE-mediated responses to allergens in parents is insufficient by itself, in a general population cohort, to predict which infants are at greatest risk of developing IgE-CMA.

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Introduction

The genetic basis for IgE-mediated food allergy is perhaps best demonstrated in the case of peanuts for which a significantly higher concordance rate of peanut allergy was noted among monozygotic (64.3%) vs dizygotic twins (6.8%).¹ It is generally presumed that atopy in the parents increases the atopic risk for the developing infant. This indeed appears to be the case for many atopic diseases, such as atopic dermatitis,² aeroallergen allergy,³ and asthma.^{4,5} In addition, in one longitudinal study, significant associations between a maternal history of atopy or asthma and a positive peanut food challenge result were noted.⁶ Interestingly, a genetic basis, the loss-of-function mutations in the filaggrin gene, has been reported to be significantly associated with increased odds of developing peanut allergy.⁷ An infant's genetic predisposition to develop food allergy, however, is subject to environmental

factors, such as the infant's age at the time of food exposure and the route of exposure.⁸ For example, early oral exposure to cow's milk protein (CMP),⁹ peanut,¹⁰ egg,¹¹ and fish¹² may protect an infant from developing an allergy to the respective food administered.

Studies that report that parental atopy can increase the risk of atopic diseases in the infant^{2–5} and in some cases even increase the risk of food allergy⁶ initially led to guidelines that recommend specific dietary restrictions for infants of atopic parents during the first months of life.^{13–16} However, the relationship between parental atopy and the development of IgE-mediated cow's milk allergy (IgE-CMA) is less clear. In the few studies in which this question was addressed, a definitive answer as to the risk of parental atopy was obscured by various factors. Either the risk of atopy was combined with other risk factors, such as length of breastfeeding,^{17–19} or the data relied primarily on self-reporting,^{13,14} which can potentially lead to a self-report bias. In some studies, only a tertiary selected population was analyzed.²⁰ In other studies, an oral food challenge (OFC) was not performed to validate the diagnosis.^{21,22}

We therefore sought to analyze whether parental atopy was an independent risk factor for the development of IgE-CMA in their respective infants. A recently identified cohort of IgE-CMA allergic patients (n = 66) from a large-scale, longitudinal, prospective

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study⁹ was used. Parental atopic status was identified by self-reporting of diseases related to atopy and skin prick test (SPT), an objective measure of atopy. Two subgroups from the cohort were identified: those who became tolerant of milk by the age of 4 years and those in whom the IgE-CMA persisted beyond the age of 4 years.²³ Findings from these parents were then compared with the parental atopic status of a control group randomly chosen from the 12,638 healthy infants.

Methods

Study Population

The research protocol was approved by the Helsinki Review Board of the Assaf Harofeh Medical Center. Written consent was obtained from participants. A cohort of 12,638 healthy infants (defined by not having any symptoms related to cow's milk–derived formulas) was previously identified in a large-scale, prospective study analyzing the incidence of IgE-CMA.⁹ Infants with IgE-CMA were defined by a suggestive history of an immediate response, a positive SPT response, and, in most cases, a positive challenge result to CMP.⁹ The feeding characteristics of these infants were previously described, and of interest, 64 of 66 infants were exclusively breastfed for longer than 2 weeks.⁹ We used Matlab's randperm function to randomly choose 232 infants from this healthy cohort of 12,638 healthy infants to be used as a control group. We succeeded in recruiting 156 of these 232 families (312 parents) for evaluation, including the completion of a questionnaire evaluating for their atopic history and atopic status. Within the control group, 92 mothers (59%) and 80 fathers (51%) agreed to undergo an SPT. Thus, we evaluated the risk of parental atopy for IgE-CMA by comparing the control group based on self-reporting ($n = 156$) and the one based on the SPT ($n = 92$) to the parents of the allergic children with IgE-CMA originally identified in our study ($n = 66$). In addition, we compared the control groups with the parents of a subgroup of these infants with prolonged IgE-CMA ($n = 25$). The latter group was evaluated every 6 months until a median age of 46 months (range, 34–57 months). Questionnaires were filled between the ages of 2 and 3 years, and at the time of that evaluation they still reacted to milk on an OFC test. In most of these patients, their IgE-CMA persisted beyond the age of 4 years, as previously described.²³ Thus, we use the term *persistent IgE-CMA* in the remainder of this article to describe this subgroup.

Determination of Atopic Status

Parents were asked whether they had been diagnosed as having bronchitis (chronic cough), atopic dermatitis, food allergies, asthma, or "other" allergic disease, including allergic rhinitis or hay fever. SPTs

were performed to the following food and environmental allergens: milk, soy, egg, peanut, sesame, and *Alternaria* at 1:10 (wt/vol); *Parietaria judaica*, dog hair, sagebrush, and olive tree at 1:20 (wt/vol); *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (5,000 AU/mL), mix grasses (100,000 BAU/mL), cat hair (5,000 BAU/mL), and cat pelt (10,000 BAU/mL); and histamine (1 mg/mL) positive and saline negative controls. A response was considered positive if the wheal was 3 mm or larger for one or more of the allergens.⁵

Statistical Analyses

The Fisher exact test and χ^2 test were used to analyze the relationship between categorical variables. A 2-tailed Fisher exact test was used to compare SPT results between control and allergic groups. $P < .05$ was considered significant. Multiple-testing corrections were ignored. In one analysis, we used imputation, taking into account the self-reports, to handle missing SPT results for parent self-reporting but not undergoing SPTs. The SPT-positive incidences in each self-reporting category were grouped together for fathers and mothers, control and IgE positive, after verifying that there is no significant difference in these rates between the groups. For example, 68 of the tested parents (from both the IgE-CMA and control groups) reported positive atopy, and 49 of these 68 (72%) exhibited at least 1 positive SPT result (Table 1). Thus, approximately 72% of the control group who did not take the SPT tests but self-reported positive atopy (14 of the 19 parents) would have been SPT positive in at least 1 SPT. In contrast, only 76 of the 226 parents (34%) who reported not having atopy and who were tested have had at least 1 positive SPT result. Thus, similarly, approximately 34% of parents who reported not having atopy and who were not tested (39 of the 115) would have had at least 1 positive SPT result. These values were added to the actual positive and negative SPT results, respectively, to give a hypothetical total count of positive and negative SPT results.

The power of our statistical tests was, by and large, dictated by the size of the (smaller) IgE-CMA group. For the comparison of SPT results between the IgE-CMA group and the control group, the proportion of positive results in the control group was 42%, whereas that in the IgE-CMA group was 40%. Given our IgE-CMA group size, detection with a power of 0.9 requires the latter proportion to be higher than 60%, with the latter number depending only weakly on the size of the control group.

Results

The demographic characteristics of the control group ($n = 156$) and those of the total population of healthy infants ($n = 12,482$) are

Table 1
Parental allergen SPT results for the IgE-CMA and control groups stratified by self-reports

No. of allergens	Mothers						Fathers					
	SPT positive (≥ 3)	SPT positive (≥ 2)	SPT positive (≥ 1)	SPT negative	Not tested	Total	SPT positive (≥ 3)	SPT positive (≥ 2)	SPT positive (≥ 1)	SPT negative	Not tested	Total
IgE-CMA ($n = 66$)												
Self-reported positive	6	7	10 ^a	8 ^a	1	19	5	7	8 ^a	1 ^a	1	10
Self-reported negative	5	10	13 ^b	32 ^b	1	46	5	11	17 ^{**}	33 ^b	3	53
NA					1	1					3	3
Control ($n = 156$)												
Self-reported positive	8	14	18 ^a	5 ^a	7	30	2	7	13 ^a	5 ^a	12	30
Self-reported negative	8	14	25 ^b	44 ^b	57	126	6	12	21 ^b	41 ^b	58	120
NA					0	0					6	6
Persistent IgE-CMA ($n = 25$)												
Self-reported positive	4	4	6	4	0	10	1	2	3	0	0	3
Self-reported negative	2	4	4	11	0	15	3	6	6	15	0	21
NA					0	0					1	1

Abbreviations: IgE-CMA, IgE-mediated cow's milk allergy; NA, not applicable; SPT, skin prick test.

^aA total of 68 tested parents (27 IgE-CMA parents and 41 control parents) reported testing positive for atopy.

^bA total of 226 tested parents (95 IgE-CMA parents and 131 control parents) reporting testing negative for atopy.

given in Table 2. No statistically significant differences between the 2 groups were observed in terms of sex, gestational age, birth weight, maternal age, type of delivery, number of siblings, location of residence, and age of CMP introduction. However, the percentage of non-Jewish infants in the control was significantly lower than that in the total healthy infants cohort ($P = .007$) (Table 2) due to a lower recruitment rate from the computer-generated randomly selected set ($n = 232$). In addition, we compared the risk factors between the parents of the children with IgE-CMA ($n = 66$) cohort and the parents of this randomly selected control group ($n = 156$) (Table 3). Demographic details, such as gestational age, birth weight, maternal age, dwelling, and dairy consumption by the mother, were not significantly different between the control group selected from the healthy infant population and the IgE-CMA group (data not shown). Occurrences of potential confounding risk factors, such as incidental exposure to milk in the nursery (by history), parental educational level, presence of pets at home, and smoking exposure, were similar between the 2 groups (Table 3).

The atopic background of the parents in this control group was analyzed by self-reports of a physician diagnosis of bronchitis, atopic dermatitis, food allergies, asthma, or allergic rhinitis or hay fever. For a subgroup of the control group, the atopic background was analyzed by the more objective criterion of SPT. No differences in maternal or paternal self-reported atopy were noted between the 2 groups (Fig 1A), even when individual atopic diseases were evaluated (data not shown). We reasoned that patients with persistent IgE-CMA may reflect a higher-risk group with a concomitant higher likelihood of genetic risk and thus compared their parental atopy self-reports ($n = 25$) with those of the control group ($n = 156$). Interestingly, maternal but not paternal self-reporting was higher in the persistent IgE-CMA group compared with the control group ($P = .04$, Fig 1A).

However, when we compared SPT reactivity as an objective measure of atopic tendency, the incidence of maternal and paternal positive SPT reactivity (for at least 1 allergen) was similar among controls ($n = 92$), patients with IgE-CMA ($n = 63$), and patients with persistent IgE-CMA ($n = 25$) (Fig 1B). In particular, a positive SPT result for milk was rare in parents from both groups

Table 2
Demographics and risk factors of the infant control group selected from the healthy infants population compared with the full healthy infant population^a

Variable	Control group ($n = 156$)	Healthy infants ($n = 12,482$)	<i>P</i> value
Sex			
Male	81 (51.9)	6,328 (50.7)	.76
Female	75 (48.1)	6,154 (49.3)	
Gestational age, mean $\pm$ SD, wk	39.2 $\pm$ 2.06	39.15 $\pm$ 1.9	.76
Birth weight, mean $\pm$ SD, kg	3.201 $\pm$ 0.42	3.196 $\pm$ 0.552	.91
Maternal age, mean $\pm$ SD, y	29.63 $\pm$ 5.38	29.69 $\pm$ 5.23	.88
Type of delivery			
PS	139 (89.1)	10,557 (84.6)	.12
CS	17 (10.9)	1,925 (15.4)	
No. of siblings	2.26 $\pm$ 1.53	2.35 $\pm$ 1.53	.42
Dairy product consumption by mother	156 (100)	12,375 (99.2)	
Ethnicity			
Jewish	138 (88.5)	9,651/12,111 (79.7)	.007
Non-Jewish ^b	18 (11.5)	2,460/12,111 (20.3)	
Age of CMP introduction, mean $\pm$ SD, d	67.62 $\pm$ 99.27	56.94 $\pm$ 86.22	.12
Dwelling			
City	134 (85.9)	10,771 (86.3)	.89
Other ^c	22 (14.1)	1,711 (13.7)	

Abbreviations: CS, caesarean section; PS, partus spontaneous.

^aData are presented as number (percentage) of patients unless otherwise specified. Data are $\pm$ 1 SD where indicated.

^bThe non-Jewish population consists mostly of Arab-Muslim mothers (62.6%) and Arab-Christian mothers (5.5%), and for the rest "no religion" was specified.

^cAny nonurban living is included.

Table 3

Comparison of risk factors for IgE-CMA between the control group selected from the healthy infant population and the IgE-CMA group^a

Risk factor	IgE-CMA ($n = 66$)	Control infants ($n = 156$)	<i>P</i> value
Incidental exposure in nursery	0.93 $\pm$ 1.17	1.22 $\pm$ 1.59	.21
Maternal educational level, mean $\pm$ SD, y	13.8 $\pm$ 2.73	13.32 $\pm$ 3.32	.30
Paternal educational level, mean $\pm$ SD, y	13.85 $\pm$ 3.14	13.47 $\pm$ 3.33	.43
Animals in home	17/65 (26.2)	47 (30.1)	.72
Maternal smoking	14/64 (21.9)	26/155 (16.8)	.37
Paternal smoking	20/63 (31.8)	49/149 (32.9)	.87

Abbreviation: IgE-CME, IgE-mediated cow's milk allergy.

^aData are presented as number (percentage) of patients unless otherwise specified. Data are $\pm$ 1 SD where indicated.

(1 of 122 parents in the IgE-CMA group and 3 of 173 in the control group), with no sign of differences between the groups. We also tested whether positive SPT reactivity in multiple tests correlated with an increased likelihood of atopic risk. Previous studies have reported that maternal risk to confer asthma, for example, was highest among those parents sensitized to the greatest number of aeroallergens.⁵ To test this hypothesis, we next evaluated maternal and paternal testing based on any multiple of aeroallergen positive reactivity. The data are stratified for mothers and fathers by their SPT reactivity and self-reported atopic status (Table 1). No significant differences were found whether maternal and paternal SPT data were combined, evaluated independently, or based on any multiple of aeroallergen positive reactivity. Furthermore, to control for the risk factor associated with the age at first exposure to CM, we compared only parents of infants whose first CM exposure was between 75 and 194 days after birth, shown to be at the highest risk of CMA induction.⁹ Still, no differences in SPT reactivity were noted between the groups (data not shown).

We next explored whether parents who believe they are atopic will be more cooperative when asked to undergo a SPT. Therefore, we compared infants of the parental control group who underwent the SPT ($n = 92$) with those who refused ($n = 64$) (Table 4). Although many of the infant-related and parental-related demographic details were similar between the groups, mothers who refused a SPT were younger ($P = .01$) and the gestational age of their children at birth was slightly older ($P = .02$). Most importantly,

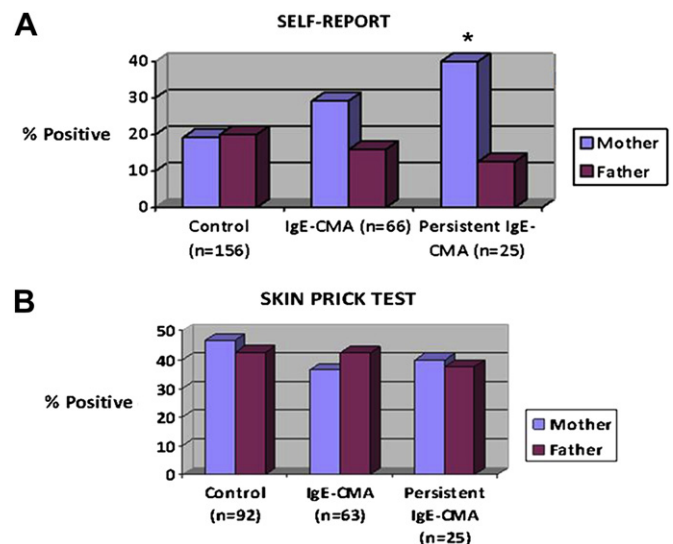


Figure 1. Relationship of parental atopic status to the development of IgE-mediated cow's milk allergy (IgE-CMA) in their children based on self-reports of atopy (A) and skin prick tests (B). Maternal but not paternal self-reporting of atopic history was higher in the persistent IgE-CMA group compared with the control group ($P = .04$). * $P < .05$.

Table 4

Comparison of demographics and risk factors of controls in whom parental SPT was performed vs those who refused^a

Variable	SPT performed (n = 92 infants)	SPT refused (n = 64 infants)	P value
Infant related			
Sex			
Male	51 (55.4)	30 (46.9)	.29
Female	41 (44.6)	34 (53.1)	
Gestational age, mean $\pm$ SD, wk	38.87 $\pm$ 2.34	39.67 $\pm$ 1.46	.02
Birth weight, mean $\pm$ SD, kg	3,153 $\pm$ 628	3,271 $\pm$ 412	.16
Age of CMP introduction, mean $\pm$ SD, d	68.43 $\pm$ 103.55	68.45 $\pm$ 93.56	.90
Type of delivery			
PS	79 (85.9)	60 (93.8)	.12
CS	13 (14.1)	4 (6.3)	
No. of siblings	2.27 $\pm$ 1.51	2.23 $\pm$ 1.57	.88
Ethnicity			
Jewish	81 (88.1)	57 (89.1)	.29
Non-Jewish ^b	11 (11.9)	7 (10.9)	
Pets	62 (67.4)	47 (73.4)	.16
Dwelling			
City	77 (83.7)	57 (89.1)	.34
Other ^c	15 (16.3)	7 (10.9)	
Parental related			
Maternal age, mean $\pm$ SD, y	30.52 $\pm$ 5.58	28.34 $\pm$ 4.82	.01
Maternal dairy consumption	92 (100)	64 (100)	
Maternal educational level, mean $\pm$ SD, y	13.14 $\pm$ 3.83	13.56 $\pm$ 2.45	.44
Paternal educational level, mean $\pm$ SD, y	13.81 $\pm$ 3.86	13.03 $\pm$ 2.45	.14
Smoking			
Maternal	15/91 (16.5)	11 (17.2)	.91
Paternal	31/85 (36.5)	18 (28.1)	.28
Positive for atopy by self-report (maternal/paternal)	34 (37.0)	17 (10.9)	.17
Positive for atopy by self-report (maternal)	23 (25.0)	7 (10.9)	.03
Positive for atopy by self-report (paternal)	18/86 (20.9)	12 (18.8)	.74

Abbreviations: CMP, cow's milk protein; CS, caesarean section; PS, partus spontaneus; SPT, skin prick test.

^aData are presented as number (percentage) of patients unless otherwise specified. Data are $\pm$ 1 SD where indicated.

^bThe non-Jewish population consists mostly of Arab-Muslim mothers (62.6%) and Arab-Christian mothers (5.5%), and for the rest "no religion" was specified.

^cAny nonurban living is included.

we found that mothers who refused a SPT were less likely to self-report atopy ($P = .03$), in concordance with the suspected bias. In contrast, positive paternal self-reports did not differ according to whether a SPT was performed (Table 4). To overcome this potential bias, we have reanalyzed our data extrapolating imputation as described in the "Methods" section. Even after accounting for self-reporting, no significant differences were found between the control and IgE-CMA groups whether maternal and paternal SPT data were combined, evaluated independently, or based on the likelihood of being sensitized.

Discussion

Substantial evidence indicates that the presence of parental atopy is a risk factor for the development of atopic diseases in their children.^{2–6} A link between a parental history of atopy or a personal history of atopic dermatitis and food allergy was recently highlighted in a National Institute of Allergy and Infectious Diseases-sponsored expert panel on food allergy.²⁴ However, Saarinen et al²⁵ evaluated children with persistent IgE-CMA (median age, 8.6 years) and noted that although a family history of atopy (derived from a questionnaire on atopy) was a risk factor for asthma, allergic rhinoconjunctivitis, and atopic eczema in their children, it was not a risk factor for the development of IgE-CMA. This study addresses whether parental atopy can reliably be used in a population cohort

to define infants more likely to develop IgE-CMA. The self-reporting of diseases related to atopy among parents of our IgE-CMA cohort ($n = 66$) was not found to be different from that of the parental control group. However, in the subgroup with persistent IgE-CMA ($n = 25$), maternal but not paternal self-reporting of atopic diseases was seen to be increased, similar to a previous report.²⁰

The maternal vs paternal contribution to CMA risk in the child was surprising, and we sought to confirm these findings using a more objective standard for atopy. Using the objective criteria of a positive SPT result, both maternal and paternal atopy did not confer a risk for the development of IgE-CMA in the child. One potential explanation of these results is an awareness bias in the maternal caretakers, which is more likely to manifest over time, while caring for a child with persistent IgE-CMA. Thus, our conclusions based on SPT results in the parents are in agreement with those of Saarinen et al, suggesting that familial atopy is not a risk factor for persistent IgE-CMA.

Reports from the literature may be difficult to compare directly with the results of our study. First, it is important to distinguish between those analyzing an infant population^{16,17,26–28} from those describing results derived from older children (≥ 4 years).^{15,17,25,29} The latter is a selected group of patients with persistent IgE-CMA often enrolled in a tertiary care center setting.²⁰ Second, many reports that describe an association between family history and food allergy do not segregate results for each food item^{21,22,30} or may rely solely on a questionnaire completed by the parents, not supplemented by any objective criteria, such as SPT or specific IgE.^{17,25–29} Finally, some reports describe food allergy in patients, but the diagnosis was made without an OFC being performed for confirmation.^{20–22,29} The more than 98% prospective recruitment of a newborn cohort, the reliance on an OFC for the diagnosis of IgE-CMA in the infant,⁹ and the assessment of parental atopy by self-report and SPT reactivity are particular features of this study.

Our study has several limitations that we took into account when analyzing the data. First, a comparison within the parents of the healthy infant cohort revealed that parents who agreed to undergo a SPT were more likely to report allergies. Thus, we extrapolated from those who underwent a SPT to those who reported allergy and were not tested, taking into account their reported status. Even after taking into account those who did not perform an SPT, no significant differences were found between the control and IgE-CMA groups whether evaluating the parents singly or together. Second, although the characteristics and potential risk factors of the control group ($n = 156$) were similar to the total healthy infants birth cohort ($n = 12,482$), a statistical difference was noted between the ethnicity makeup between these groups. This finding is possibly a reflection of a reluctance of the healthy non-Jewish population to come for a clinical study. Studies that compared the atopic predisposition between these 2 populations, however, are varied.^{31–34} In terms of IgE-CMA, one study did not demonstrate a greater risk between these groups,³⁴ whereas in our population-based study, significantly less IgE-CMA was seen in the non-Jewish population, although this was likely a reflection of an earlier introduction of CMP.⁹ However, our results did not change when we limited the comparisons to the Jewish population (63 of 66 of the IgE-CMA group and 138 of 156 of the control group).

In summary, on the basis of our data, parental atopic status is not an indicator of a higher risk to develop IgE-CMA in a general population cohort. Thus, it appears there is no need to restrict CMP-based formula to infants born to atopic parents.

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