

Latex allergy and latex sensitization in children and adolescents with meningocele

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Background: The high prevalence of clinical latex allergy and latex sensitization in children with meningocele has been widely reported. It has also been noted that these same children have a higher than expected prevalence of atopic disease. It would be useful to have a safe, sensitive, and specific skin test to detect latex sensitivity and to know how well this test compares with available in vitro tests. It would likewise be helpful to know as fully as possible the characteristics of the individual and to evaluate the relative importance of factors suspected to contribute to clinical latex allergy and latex sensitization in this population.

Methods: A group of 116 children and adolescents 1 to 20 years of age were recruited for the study. An extensive history of latex allergy, atopic diseases, and surgical procedures was taken on all subjects. Each subject had either a latex skin test or an in vitro study for latex-specific IgE, and 67 subjects had both tests simultaneously. Eighty-five subjects had epicutaneous skin tests to a panel of environmental allergens.

Results: Overall, 25 of 116 (21.5%) subjects had a history of clinical latex allergy, and 51 of 116 (44%) were sensitized to latex. The sensitivity and specificity of skin tests for clinical latex allergy were slightly greater than for the in vitro test (100% vs 95.8% and 82.3% vs 68.9%, respectively). The positive predictive value and negative predictive value of skin testing for clinical latex allergy were also greater (67.6% vs 50% and 100% vs 98.1%, respectively). Age was found to be a significant variable for both latex allergy and latex sensitization. The number of surgical procedures undergone and the presence of positive skin test responses to environmental allergens were significantly correlated with latex sensitization but not with clinical allergy to latex.

Conclusions: A sensitive, specific, and safe skin test for latex sensitivity appears superior to in vitro testing for latex allergy. Age, number of surgical procedures, and the presence of positive allergen skin test responses are significantly correlated with latex sensitization. Age alone is significantly correlated with clinical allergy to latex. (*J Allergy Clin Immunol* 1998;101:741-6.)

Key words: Latex, clinical allergy, sensitization, age, surgical procedures, atopic status, skin prick test, Ala STAT test

IgE-mediated allergic reactions to latex have been recognized with increasing frequency in recent years,

Abbreviations used

MM: Meningocele
SPT: Skin prick test

and several groups have been identified as being at high risk for having this form of latex hypersensitivity. The identified risk groups include those with occupational latex exposure (particularly latex glove wearers),¹⁻⁴ patients exposed to latex rubber during medical procedures or by instrumentation (where the risk appears related to early and repeated exposure, such as that experienced by patients with meningocele [MM]),⁵⁻⁹ and individuals with oral allergy syndrome or progressive food allergy induced typically by tropical fruits and vegetables, which cross-react with rubber latex. Previous reports of patients with MM have indicated that between 10% and 73% have a history of some type of clinical allergic reaction to latex,^{7,10} varying in severity from contact urticaria to anaphylactic shock.^{5, 7, 8, 11-16} Reports document in vitro IgE assays to be positive for latex allergens in between 34% and 72% of subjects with MM,^{6, 13} and skin prick tests (SPTs) are positive in 49% to 65% of tested patients.^{9, 17} The high prevalence of latex sensitization in patients with MM is thought to be the result of degree of exposure to latex rubber and possibly reflects factors unique to MM itself.^{8-10, 12, 18, 19} Beginning with the surgical closure of their spinal defect, these patients often undergo multiple surgical procedures for orthopedic, urologic, and neurologic problems and are thus exposed intraoperatively to several sources of latex. They are likely to have further exposure as part of ongoing daily bladder catheterization and bowel management programs. Taken in aggregate, these exposures are thought to constitute a heavy and enduring burden of latex allergen contact beginning early in life. Because patients with MM comprise the majority of subjects reported to have latex-induced anaphylactic reactions, there is a need to identify individuals with MM who have been sensitized to this product.¹³ Additionally, it is desirable to more closely identify the factors that predispose patients with MM to develop latex hypersensitivity in the hope that they might be avoided, although a number of reports have previously evaluated these factors.^{8-10, 13, 15} The following study was carried out to confirm the previously reported positive and negative predictive power of SPTs and in vitro testing for patients in whom clinical latex allergy has been reported

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Supported by a grant from the Nemours Foundation.

Received for publication Mar. 20, 1997; revised Feb. 25, 1998; accepted for publication Feb. 27, 1998.

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0091-6749/98 \$5.00 + 0 1/1/89870

TABLE I. Characteristics of the group with MM

Characteristics	
Total study group	116
Age range (yrs)	1-20
Sex	
M	58
F	58
Race	
White	105
Black	7
Asian	2
Unknown	2

and to identify more specifically the factors that predispose to latex hypersensitivity in individuals with MM.

METHODS

Subjects

One hundred sixteen patients with myelodysplasia (age range, 1 to 20 years) who were not acutely ill and who attended the Spinal Dysfunction Clinic at the duPont Hospital for Children were included in this study, which was carried out from December 1992 to February 1994. Subjects were unselected; no attempt was made to recruit or exclude latex-sensitive subjects. Enrolled patients, their parents, or guardians gave written informed consent for the proposed studies using a form approved by the institutional review board.

Basic information

The parents or guardians were administered a questionnaire, which elicited an overview of the patient's medical condition and assessed the history of immediate hypersensitivity reactions to latex, including itching, hives, rhinoconjunctivitis, bronchospasm, angioedema, or hypotension. The questionnaire also documented the number of surgical procedures and identified coexisting atopic conditions, including asthma, allergic rhinitis, rhinoconjunctivitis, atopic dermatitis, and food sensitivity in the patient.

Latex sensitivity testing

Latex sensitivity testing was carried out by both in vivo and in vitro methods, although not all subjects consented to both. Epicutaneous testing (SPTs) used latex proteins, which were a gift from Donald Beezold, PhD. They were derived from three lots of ammoniated latex (Micotex, Unitex, and Dynaten) obtained from Guthrie Latex, Inc. (Tuscon, Ariz.). These lots were mixed, and the dialyzed extract was lyophilized. To determine the antigenic protein content, the extract was reconstituted and analyzed by LEAP assay by using an internal standard developed by gravimetric analysis of purified ammoniated latex protein. The extract was adjusted to a concentration of 1 mg/ml in phosphate-buffered saline containing 30% glycerol. The material was sterilized by passage through a 0.45 μ m filter and diluted as needed for skin testing. Dilutions of this material of 1:1000 and 1:100 were made, and the SPTs were carried out with a sterile 25-gauge needle. A positive SPT response was defined as a wheal 3 mm larger than that produced by the negative saline control. In vitro testing for latex-specific IgE was carried out on serum collected from patients by the Ala STAT, an ELISA assay performed in the Allergy Research Laboratory of Henry Ford Hospital. A result

TABLE II. Latex sensitivity test results

	Positive SPT responses (%)	Positive Ala STAT results (%)
Total patients tested by either method*	34/85 (40)	46/98 (46.9)
Total patients tested by both methods†		
Positive history	22/22 (100)	21/22 (95.4)
Negative history	8/45 (17.7)	16/45 (35.5)
Sensitivity for clinical latex allergy		
Total group	23/23 (100)	23/24 (95.8)
Patients having both tests	22/22 (100)	21/22 (95.4)
Specificity for clinical latex allergy		
Total group	51/62 (82.3)	51/74 (68.9)
Patients having both tests	37/45 (82.2)	29/45 (64.4)
Positive predictive value for clinical latex allergy		
Total group	23/34 (67.6)	23/46 (50)
Patients having both tests	22/30 (73.3)	21/37 (56.8)
Negative predictive value for clinical latex allergy		
Total group	51/51 (100)	51/52 (98.1)
Patients having both tests	37/37 (100)	29/30 (96.7)
Concordance		
Positive SPT responses	—	29/30 (96.7)
Negative SPT responses	—	29/37 (78.4)
Positive Ala STAT results	29/37 (78.4)	—
Negative Ala STAT results	29/30 (96.7)	—

*Total patients tested by either method = 116; patients with positive history = 25 and patients with negative history = 91.

†Total patients tested by both methods = 67.

of Class I Ala STAT or greater was considered to be a positive result as recommended by the Laboratory.²⁰ Patients with IgE antibody to latex produced by either SPT or Ala STAT were considered latex sensitized.

Allergen SPTs

Allergen SPTs were carried out by using the Multi-Test system. Extracts of dust mite, ragweed, grass, tree mix, and mold mix, as well as glycerin saline and histamine controls, were applied to the skin of the forearm and read after 15 minutes. Wheal and erythema were measured, and SPT responses were considered positive if the wheal was 3 mm larger than that produced by the saline control. A positive reaction to two or more allergens was considered positive SPT evidence for atopy.

History of allergy

Clinical allergy to latex was considered to be present if there was a history of itching, hives, angioedema, rhinoconjunctivitis, bronchospasm, faintness, or hypotension occurring on multiple occasions in response to latex exposure. A subject was considered historically atopic if allergic rhinitis, rhinoconjunctivitis, atopic dermatitis, or asthma were present; if acute nasal, ocular, or wheezing symptoms developed repeatedly on contact with dogs, cats, or house dust; or if specific foods produced hives or oral allergy syndrome on multiple occasions.

TABLE III. Age-related sensitivity

Age range (yrs)	Clinical latex allergy	Positive latex SPT responses	Positive Ala STAT results	Positive allergy history	Positive allergy SPT responses
0-5 (<i>n</i> = 35)	2.9% (1/35)	13.0% (3/23)	20.7% (6/29)	11.4% (4/35)	17.4% (4/23)
6-10 (<i>n</i> = 29)	20.7% (6/29)	33.3% (7/21)	43.5% (10/23)	37.9% (11/29)	47.6% (10/21)
11-15 (<i>n</i> = 36)	33.3% (12/36)	57.1% (16/28)	61.3% (19/31)	30.6% (11/36)	39.3% (11/28)
16-20 (<i>n</i> = 16)	37.5% (6/16)	61.5% (8/13)	73.3% (11/15)	43.8% (7/16)	46.2% (6/13)

Statistical analysis

Sensitivity, specificity, and positive and negative predictive value were calculated by using standard definitions. Multivariate logistic regression analysis was used to examine the association between clinical history of latex allergy and latex sensitization detected by SPT or Ala STAT and the variables of age, number of surgical procedures, and SPTs to environmental allergens.

RESULTS

The composition of the study group is presented in Table I. As shown, 25 of 116 (21.5%) subjects are clinically allergic to latex as indicated by repeated immediate reactions on latex exposure. Considering the most serious clinical reaction, these included six with urticaria, six with angioedema, six with bronchospasm, three with rhinoconjunctivitis, and four with hypotension. There were 116 subjects tested by either SPT or Ala STAT, and of these, 51 of 116 (44%) demonstrated evidence of latex sensitization. Sixty-seven subjects were tested by both methods. On the basis of these data, the sensitivity, specificity, and positive and negative predictive values for detection of clinical latex allergy, as well as concordance between the methods, were calculated as shown in Table II. SPTs are found to be more specific tests than Ala STAT (82.2% vs 64.4%), but the sensitivity of both methods is comparable in identifying the population allergic to latex (100% and 95.4%). The negative predictive value of both SPT and Ala STAT for clinical allergy is strong (100% and 96.7%, respectively); however, the positive predictive value of both methods is considerably less, with SPTs slightly, but not significantly, better (73.3% vs 56.8%, $p = 0.34$).

Table III shows the prevalence of latex sensitization, atopic history, and positive allergen SPT responses in cohorts of children and adolescents with MM of increasing age. Clinical latex allergy, positive latex SPT responses, positive Ala STAT results, atopic history, and allergy skin tests all show increased prevalence with increasing age of the subjects studied. Although latex allergy, latex sensitization by SPT or Ala STAT, and allergy history increase progressively with the age of the subject, the maximal prevalence of positive environmental allergen SPT responses is reached in the 6 to 10 year age group and does not increase in the older age groups. It was our observation (data not shown) that neither latex allergy nor latex sensitization were found in any subject 0 to 4 years of age but began to appear among the 5-year-old subjects. With one exception, the same was true of history of atopy and positive allergen SPT

TABLE IV. Logistic regression: Latex sensitization overall model*

Variable	Coefficient	<i>p</i> Value	Odds ratio
Intercept	-3.0471	0.0001	
Age	0.1072	0.04	1.113
No. of surgical procedures	0.2362	0.008	1.266
Allergen SPT	1.3700	0.017	3.935

Area under ROC curve = 0.831.

* $p = 0.0001$.

response. Sensitization to both latex and environmental allergens increased greatly in patients between 5 and 10 years of age.

The results of a multivariate logistic regression analysis of latex sensitization shown by positive SPT responses or Ala STAT results as the dependent variable and age, number of surgical procedures, and the number of positive environmental allergen SPT responses as independent variables are shown in Table IV. All of these independent variables show a significant correlation with latex sensitization. When multivariate regression analysis was carried out with clinical latex allergy as the dependent variable, only age correlated significantly with clinical latex allergy ($p > 0.03$), whereas number of surgical procedures and allergen skin tests were not significantly related. Gender was evaluated and was not shown to be a significant variable in either latex allergy or latex sensitization after controlling for age and number of procedures. More male subjects were shown to be allergic to latex (27.5% vs 15.5%) and sensitized latex (41.3% vs 25.5%), but the differences were not shown to be statistically significant.

Correlations between race and latex allergy or sensitization were not analyzed because of the small number of nonwhite subjects.

DISCUSSION

This study confirms some observations by other authors, fails to confirm others, and may offer insights into the development of latex and environmental allergen sensitivity in this patient population. The findings of 11 reports describing 25 or more patients with MM are shown in Table V. The findings that we report above are within the range previously reported for prevalence of clinical latex allergy, latex sensitization as determined by SPT or Ala STAT, and history of atopy among patients with MM. In our study when SPT responses and Ala

TABLE V. Summary of latex allergy in MM

Author	No. of subjects	Clinical latex allergy (%)	Positive latex RAST or ELISA results (%)	Positive latex SPT responses (%)	Atopic history (%)	RAST or SPT sensitive but clinically nonallergic (%)	No. of surgical procedures identified as risk
Moneret-Vautrin ¹⁵	<i>n</i> = 25	5/25 (20%)	NA	4/25	11/25 (44%)	5/13 (38%)	+
Yassin ⁹	<i>n</i> = 76	24/76 (32%)	ND	49/76 (64.5%)	28/76 (39%)	25/47 (51%)	+
Pearson ¹⁸	<i>n</i> = 110	13/53 (25%)	ND	ND	21/110 (19%)	NA	+
Kelly ¹³	<i>n</i> = 75	14/75 (19%)	ELISA: 37/52 (72%); RAST: 31/51 (61%)	29/49 (59%)	12/41 (29%)	14/27 (52%)	+
Slater ⁶	<i>n</i> = 32	5/32 (16%)	4/32 (34%)	ND	19/32 (59%)	NA	—
Tosi ⁷	<i>n</i> = 93	9/93 (10%)	35/93 (38%)	ND	22/93 (24%)	25/35 (71%)	—
Ellsworth ¹⁶	<i>n</i> = 50	10/50 (20%)	26/45 (58%)	21/43 (49%)	ND	16/45 (36%)	+
Friday ⁸	<i>n</i> = 107	34/107 (32%)	58/107 (59%)	ND	ND	24/107 (22%)	+
Konz ¹⁰	<i>n</i> = 36	26/36 (73%)	23/36 (64%)	ND	15/36 (42%)	None	+
Nieto ¹⁹	<i>n</i> = 100	15/100 (15%)	ND	NA	11/100 (11%)	14/29 (48%)	+
Capriles-Hulett ¹⁷	<i>n</i> = 93	3/93 (3.2%)	ND	4/93 (4.3%)	34/93 (36.6%)	1/4 (25%)	—
Mean		24.1%	55.1%	44.2%	33.7%	42.8%	
Range		(3.2%-73%)	(34%-72%)	(49%-65%)	(11%-59%)	(22%-71%)	
No. of studies reporting		<i>n</i> = 11	<i>n</i> = 6	<i>n</i> = 4	<i>n</i> = 9	<i>n</i> = 8	<i>n</i> = 8

ND, Not done; NA, not ascertainable.

STAT results are compared in ability to detect subjects allergic to latex, both tests have comparable sensitivity, but the specificity and positive predictive value of the SPT is greater. Our data differ from those of Kelly et al.²¹ and Hamilton and Adkinson²² who found that SPT responses were more frequently positive. We found Ala STAT results more often positive. The reason for these differences is not clear but may be related to difference in SPT reagent potency in the report by Kelly et al. because that report described systemic reactions from skin testing. Hamilton and Adkinson studied an adult population, which may have reacted differently. As can be seen in Table II, positive Ala STAT results exceeded the SPT responses only in the group that had a negative history of latex sensitivity. A possible explanation for the increased number of positive Ala STAT results in our study is that the assay is detecting cross-reacting IgE antibodies against food²³ or pollen allergens.²⁴ Review of the eight subjects having positive Ala STAT results but negative latex skin test responses reveals that five of the eight had positive immediate hypersensitivity test responses to the environmental allergens. The greater number of positive Ala STAT assay results account for the poor concordance between the positive Ala STAT results and positive SPT responses and between negative SPT responses and negative Ala STAT results. Although no approved latex SPT reagent is currently available in the United States, our findings and the report of Hamilton and Adkinson²² suggest that development of such a reagent would be useful, safe, and practical.

We find that increasing age correlates significantly with both clinical latex allergy and latex sensitization. Despite using the same statistical method, we cannot

confirm the findings of Nieto et al.¹⁹ who reported that multivariate logistic regression analysis selected number of operations as the variable that contributed most to the process of latex sensitization. In contrast, we find increasing age to be a significant variable for both latex allergy and sensitization, whereas number of surgical procedures correlates only with latex sensitization. It is not clear why our findings differ, but the fact that we observed no latex sensitization or allergy below age 5 years, whereas Nieto noted 13% of subjects to be sensitized at that age, suggests population differences.

Our study was carried out from 1992 to 1994, and latex avoidance for patients with MM was implemented in mid-1993 at our facility. Children in our study would have been 0 to 15 years of age in 1988, when latex allergen is thought to have appeared in large quantity, and exposure would have continued through mid-1993. Because it has been suggested that allergen exposure early in life is most likely to elicit atopy, the younger subjects might be expected to have a higher prevalence of latex allergy and latex sensitization.²⁵ This was not found. Instead, as shown in Table III, the prevalence of latex allergy and sensitization seemed to be a function of advancing age and possibly of more surgical procedures, rather than age at exposure.

Investigators have noted the high prevalence of atopy in patients with MM.^{13, 15} In this study the prevalence of both atopic disease history and SPTs for environmental allergens are higher than in epidemiologic studies of comparably aged children. The NHANES II study found 20% of children 6 to 11 years of age had positive SPT responses compared with 48% in our data.²⁶ Among Swedish 7-year-old subjects, 15.1% had atopy by paren-

tal reports,²⁷ compared with 37.9% in our group. The cause of the increased atopy in MM is unknown, although Konz et al.¹⁰ have postulated disordered neural immune interaction, suggesting that patients with MM are a unique population in their tendency to develop atopy. We suggest an alternative explanation. It has been noted that populations intensely exposed to strong allergens have high rates of sensitization. Animal laboratory technicians, for example, have sensitization rates of 19% to 72%.²⁸⁻³⁰ These high prevalences are similar to the latex-sensitization prevalence in patients with MM but offer no explanation of the frequent sensitization to unrelated allergens at an early age in patients with MM. Atopic sensitization is thought to begin when naive T cells undergo *immune deviation* on allergen exposure into the T_{H2} developmental pattern, leading to production of IL-4 and IL-13. The former is also produced by activated mast cells and basophils.^{31,32} It is known that naive T cells exposed to IL-4 during antigen stimulation develop into T_{H2} cells preferentially.^{33,34} Children with MM who have developed atopic sensitivity to latex and continue to be exposed to that allergen may have sufficient ongoing production of these cytokines to influence local reactions to subsequently encountered allergens toward atopic sensitization. This phenomenon could produce more environmental allergy and atopy manifesting at a younger age in these patients. The recent report of a normal prevalence of atopy in subjects with MM having little latex exposure would support this mechanism as being operative.¹⁷ The fact that patients with MM are sensitized to latex protein fractions that are different from those of health care workers might suggest that they are a unique group. However, it has also been proposed that this sensitization may result from frequent exposure to water-insoluble proteins during surgery and in bladder catheterization and bowel programs.^{35,36} We suggest that patients with MM have a high prevalence of latex allergy because of early and intense exposure to that potent allergen and that their latex allergy facilitates development of other allergies.

We thank Ms. Bernadette Toner and Ms. Margaret Scatasti for their expert secretarial assistance.

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Correction

The following correction applies to the article by Peng, Li, and Simons entitled "Immunoblot analysis of salivary allergens in 10 mosquito species with worldwide distribution and the human IgE responses to these allergens," which appeared in volume 101, part 1, pp. 498-505, 1998, of The Journal.

Only half of Figure 3 appears in the text. We here reprint Figure 3 and its legend in their entirety.

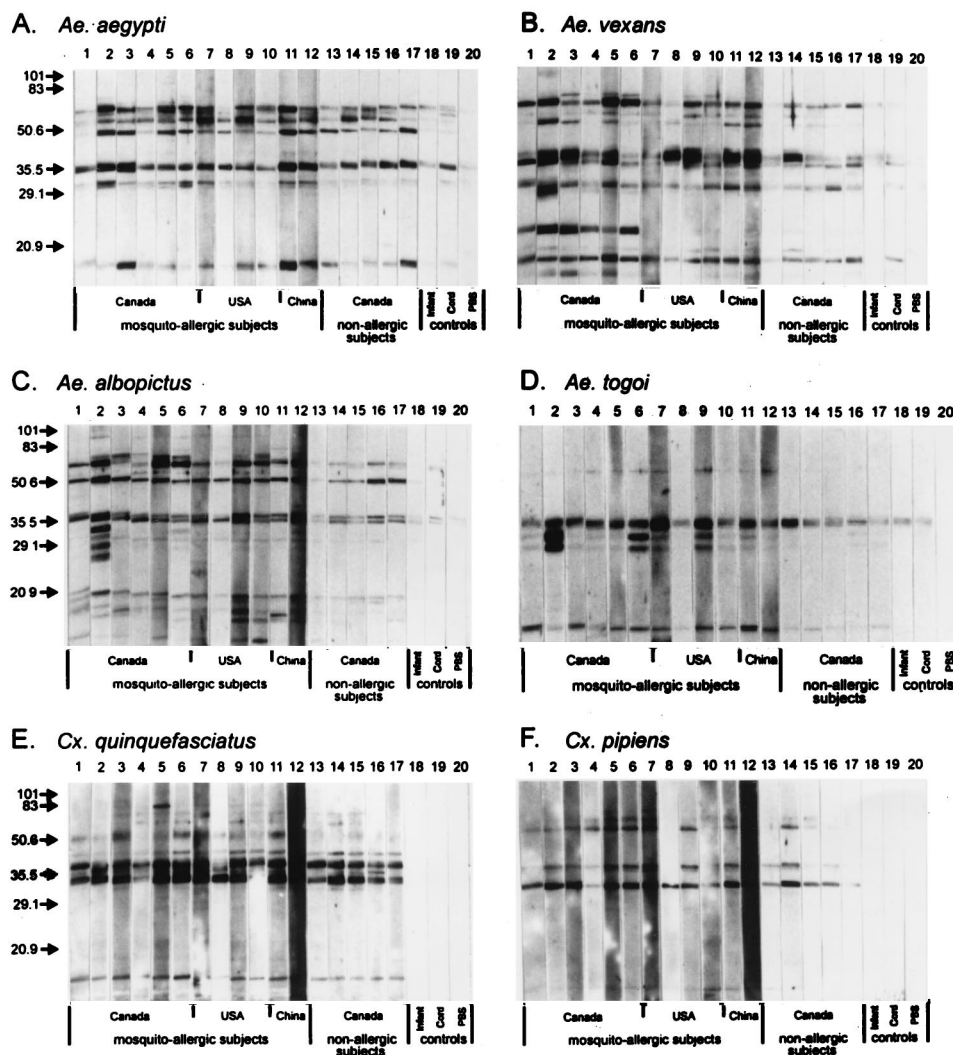


FIG. 3. IgE responses to salivary allergens of six mosquito species in subjects allergic to mosquitoes and nonallergic subjects. Proteins of saliva or salivary gland extracts separated by SDS-PAGE were transferred to nitrocellulose membranes. Membranes were sequentially incubated with sera from subjects allergic to mosquitoes (strips 1 to 12) or sera from nonallergic subjects (strips 13 to 17), monoclonal anti-human IgE, and enzyme-conjugated goat anti-mouse IgG as described in Methods section. Infant serum (strip 18), cord serum (strip 19), and PBST (strip 20) were used as negative controls. Six mosquito species used were *Ae. aegypti* (A), *Ae. vexans* (B), *Ae. albopictus* (C), *Ae. togoi* (D), *Cx. quinquefasciatus* (E), and *Cx. pipiens* (F). In *Ae. vexans* a 68 kd species-shared allergen, Aed a 1, is indicated by arrow a, and a 23 kd *Ae. vexans*-specific allergen is indicated by arrow b.