

**TABLE I.** Clinical manifestations observed in the DBPCFCs

|                           | Group with<br>peach allergy<br>(N = 71) | Group with<br>apple allergy<br>(N = 40) | Total<br>(N = 111) |
|---------------------------|-----------------------------------------|-----------------------------------------|--------------------|
| OAS                       | 66 (92.9%)                              | 34 (85%)                                | 100 (90.1%)        |
| Abdominal pain            | 14 (19.7%)                              | 5 (12.5%)                               | 19 (17.1%)         |
| Rhinoconjunctivitis       | 10 (14%)                                | 7 (17.5%)                               | 17 (15.3%)         |
| Skin itching              | 10 (14%)                                | 5 (12.5%)                               | 15 (13.5%)         |
| Urticaria                 | 7 (9.8%)                                | 2 (5%)                                  | 9 (8.1%)           |
| Cough                     | 3 (4.2%)                                | 2 (5%)                                  | 5 (4.5%)           |
| Vomiting                  | 5 (7%)                                  | 0                                       | 5 (4.5%)           |
| Diarrhea                  | 1 (1.4%)                                | 0                                       | 1 (0.9%)           |
| Only local symptoms       | 48 (67.6%)                              | 29 (72.5%)                              | 77 (69.3%)         |
| Local + systemic symptoms | 20 (28.2%)                              | 9 (22.5%)                               | 29 (26.1%)         |
| Only systemic symptoms    | 3 (4.2%)                                | 2 (5%)                                  | 5 (4.5%)           |

No statistical differences were found between the peach and apple groups.

and included antihistamines in 19 patients, corticosteroids in 14, antacids in 6, and inhaled salbutamol in 1. Epinephrine was administered in 6 subjects. All the reactions subsided within 60 minutes, and only 1 delayed reaction was reported in a patient who experienced immediate transient OAS, and hours later at home had abdominal pain and vomiting.

In this study, most of the patients (69.3%) presented only mild symptoms (OAS) during the challenges, and 80.2% of the reactions subsided spontaneously. Therefore, we can conclude that DBPCFCs with peach and apple, in our LTP-sensitized population, are safe, if performed in an adequate setting and by trained personnel.

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## The value of sesame-specific IgE levels in predicting sesame allergy

To the Editor:

Recently, sesame has been recognized as an increasingly frequent and potentially severe allergen. Accurate, safe, and cost-effective diagnostic techniques are, therefore, essential.<sup>1</sup> Serum levels of sesame-specific IgE can be quantified by a commercially available test; however, its diagnostic value has not been established. The normal range of sesame-specific IgE in individuals who tolerate sesame is unknown, and there are no established thresholds that predict clinical reactivity.

We conducted a study to (1) define the performance characteristics (sensitivity, specificity, positive and negative predictive values) of sesame-specific IgE and (2) determine a threshold that differentiates allergic from tolerant children. The Research Ethics Board of the Montreal Children's Hospital approved the study.

A retrospective cohort of children with sesame allergy, age 2 to 18 years, was identified through a chart review of all patients presenting to the Montreal Children's Hospital Allergy Clinic who had serum levels of sesame-specific IgE measured between January 2001 and September 2005. A child was considered to have sesame allergy with either (1) a convincing history of an allergic reaction and a positive skin prick test (SPT) to sesame or (2) a positive food challenge to sesame.

A convincing history was defined as a minimum of 2 mild symptoms or signs (pruritus, urticaria, flushing, and/or rhinoconjunctivitis) or 1 moderate (angioedema, change in voice, coughing, nausea, vomiting, and/or abdominal pain) or severe (wheezing, stridor, cyanosis, and/or circulatory collapse) symptom or sign in the context of a clear ingestion of sesame.

A control group of sesame-tolerant children, age 2 to 18 years, was identified prospectively through the Montreal Children's Hospital Allergy Clinic between October 2003 and June 2006 and retrospectively through the chart review described. Children younger than 2 years were excluded because this age group generates lower IgE levels.<sup>2</sup> A child was considered not to have sesame allergy if either (1) on history, the child tolerated a usual portion of sesame on a regular basis or (2) the child had a negative food challenge with sesame. For patients recruited prospectively, if blood tests were indicated for evaluation of the presenting complaint, consent was obtained for measurement of sesame-specific IgE.

**TABLE I.** Demographic and clinical characteristics of children allergic to sesame and tolerating sesame

|                                                        | Allergic to sesame (N = 28) | Tolerating sesame (N = 73) |
|--------------------------------------------------------|-----------------------------|----------------------------|
| Age at time of Unicap (y), mean (SD) (95% CI)          | 6.9 (3.1) (5.7, 8.1)        | 7.5 (3.8) (6.6, 8.3)       |
| Percent male (95% CI)                                  | 67.9 (47.6, 84.1)           | 71.2 (59.4, 81.2)          |
| Unicap value (kU <sub>A</sub> /L),* mean (SD) (95% CI) | 27.0 (30.4) (15.2, 38.8)    | 5.4 (17.5) (1.4, 9.5)      |
| Median (interquartile range)                           | 16.0 (5.9, 36.0)            | <0.35 (<0.35, 1.22)        |
| Range                                                  | 0.46, >100                  | <0.35, >100                |
| Interval between reaction and Unicap (y), mean (SD)    | 3.9 (2.9)                   |                            |
| Median (interquartile range)                           | 3.4 (1.3, 7.3)              |                            |
| Range                                                  | 0.17, 7.9                   |                            |
| SPT value (mm),† mean (SD) (95% CI)                    | 8.8 (4.9) (6.9, 10.7)       |                            |
| Atopic features,‡ proportion (%)                       |                             |                            |
| Asthma                                                 | 16/19 (84.2)                | 37/66 (56.1)               |
| Eczema                                                 | 20/21 (95.2)                | 45/62 (72.6)               |
| Rhinitis                                               | 10/11 (90.9)                | 25/56 (44.6)               |
| Food allergies (other than sesame)                     | 27/28 (96.4)                | 67/68 (98.5)               |
| Peanut allergy                                         | 15/28 (53.6)                | 48/73 (65.8)               |
| Family history of atopy,‡ proportion (%)               | 17/19 (89.5)                | 52/61 (85.2)               |

Unicap refers to the measurement of sesame-specific IgE.

\*Unicap was set at 0.34 kU<sub>A</sub>/L when measured as <0.35 kU<sub>A</sub>/L and at 101 kU<sub>A</sub>/L when measured as >100 kU<sub>A</sub>/L.

†SPT value is sesame wheal minus saline wheal.

‡Based on nonmissing data.

**TABLE II.** Performance characteristics of sesame Unicap testing at various cutoff points

| Unicap cutoff (kU <sub>A</sub> /L) | No. at or exceeding threshold | No. of children with allergy among those exceeding threshold | Sensitivity (%), (95% CI) | Specificity (%), (95% CI) | Positive predictive value (%), (95% CI) | Negative predictive value (%), (95% CI) | Prevalence of sesame allergy = 1%       |                                         |
|------------------------------------|-------------------------------|--------------------------------------------------------------|---------------------------|---------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|
|                                    |                               |                                                              |                           |                           |                                         |                                         | Positive predictive value (%), (95% CI) | Negative predictive value (%), (95% CI) |
| ≥0.34*                             | 101                           | 28                                                           | 100 (87.7, 100)           | 0.0 (0.0, 4.9)            | 27.7 (19.3, 37.5)                       | —                                       | 1                                       | —                                       |
| ≥0.35                              | 64                            | 28                                                           | 100 (87.7, 100)           | 50.7 (38.7, 62.6)         | 43.8 (31.4, 56.7)                       | 100 (90.5, 100)                         | 2.0 (1.6, 2.6)                          | 100 (99.8, 100)                         |
| ≥1                                 | 48                            | 26                                                           | 92.9 (76.5, 99.1)         | 69.9 (58.0, 80.1)         | 54.2 (39.2, 68.6)                       | 96.2 (87.0, 99.5)                       | 3.1 (2.2, 4.5)                          | 99.9 (99.7, 100)                        |
| ≥3                                 | 36                            | 22                                                           | 78.6 (59.0, 91.7)         | 80.8 (69.9, 89.1)         | 61.1 (43.5, 76.9)                       | 90.8 (81.0, 96.5)                       | 4.2 (2.5, 6.9)                          | 99.7 (99.5, 99.9)                       |
| ≥7                                 | 27                            | 20                                                           | 71.4 (51.3, 86.8)         | 90.4 (81.2, 96.1)         | 74.1 (53.7, 88.9)                       | 89.2 (79.8, 95.2)                       | 7.9 (3.8, 15.7)                         | 99.7 (99.5, 99.8)                       |
| ≥20                                | 17                            | 12                                                           | 42.9 (24.5, 62.8)         | 93.2 (84.7, 97.7)         | 70.6 (44.0, 89.7)                       | 81.0 (70.9, 88.7)                       | 7.1 (2.6, 16.9)                         | 99.4 (99.2, 99.6)                       |
| ≥40                                | 9                             | 7                                                            | 25.0 (10.7, 44.9)         | 97.3 (90.5, 99.7)         | 77.8 (40.0, 97.2)                       | 77.2 (67.2, 85.3)                       | 13.0 (2.5, 44.5)                        | 99.2 (99.1, 99.4)                       |
| ≥101                               | 4                             | 2                                                            | 7.1 (0.9, 23.5)           | 97.3 (90.5, 99.7)         | 50.0 (6.8, 93.2)                        | 73.2 (63.2, 81.7)                       | 4.4 (2.7, 20.1)                         | 99.0 (99.0, 99.2)                       |

Unicap refers to the measurement of sesame-specific IgE.

\*Unicap was set at 0.34 kU<sub>A</sub>/L when measured as <0.35 kU<sub>A</sub>/L and at 101 kU<sub>A</sub>/L when measured as >100 kU<sub>A</sub>/L.

Skin prick tests to sesame were performed using a commercially prepared extract from ALK-Abelló (Port Washington, NY). Negative controls with saline and positive controls with histamine were performed concurrently. A positive SPT was defined as a wheal diameter at least 3 mm greater than the negative control.<sup>3</sup>

Serum samples were analyzed for sesame-specific IgE using Phadia's ImmunoCAP fluorescence enzyme immunoassay (Uppsala, Sweden) between January 2001 and June 2006. The sesame allergen is derived from sesame seed extract, and all components of the native seed are included (C. Lampman, product specialist, allergy/immunology, Somagen Diagnostics Inc, personal communication, March 2006).

Food challenges were conducted when there was diagnostic uncertainty either because of a questionable history or a negative SPT despite a convincing history. Patients with a history of anaphylaxis were not challenged. Challenges were performed as single-blind or open using either sesame seeds or sesame snacks.

Twenty-five of 28 children with sesame allergy had a convincing history and positive SPT to sesame, and 3 were labeled

allergic on the basis of a positive food challenge. These 3 had itchiness and/or gastrointestinal symptoms and/or generalized hives after a cumulative dose of sesame between 4.1 mL and 10 mL. Sixty-nine of 73 controls had a history of tolerating sesame, whereas 4 had a negative sesame challenge in the context of a questionable history. These 4 tolerated a cumulative dose between 5 mL and a 15-cm × 3-cm sesame seed bar.

The mean sesame-specific IgE level of the children with sesame allergy exceeded that of the tolerant children: 27.0 kU<sub>A</sub>/L versus 5.4 kU<sub>A</sub>/L (Table I). The mean difference and 95% CI between the groups was 21.6 kU<sub>A</sub> (9.2-34.0 kU<sub>A</sub>/L). There were no patients with sesame allergy with a sesame-specific IgE <0.35 kU<sub>A</sub>/L. Thirty-seven of 73 tolerant children had a sesame-specific IgE <0.35 kU<sub>A</sub>/L. Two patients each in the allergic and tolerant groups had a sesame-specific IgE >100 kU<sub>A</sub>/L.

Sensitivity was highest at a lower cutoff value, whereas specificity increased at higher values (Table II). The positive predictive value increased up to a threshold of 7 kU<sub>A</sub>/L. Of the 17 patients whose sesame-specific IgE was ≥20 kU<sub>A</sub>/L, 5

tolerated sesame. Given that the predictive values depend on the prevalence of sesame allergy, these values were recalculated with a presumed prevalence of sesame allergy of 1% (Table II).

We have conducted the first study to evaluate the diagnostic value of sesame-specific IgE. We were unable to establish a threshold, in our population, with a 95% positive predictive value. At a sesame-specific IgE threshold of 7 kU<sub>A</sub>/L, the positive predictive value was 74.1% and did not increase monotonically at higher thresholds. The significance of lower positive predictive values at higher thresholds is uncertain because these were based on a small number of cases. Of the 5 of 17 patients with sesame-specific IgE  $\geq 20$  kU<sub>A</sub>/L who tolerated sesame, all were allergic to peanut. Because one of the major sesame allergens, Ses I 3, has 80% homology with a major peanut allergen, Ara h 1,<sup>4</sup> it is possible that the peanut-specific IgE in these patients was falsely detected as sesame-specific IgE.

Our study does demonstrate, however, that a sesame-specific IgE  $<0.35$  kU<sub>A</sub>/L is useful in excluding a diagnosis of sesame allergy. Although patients with a sesame-specific IgE exceeding this value may not have sesame allergy, none of our patients with a value  $<0.35$  kU<sub>A</sub>/L had sesame allergy.

Although our study is limited by a small sample of cases, the sample size is similar to that in the study by Sampson<sup>5</sup> of wheat and soy IgE, which also did not predict allergy. It is possible that a larger sample would be successful in establishing a threshold. Another potential limitation of our study is that allergy or tolerance to sesame was usually determined by history rather than the gold standard food challenge. Although history is subject to recall and reporting bias, we applied strict inclusion and exclusion criteria. Furthermore, other studies have relied on clinical history to define their allergic cohort.<sup>6-8</sup> The several year delay between convincing reaction and measurement of sesame-specific IgE is also a limitation of our study because it raises the concern that the sesame allergy may have resolved at the time of the IgE measurement. However, this delay was unavoidable because measurement of sesame-specific IgE was not available at our institution until several years after the children's reactions in some cases. At the time of the IgE measurement, all children were still considered by their treating allergist to have sesame allergy because they had had a recent positive SPT to sesame (23 of the children with sesame allergy) or a recent reaction, either accidental or during a food challenge (5 children). In the 23 with a persistently positive SPT in the context of a convincing history, a challenge was considered too risky. It should be noted that the potential misclassification as allergic of a child who may have a resolved sesame allergy would not change the conclusion of our research—that is, a sesame-specific IgE  $<0.35$  kU<sub>A</sub>/L is useful in excluding a diagnosis of sesame allergy.

Considering our relatively small sample, a sesame-specific IgE  $<0.35$  kU<sub>A</sub>/L should still be interpreted in the context of the history and SPT. With the exception of individuals with convincing histories of sesame allergy, we suggest that challenges should be offered to all patients to confirm the diagnosis of sesame allergy, irrespective of SPT or sesame-specific IgE values. In those with a sesame-specific IgE level  $<0.35$  kU<sub>A</sub>/L, the risk of an allergic reaction is low. Further, the clinician should be aware of the potential for patients with peanut allergy to be falsely labeled as having sesame allergy if this diagnosis is solely based on the sesame-specific IgE. We suggest that if a patient clearly tolerates sesame, it is not warranted to obtain a sesame-specific IgE. Alternatively, if the patient's history is truly convincing of a significant

allergic reaction to sesame, regardless of the SPT result or sesame-specific IgE level, the patient should be considered allergic, because anaphylaxis to sesame has been described with negative SPT and IgE levels.<sup>7,9</sup>

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## Pharmacogenomics and outcome of asthma: No clinical application for long-term steroid effects by *CRHR1* polymorphisms

### To the Editor:

Worldwide, millions of patients are affected by asthma, an inflammatory airway disease. Corticosteroids suppress virtually every step of the inflammatory cascade and constitute the cornerstone of asthma treatment. Their beneficial effects on a group level are well accepted, but the individual response to inhaled corticosteroids (ICSs) varies widely. The latter might be due to an underlying genetic background, as suggested by Tantisira and colleagues.<sup>1,2</sup> They have shown that 3 haplotype-tagging single nucleotide polymorphisms (SNPs) in the corticotropin-releasing hormone receptor 1 gene (*CRHR1*) are associated with lung function improvement after 8 weeks' treatment with ICSs in patients