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Mammalian meat-induced anaphylaxis: Clinical relevance of anti-galactose- α 1,3-galactose IgE confirmed by means of skin tests to cetuximab

To the Editor:

Severe anaphylaxis is often associated with food allergy. Classically, the diagnosis of food allergy is established through a careful evaluation of a patient's allergy history, including skin tests and *in vitro* tests. If the specific trigger cannot be established, then the patient might be diagnosed with idiopathic anaphylaxis, which is a major concern for both the patient and the physician. Some of these cases are due to rare food allergies.¹ Recently, a new specific IgE to galactose- α 1,3-galactose (α -gal) was shown to be linked with anaphylaxis or angioedema reactions to mammalian meats.^{2,3} The present study reports on 2 cases of anaphylaxis to mammalian meats, which were evaluated by using an in-house α -gal IgE immunoassay⁴ and novel intradermal tests (IDTs) to cetuximab. Cetuximab is an mAb presenting the α -gal oligosaccharide in the Fab portion of the heavy chain.

Two patients were referred to our department in 2008 with idiopathic anaphylaxis diagnoses after undergoing inconclusive allergy tests. Patient 1 was a 53-year-old man who had an anaphylactic shock in 2006 ninety minutes after consuming pork offal. He experienced recurrent episodes of delayed urticaria 4 hours after ingesting pork, beef, and horse, lamb, and rabbit meats. Consumption of milk and poultry did not result in allergic reactions. The patient had asthma in childhood.

Patient 2 was a 48-year-old woman who experienced an anaphylactic shock in 2004 two hours after eating a meal that included pork offal (kidney) and 7 episodes of urticaria that occurred at night. Retrospectively, the anamnesis indicated that she had consumed mammalian meat 6 hours before the allergic reaction. She consumed milk and poultry without incident. In

TABLE I. Prick-in-prick tests and IDT results for 3 patients (in millimeters)

	Patient 1	Patient 2	Pork-cat syndrome (control subject)
Negative control to saline	0	0	0
Positive control to 9% codeine	2.5	6	3
Raw beef meat	3	3	0
Cooked beef meat	2.5	0	0
Raw and cooked veal meat	0	nd	2.5
Raw and cooked pork meat	0	1.5 and 0	0
Pork kidney	2.5	2.5	0
Raw and cooked lamb meat	0	0	0
Raw rabbit meat	2	nd	2.5
Cooked rabbit meat	1	nd	Nd
Other food allergens	0	0	0
Cetuximab, 5 μ g/ml	9	9	0

A positive prick-in-prick test result was a 3-mm-diameter wheal when the negative control produced negative results and the 9% codeine control result was positive.

childhood the patient had atopic dermatitis. She had 2 pets (a cat and a dog) and used to go horseback riding.

Both patients had a background of atopy with sensitization to *Dermatophagoides pteronyssinus*. The total IgE levels measured were 38 kU/L for patient 1 and 454 kU/L for patient 2. The serum tryptase levels were normal in both patients. Prick-in-prick tests were performed to raw and cooked mammalian meats, as well as to 30 common foods. Both patients had slightly positive prick-in-prick test results, these being only to raw beef and pork kidney (Table I).

IDTs to cetuximab (Erbix; Merck Serono, Geneva, Switzerland) were conducted at concentrations of 5, 50, and 500 μ g/mL. For both patients, the IDT results were positive at the lowest concentration (5 μ g/mL) and produced a mean wheal diameter of 9 mm (ie, the reaction was 3 times larger than the wheal of injection; Fig 1). Increased concentrations of cetuximab elicited impressive skin reactivity. Eight control subjects with atopy who were suspected of having meat allergies were also evaluated with IDTs to cetuximab. One of these control subjects had allergic rhinitis to cat and allergy to pork meat, referred to as "pork-cat syndrome," that was mediated by specific IgE antibodies to serum albumin. All 8 control subjects had negative results to cetuximab up to 500 μ g/mL.

Specific IgE antibodies were present for beef, pork, and rabbit meat in both patients (Table II). Specific IgE antibody levels to α -gal were measured, as described by Chung et al,² and were 4.82 kU/L in patient 1 and 0.28 kU/L in patient 2. Five control sera were tested; all were negative for IgE antibodies to α -gal. Both patients exhibited specific IgE antibodies to cat epithelia in the absence of IgE to Fel d 1, and patient 2 showed only a slight sensitization to cat albumin. Both patients had negative results for IgE antibodies to pork albumin. In contrast, the control subject with pork-cat syndrome had specific IgE antibodies that were greater than 100 kU/L against cat albumin and 9.41 kU/L against pork albumin but had no anti- α -gal IgE antibodies (Table II).

Allergies to meats are rarely identified. The Circle for Clinical and Biological Investigations in Food Allergy (CICBAA) database has recorded 1037 documented food allergies and contains data on 14 cases of allergies to mammalian meats, including 10 (1.3%) of 726 cases in children and 4 (1.2%) of 311 cases in

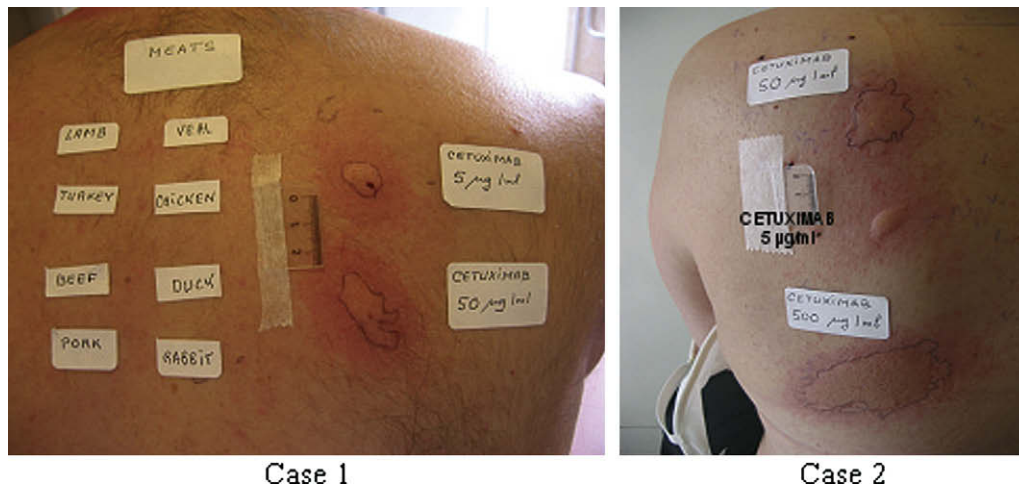


FIG 1. IDTs to cetuximab. Cetuximab (0.05 mL) at concentrations of 5, 50, and 500 $\mu\text{g}/\text{mL}$ (10^{-1} , 10^{-2} , and 10^{-3} dilutions of the commercial drug, respectively) was intradermally injected. The diameter of the injection papula was 3 mm. The positive response criteria included a doubling of the wheal diameter size measured 15 minutes after the injection, a pink wheal color, and a surrounding erythema.

TABLE II. Specific IgE levels (in kilounits per liter) in 3 subjects as measured with ImmunoCAP (Phadia, Uppsala, Sweden)

	Patient 1	Patient 2	Pork-cat syndrome (control subject)
Beef	3.43	20	6.11
BSA	ND	ND	10.8
Pork	2.38	13	6.48
Pork serum albumin	<0.10	<0.10	9.41
Rabbit	0.62	1.12	ND
Cat epithelia	2.28	20.3	>100
Cat albumin	<0.10	0.14	>100
Fel d 1	<0.10	<0.10	3.01
α -Gal	4.82	0.28	<0.10

adults. In children beef allergies were implicated in 8 cases and were associated with pork allergies in 2 cases and with milk allergies in 2 cases. Two cases in children were isolated pork allergies. In adults allergies to pork were reported 3 times and were associated with allergies to rabbit meat in 2 cases.

BSA is the most common allergen that explains cross-allergies between milk and beef and lamb.⁵ Other identified allergens were more rare; these included gamma globulins, tropomyosin, and actin.⁵ In pork-cat syndrome the allergen is pork albumin, which can cross-react with cat albumin because of its 82% amino acid sequence homology.^{6,7} In addition, specific allergens could be involved in allergies to offal that contrast with a tolerance to meats of similar origin.⁸

Mammalian meat allergies can be related to sensitization to the α -gal oligosaccharide epitope, a glycosylation modification in nonprimate mammalian proteins.^{2,3,9} However, the clinical relevance of IgE antibodies against α -gal is unclear. Hence in patient 2 an allergic reaction is not observed after each meal containing meat. Although the level of specific IgE antibodies was low in this patient, strong skin sensitization was observed on the IDTs to cetuximab. The lack of a correlation between allergen

consumption and the reaction might be linked to variability in meat digestion, as altered by the association of other food variables, which is known as the matrix effect.

Pork-cat syndrome has been shown to be due to cross-reactivity between cat and pork albumins.⁷ The control subject with this syndrome had no specific IgE antibodies to α -gal. This result is consistent with the theory that only protein epitopes are implicated in pork-cat syndrome and with the fact that albumins are not glycosylated.

The strong skin reactivity observed might depend on several parameters. First, there are 2 α -gal epitopes per molecule of cetuximab, making cetuximab a divalent molecule that can bridge a membrane IgE. These epitopes are presented opportunistically to membrane IgE antibodies, with a constant distance between the 2 epitopes that is determined by the Fab.

Second, the intradermal injection of this cetuximab offers a huge quantity of accessible epitopes. Injection of 0.05 mL of 5 $\mu\text{g}/\text{mL}$ cetuximab offers a total of 10^{12} cetuximab molecules and, consequently, 2×10^{12} α -gal molecules.

Third, the measured skin reactivity demonstrates that numerous specific IgE antibodies are present on mast cells. Therefore skin sensitization can be much higher than the circulating specific IgE level predicts. The reactive concentration of cetuximab, as measured with the IDT, was estimated to be 100-fold greater in the 7 control subjects than in the allergic patients (500 vs 5 $\mu\text{g}/\text{mL}$, respectively). Therefore this diagnostic tool could be used to accurately identify mammalian meat allergies in patients given diagnoses of idiopathic anaphylaxis and eosinophilic esophagitis, gastroenteritis, or colitis.¹⁰

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17q12-21 variants interact with smoke exposure as a risk factor for pediatric asthma but are equally associated with early-onset versus late-onset asthma in North Americans of European ancestry

To the Editor:

Gene-environment interactions contribute to asthma.¹ The first common genetic risk factor identified for pediatric asthma by means of genome-wide association is the 17q12-21 locus harboring the *ORMDL3* gene. *ORMDL3* encodes a gene product of uncertain function that localizes to the endoplasmic reticulum.^{2,3} Association between asthma and 17q12-21 was identified in white subjects of Northern European ancestry² and has been established as a risk factor for early pediatric asthma through replication studies in multiple independent cohorts of the same ancestral background, including our own study.³⁻⁶

A recent study of 17q12-21 variants in white subjects reported the association was significantly stronger in subjects with early tobacco smoke exposure.⁴ This study also found that the genetic variations were more strongly associated with early-onset asthma (before age 4 years) than with late-onset asthma (after age 4 years). Our own prospective birth cohort also suggested that upstream *ORMDL3* variants were associated mainly with asthma of onset at less than age 3 years,⁶ yet these findings need further replication. Here we sought to confirm the smoking and age-of-onset findings in a larger study using a case-control design.⁷ We used 2 pediatric asthma cohorts, one of self-identified white subjects and one of self-identified African American subjects. Both were recruited at the Children's Hospital of Philadelphia

(CHOP) from greater Philadelphia area residents. This study was approved by the Institutional Review Board at CHOP and included intake surveys, sample collection, genotyping, and linkage to electronic medical records (EMRs).

Patients and control subjects were recruited from outpatient settings within the CHOP Health Care Network between 2006 and 2008. Case status was determined by self-report of asthma on the intake questionnaire plus diagnosis or treatment of asthma in the EMR. Control status was defined by the absence of any diagnosis or medical treatment consistent with asthma. The white cohort included 920 cases and 3804 control subjects; the African American cohort included 1844 cases and 3488 control subjects. Among white subjects, mean age at the start of follow-up was 6 years, and 54% of subjects were male. Mean age at the start of follow-up among white asthmatic subjects was 5.2 years (SD, 4.8; range, 0-16.0 years). Mean age of asthma onset was 6.8 years (SD, 4.9; range, 0.4-17.5 years). Among African American subjects, mean age at the start of follow-up was 4 years, and 51% of subjects were male. Mean age at the start of follow-up among African American asthmatic subjects was 3.3 years (SD, 4.2; range, 0-13.7 years). Mean age of asthma onset was 4.6 years (SD, 4.6; range, 0.1-16.3 years). Compared with previously published research using these cohorts,³ more asthma cases were available, and a more rigorous case definition was used that required evidence of asthma both on a questionnaire and in the EMRs.

The EMRs document all encounters between the subject and the CHOP health care system, including outpatient prescriptions, *International Classification of Diseases-Ninth Revision* diagnoses, and laboratory results. We assumed that diagnostic codes for asthma or asthma medications before a given age indicated asthma of onset before that age. Smoking exposure was estimated by using the intake questionnaire, which asks parents whether a smoker lives in the house with the pediatric subject. Genotyping was performed with Illumina HumanHap550 BeadChips.⁸

Heterogeneity was assessed by using the Breslow-Day test. For this test, control subjects were randomly assigned to the early- or late-onset groups.

In white subjects the association between the 17q12-21 variants and predisposition to asthma was replicated (Table I). The most strongly associated single nucleotide polymorphism (SNP) was rs2305480, which is consistent with the recent study.⁴ Statistically significant effect-measure modification by means of smoke exposure in childhood seen in that study was also replicated (Table I).

No trend toward heterogeneity of effect by age was present in white subjects. Odds ratios between the early- and late-onset groups were nearly identical (Table I). Analysis using ordered subsets, each restricted to asthma onset before a given age, showed no evidence for increasing effect size or changing odds ratios at any maximum age of onset. Odds ratios across the age range were roughly constant, and statistical significance increased as higher ages of onset were included in the analysis (Fig 1).

A statistical false-negative result for age-of-onset is possible. However, sample size in this study was comparable with that seen in the original report, and there is no trend in the direction expected. Direct comparison of major allelic frequencies in subjects with early-onset compared with late-onset asthma indicated at most modest differences (eg, for rs7216389, the ratio was 0.97 [95% CI, 0.79-1.19]), making it unlikely (excluding misclassification) that this study missed a greater than 20% increase in the odds ratio.