

ORIGINAL ARTICLE

ANAPHYLAXIS

Anaphylaxis to pork kidney is related to IgE antibodies specific for galactose- α -1,3-galactose

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Abstract

Background Carbohydrate-specific IgE antibodies present on nonprimate mammalian proteins were incriminated recently in delayed meat anaphylaxis. The aim of this study was to explore whether anaphylaxis to mammalian kidney is also associated with galactose- α -1,3-galactose (α Gal)-specific IgE.

Methods Fourteen patients with anaphylaxis to pork or beef kidney underwent prick tests to meat and kidney. Some patients also underwent skin tests to Erbitux[®] (cetuximab). IgE antibodies to α Gal, swine urine proteins, beef and pork meat, serum albumin proteins, cat, and r*Fel d* 1 were measured by ImmunoCAP[®]. The α Gal levels were estimated in meats and kidney by ELISA inhibition assay. Cross-reactivity between α Gal and pork kidney was studied with the ImmunoCAP[®] inhibition assay.

Results Among the 14 patients, 12 presented with anaphylactic shock. Reactions occurred within 2 h from exposure in 67% of patients. Associated risk factors were observed in 10 cases, and alcohol was the main cofactor. Three patients underwent an oral challenge to pork kidney, and anaphylaxis occurred after ingestion of small quantities (1–2 g). Prick tests to kidney were positive in 54% of patients. All tested patients showed positive skin tests to Erbitux[®]. All patients tested positive for IgE to α Gal, with levels ranging from 0.4 to 294 kU/l. IgE binding to α Gal was inhibited by raw pork kidney extract (mean, 77%; range, 55–87%), which showed a high amount of α Gal determinants.

Conclusions Pork or beef kidney anaphylaxis is related to α Gal IgE. Its peculiar severity could be due to an elevated content of α Gal epitopes in kidney.

Allergy to mammalian meat, especially kidney, is rare, with few published reports of anaphylaxis occurring after its ingestion (1, 2). According to the French Allergovigilance Network, only one case of anaphylaxis to pork or beef kidney (P&BK) was reported in 2002 (3). In most cases of allergy to kidney, the involved allergens are not clearly defined (1, 2, 4). Cross-reactivity between pork and cat albumins (pork–cat syndrome) has been described (5, 6). More recently, Commins et al. reported semidelated clinical reactions after ingestion of mammalian meats, which they linked to the carbohydrate galactose- α -1,3-galactose (α Gal) expressed on nonprimate mammalian proteins (7).

Because the kidney is an internal organ, it differs from previously studied mammalian flesh involving skeletal muscle tissue. Therefore, the objective of this study was to explore whether anti- α Gal IgE antibodies are involved in kidney anaphylaxis.

Material and methods

Patients

Seventeen cases of anaphylaxis after P&BK ingestion were referred to our clinic between 2001 and 2010. Among them,

14 patients for whom frozen sera samples were available were selected for the study.

Skin testing

Prick tests (PTs) to raw meat (beef, pork, lamb, horse, veal, rabbit, chicken, duck, and turkey), P&BK, other mammalian offal, and milk were performed in accordance with previously published methodology (8). Patients also underwent PTs to commercial aeroallergen extracts (cat and dog dander, *Blattella germanica*, *Dermatophagoïdes pteronyssinus*, *Alternaria alternata*, grass, ash, birch, and mugwort pollens) (Stalergènes, Antony, France). A PT was considered positive if the wheal diameter was at least 3 mm larger than the diameter of the negative control and/or >50% of the diameter of the positive control (10% histamine chlorhydrate or 9% codeine sulfate). Patients also underwent prick and intradermal tests to cetuximab (Erbix[®]; Merck Serono, Geneva, Switzerland) (9).

Oral challenge

Three patients underwent a double-blind placebo-controlled oral food challenge (DBPCFC) with cooked pork kidney. The dose of pork kidney was increased every 20 min, as follows:

- First day: 15, 50, 150, 285, and 465 mg [cumulative dose (CD): 965 mg]
- Second day: 500 mg, 1 g, 2 g, and 3.5 g (CD: 7 g)
- Third day: 5, 10, 20, 40, and 75 g (CD: 150 g)

Patients were discharged from hospital 20 h after the last ingestion.

Serum analyses

Specific IgE antibodies to swine urine proteins, meats (beef and pork), albumin (pork, beef, and cat), cat dander, and rFel d 1 were measured with the commercially available ImmunoCAP[®] assay (Phadia, Uppsala, Sweden). IgE antibodies specific to α Gal were assayed as previously described (9, 10). When the specific IgE level in serum was >100 kU/L, the serum was diluted to obtain more precise values.

Meat and kidney extracts

Biological analyses were performed with raw and cooked products. Meat was cooked by steaming for 10 min at 100°C. Meats and kidney were homogenized in Tris buffer (20 mM, pH 7.4) with Ultraturax. The protein concentrations in supernatants were determined by Bradford assay.

ELISA inhibition

For inhibition, the anti- α Gal monoclonal antibody (mAb) M86 (Enzo Life Sciences, Farmingdale, NY, USA; 1/5 dilution) was preincubated with meat and kidney extracts (10 μ g proteins/ml) for 20 h before the assay. For ELISA, biotinylated α Gal (GlycoTech, Gaithersburg, MD, USA)

(50 ng) bound to streptavidin-coated microplate wells (Pierce) was incubated with M86 alone or preincubated with extracts. After 2 h of incubation with alkaline phosphatase-labeled rat anti-mouse IgM (Southern Biotech, Birmingham, AL, USA), the substrate (p-nitrophenylphosphate) was added. Absorbance was read at 405 nm. Reported values represent the means of two wells.

Results are expressed as the percent inhibition of anti- α Gal mAb to α Gal coated on the plates by meats and kidney extracts. The relative levels of α Gal in the meats and kidney were deduced from a comparison of the percent inhibition values.

ImmunoCAP[®] inhibition assay

Patient sera were incubated overnight with diluent (Phadia, Uppsala, Sweden) (no inhibition group) or raw pork kidney extract (1.7 mg/ml of protein) (inhibition group). Specific IgE to α Gal were determined with ImmunoCAP[®], as previously described by Jacquenet et al. (9).

Results

Fourteen patients (six women and eight men; 55 $\pm$ 14 years old) were referred to our clinic for anaphylaxis after ingestion of mammalian kidney (most frequently pork kidney) (Table 1). Anaphylaxis was generally severe (12 anaphylactic shocks, with loss of consciousness in four cases) and occurred with a delay ranging from 10 min to 5 h after kidney ingestion. A total of nine and four patients presented with immediate anaphylaxis [$\leq$ 2 h, according to Boyce et al. (11)] and semidelayed anaphylaxis, respectively. Associated risk factors were found in 10/14 patients, including eight cases of alcohol, two cases each of physical exercise or β -blockers, and one case each of angiotensin-converting enzyme (ACE) inhibitor, aspirin, or sartin. Seven patients (50%) reported allergic symptoms after ingestion of P&BK, but were tolerant to meats of the same species. Anaphylaxis after ingestion of other offal was also observed in two cases. Less severe reactions (urticaria with or without angioedema) occurred after beef, pork, lamb, horse, or rabbit meat ingestion in five cases (Table 1).

Three patients agreed to undergo a DBPCFC to kidney (Table 1). The challenge was positive in all cases, with a very low amount of kidney. Two anaphylactic reactions occurred after ingestion of only 0.97 or 2.1 g of pork kidney. In all cases, clinical reactions were observed within 10–20 min after ingestion of the last dose (Table 1).

Skin testing

Prick tests to aeroallergens were positive in 6/13 patients (46%), including one and four cases that were positive to cat and dog dander, respectively. Prick tests to kidney were positive in 7/13 patients for pork kidney and 2/9 for beef kidney. All PTs to cow's milk and poultry were negative. The PTs to raw meat were positive in 7/14 cases, mostly to beef. The PTs to other offal were positive in 7/8 tested patients, mostly for pork tripe (Table 2).

Table 1 Clinical characteristics of patients allergic to kidney

Patient (no.)	Age (year)	Sex	Kidney Allergy			Other mammalian meat or offal allergies			DBPCFC to pork kidney		
			Symptoms	Delay	Associated risk factors	Meat or other offal	Symptoms	Other allergic reactions	Symptoms	CD (g)	Delay (min)
1	55	M	AS with loss of Con	15 months	No	No	No	Allergic rhinoconjunctivitis	nd	nd	nd
2	54	M	Generalized U	1 h	No	No	No	Allergic rhinitis to rabbit	nd	nd	nd
3	59	M	AS with loss of Con	5 h	Alcohol*, Sartan	Pork and beef meat	Generalized U	No	nd	nd	nd
4	75	M	AS	2 h	no	Beef liver and tongue, veal head, pork intestine	no	No	nd	nd	nd
5	53	F	Several AS and one with loss of Con	2 h	Alcohol*		Recurrent Ax 30 min to 8 h after ingestion	No	Paino-plantar pruritus	7	20 min
6	50	F	AS	1.5 h	Alcohol, β -blockers*	Raw beef meat, pork	Acute U, AO	No	↓ blood pressure and paino-plantar pruritus	0.97	10 min
7	54	M	Several AS	1.5 h	Alcohol, physical exercise*	Beef, pork, lamb, horse meats	Ax, acute U, 2–5 h after ingestion	Asthma during childhood	nd	nd	nd
8	48	F	AS	nd	Alcohol*	Beef, pork, lamb, horse, and rabbit meats	Acute U	no	nd	nd	nd
9	26	F	AS	1.5 h	no	no	no	no	nd	nd	nd
10	75	M	AS with loss of Con	3 h	Alcohol, ACE inhibitor	no	no	Aspirin hypersensitivity	nd	nd	nd
11	62	M	AS	2.5 h	Alcohol*, physical exercise	Beef, pork, and rabbit meats	Ax 2–3 h after ingestion	Ketoprofen hypersensitivity	nd	nd	nd
12	46	M	Acute U and AO	>2 h	Alcohol*	Beef and lamb meat	Several Ax, One AS with loss of Con, 6 h after	Wasp venom anaphylaxis	nd	nd	nd
13	75	F	AS	2 h	β -Blockers	no	no	no	nd	nd	nd
14	35	F	AS	10 min–1 h	Aspirin	Beef tongue, pork and veal meat, pork intestines	Generalized U, 2 h after ingestion	no	AS	2.1	20 min

ACE, angiotensin-converting enzyme; AO, angioedema; Ax, anaphylaxis; AS, anaphylactic shock; CD, cumulative dose; Con, consciousness; DBPCFC, double-blind placebo-controlled oral food challenge. nd, not done; U, urticaria;

*Risk factor also associated with reaction to meat or other offal.

Table 2 Skin testing

Patient (no.)	PT					Positive PT		Threshold of positive IDT (or PT) to Erbitux® (μ g/ml)
	Cat	Dog	Other aeroallergens	Pork kidney	Beef kidney	Mammalian raw meat	Other offal	
1	+	+	<i>Dermatophagoïdes pteronyssinus</i> , <i>Blattella germanica</i>	+	nd	None	nd	50
2	—	—	Rabbit	+	+	Beef, pork, and lamb	Pork intestine and liver	5
3	—	—	—	+	—	None	Pork intestine	500
4	—	—	—	—	nd	None	nd	nd
5	—	—	<i>D. pteronyssinus</i>	—	—	None	Beef liver	nd
6	—	—	—	—	—	Beef, pork, and lamb	Pork intestine and liver	5
7	—	+	<i>D. pteronyssinus</i>	+	+	Beef, pork, and lamb	Veal and pork liver	5
8	—	+	<i>D. pteronyssinus</i>	nd	nd	Beef	nd	50
9	—	—	—	+	nd	None	nd	5
10	—	—	—	—	—	Veal, lamb	Pork intestine	5
11	—	—	—	+	—	Beef, pork, lamb, and rabbit	None	5
12	nd	nd	nd	—	—	None	nd	nd
13	—	—	—	—	nd	None	nd	nd
14	—	+	—	+	—	Beef, lamb, and horseflesh	Beef tongue	5

IDT, intradermal test; nd, not done; PT, prick test.

Intradermal tests to Erbitux® can be used to determine a sensitization to α Gal determinants (9). All patients tested ($n = 10$) showed positive prick or intradermal tests to 5–500 μ g/ml Erbitux® (Table 2).

Serum analyses

IgE antibodies to pork meat were detected in 11/14 patients (79%), with specific IgE levels ranging from 0.4 to 34.3 kU/l (median, 3.2 kU/l). IgE antibodies to beef were detected in

11/12 patients (92%), with specific IgE levels ranging from 0.15 to 33.5 kU/l (median, 1.8 kU/l) (Table 3).

When tested, IgE antibodies to pork serum albumin were slightly detected (5/9; range, 0.1–0.8 kU/l), but IgE antibodies to beef serum albumin were never detected. When tested, no specific IgE antibodies to cat allergens (dander, rFel d 1 or albumin) were detected. IgE reactivity to swine urine proteins was positive in 12/13 patients (range, 0.2–37.4 kU/l; median, 2.9 kU/l). All cases tested positive for IgE antibodies to α Gal (median, 14.3 kU/l; range, 0.4–294 kU/l) (Table 3).

Table 3 Serum analyses

Patient (no.)	Total IgE (kU/l)	Specific IgE (kU/l)									
		α Gal	Inhibition of α Gal*	Swine urinary proteins	Pork meat	Beef meat	Pork serum albumin	Beef serum albumin	Cat	rFel d 1	Cat albumin
1	975	231.5	84%	37.4	34.3	nd	nd	nd	28	<0.1	nd
2	351	7.5	87%	2.9	1.1	1.6	0.1	nd	nd	<0.1	<0.1
3	289	78.3	77%	2.9	3.2	3.6	nd	<0.1	nd	<0.1	<0.1
4	nd	0.4	nd	<0.1	<0.1	nd	nd	nd	<0.1	nd	nd
5	59	12.9	81%	1.0	<0.1	<0.1	nd	<0.1	nd	nd	nd
6	33	77.4	75%	3.4	0.9	1.8	0.4	nd	nd	<0.1	<0.1
7	30	16.8	nd	4	2.4	3.4	<0.1	nd	0.1	<0.1	<0.1
8	304	294	nd	29.3	13	20.7	0.2	<0.1	nd	<0.1	<0.1
9	nd	4	nd	0.9	1.2	1	nd	nd	1.5	nd	nd
10	680	96.3	80%	17.6	7.7	18.3	0.8	nd	0.9	<0.1	<0.1
11	117	7.8	nd	2	22	33.5	0.45	<0.1	<0.1	<0.1	<0.1
12	119	1.8	nd	0.6	0.4	0.9	<0.1	nd	<0.1	<0.1	<0.1
13	23	2.5	79%	0.2	<0.1	0.15	<0.1	nd	<0.1	<0.1	<0.1
14	70	15.7	55%	nd	24.3	0.9	<0.1	<0.1	35.4	<0.1	<0.1

Nd, not done.

*Inhibition assay of specific IgE to α Gal with pork kidney.

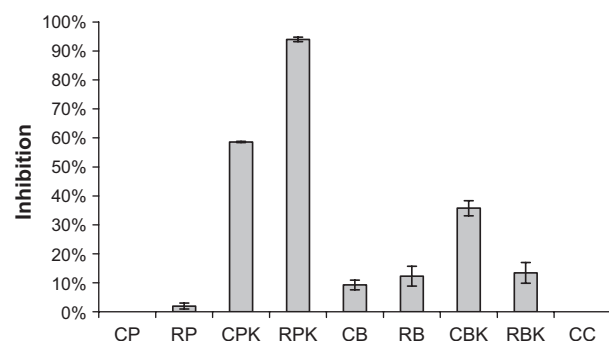


Figure 1 Inhibition of α Gal binding after preincubation with different mammalian meats and offal and poultry (CP, cooked pork; RP, raw pork; CPK, cooked pork kidney; RPK, raw pork kidney; CB, cooked beef; RB, raw beef; CBK, cooked beef kidney; RBK, raw beef kidney; CC, cooked chicken).

A strong correlation was observed between IgE to α Gal and IgE to swine urine proteins ($r = 0.93$; $P < 0.0001$). No statistically significant correlation was found between IgE to α Gal and IgE to pork meat or beef meat ($r = 0.48$, $P = 0.09$ and $r = 0.42$, $P = 0.17$, respectively).

The α Gal levels in meats and kidney were estimated by an ELISA inhibition assay (Fig. 1). The ability of meats and kidney to inhibit the binding of anti- α Gal mAb to α Gal coated on microplates reflects the α Gal content of the meats and kidney (i.e., high inhibition indicates high α Gal content). Kidneys had higher amounts of α Gal (94% inhibition for raw pork kidney, 59% for cooked pork kidney, 36% for cooked beef kidney, and 13% for raw beef kidney) than meats (12% for raw beef, 9% for cooked beef, and 2% for raw pork). Cooked pork and chicken contained no α Gal.

Based on the above results, raw pork kidney extract was chosen for preincubation with patient sera to verify its ability to inhibit α Gal-specific IgE binding by ImmunoCAP[®]. Raw pork kidney extract inhibited IgE binding to α Gal in all sera tested (mean, 77%; range, 55–87%). This finding shows that α Gal-specific IgE antibodies are able to interact with α Gal determinants in kidney.

Discussion

The results of this study confirm that allergy to P&BK often induces severe anaphylaxis (2). All tested patients showed a positive intradermal test to Erbitux[®] (Table 2). Substantial amounts of α Gal determinants were observed in kidney, especially pork kidney (Fig. 1). All patients had specific IgE antibodies to α Gal, and pork kidney inhibited specific IgE binding to α Gal (Table 3). Taken together, our results suggest that specific IgE antibodies to α Gal are probably involved in P&BK anaphylaxis.

In a previous study, immunoblots performed with sera of patients suffering from allergy to pork kidney and red meats evidenced multiple IgE reactive bands (1). In light of our results and because of the ubiquitous character of α Gal glycosylation in nonprimate mammalian proteins (12) and lipids (13), this IgE multibinding may be interpreted as a sensitiza-

tion to α Gal determinants rather than to different proteins and/or protein epitopes.

The first description of anaphylaxis after pork ingestion was related to an IgE cross-reactivity between pork and cat albumins (i.e., pork–cat syndrome) (5). In the present study, when observed, IgE levels to beef, pork, and cat serum albumin were very low (Table 3). This low IgE response could be due to a slight sensitization to animal albumin (which bears no α Gal determinants), or may be related to trace contamination of glycosylated proteins in the albumin extracts.

We observed that allergenicity to P&BK was stronger than allergenicity to other offal or skeletal muscles, on the basis of the symptom severity, skin tests results, and shorter delay of symptom occurrence after kidney ingestion. One patient tolerating mammalian meat experienced anaphylactic shock after a DBPCFC with only 2.1 g of pork kidney. The higher amount of α Gal determinants in kidney than in meat (Fig. 1) may explain several of the observed results, including why some patients reacted only after kidney ingestion and why the cumulative reactive dose of pork kidney during oral challenge was very low (Table 1). Moreover, this finding may explain why symptoms generally occurred with a shorter delay than that of previously described anaphylactic reactions to mammalian meat (7), even in the absence of alcohol, drugs, or physical exercise (14, 15). During the oral challenge, reactions were observed within 10–20 min after ingestion of the last dose. Given that the doses were ingested every 20 min, we cannot be certain about the delay because the patient may have been reacting to a previous dose. However, as the interval between the first and the last dose is of 60 min at most, we can assert that all patients reacted within 80 min. Thus, it must be stressed that traces of kidney (e.g., hidden in ground meat) may be involved in severe reactions.

Despite the strong allergenicity of kidney, it is interesting that two of the patients who presented with anaphylactic shock to P&BK had negative PTs and no IgE antibodies to meat and/or kidney (Tables 2 and 3). In such cases, the involvement of kidney allergy can only be proven through the measurement of anti- α Gal IgE, through an intradermal test to Erbitux[®], or through an oral challenge to kidney (which may be relatively dangerous). A high correlation was found between the levels of IgE to α Gal and to swine urinary proteins. Because there currently is no commercially available assay for anti- α Gal IgE, the measurement of specific IgE to swine urinary proteins (which is an available assay) may be helpful as a diagnostic tool.

We can propose three possible causes of IgE sensitization to α Gal epitopes. First, because Erbitux[®] is produced by a mouse cell line that expresses the gene for α Gal, primary exposure to cetuximab could be involved. Chung et al. showed that, in most subjects with hypersensitivity reactions to cetuximab treatment, IgE antibodies to alpha-Gal were present before the treatment. Thus, cetuximab was not the cause of sensitization (10). In our study, one patient was previously treated for cancer, but no patient had been exposed to cetuximab. Therefore, the IgE sensitization to α Gal among our patients could not be attributed to this drug.

Second, a relationship between specific IgE to α Gal and a history of bites from ticks of the genus *Amblyomma* or *Ixodes* has been reported in the USA and Australia (16, 17). In France, ticks belong to the *Ixodes* genus; therefore, the same link could be hypothesized in the present study. Indeed, six patients reported previous tick bites (patients 1, 6, 7, 11, 13, and 14). The bites had occurred several months or years before the first report of kidney anaphylaxis. Only one patient had observed an abnormal pruriginous local reaction after the tick bite (patient 13), which was 8 years before the anaphylactic shock to pork kidney.

Third, because pig urine can cause asthma (18, 19), and because we observed a strong correlation between the levels of IgE antibodies to α Gal and to swine urinary proteins, we speculate that the inhalation of glycosylated proteins in pet urine could cause sensitization. The questionnaire showed that 6/10 patients were living with mammalian pets (cats, dogs, horses, and/or rabbits).

Conclusion

Allergy to P&BK induces severe anaphylaxis, probably mediated by IgE antibodies to α Gal. The allergenic reactivity of kidney is stronger than that of mammalian meat. In the case of kidney allergy, patients should be instructed to avoid mammalian offal. If no reaction after meat ingestion has been previously reported, then ingestion of mammalian meat may be allowed; however, the patient should be instructed to avoid risk factors, especially physical exercise, within 4 h after meals combined with alcohol, aspirin, or NSAID consumption.

Conflict of interest

C. Richard and S. Jacquenet are employees of Genclis SAS, a diagnostics company. G. Kanny has received honoraria from Genclis.

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