



Case series of anaphylactic reactions after rabies vaccinations with gelatin sensitization

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Abstract Side effects due to allergic reactions to vaccine antigen or to additives such as chicken protein or gelatin have been known for some time. Recent findings regarding reactions mediated via the carbohydrate epitope galactose-alpha-1,3-galactose (alpha-gal), a constituent of animal gelatin, broaden the spectrum of gelatin-related allergies. This case series presents four patients who developed anaphylactic reactions following rabies vaccination using the vaccine Rabipur®. After appropriate allergy testing by skin prick testing and the determination of specific IgE to allergens in the vaccine, triggering by alpha-gal could be excluded and an allergy to gelatin was detected. The absence of allergic symptoms following the consumption of gelatin could potentially be explained through intestinal hydrolysis resulting in a loss of allergenic potency. Further implications related to the use of gelatin-containing infusions in emergency medicine are discussed.

Abbreviations

alpha-gal	Galactose-alpha-1,3-galactose
IgE	Immunoglobulin E
ImmunoCAP	Method to determine the level of specific IgE antibodies
kUa/l	Kilounits of antigen per liter

Introduction

With a probability of 1:1 million, anaphylaxis following vaccination is an extremely rare event [1]. In addition to the actual vaccine antigen, other triggers can include additives such as antibiotics, preservatives, gelatin, and chicken protein. The allergic reactions best investigated are those to chicken protein as a vaccine constituent. Taking into consideration the latest results, the concentration in vaccines is limited to a maximum dose of 2 µg/ml, thus, making anaphylaxis highly unlikely even in egg-allergic individuals [2]. In contrast, our understanding of vaccine reactions in persons suffering from gelatin allergy is comparatively sparse. Gelatin is a protein mixture primarily composed of hydrolyzed collagen [3]. Other frequent components of animal gelatin include carbohydrate epitopes such as galactose or the 1,2-linked disaccharide of glucose and galactose, as well as galactose-alpha-1,3-galactose (alpha-gal) [4]. The latter does not only occur in muscle meat, but also in numerous other body cells (e.g., innards, connective tissue cells) of mammals that are not primates of the old world. Allergies to “red meat” (beef, pork, lamb) and innards that are associated with elevated IgE titers to alpha-gal have been described. Therefore a vaccine reaction to gelatin is not necessarily due to a purely protein-mediated allergic reaction, but can also be caused by IgE antibodies to alpha-gal [3]. Four cases are described below in which anaphylactic reactions to gelatin developed in association with rabies immunization.

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Case presentation

Case 1

A 24-year-old woman was immunized against rabies and Japanese encephalitis at the vaccine center of the University Hospital Mainz, Germany. The patient's own history as well as in her family history showed no previous anaphylactic reactions to vaccinations. The patient had tolerated all previous routine vaccinations well. However, she was known to have multiple food allergies and pollinosis.

Progressive swelling of the tongue occurred shortly after injection of the vaccines Rabipur® and Ixiaro®. The patient received an intramuscular injection of 300 µg epinephrine (Fastject®), 250 mg prednisolone (Solu-Decortin®), 4 mg dimetindene maleate, and 55.8 mg ranitidine intravenous.

Allergy testing with ImmunoCAP measured a total IgE of 146 kUA/l. This was consistent with the patient's atopic predisposition (allergic rhinitis). She was also tested for egg white, gelatin, beef, and alpha-gal. The results were negative apart from a clear reaction (ImmunoCAP class 3) to gelatin.

Case 2

At the Institute of Tropical Medicine belonging to the University Hospital Tübingen, Germany, a 24-year-old woman received the second injection (Rabipur®) for rabies immunization, together with a typhus vaccination. Here again, there was no indication of previous allergic reactions to vaccines. Allergic rhinoconjunctivitis due to allergy to tree pollens was a known incidental finding.

Generalized urticaria and vomiting developed following injection of the vaccine.

Allergy testing was performed several weeks later. In a first step, skin prick testing with egg yolk, egg white, beef and pork was conducted, to which the patient tested negative. Intradermal testing with gelafundin 4% was performed afterwards. This caused generalized urticaria. The ImmunoCAP assay that was additionally performed detected a total IgE of 64 kUA/l, as well as specific IgE antibodies to gelatin (ImmunoCAP class 4), but no specific IgE antibodies to chicken protein or alpha-gal.

Case 3

A 25-year-old woman received rabies immunization (Rabipur®) from her primary care physician. Similar to the aforementioned patients, case 3 showed no predispositions for allergic reactions against vaccines. Allergic rhinitis and pollinosis were known.

Generalized urticaria developed 2 h after the third Rabipur® injection. Symptoms improved rapidly following intravenous administration of antihistamines.

Skin prick testing with egg yolk, egg white, gelafundin 4%, beef, and pork was performed a few weeks subsequently. Serological determination of total IgE and determination of gelatin and alpha-gal were performed. A marked reaction was observed for gelatin, both serologically in the ImmunoCAP assay (ImmunoCAP class 2) and in skin prick testing. All other results were inconspicuous.

Case 4

As in the previous cases, this patient was immunized against rabies with the vaccine Rabipur®. Again, patient and family history of vaccine reactions were unremarkable. Allergic rhinitis to grass as well as cat and horse dander was determined as an incidental finding.

Following the third immunization, the patient developed urticaria on the ears and neck, as well as hypotension with systolic values of around 90 mmHg.

Shortly thereafter, a total IgE of 468 kUA/l and specific IgE to egg yolk, egg white, porcine serum albumin, alpha-gal, and gelatin were determined. With ImmunoCAP class 3, gelatin yielded a positive result. All other tests were negative. Skin prick testing with gelatin powder, hard gelatin capsules, gelafundin 4%, and polygeline produced markedly positive reactions in all test areas. In this particular case, negative prick testing with the Rabipur® excipients amphotericin and neomycin was additionally performed.

Discussion

For a vaccine reaction to occur, previous sensitization needs to have taken place. Sensitization can be induced by gelatin-containing vaccines, drugs or the consumption of gelatin-containing foods [5]. Alpha-gal-sensitized patients may also react allergic to gelatin. Sensitization to alpha-gal generally occurs via tick bites and typically results in delayed, sometimes cofactor-dependent allergic reactions following the consumption of meat or innards (beef, pork, and lamb), and also occasionally animal-derived gelatin [6]. As a result, sensitization to the carbohydrate epitope alpha-gal increases the likelihood of an allergic reaction to gelatin-containing vaccines [2] produced using gelatin derived from mammalian connective tissue. An increasing number of reports from other centers on alpha-gal-mediated allergic reactions following vaccinations support this finding—most recently for the zoster vaccine approved in May 2018 [7].

By determining specific IgE values, it is possible to differentiate between a purely protein-mediated gelatin allergy and an alpha-gal-mediated reaction.

Regarding alpha-gal there are currently no standardized solutions available for prick testing [6]; therefore, pork or beef are used exemplarily and the specific IgE antibodies against alpha-gal are determined. Alpha-gal-specific IgE was not detected in any of the patients presented here, whereas IgE antibodies to

Table 1 Results of ImmunoCAP IgE determination

	Case 1		Case 2		Case 3		Case 4	
	ImmunoCAP class	Level	ImmunoCAP class	Level	ImmunoCAP class	Level	ImmunoCAP class	Level
Total IgE	—	146 kUA/l	—	64.7 kUA/l	—	17.3 kUA/l	—	468 kUA/l
Egg white	0	0.01 kUA/l	0	0.02 kUA/l	n. s.	n. s.	0	<0.35 kUA/l
Gelatin (beef, cross-reactivity to pork)	3	9.65 kUA/l	4	18.3 kUA/l	2	1.1 kUA/l	3	11.1 kUA/l
Alpha-Gal	0	0.02 kUA/l	0	0.00 kUA/l	0	<0.35 kUA/l	0	<0.35 kUA/l

ImmunoCAP class 0: negative; class 1: borderline; class 2–6: elevated
class 0: < 0.35 kUA/l; class 1: 0.35–0.7 kUA/l; class 2: 0.7–3.5 kUA/l; class 3: 3.5–17.5 kUA/l
class 4: 17.5–50 kUA/l; class 5: 50–100 kUA/l; class 6: > 100 kUA/l; n. s. not specified; kUA/l kilounits of antigen per liter

gelatin were (Table 1). In addition, skin prick testing to gelatin produced a reaction, an example of which is shown for the patient in case 4 in Fig. 1.

Since in three of the four cases the reaction only occurred after the second vaccination, sensitization or a booster effect due to the first injection can be assumed.

**Fig. 1** Skin prick testing with gelatin, case 4

Other constituents of the Rabipur® vaccine, such as amphotericin B, chlortetracycline, and neomycin, were tested only in case 4. Therefore, these cannot be definitively excluded as triggers in the other cases. However, the likelihood is extremely low, since barely any cases are reported in the literature [9]. Taking all test results into consideration, the patients' reactions can most likely be attributed to the polygeline contained in the Rabipur® rabies vaccine (a urea and hydrolyzed gelatin mixture), since neither Ixiaro® nor Typhim® contain gelatin or other potent allergens.

Allergic reactions to the polygeline contained in Rabipur® are generally rare and occur more frequently after administration of vaccines that contain milligram concentrations of gelatin, such as MMR (measles–mumps–rubella), zoster, and varicella [10]. The most common side effects caused by Rabipur® include pain and/or injection site induration, as well as fever and cephalgia. A number of studies have shown all three injections (day 0, 7, 21) required for basic immunization to be generally well tolerated [11].

Not all patients experiencing vaccine reactions in proven gelatin allergy additionally react to the gelatin contained in numerous foods; this also applies to the cases presented here, in which no allergic reaction occurred following the consumption of relevant foods. Gelatin-containing foods may be tolerated due to the possible denaturing of gelatin occurring in the gastrointestinal tract, as this could lead to the loss of potential allergenicity [12].

Furthermore, new insights into alpha-gal are relevant in emergency medicine. Gelatin-containing solutions are often used in Europe as plasma expanders [13], and anaphylactic and anaphylactoid reactions have been described following their administration. Since gelatin allergy was confirmed in the majority of patients, this was seen as a causal factor of the reaction to plasma expanders [14]. Reactivity now also seems to be possible due to alpha-gal sensitization [8]. All patients with allergy to alpha-gal and/or gelatin are advised to carry an allergy passport containing the warning note “Please avoid gelatin-containing intravenous and intramuscular preparations” [15]. In

the case of alpha-gal allergy, cetuximab should additionally be avoided, and potentially also other animal-derived medical products, such as heparins and biological heart valves [16].

Conflict of interest F. Bradfisch, M. Pietsch, S. Forchhammer, S. Strobl, H.M. Stege, R. Pietsch, S. Carstens, K. Schäkel, A. Yazdi and J. Saloga declare that they have no competing interests.

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