



Vaccination-associated anaphylaxis in adults: Diagnostic testing ruling out IgE-mediated vaccine allergy

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ABSTRACT

Re-vaccinations in patients with a history of anaphylaxis after vaccine injection have to be avoided because of the potential risk of recurrent anaphylaxis. However, without diagnostic work-up vaccine allergy remains a presumption and necessary vaccinations may be unjustified withheld. In the last 7 years all patients referred to our allergy clinic with a diagnosis of vaccination-induced anaphylaxis were subjected to allergologic diagnostic procedures to identify IgE-mediated allergy. We evaluated 38 patients with a history of vaccination-associated anaphylaxis. The diagnostic procedure included skin testing and challenge tests, i.e. re-vaccination with the suspected vaccine. In all 38 patients negative skin tests and tolerated challenge tests ruled out IgE-mediated allergic anaphylaxis to vaccine components. Diagnostic testing after suspected vaccination-induced anaphylaxis should be performed to rule out IgE-mediated allergy to the incriminated vaccine and its constituents and to enable future vaccinations with the tested compounds. Therefore, a history of anaphylaxis after vaccination may not be an absolute contraindication for re-vaccination.

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1. Introduction

Vaccinations induce an immune reaction against the vaccinated antigen and may cause both local and systemic side effects. Systemic inflammatory reactions within 1–2 days after injection are not uncommon and may include fever, nausea, vomiting and myalgia resolving within 3 days [1]. More rarely, circulating antigen-antibody complexes may induce over 6–12 h a serum sickness-like disease or an exanthematous rash, whereas on subsequent exposures delayed-type hypersensitivity due to the stimulation of antigen-specific T cells peaks within 2 days [2,3].

In contrast to these delayed-type hypersensitivity reactions, anaphylaxis develops within minutes to 1 h after contact with the causative trigger. Objective anaphylaxis symptoms include urticaria, angioedema, bronchospasm, hypotension, and shock [4]. Anaphylaxis may start with relatively minor symptoms but may also rapidly progress to a life-threatening respiratory and cardiovascular reaction. However, at onset of anaphylaxis symptoms it is impossible to predict the ultimate severity of the entire episode [5]. Common causes of anaphylaxis include foods, hymenoptera stings, allergen immunotherapy, and drugs, whereas vaccination-induced anaphylaxis is a rare event [3,4].

It is recommended that a history of vaccination-associated anaphylaxis is a contraindication to receipt of that vaccine [2]. Vaccine solutions contain both antigenic and non-antigenic components including antibiotics, stabilizers and preservatives. Immunoglobulin E (IgE)-mediated allergy may be due to the antigenic compound or to any of the adjuvants. Culture contaminants in live virus vaccines, which have been grown on egg-derived media were of particular concern, but stabilizers (gelatine) or antibiotics (neomycin) also caused allergic reactions responsible for anaphylaxis [6–8]. Several of these adjuvants are also found in other vaccine solutions and without allergologic testing all vaccines containing any of the constituents of the incriminated vaccine have to be avoided in the future.

During the past 7 years we evaluated all patients who presented with a history of anaphylaxis after vaccination by using a standardized allergologic work-up. Aim was to identify and differentiate IgE-mediated allergy and non-allergic vaccination-associated anaphylaxis symptoms. Furthermore, we proofed indirectly the reliability of reporting vaccine-induced allergic anaphylaxis by health care professionals.

2. Methods

2.1. Terminology

The terminology used to characterize allergic and allergy-like reactions is confusing. The report of the European Academy of

Abbreviation: IgE, immunoglobulin E.

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Table 1
Grading system for anaphylaxis (modified from [10]).

Grade	Symptoms
1 (mild): skin and subcutaneous tissue only	Generalized urticaria, periorbital oedema or angioedema
2 (moderate): features suggesting respiratory, cardiovascular or gastrointestinal involvement	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), tachycardia, chest or throat tightness, or abdominal pain
3 (severe): hypoxia, hypotension or neurological compromise	Cyanosis, hypotension (systolic blood pressure <90 mmHg in adults), confusion, collapse, loss of consciousness, incontinence

Allergy and Clinical Immunology published in 2001 “A revised nomenclature for allergy” has gained substantial international recognition [9]. Hypersensitivity means objectively reproducible symptoms initiated by exposure to a dose tolerated by normal persons. Allergy means hypersensitivity mediated by specific immunological mechanisms. Anaphylaxis is a severe, generalized or systemic hypersensitivity reaction. Anaphylaxis is sub-classified as IgE-mediated allergic anaphylaxis when the reaction is mediated by allergen-specific IgE, or non-allergic anaphylaxis due to whatever non-immunologic cause (formerly anaphylactoid reaction).

2.2. Patients

From 2000 to 2007, all patients referred to our allergy clinic with a diagnosis of vaccine-induced allergic anaphylaxis were subjected to standardized allergy testing. A further requirement for performing the diagnostic procedure was the medical necessity for initiation or continuation of a vaccination. All patients were referred by health care professionals, i.e. general practitioners, consultants, or allergologists, all suspecting allergic anaphylaxis due to vaccine injection. After a thorough review of patient files all available clinical data were collected including history of allergies (most importantly egg and antibiotics), type of vaccine, date of administration, time interval from injection to onset of symptoms, treatments administered (epinephrine, intravenous fluids, antihistamines, corticosteroids, bronchodilators), and severity of clinical symptoms (Table 1) [10]. Grade 1 consists of cutaneous symptoms such as urticaria and angioedema; grade 2 and 3 include symptoms of the following organ systems: cardiovascular (hypotension, tachycardia), respiratory (dyspnoea, bronchoconstriction), and digestive (vomiting, abdominal pain, incontinence). A patient was classified as atopic when there was a medically recorded history of allergic rhinitis, atopic dermatitis, positive skin prick tests with aeroallergens, and/or allergic asthma with use of bronchodilators.

2.3. Skin tests

Written informed consent for allergologic work-up was obtained. Since determination of potential allergy is part of routine diagnostic practice in our allergy clinic, further ethical approval was not required. We performed prick tests on the volar forearm with the culprit vaccine according to published recommendations [11]. The vaccine preparations were used undiluted for the prick tests and physiological saline solution was used as negative, histamine as positive control. In individual cases allergic or non-allergic hypersensitivity to other drugs administered concomitantly with the vaccine and latex allergy (natural rubber latex from, e.g. stoppers, tubes, gloves) which may be responsible for the symptoms as well were excluded using skin and challenge tests.

2.4. Challenge tests

Patients with negative skin tests were offered challenge tests, i.e. re-vaccination with the suspected vaccine if these vaccines

were indicated and if the patient was not acutely ill or immunosuppressed. The patients were challenged using standardized doses of the vaccine: 10%; 30%; 60%; total 100% of the normal vaccination dose. General principles of our challenge protocol were as follows: (i) the time interval since the anaphylactic reaction was at least 2 weeks; (ii) during the entire challenge procedure the patient was observed and equipment for emergency treatment was available; (iii) the dosage of the vaccine increased stepwise to a normal dose with intervals of 1 h between the individual doses; (iv) strict adherence to absolute and relative contraindications for drug challenge tests; (v) prior to challenge testing written informed consent was obtained from each patient following a discussion of the risks and benefits of re-vaccination.

3. Results

3.1. Patients

Thirty-eight patients were evaluated, 28 females and 10 males referred by health care professionals from 2000 to 2007 with signs and symptoms within 1 h after vaccination strongly suggesting anaphylaxis. The referring health care professional made the final diagnosis allergic anaphylaxis/anaphylactic shock due to injection of the suspected vaccine. The average age at the time of the anaphylaxis episode was 48 years (ranging from 13 to 79 years) (Table 2). Ten patients were considered atopic due to a positive skin prick test with aeroallergens or a history of atopic dermatitis, allergic rhinitis or asthma. The vaccines administered to the patients included tetanus-/diphtheria-toxoid (17×), followed by hepatitis A/B (8×), tick-borne encephalitis (7×), and influenza (6×) (Table 3). The latency between injection of the vaccine and onset of symptoms was recorded as virtually immediate ($n=5$), less than 5 min ($n=3$),

Table 2
Clinical features of the subjects studied.

No. of patients	38
Male/female	10/28
Mean age, years (range)	48 (13–79)
Age group, years	
11–18	5
19–49	12
50–65	15
>65	6
Patients with atopic disease	10
Latency	
Immediate	5
<5 min	3
5–15 min	3
<30 min	6
30 min–1 h	21
Anaphylaxis	
Grade 1	20
Grade 2	9
Grade 3	9

Table 3

Antigenic and non-antigenic constituents of the tested vaccines. TBE; tick-borne encephalitis.

		Influenza 6	Tetanus-, diphtheria- toxoids 17	TBE 7	Hepatitis A/B 8	Total 38
Sources	Yeast cells				6	6
	Human MRC-5 fibroblasts				4	4
	Chicken embryo fibroblasts	6		7		13
Antibiotics	Neomycin	3		7	1	11
	Gentamicin	2		7		9
	Chlortetracycline			1		1
	Polymyxin B	1				1
Stabilizers	Formaldehyde	5	17	7	2	31
	Protamin sulfate			6		6
	Cetrimonium bromide	1				1
	Polysorbate/Tween	3			1	4
	Octoxinol/Triton-X	3				3
	Human albumin			6		6
	Lecithine	1				1
	Hydrocortisone	1				1
	Thiocyanate				1	1
	Sucrose	2		6		8
Preservatives	Thiomersal	1	1		1	3
	Sodium borate				1	1
	2-Phenoxyethanol		1		4	5
Adjuvants	Aluminium hydroxide		16	7	6	29
	Aluminium phosphate		1		4	5

5–15 min ($n=3$), 15–30 min ($n=6$), and 30 min to 1 h ($n=21$). None of the patients had experienced a prior adverse reaction to a vaccination. Episodes of vaccine-associated anaphylaxis were classified as grade 1 ($n=20$), grade 2 ($n=9$), and grade 3 ($n=9$) (Table 2). Five reactions resolved without treatment, 32 required the use of antihistamines, intravenous fluid, corticosteroids or bronchodilators, and one required epinephrine. The history concerning allergy to hen's egg, yeasts or antibiotic drugs was negative in all patients.

3.2. Skin tests

Results of the diagnostic procedure are summarized in a flow chart (Fig. 1). In all 38 patients skin prick tests with the culprit

vaccines were completely negative. The mandatory allergologic work-up in case of a positive skin test is depicted in Fig. 1, however due to negative skin test results in all of our patients, has not been performed [12].

3.3. Challenge tests

No cutaneous or systemic symptoms occurred during controlled vaccination with negatively skin tested vaccines. After the controlled challenge test vaccination was again indicated in 10 patients and all tolerated the procedure without side effects.

4. Discussion

Vaccination is generally well tolerated although approximately 1% of patients who receive vaccines develop adverse reactions. Vaccination reactions range from a mild inconvenience, such as local reactions associated with mild fever, to a life-threatening emergency. There is considerable fear of anaphylaxis, characterized by generalized urticaria, acute bronchospasm, and profound hypotension, which is a serious, potentially life-threatening reaction occurring within 1 h after vaccine injection. Therefore, a history of vaccination-induced anaphylaxis is a contraindication for re-vaccination with the same vaccine or its constituents [2]. However, such conservative recommendations may reduce unnecessarily the vaccination coverage of patients believed to be at risk for anaphylaxis. Surprisingly, in our series all patients who previously experienced vaccination-associated anaphylaxis were skin test negative, tolerated the following vaccine shots, and subsequently completed the course of all indicated vaccine doses without side effects. Therefore allergologic testing seems to be important to reassure patients of safety of the procedure and to encourage them to have the vaccination done.

Anaphylaxis is the most serious vaccine-associated adverse reaction but with the currently used vaccines an extremely rare event. The incidence of anaphylactic reactions to vaccines was recently calculated to be 0.65 cases per million doses [13]. It is virtually impossible to estimate the incidence of vaccination-induced allergic anaphylaxis because calculation relies mostly on reporting of retrospective cases. The most frequently reported allergic

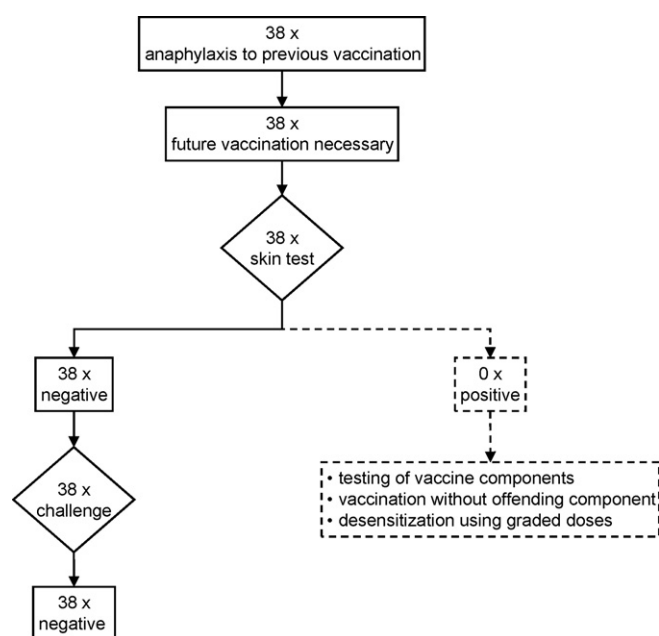


Fig. 1. Steps and results of the allergologic work-up in 38 patients with a history of anaphylaxis in temporal relation to vaccination.

Table 4

Clinical factors that may have contributed to the anaphylaxis episode and differential diagnoses.

Identifiable contributing factors in 15 patients	
Asthma	5
Thyroid disease	1
Emotional stress	2
β -blockers	4
Exercise	3
Possible differential diagnoses in 10 patients	
Vasodepressor (vasovagal) reaction	3
Panic attack	1
Vocal cord dysfunction	1
Urticaria/angioedema	5

hypersensitivity reactions to vaccines were not due to the vaccine antigen itself but to additional components in vaccine solutions such as hen's egg proteins and gelatine. In our study 13 vaccines were produced in biological culture preparations derived from chicken's embryo, namely the vaccines against influenza and tick-borne encephalitis. The egg protein content is highly variable according to the manufacturing process, e.g. higher in vaccines produced in chicken's embryo than in those produced in chicken's fibroblasts [14]. In the literature, multiple examples of uneventful administration of egg-containing vaccines to children with known egg hypersensitivity and reports of anaphylaxis to egg-derived vaccines in patients without a history of egg allergy have cast doubt on the theory that egg proteins in the vaccine are major causative agents [15–17]. Recombinant hepatitis B vaccine is produced in *Saccharomyces cerevisiae* cultures, but there are very few cases of vaccine reactions attributed to yeast allergy [18]. Gelatine hypersensitivity was a major cause of anaphylaxis to measles, mumps, rubella, and varicella vaccines in Japan [7,19]. Nowadays, removal of gelatine from vaccines has dramatically diminished the incidence of vaccine-related anaphylaxis in Japan [20]. In our series no case of anaphylaxis could be attributed to hypersensitivity to gelatine. Some vaccines in our series contained neomycin, gentamicin, chlortetracycline and polymyxin B. Importantly, contact dermatitis to these antibiotics is not a contraindication to immunization with the corresponding vaccines [2].

The evaluation of patients with suspected vaccine-induced anaphylaxis should include appropriate skin tests ensuring that patients with an IgE-mediated allergy are not missed [2,3,14]. However in the literature there are no data regarding sensitivity and specificity of skin tests with vaccines. Because of the lower risk of false positive reactions and therefore increased specificity, we preferentially use prick testing with undiluted vaccines. In a recent study, the authors demonstrated that intradermal testing with 1:10 diluted vaccine (measles and influenza) was more suitable than prick testing with the undiluted vaccine for predicting an immediate-type reaction [21]. Combined prick (undiluted vaccine) and intradermal (1:10 dilution) testing may therefore increase the sensitivity of skin tests. However, careful controlled challenge testing may be attempted to verify negative skin test results. In our series 38 anaphylaxis episodes had been attributed to vaccines, but negative skin tests followed by tolerated challenge tests demonstrated that all these reactions were in fact not induced by an IgE-mediated vaccine allergy.

How can we explain the anaphylaxis episode leading to the incorrect diagnosis of vaccine-induced allergic anaphylaxis? Retrospectively, an accurate diagnosis in these cases cannot be made. However, we have identified in 15 of our patients risk factors and in 10 differential diagnoses which may have triggered anaphylaxis or may have imitated such symptoms, respectively (Table 4). In most cases the direct release of histamine and other mediators may have been responsible for the anaphylaxis symptoms after appli-

cation of the vaccine either directly by an effect of the vaccine solution and non-specific binding of vaccine components on membrane receptors or indirectly by complement-/kinin-activation [22]. In immunoglobulin G (IgG)- or complex complement-mediated anaphylaxis a critical concentration of antigens capable of forming complement-fixing immune complexes and peptides split from activated complement components can act on mast cells and basophils to induce the release of anaphylaxis mediators [22]. Therefore, irrespective of the individual history it is recommended that vaccines should always be administered in health care settings adequately equipped to treat anaphylaxis and all vaccinated patients should be observed for up to 1 h after immunizations.

Patients exposed to drugs frequently experience side effects that are not a result of pharmacological action or hypersensitivity. In our cohort of patients, the strikingly higher occurrence of vaccination-associated anaphylaxis in women is difficult to explain on a pathophysiological basis. This implies that a psychosomatic component in a subgroup of patients with vaccination-associated anaphylaxis may exist. So-called nocebo reactions have been well described [23]. However, about three quarters of health care professionals are not aware of such nocebo phenomena [24]: approximately one quarter of patients taking placebo report adverse side effects [25,26]. Barsky and Borus identified several factors which appear to be associated with the nocebo phenomenon: patients' expectations of adverse effects, a process of conditioning in which the patients learn from prior experiences, and psychological characteristics such as anxiety, depression, and the tendency to somatise [27].

Naturally, after anaphylaxis in temporal relationship to the application of a vaccine, other causes for the symptoms have to be considered. During vaccination the patient may come in contact with natural rubber latex [28]. Also concomitantly taken non-steroidal anti-inflammatory drugs, β -blockers or angiotensin-converting enzyme inhibitors can trigger symptoms of anaphylaxis [29]. Finally, vaccine injections may be capable to precipitate symptoms of occult mastocytosis [30]. Careful clinical history, certain laboratory tests (i.e. tryptase measurement, IgE specific for natural rubber latex), skin tests, and drug challenge tests helped to exclude these differential diagnoses in our patients.

In conclusion, allergic hypersensitivity to vaccine constituents administered to adults seems to be very rare. However, in daily practise it may be difficult to distinguish allergic anaphylaxis from differential diagnoses and facilities and personnel should be prepared for treating immediate-type hypersensitivity reactions in all settings where vaccines are administered. In order not to miss IgE-mediated allergy, all patients with a history of anaphylaxis should be subjected to an allergologic work-up. Most cases with even severe clinical symptoms may be due to a non-allergic mechanism. Skin testing and subsequent vaccination appears to be useful for ruling out the presence of an IgE-mediated allergy ensuring that the incriminated vaccine and its constituents can be used safely in the future.

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