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Anaphylaxis to vaccination and polyethylene glycol: a perspective from the European Anaphylaxis Registry

To the Editor,

The COVID-19 pandemic is currently one of the most important health challenges, and the recently approved vaccines can save millions of lives. However, the fact that anaphylaxis might occur after vaccination has raised much concern. Currently, Centers for Disease Control and Prevention (CDC) reported the rate of 2.5–4.7 cases/million mRNA vaccine doses administered.[1] The allergen(s) causing these reactions remain unknown. Polyethylene glycol (PEG) has surfaced as a possible elicitor, considering that this ingredient has previously been identified as an allergen.[2,3]

The European Anaphylaxis Registry is a database of anaphylaxis cases collected from more than a hundred tertiary allergy centres from twelve European countries and Brazil.[4] Herein, the data from 13 354 cases, reported between 2007 and 2020 was screened to identify reactions caused by vaccination or PEG. Table 1 presents anaphylaxis cases caused by vaccination; 14 of such reactions were reported (14/2350; 0.6% of all reactions caused by drugs). The majority of them were observed in children (10/14). Four patients had an atopic background. Reactions to all major types of vaccines were reported. More than half of the reactions (8/13) occurred within 10 min after immunization; however, four reactions had a delayed onset (>1 h). Six reactions were classified as moderate and eight reactions as severe.[5]

Table 2 presents data on reactions to PEG. Six reactions to PEG and one to polysorbate (a possibly cross-reactive allergen) were identified (7/2350; 0.3% of all drug-induced anaphylaxis cases). All patients were adults. An atopic background was reported in three cases. The basal tryptase was within normal range in all patients with available data (4/4). The time between exposure and onset of the symptoms was within half an hour (6/6). All reactions manifested with skin and cardiovascular symptoms, two of them were classified as severe and five as moderate.[5]

The Anaphylaxis Registry is not a population-based database, and it is not suitable to estimate incidence. However, a very low number of reactions reported to vaccinations (14/13 354) or PEG (6/13 354) suggests that these reactions are very rare, confirming previously published data (incidence of anaphylaxis to vaccination in the USA was recently estimated as 1.3/1 000 000[6]). The reactions to PEG in the registry might be underreported (and reported as idiopathic anaphylaxis or misdiagnosed, for example as anaphylaxis to corticosteroids, paclitaxel or local anaesthetics), as PEG is a commonly used additive, which might have been 'overlooked' in some cases.

The rate of patients with an atopic background in our study [29% (4/14) for vaccine and 43% (3/7) for PEG anaphylaxis] was very similar to the one reported by CDC (29%; 6/21)[7] and in the currently published case series of 10 Danish patients allergic to PEG (30%; 3/10).[2] This rather low rate of patients with an atopic background, might suggest that these reactions have distinct/additional pathomechanisms[8,9] than, for example common food anaphylaxis. Our study does not suggest that mastocytosis is an underlying disease in these reactions.

Vaccines are an extremely effective method to prevent illnesses and death, and they are safe from an allergist's point of view with only very rare instances of severe reactions. Nevertheless, partially due to misleading information, many patients with allergies feel anxious in terms of getting the SARS-CoV-2 vaccination.[10] This might lead to lower immunization rate and hence higher mortality and morbidity due to this now preventable disease. Therefore, identifying whether PEG is the antigen responsible and determining the mechanisms of these reactions are of great importance. Here, more data on the cases (including data on comprehensive allergological work-up) should be urgently made available to help the scientific community to identify the patients who are truly at risk and thus raise the acceptance of the vaccine.

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Conflict of interest

MW declares the receipt of honoraria or consultation fees by the following companies: ALK-Abelló Arzneimittel GmbH, Mylan Germany GmbH, Leo Pharma GmbH, Sanofi-Aventis Deutschland GmbH, Regeneron Pharmaceuticals, DBV Technologies S.A, Stallergenes GmbH, HAL Allergie GmbH, Allergopharma GmbH & Co.KG, Bencard Allergie GmbH, Aimmune

Table 1 Anaphylaxis† to vaccines

Age	Sex	Vaccination	Country	Interval	Severity‡	Symptoms	Atopic comorbidities	Diagnostic procedures
2 months	F	Pentavalent vaccine (diphtheria, pertussis, tetanus, Haemophilus influenzae type b. (Hib) and hepatitis B)	Brazil§	>2 h	II	Urticaria, angioedema Dyspnoea	None	Not performed
4 months	M	Pentavalent vaccine (diphtheria, pertussis, tetanus, Hib and hepatitis B), Inactivated polio vaccine, Pneumococcal conjugate vaccine (PCV13) Oral human rotavirus vaccine	Brazil§	<10 min	II	Rhinitis Vomiting Wheezing	Food allergy	sIgE
1	F	Tetra viral vaccine (measles, mumps, rubella and varicella vaccine)	Brazil§	30–60 min	III	Vomiting Wheezing Reduction of alertness	None	Neg. prick test pos. i.d. test
1	F	Influenza	Brazil§	>2 h	II	Urticaria, angioedema Dyspnoea	None	Not performed
1	M	Measles Yellow fever	France	<10 min	III	Cough, cyanosis Hypotension, tachycardia	None	Neg. prick and i.d. test
2	M	DTP (diphtheria, tetanus, pertussis) Oral polio vaccine	Brazil§	<10 min	III	Erythema Stridor Reduction of alertness	AD, ARC, asthma	Not performed
3	F	Pneumococcal polysaccharide vaccine 23	France	<10 min	III	Urticaria, angioedema Wheezing Hypotension	None	Neg. prick test pos. i.d. test
5	M	Yellow fever	Brazil§	<10 min	II	Urticaria, angioedema Abdominal pain, nausea Cough Chest pain, tachycardia	ARC, asthma, food allergy to egg	Pos. prick test and sIgE to egg
17	M	Hepatitis A + B	Germany	Unknown	II	Urticaria, angioedema Nausea, diarrhoea Dyspnoea	None	Unknown¶
21	M	Rabies	Germany	<10 min	III	Erythema, pruritus Nausea, vomiting Dizziness, hypotension, Tachycardia	Unknown	Pos. sIgE to gelatin (CAP class 4)
22	F	Rabies	Germany	<10 min	II	Urticaria, angioedema Abdominal pain, diarrhoea	None	Not performed
23	F	Hepatitis B	Switzer-land	<10 min	III	Erythema Reduction of alertness	None	Not performed
27	F	Influenza	Austria	1–2 h	III	Pruritus, urticaria Dyspnoea, wheezing Hypotension, loss of consciousness	Asthma	Neg. prick test pos. i.d. test
47	F	Influenza	Germany	>2 h	III	Angioedema Dyspnoea Dizziness, hypotension	None	Not performed

AD, atopic dermatitis; ARC, allergic rhinoconjunctivitis.
†Cases fulfilling the modified NIAID/FAAN criteria described in Ref. 4. ‡Severity was classified according to grading by Brown[5] (II – moderate; III – severe). §The collaborating centre in Brazil is a reference centre for allergic reactions to vaccines resulting in a relatively high number of reactions to vaccines reported from this country. ¶This questions were not asked in the older version of questionnaire when the case was reported.

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Table 2 Anaphylaxis† to PEG and polysorbate

Age	Sex	Substance	Country	Interval	Severity‡	Symptoms	Atopic comorbidities	Baseline tryptase	Diagnostic procedures
26	F	PEG	Germany	<10 min	II	Erythema, pruritus, urticaria Chest tightness	ARC, asthma	4 μg/l	Not performed
34	M	PEG	Italy	10–30 min	II	Urticaria Vomiting Dyspnoea Chest tightness	Asthma	Unknown	Neg. prick pos. i.d. test
40	F	PEG	France	<10 min	III	Urticaria Hypotension	None	4 μg/l	Neg. prick
42	F	PEG (as additive in medroxyprogesterone-acetat depo injection)	Germany	<10 min	II	Pruritus, rhinitis Nausea Tachycardia	None	1 μg/l	Neg. prick pos. i.d. test
50	M	PEG	France	Unknown	III	Pruritus, urticaria Loss of consciousness	None	Unknown	Pos. prick test and oral provocation
50	M	Polysorbate	Switzerland	<10 min	II	Urticaria, Dizziness, Sight disorder	ARC	3 μg/l	Pos. prick test and oral provocation
67	F	PEG	France	<10 min	II	Urticaria, angioedema Dizziness	None	Unknown	Pos. prick neg. i.d. test

AD, atopic dermatitis; ARC, allergic rhinoconjunctivitis.
†Cases fulfilling the modified NIAID/FAAN criteria described in Ref. 4; additionally, two mild reactions were reported in the registry (patients with skin symptoms only, not fulfilling the inclusion criteria; both patients were women with atopic background; data not shown). ‡Severity was classified according to grading by Brown[5] (II – moderate; III – severe)

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Author contributions

MK performed data analysis and wrote the manuscript. JMR, LFE, AK, MBB, KSH and SDB collected the data, contributed to the interpretation of data and revised the manuscript critically for important intellectual content. MW managed data acquisition, contributed to the interpretation of data and revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript for publication.

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Stevens–Johnson syndrome induced by tonic water

Editor

Tonic water is known to cause fixed eruptions (FEs), but severe drug eruption is rarely reported to date. Here we describe the first case of Stevens–Johnson syndrome (SJS) induced by intake of tonic water. We must notice that the FE induced by tonic water can be severe due to repeated intake.

A 26-year-old man presented with a 1-year history of a recurrent rash. He noticed that the symptom had appeared one day after drinking gin and tonic and regressed within a week leaving hyperpigmentation. At first, the lesion was an erythematous plaque on his upper lip, and the extent of the lesion had spread to most of his body surface as the symptoms had relapsed. Physical examination revealed high fever (39.6°C), erosions on his lips and scrotum, and generalized, ill-defined, coalescing, erythematous macules (Fig. 1). A biopsy of the lesion revealed vacuolization of the basal cell layer, necrosis of keratinocytes surrounded by lymphocytes and a sparse perivascular lymphoid infiltrate, confirming the diagnosis of SJS. He was treated orally with corticosteroids, and the rash had resolved leaving hyperpigmentation. The corticosteroids were tapered and finished after the symptom regressed.

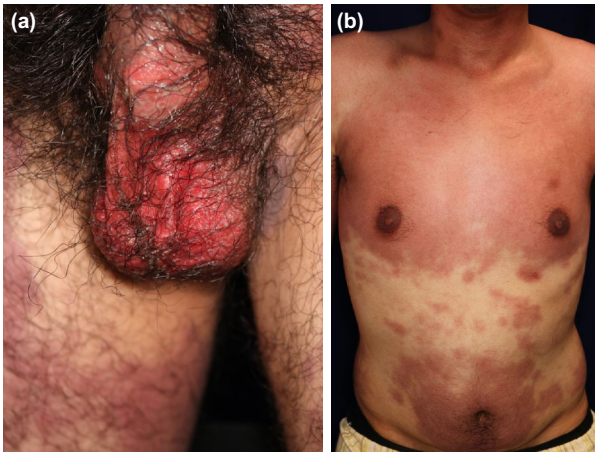

Figure 1 Clinical images of Stevens–Johnson syndrome induced by tonic water; (a) an erosion on the patient's scrotum, and (b) erythematous macules on his trunk.

One month later, a closed patch test (PT) was conducted with several kinds of tonic water (Schweppes®[Coca-Cola, Tokyo, Japan], CANADA DRY®[Coca-Cola] and Wilkinson®[Asahi, Tokyo, Japan]), gin, quinine (20% in petrolatum), quinine chloride (20% in petrolatum) and optical isomers of quinine (quinidine and hydroxychloroquine, 20% in petrolatum) on both affected and unaffected skin areas with positive results only to quinine and quinine chloride on the affected skin according to criteria of The International Contact Dermatitis Research Group. The erythema and infiltration extended around both of the test sites (Fig. 2). Lymphocyte stimulation tests (LSTs) with quinine and quinine chloride were negative. The diagnosis of SJS induced by tonic water was made. We did not perform an oral challenge test (OCT) due to severity of his symptom.

Quinine is an antimalarial drug, and tonic water was developed to ease the bitter taste of quinine by adding sugar and citrus extract. Various manifestations of hypersensitivity to quinine, and tonic water including quinine, have been reported.[1] Although immediate reactions such as anaphylaxis and allergic urticaria are reported, the most reported hypersensitivity to tonic water is FE.[2,3] It typically involves the lips, appears after drinking tonic water and disappears spontaneously, leaving residual hyperpigmentation. The symptoms are usually recurrent because patients are not aware that tonic water is an allergen. Repeated intake of tonic water can worsen the extent of eruptions but they rarely progress to severe eruptions such as toxic epidermal necrolysis (TEN) and generalized bullous fixed eruption (GBFE).[4,5]

Stevens–Johnson syndrome is a life-threatening cutaneous hypersensitivity reaction, typically to a medication. SJS induced by food has been rarely reported.[6]

Patch tests and OCTs are useful to identify tonic-water-induced eruptions. We searched for tests conducted in 23 previously published cases of FEs, and in a case of GBFE and TEN, due to tonic water, in the English and Japanese literature.[3–5,7–9] LSTs were negative in the two cases tested. PTs on unaffected skin were negative in all seven cases tested, while PTs on affected skin were 52.6% (10/19) positive. PTs on affected regions were 33.3% (3/9) positive by tonic water, while 61.5% (8/13) was positive by quinine. OCTs were 100% (15/15) positive. However, some cases needed further corticosteroid therapy to treat the eruption re-provoked by the OCT.[9] These results suggest that PTs on affected regions, especially using quinine, are useful to confirm the diagnosis of tonic-water-induced eruptions.

This is the first report of SJS induced by tonic water. We emphasize that FEs can progress to SJS and patients must be educated to avoid suspected foods.

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The patient in this manuscript has given written informed consent to publication of his case details.

