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Dextran-specific IgG response in hypersensitivity reactions to measles-mumps-rubella vaccine

To the Editor:

Measles-mumps-rubella (MMR) vaccination is a very safe and effective health intervention. However, hypersensitivity reactions to this vaccine have been reported by various authors.[1,2] In the past, allergic reactions were attributed to egg proteins. Because the majority of severe reactions were observed in egg-tolerant individuals, sensitization to other components was evaluated, and gelatin allergy was demonstrated.[1]

In Italy an increase of immediate allergic reactions in children vaccinated with a brand of MMR vaccine, Morupar (Chiron, Siena, Italy), caused alarm among public health personnel a few years ago. Moreover, allergic reactions, including anaphylaxis, after administration of the same MMR vaccine were reported in Brazil during a national vaccination campaign.

The potentially allergenic components of the Morupar vaccine included neomycin sulfate (up to 10 μg/dose), as well as residual traces of egg proteins, hydrolyzed casein, and Dextran 70 (Sigma-Aldrich, St Louis, Mo), the concentration of which could not be precisely stated by the manufacturer. Gelatin and latex were not present, according to the manufacturer's certification. A detailed analysis of vaccine adverse event reports was performed, and the reactions were discussed at the international level with vaccine safety experts (see acknowledgements). Allergy to a vaccine component was suspected. Neomycin was ruled out because it mainly causes late hypersensitivity reactions; egg proteins and casein were considered improbable causes because all but 1 of the patients tolerated the ingestion of eggs and milk. Therefore dextran, which was present in this brand only, was singled out as the potential culprit.

Clinical dextrans, including 40, 60, 70, and 75 dextrans, have been widely used for postoperative thromboembolic prophylaxis and as plasma volume expanders.[3] Hypersensitivity reactions to intravenous dextran therapy have been recognized since the 1960s.[4] The reported incidence of anaphylactic-like reactions has ranged from 0.03% to 1.10% of patients and has been attributed to the active ingredient and not to contaminants.[5,6] Immune complex–mediated reactions caused by naturally occurring dextran-reactive antibodies are considered the most likely pathogenetic mechanism,[7] with complement activation and anaphylotoxin release.[5] Increased IgG levels to dextran have been demonstrated in patients with hypersensitivity reactions; an IgE-mediated mechanism has been also postulated but ruled out by most of the studies.[3,7]

With regard to vaccines, hypersensitivity reaction to BCG vaccine containing high-molecular-weight (100 kd) dextran has been described in a newborn subject and explained by the binding of passively transferred maternal dextran-reactive IgG.[8] These antibodies were found at high titers in the maternal serum a few days after the reaction. Reactions are unpredictable because dextran-reactive antibodies at low titers have been demonstrated in healthy individuals and might be due to sensitization to cross-reactive bacterial polysaccharides.[3]

To confirm the hypothesis of dextran-induced reactions, we collected clinical data and serum samples of children referred to the Green Channel, the Regional Reference Center for Prevaccination Consultancy, and the Adverse Event Following Immunization Surveillance.

Of 28 children who reported hypersensitivity reactions to Morupar, a group of 12 children was available for analysis and blood collection after informed consent was provided by their parents, who refused the offered skin tests. The clinical history of children with Morupar reactions was recorded. Sera were collected within a time interval of 2 to 24 months after the reaction (Table I). Total and specific IgE levels to the vaccine components casein (whole and hydrolyzed), egg white, ovalbumin, and ovomucoid were determined by using the ImmunoCap System (Phadia, Uppsala, Sweden). Dextran-specific IgG, IgE, and IgM levels were measured by using a time-resolved fluorescence immunoassay (DELFIA; PerkinElmer, Waltham, Mass). Dextran 70 was used for coating the Delfia plate. Plates were incubated with sera in diluting buffer (PerkinElmer). Bound antibodies were detected with a europium-labeled anti-human IgG, IgE, or IgM antiserum (PerkinElmer).

Because of the high prevalence of dextran-reactive antibodies in healthy individuals, we also analyzed the sera of 11 age- and sex- matched control subjects referred to our center for consultancy because of previous adverse reactions in temporal relationship with other vaccine administrations; also tested was a group of 10 healthy donors who had never received Morupar, along with 4 children previously vaccinated with Morupar with no history of adverse reactions.

In 3 of 12 children with Morupar reactions, a positive familial history of atopy was reported. All but 1 of the children tolerated hen's eggs and cow's milk and derivatives. They were all vaccinated with vaccines that did not contain dextran (diphtheria, tetanus, pertussis, polio, and hepatitis B) without adverse reactions. Patients 10 to 12 had previously tolerated a first MMR dose not containing dextran. Details about personal data and types of reactions are reported in Table I. The degree of reactions ranged from mild to severe. Three cases reached grade II severity and 1 reached grade III severity, as per Ring's classification of dextran-induced reactions[3]; the latter case also meets level 1 of the Brighton Collaboration anaphylaxis case definition.[9]

Total IgE levels of the 12 children ranged from 5 to 550 kU/L. IgE measurements to casein were negative in all the children. Low levels of specific IgE to egg proteins were found in 2 children, with one of them being egg tolerant.

The patients and control groups were then tested for specific IgG to dextran 70. The cutoff was fixed at 170,000, being higher than the mean plus 2 SDs of europium counts (EC) in the unexposed and exposed control groups (mean, 69,130; SD, 46,120 × 2). Nine (75%) of 12 patients showed increased levels of specific IgG to Dextran 70 above the cutoff value. Moreover, IgG antibody measurements to Dextran 70 were negative

TABLE I. Personal, clinical, and serologic data of patients and control subjects

	Sex/age (y)	Symptoms after Morupar vaccine	Treatment	Serum collection (mo)*	Total IgE (kU/L)	Specific IgE (kUA/L)				Dextran 70 IgG × 10^3†	Dextran 70 IgE × 10^3‡
						Egg white	OA	OM	Casein		
Patients											
1	M/1.5	Immediate urticaria	IM AH	12	67	0.47	0.48	<0.35	<0.35	99	38
2	M/1.5	Delayed urticaria	None	24	550	<0.35	<0.35	<0.35	<0.35	33	56
3	F/1.5	Immediate exanthema	None	5	14	<0.35	<0.35	<0.35	<0.35	**530**	43
4	M/1.5	Immediate erythema	None	3	3.6	<0.35	<0.35	<0.35	<0.35	**1700**	15
5	F/1.5	Immediate cyanosis, cough, dyspnea	IV GC	7	5.9	<0.35	<0.35	<0.35	<0.35	**260**	33
6§	M/1.5	Immediate erythema and cough	IM AH IV GC	9	51	<0.35	<0.35	<0.35	<0.35	**350**	66
7	M/1.5	Immediate erythema and dyspnea	IM AH IV GC	4	5	<0.35	<0.35	<0.35	<0.35	**200**	88
8	M/1.5	Immediate erythema, angioedema	IM AH IV GC	2	13.4	<0.35	<0.35	<0.35	<0.35	**730**	68
9	F/5	Immediate urticaria	IV GC	4	6.8	<0.35	<0.35	<0.35	<0.35	**1800**	18
10‖¶	M/12	Dyspnea, facial edema, urticaria	IM AH IV GC	5	1219	2.2	2.4	0.7	<0.35	**2000**	18
11‖	F/14	Urticaria, dyspnea	IM AH IV GC	19	83	<0.35	<0.35	<0.35	<0.35	150	15
12‖	M/12	Apnea, hypotonia, neck edema, loss of consciousness, fecal and urinary incontinence	SC epinephrine, artificial ventilation	5	25	<0.35	<0.35	<0.35	<0.35	**460**	11
Unexposed control subjects		Symptoms after other vaccines									
1	M/13	Immediate urticaria to HB vaccine	IM AH	11	ND	ND	ND	ND	ND	70	57
2	M/0.6	Immediate erythema and facial edema after Hexavalent vaccine	IM AH IV GC	12	ND	ND	ND	ND	ND	45	74
3	M/6	Immediate erythema after DTP vaccine	None	24	ND	ND	ND	ND	ND	21	31
4	F/12	Cephalalgia after HB vaccine	None	6	ND	ND	ND	ND	ND	**183**	14
5	F/11	Cough, bronchospasm after HB vaccine	Inhaled β_2-agonist	5	1029	<0.35	<0.35	<0.35	<0.35	82	44
6	M/2¶	Local reaction to Hexavalent vaccine	None	12	23	3.7	17	14	0.37	53	43
7	M/2.5	Facial edema after Hexavalent vaccine	IV GC	32	17	<0.35	ND	ND	ND	42	56
8	M/12	Bronchospasm after HB vaccine	Inhaled β_2-agonist	7	ND	ND	ND	ND	ND	65	10
9	M/0.6	Urticaria after DT vaccine	IM AH	6	ND	ND	ND	ND	ND	25	16
10	M/5	Local reaction to DT vaccine	None	6	ND	ND	ND	ND	ND	22	16
11	F/9	Local reaction to DT vaccine	None	8	ND	ND	ND	ND	ND	127	10
Exposed control subjects		Symptoms after Morupar vaccine									
12	F/3	None	NA	17	ND	ND	ND	ND	ND	108	15

(*Continued*)

TABLE I. (*Continued*)

	Sex/age (y)	Symptoms after Morupar vaccine	Treatment	Serum collection (mo)*	Total IgE (kU/L)	Specific IgE (kUA/L) Egg white	OA	OM	Casein	Dextran 70 IgG × 10^3†	Dextran 70 IgE × 10^3‡
13	M/3	None	NA	16	ND	ND	ND	ND	ND	29	20
14	F/2	None	NA	11	ND	ND	ND	ND	ND	53	33
15	F/2	None	NA	9	ND	ND	ND	ND	ND	112	18

OA, Ovalbumin; *OM*, ovomucoid; *M*, male; *IM*, intramuscular; *AH*, H1 antihistamines; *F*, female; *IV*, intravenous; *GC*, glucocorticoids; *SC*, subcutaneous (despite international recommendations); *HB*, hepatitis B; *ND*, not determined; *DTP*, diphtheria-tetanus-pertussis; *DT*, diphtheria-tetanus; *NA*, not applicable.
*Months after the reaction.
†Europium counts: fixed cutoff value, 170,000 (mean of controls + 2 SD: 69,130 + 46,120 × 2). Positive results are shown in boldface.
‡Europium counts: fixed cutoff value, 79,000 (mean of controls + 2 SD: 30,470 + 20,050 × 2).
§Reported erythema after cow's milk–based formula intake.
‖II MMR dose.
¶Inhalant allergy, asthma, and egg intolerance.

(<170,000 EC cutoff value) in subjects who had received Morupar but who did not have any reaction. Only one of the 11 children with a history of reactions to other vaccines had an IgG level to Dextran 70 greater than the cutoff value. A further group of 10 healthy subjects, aged 1 to 40 years (mean, 29 years), with no history of vaccine adverse reactions and no exposure to Morupar had Dextran 70 IgG levels ranging between 60,000 and 128,000 EC. Specific IgE levels to Dextran 70 did not differ in patients and control subjects (Table I).

These patients had no previous vaccine-related adverse events; only one of them had egg-induced allergic reactions, and another reacted to cow's milk–based formula. Moreover, 3 of them, including the subject with egg allergy, had previously tolerated another brand of MMR vaccine that contained traces of egg proteins without reactions. Although reactivity to injected egg proteins cannot be excluded as a possible culprit in 2 children with specific IgE to egg proteins, we conclude that the majority of hypersensitivity reactions to Morupar are dextran induced. The clinical relevance of dextran-specific IgG levels is strengthened by its negativity in one child who had a delayed-type reaction (patient 2); 2 further negative test results might be the result of delayed blood collection (patients 1 and 11). Dextran 70–specific IgM levels were also determined in patients and control subjects, but a level higher than the cutoff value was only found in patients 9 and 10 (data not shown).

We think that investigation of vaccine-related adverse events is important for a better understanding of mechanisms and causes and to maintain public confidence in immunization programs. At the individual level, this information is important because in the future, 9 of these children will be called in for a second administration of MMR vaccine.

Because of numerous cases of immediate allergic reactions, including cases of anaphylactic shock reported in Italy and Brazil, Morupar was subsequently withdrawn from the market. MMR vaccines currently used in Italy do not contain dextran.

Presently, with so many new products coming on the market, we suggest that vaccines should be produced without dextran, which seems to be a replaceable component. In the rare cases of plasma expanders being administered to these patients, another drug should be used.

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