Allergol Immunopathol (Madr). 2010;38(6):341–346

Allergologia et immunopathologia

www.elsevier.es/ai

RESEARCH LETTERS

Hypersensitivity reactions following measles-mumps-rubella vaccine and dextran-specific IgG response

To the Editor,

In the context of a mass vaccination campaign, rare adverse events can be detected through passive surveillance.[1] The Brazilian Post-Vaccine Adverse Event Surveillance System received notifications of allergic reactions at a rate of 0.95 cases/100,000 doses of the Measles-Mumps-Rubella vaccine (MMR) produced in Italy (Morupar® Chiron), in the period from 2000 to 2003. However on August 21st 2004 (the first day of the National Measles Follow-up Campaign), an increase in allergic reactions was reported with a rate of 11.56 cases/100,000 doses administered of this vaccine. As a result, and as a preventive measure, the use of this product was discontinued in Brazil. (Ministério da Saúde. Brasília. – Nota Técnica N°97/04).

Studies have shown an association between anaphylaxis following administration of the MMR vaccine and subsequent detection of anti-gelatin IgE antibodies. [2,3] According to the manufacturer's certification, the gelatin was not present and the Morupar® vaccine had residual traces of egg, hydrolysed casein and dextran 70.

Dextran, a high-molecular-weight polysaccharide used as a stabiliser in some vaccines, is rarely associated with hypersensitivity reactions. These reactions result from circulating immune complexes formed by preexisting anti-dextran IgG antibodies and dextran injected with the vaccine, causing complement activation and mast cell and basophil degranulation by anaphylatoxins.[4]

We evaluated 19 children (aged 34.9±16.3 months) who reported reactions within two hours after receiving the vaccine, in Curitiba, state of Paraná. Thirty-one age/gender matched children, living in the same area, who had received on the same date and who had no adverse reactions were included as a control group. Blood samples were collected approximately five to six weeks after vaccine administration, while skin tests were performed four to seven months after vaccination.

Serum specific IgE antibodies (casein, egg) were determined by a fluoroenzyme immunoassay method (Immuno-CAP-Pharmacia®) and levels greater than 0.35 KU/L were considered positive.

Levels of specific IgE and IgG to dextran 70 were determined by a time-resolved fluorescent lanthanide immunoassay (DELFIA, PerkinElmer, Boston, MA, US). The dissociation-enhanced method can be used to study antibody binding to solid-phase proteins or peptides. Dextran 70 from *Leuconostoc ssp* (Molecular weight ~70 kDa, Fluka, Sigma Aldrich, Milan, Italy) was used at a concentration of 400 μg/ml to coat the Delfia plates. Serum samples were diluted 1:50 in bovine serum albumin 1% and incubated overnight at 4–8 °C. Bound antibodies were detected by a europium-labelled anti-human IgG or IgE antiserum (Perkin-Elmer). Optical density values higher than the mean plus two standard deviations of europium counts in the control group were considered positive.

For allergy skin tests we used undiluted vaccine from the same batch as that employed in the Vaccination Campaign.

The study was approved by the Federal University of Parana's Institutional Review Board of Hospital de Clinicas, and a voluntary informed-consent was signed by children's guardians.

No prior allergic reactions to vaccines were reported in either group, and there was no association with history of atopy or allergic reactions to medication and/or food.

Of the children evaluated, all developed skin manifestations (erythema, urticaria or angioedema), associated or not with other systems. All of them received oral antihistamines, two received oral corticosteroids, and subcutaneous adrenaline complemented the therapy.

Demographic and laboratory data of subjects and controls are shown in Table 1.

Casein-specific IgE was not detected in all the subjects. Two controls showed levels > 0.35 KU/L of specific IgE to egg.

Sera from the case and control groups were tested for specific IgE and IgG to dextran 70, which was the most suspected causal component in the Italian case series [5]. All the children had specific IgE to dextran 70 below the cut-off value (167,336; mean 93,092, SD 37,122). The cut-off for specific IgG was fixed at 1,433,119, which is higher than the mean plus 2 SDs of europium counts in the control group (mean, 422,899; SD, 505,109 × 2). Sixteen out of 19 cases (84%) and one out of 31 controls (3%) presented specific IgG levels above the cut-off value (Table 1).

Positive skin prick test with the Morupar vaccine was observed in five out of 18 cases and in none of the 22 controls tested. These five patients also showed high levels of specific IgG to dextran 70, with negativity of specific IgE.

The determination of specific IgE to casein and egg allowed us to exclude that these proteins were part of the cause of reactions to the Morupar vaccine. According to the results of dextran-specific antibodies, immediate allergic reactions reported in Brazil could be possibly induced by dextran 70 like those reported in Italy.[5]

Table 1 Demographic data, serologic and prick test results of cases and control subjects

Cases	Age (months)	Gender	Specific IgE(kU/L)		Dextran 70 IgG	Dextran 70 IgE	Prick test
			Casein	Egg white			
1	40	F	<0.35	<0.35	**2,046,917**	124,299	Positive
2	23	F	<0.35	<0.35	**1,760,366**	94,160	Negative
3	43	M	<0.35	<0.35	15,943	33,425	Negative
4	34	F	<0.35	<0.35	**1,858,396**	110,011	Negative
5	14	F	<0.35	<0.35	1,193,181	98,350	Negative
6	55	F	<0.35	<0.35	**1,969,370**	139,781	Negative
7	57	M	<0.35	<0.35	**2,177,109**	113,300	Negative
8	54	F	<0.35	<0.35	**1,564,207**	82,105	Negative
9	37	F	<0.35	<0.35	**1,773,746**	144,329	Positive
10	41	M	<0.35	<0.35	**1,798,760**	109,966	Positive
11	16	M	<0.35	<0.35	**2,019,567**	119,839	Negative
12	32	M	<0.35	<0.35	**1,501,322**	148,892	Negative
13	55	F	<0.35	<0.35	**1,857,291**	129,189	Positive
14	13	F	<0.35	<0.35	**1,923,830**	128,222	Negative
15	52	F	<0.35	<0.35	**2,047,325**	106,648	Positive
16	15	M	<0.35	<0.35	**1,785,574**	99,988	Negative
17	20	F	<0.35	<0.35	**1,717,535**	99,940	Negative
18	14	F	<0.35	<0.35	**1,894,459**	103,162	Negative
19	49	M	<0.35	<0.35	592,071	38,380	ND
Controls							
1	24	F	<0.35	<0.35	818,652	68,916	Negative
2	24	F	<0.35	<0.35	1,159,819	104,267	Negative
3	58	F	<0.35	<0.35	51,912	67,927	Negative
4	25	F	<0.35	<0.35	79,455	76,974	Negative
5	27	F	<0.35	<0.35	622,043	128,462	Negative
6	57	M	<0.35	<0.64	298,816	17,480	Negative
7	50	M	<0.35	<0.35	936,896	68,822	ND
8	52	M	<0.35	<0.35	27,610	82,077	Negative
9	36	F	<0.35	<0.35	110,355	31,535	Negaitive
10	15	M	<0.35	<0.35	60,946	50,172	ND
11	49	F	<0.35	<0.35	16,803	15,281	Negative
12	23	F	<0.35	<0.35	777,216	79,284	ND
13	29	F	<0.35	<0.35	318,863	143,238	ND
14	24	F	<0.35	<0.35	17,682	65,217	Negative
15	15	M	<0.35	<0.35	45,897	90,983	Negative
16	13	F	<0.35	<0.35	45,887	99,016	Negative
17	44	F	<0.35	<0.35	**1,991,596**	154,322	ND
18	55	F	<0.35	<0.35	229,436	130,985	ND
19	32	M	<0.35	<0.35	50,786	70,602	Negative
20	49	F	<0.35	<0.35	1,068,770	69,044	Negative
21	54	M	<0.35	<0.35	1,095,377	112,356	Negative
22	55	M	<0.35	<0.35	117,545	120,092	Negative
23	32	F	<0.35	<0.35	135,736	139,116	Negative
24	58	F	<0.35	<0.35	154,005	140,009	ND
25	26	M	<0.35	<0.35	128,790	83,075	Negative
26	23	F	<0.35	<0.35	72,542	114,813	Negative
27	13	M	<0.35	<0.35	116,883	119,235	Negative
28	40	M	<0.35	<0.35	1,303,248	103,162	Negative
29	28	M	<0.35	<0.35	943,154	76,433	ND
30	24	F	<0.35	<0.35	162,615	124,530	Negative
31	47	M	<0.35	<0.35	150,347	144,336	ND

Dextran 70 IgG: fixed cutoff value, 1,433,119 Europium counts, Dextran 70 IgE: fixed cutoff value, 167,336 Europium counts (positive results are written in bold). Gender: male (M), female (F); prick test: not determined (ND).

The positive allergy skin tests to MMR vaccine observed in five cases could be due to a double pathogenetic mechanism in these children, such as in certain drug allergies[6], involving specific IgG to dextran and IgE to a different component of the vaccine, although a non-specific reaction due to a direct degranulation of mast cells cannot be ruled out.

We conclude that residual dextran 70 in this particular brand of MMR vaccine, which induced high levels of specific IgG antibodies, could be the culprit of most of the hypersensitivity reactions reported in Brazil.

Research supported by

Programa Nacional de Imunizações, Ministério da Saúde, Brasília/Distrito Federal, Brazil

Secretaria de Estado da Saúde do Paraná, Curitiba/Paraná, Brazil

The Green Channel Reference Centre for Pre-vaccination Consultancy, University Hospital, Verona, Italy.

Conflict of interest

The authors contributed equally to this work and they have no conflict of interest.

Acknowledgments

We wish to thank the helpful discussion of Drs. Robert T. Chen, Karin R. Luhn and Fides Sbardelotto. We acknowledge Elizabeth Ferraz, Daniel R. C. de Freitas, Gisele C. B. Araújo, Kátia Terêncio and Gisele Madalosso for recruitment and serum collection.

doi:10.1016/j.aller.2010.02.006

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X-linked agammaglobulinaemia. Mutation A1246G (R372G)

To the Editor:

X-linked agammaglobulinaemia (XLA) is a primary immune deficiency characterised by a reduction in circulating B lymphocytes, hypogammaglobulinaemia and recurrent infections. The disease is caused by a mutation of Bruton's tyrosine kinase (Btk). Few studies in large groups of patients have been published; a large cohort of XLA patients in Eastern and Central European countries was recently published, in which the genetic and demographic features of XLA were studied; and clinical, immunological and genetic information was collected for 122 patients from 109 families.[11]

We present a case of XLA which we believe to be of interest in view of its classical clinical presentation, diagnostic confirmation based on molecular biological techniques, and positive familial history.

The patient was a three-year-old Caucasian male from Ecuador, who had arrived in Spain in June 2003. On occasion of the first routine primary care visit, the paediatrician noted retarded progression of body weight and height – 10.4 kg (percentile 3) and 89 cm (percentile 25) – without significant findings in the physical examination. History of disease: Starting at one year of age the patient developed two episodes of pneumonia (one requiring hospital admission), recurrent bronchitis, multiple upper airway conditions and one episode of gastroenteritis. Family history: three siblings had died as a result of respiratory infections – the first two at four and two years of age, respectively (corresponding to pneumonia and sepsis), and the third at four months of age, due to severe bronchitis. The mother explained that the first two deceased children were from