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Brief Communication

Anaphylaxis associated with the vaccine against measles, mumps and rubella

ABSTRACT

A case-control study was carried out aiming to describe the cases and causes of anaphylaxis associated with the vaccine against measles, mumps and rubella. A total of 22 reported cases in children who showed mucocutaneous manifestations, during the Campanha Nacional de Vacinação (Brazilian Vaccination Campaign), conducted in the city of Curitiba, Southern Brazil, in 2004, were studied. In addition, 66 children, who were next to these cases and did not show a symptomatology after the vaccine was applied, were selected. Serum measurements of antibodies for vaccine antigens and total IgE, specific IgE antibody measurements for several allergens, and skin tests were performed. Vaccine response was adequate, specific IgE measurement and skin tests showed that potential allergens in vaccines and atopy were not associated with anaphylactic reactions. Skin tests with the vaccine and dextran were positive in the cases exclusively, suggesting sensitization to certain residual components of the vaccine and possible cross-reaction with dextran.

DESCRIPTORS: Measles-Mumps-Rubella Vaccine, adverse effects. Child. Anaphylaxis. Case-Control Studies.

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INTRODUCTION

Anaphylaxis is a clinical condition with a sudden onset and of an emergency nature, involving possible risk of death. Its symptomatology results from the action of mediators that act in multiple systems (mucocutaneous, respiratory, cardiovascular and gastrointestinal), with a low risk of occurrence after application of vaccine, with a variation from 1.1 to 3.5 cases/million doses.[1]

According to the Brazilian Immunization Program,[a] during the *Campanha Nacional de Seguimento contra o Sarampo de 2004* (2004 Brazilian Follow-up Campaign against Measles), 11.56 cases of anaphylaxis /100,000 doses of the measles, mumps and rubella (MMR) vaccine applied by the Chiron Laboratory (Morupar®) were reported, resulting in the immediate suspension of the use of this product.

Any vaccine component, in addition to its antigenic part, has the potential to trigger anaphylaxis. Gelatin is a stabilizer used by certain laboratories that produce vaccines, with specific IgE having been detected in children with anaphylaxis after application of the MMR vaccine.[8] Once the Morupar® vaccine does not have gelatin in its formulation, the present study aimed to describe the cases and causes of anaphylaxis associated with this vaccine.

METHODS

The study population was comprised of children living in the city of Curitiba, Southern Brazil, aged more than one year and less than five years, who received the second dose of MMR vaccine (Morupar®, batch 7401B) on August 21st, 2004. Selection of cases was made by analyzing files of reports of post-vaccination adverse events and electronic medical charts of the city's health care service. Cases that met the following definition were considered: sudden onset of mucocutaneous manifestations (urticaria; erythema; angioedema; eye signs: conjunctival hyperemia, ocular itching, tearing), associated or not with the respiratory (nasal manifestations: nasal congestion, rhinorrhea, sneezing; hoarseness; dyspnea, laringospasm; bronchospasm), cardiovascular (hypotension; syncope; loss of consciousness; palpitation; pallor) and/or gastrointestinal systems (nausea; vomit; diarrhea; abdominal pains), within four hours after application of vaccine.[1]

According to City of Curitiba Department of Health, 61,319 doses of the MMR vaccine were applied and there were 42 reports of suspicious cases of adverse events. Of these, 22 children met the definition of case. The remaining 20 were excluded due to the criteria of exclusion: the concomitant application of the bacterial triple vaccine (diphtheria, tetanus and pertussis – DTP) and the diagnosis of diseases coinciding with the vaccination period. The children excluded were thus distributed: ten children had a fever and concomitant application of the DTP vaccine, five had skin manifestations four hours after application of vaccine and other five had a diagnosis of diseases coinciding with the vaccination period. All children had received a dose of oral vaccine against poliomyelitis, due to the overlapping of vaccination campaigns.

A control group was formed, with a random proportion of 1:3, including children who did not show a symptomatology after the application of the same vaccine and were selected by active search in the neighboring areas of confirmed cases.

From September 25th to October 6th, 2004, home interviews were conducted and the following information obtained: vaccination history, age, sex, maternal breastfeeding, allergy to vaccines, personal or family history of atopy (asthma or rhinitis) and symptomatology shown on August 21st, after application of vaccine. Blood collection was also performed in children for serological analysis.

Determination of serum IgM and IgG for vaccine antigens was performed by enzyme immunoassay (Behring®). Vaccine response was considered adequate when IgG for measles was > 0.20 UI/ml; for mumps, > 1.1 UI/ml; and for rubella, > 13 UI/ml.

Dosage of total and specific serum IgE (cow milk, casein, egg white, latex, *Dermatophagoides pteronyssinus* (Dp) was performed by fluoro-enzyme-immunoassay (IMUNOCAP-Pharmacia®), with specific IgE ≥ 0.35kU/l being considered positive. Skin tests were performed in the period between four and seven months after application of vaccine through invitation by telephone. The following commercial extracts (IPI-ASAC®) for skin sensitization were used: Dp, egg white, cow milk protein fractions (alpha-lactalbumin, beta-lactoglobulin, casein); 40,000 MW dextran solution in 5% glucose (Rheomacrodex®); neomycin sulfate (20mg/ml); bovine gelatin (20mg/ml) and Morupar® vaccine, batch 7401B. This vaccine is a lyophilized suspension comprised of the following attenuated live viruses: measles, Schwarz strain, cultivated in chicken embryo cells; mumps, Urabe AM9 strain, cultivated in chicken embryo cells; and rubella, Wistar HA 27/3 strain, cultivated in diploid human cells. Excipients: neomycin sulfate (10 µg/dose), hydrolyzed casein (17.5mg/dose) and stabilizing saline solution of up to 0.5ml.

[a] Ministério da Saúde. Programa Nacional de Imunizações. Eventos adversos pós-vacinais na campanha de seguimento contra sarampo no Brasil em 2004. Brasília; 2005. [Nota Técnica Nº97/04].

Histamine solution (10mg/ml) and physiological solution at 0.9% were used as negative and positive controls.

Immediate-reading skin tests were performed by 13 X 0.38 disposable needle puncturing (BD Plastipak®) and considered positive in the presence of papule > 3 mm in mean diameter. If the result of the puncture test with the vaccine was negative, an intradermal test was subsequently performed with a 0.02 ml injection of the same non-diluted vaccine into the volar forearm. Intradermal test was considered positive in the presence of papule > 5 mm in diameter, 15 minutes after application, in the early reading; and induration > 5 mm in diameter, 72 hours after application, in the late reading.

Puncture test was performed in 20 cases (n=22) and in 41 controls (n=66), due to five refusals (two cases and three controls) and loss of 22 children from the control group who were not located. Intradermal test was performed in 14 cases (one refusal) and 41 controls.

Data were analyzed in the R software, using parametric (Student t test) and non-parametric tests (Pearson's chi-square, U Mann-Whitney and Fisher's exact tests). A level of significance lower than 5% ($p< 0.05$) and 95% confidence interval were considered.

This study was approved by the Research Ethics Committee of the *Hospital de Clínicas da Universidade Federal do Paraná* (Paraná Federal University Clinical Hospital) and performed after parents or legally responsible adults signed an informed consent form.

RESULTS

The Table shows that there was no difference between cases and controls in terms of age, sex, maternal breastfeeding time, history of atopy and interval between doses of the MMR vaccine.

In addition, allergy associated with other vaccines was not reported in these groups.

The interval of onset of clinical manifestations varied between zero and two hours after application of vaccine (median=25 minutes), with a mean duration of three hours. There were only mucocutaneous manifestations in 15 cases (conjunctival hyperemia with generalized erythema or urticaria and/or angioedema). In five cases, there was an association with the respiratory (hoarseness and/or cough) or gastrointestinal systems (vomit and/or diarrhea) and in two cases there was an association with the respiratory and gastrointestinal systems (hoarseness and vomit) and with the respiratory and cardiovascular systems (hoarseness, cough, cyanosis and syncope). Medical care was necessary for all children and two of them were hospitalized. The treatment selected was oral antihistamines and, in certain cases, oral corticosteroid (n=3) and subcutaneous adrenalin (n=2) were associated.

Titles of IgG for mumps and rubella antigens were adequate in all children; levels were protective in all cases and in 62 controls for measles.

Serum values of total IgE varied between 3.98 and 446 kU/l in cases (geometric mean= 25.6) and between < 2.0 and 3,448 kU/l in controls (geometric mean= 77.8), $p<0.0001$.

Specific IgE for casein was not detected in either group. Positivity of specific IgE for egg, latex and cow milk did not show statistical significance among cases and controls. However, higher positivity of specific IgE for Dp was found ($p < 0.001$).

Positivity of skin test for egg, milk protein and gelatin was not significant among cases and controls, except for Dp, which was higher in controls (p=0.04). The test was negative for neomycin in all children assessed.

Skin tests with the vaccine and dextran were positive in five cases (p=0.0026). Intradermal test was positive in the early reading of nine cases ($p<0.01$).

Table. Characteristics of children who received the vaccine against measles, mumps and rubella. City of Curitiba, Southern Brazil, 2004.

Variable	Case (n=22)	Control (n=66)	p
Age in months (mean ± standard-deviation)	34.1 ± 16.6	37.1 ± 14.1	0.451[a]
Gender (male:female)	8:14	34:32	0.324[b]
Mean maternal breastfeeding time (months)	3.5	4	0.958[c]
Personal history of atopy	2	13	0.338[b]
Family history of atopy	5	28	0.196[b]
Interval between vaccine doses (days)	26 – 1.314	38 – 1.671	0.41[a]

[a] Student t test.
[b] Fisher's exact test.
[c] U Mann-Whitney test.

DISCUSSION

In Brazil, surveillance is carried out by the Ministry of Health *Eventos Adversos Pós-Vacinação* (EAPV – Post-Vaccination Adverse Events). Post-vaccination events reported in the cities are sent to the state department of epidemiological surveillance, which consolidates data in the information system of the Brazilian Immunization Program. The electronic medical charts from the City of Curitiba Department of Health enable an active search and can be useful as an instrument of surveillance of post-vaccination adverse events.

Mass vaccination is an effective way to control communicable diseases, although rare adverse events may occur and compromise the credibility of campaigns.[2]

This could justify the higher rate of anaphylaxis (35.87 cases /100,000 doses) found in the city of Curitiba, when compared to the national rate.

The diagnosis of anaphylaxis is essentially clinical, regardless of the immunological mechanism that has triggered such condition. Variability of criteria to define anaphylaxis hinders comparison with other studies.[4]

The level of severity of anaphylaxis can be defined according to the treatment established.[6] In the present study, two children had moderate anaphylaxis due to the use of adrenalin and hospitalization. The majority had mild anaphylaxis and the early clinical approach helped the favorable evolution.

Attributing the anaphylactic episode to a vaccine in particular is also hindered by the concomitant application of more than one vaccine.[1]

The great variability found among total IgE values shows its low specificity for allergic diseases, in addition to its not being recommended for screening, once the increase in serum levels may occur in several clinical situations.[5]

Frequency of positivity of specific IgE for dust mites (*D. pteronyssinus)* was higher in the control group (34.8%), suggesting that atopy is not related to anaphylaxis associated with vaccine.

Dextran, a stabilizer in certain vaccines, was associated with urticaria and angioedema cases after application of vaccine.[7] Immediate skin reaction to dextran has an unknown clinical meaning, due to the immunological mechanism being mediated by pre-existing anti-dextran IgG antibodies or activation of the complement system.[3]

Anaphylaxis associated with the Morupar® vaccine did not interfere with the vaccine response and the components analyzed (egg, casein and neomycin) were not related to the adverse event. Skin tests that were positive to the vaccine and dextran, found only in cases, suggest sensitization to other residual components, with possible cross-reaction to dextran. However, the significant loss of children in the control group, while performing skin tests, may have compromised the analysis.

Finally, opportune reporting and investigation of post-vaccination events are important to monitor the quality of products licensed in Brazil.

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