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Original article

Humoral immune response to measles and varicella vaccination in former very low birth weight preterm infants

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ABSTRACT

Introduction: Immune response to vaccination in infants born prematurely may be lower than in infants born at full-term. Some clinical factors might be associated with humoral immune response.

Objectives: The objectives of this study were to compare the immune response to measles and varicella vaccination in infants born prematurely with those born at full-term and to analyze factors associated with measles and varicella antibody levels.

Methods: Prospective study including two groups of infants aged 12 months. One group of infants born prematurely with birth-weight <1500 g and who were in follow-up at the outpatient clinic for preterm infants at the institution and other group of infants born at full-term. Infants with malformations, primary immunodeficiency diseases, born to HIV-positive mothers or who had received plasma or immunoglobulin transfusions five months before or three weeks after vaccination were excluded. Plasma antibodies were measured by ELISA and factors associated with antibody levels were assessed by linear regression.

Results: Sixty-five premature and 56 full-term infants were included. The percentage of immune individuals after vaccination against measles (100% vs. 100%) and varicella (92.5% vs. 93.2%) were similar in both groups, as well as the antibody levels against measles (2.393 vs. 2.412 UI/mL; $p = 0.970$) and varicella (0.551 vs. 0.399 UI/mL; $p = 0.114$). Use of antenatal corticosteroids decreased measles antibody levels whereas breastfeeding for more than six months increased varicella antibody levels.

Conclusions: Humoral responses to measles and varicella were similar between infants born prematurely and full-term infants. Measles antibody levels were negatively associated with antenatal corticosteroid use; varicella antibodies were positively associated with prolonged breastfeeding.

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Introduction

Even when a vaccine-preventable disease is controlled, groups of susceptible individuals can acquire natural infection and spread it to others.[1] Among those susceptible are individuals with a decreased immune response to vaccination due to an underlying condition and infants born prematurely. The latter acquire lower levels of antibodies through the placenta and may exhibit a less effective and less durable immune response to vaccination.[2] Premature birth emphasizes the immaturity of the innate and adaptive immune systems – both humoral and cellular – compared to full-term newborns.[3] Lower levels of *Haemophilus influenzae* type b, tetanus, pertussis, diphtheria, poliovirus, and hepatitis B antibodies were detected in children born prematurely with extremely low birth weight who were assessed at the age of seven years after booster doses at five years of age.[4]

Antenatal and postnatal corticosteroid use may interfere with the immune response to vaccination in premature infants.[5,6] Other factors associated with prematurity, such as transfusions of blood components, low weight gain during the postnatal period, and low breastfeeding rates may also affect the immune response to vaccination.[7,8]

Whether specific vaccines would induce a reduced immune response in premature infants, and up to what age that effect would persist still remain unclear.

In this context, the aim of this study was to compare the production of antibodies before and after measles and varicella vaccination in infants born prematurely with very low birth weight and in infants born at full term, and to identify the factors associated with antibody levels against measles and varicella.

Methods

This was a prospective study conducted from September 2007 to January 2010. The Institution's Ethics Committee approved the project, and the infants' parents/guardians were asked to sign a statement of informed consent (CEP 0562/09).

The study included two groups of infants aged 12 months who were immunized with measles, mumps, and rubella vaccine (MMR) administered at 12 months of age, according to the Brazilian immunization recommendations.[9] Varicella monovalent vaccine (*Varilrix, GlaxoSmithKline, Belgium*) was administered at 15 months of age. The premature group consisted of infants born at a gestational age of less than 37 weeks and birth-weight of less than 1500 g who were in follow up at the Institution's multidisciplinary premature outpatient clinic. The term group consisted of infants born at full-term, adequate for gestational age, with no neonatal clinical complications, discharged from the maternity unit within 2–3 days and followed at a pediatric outpatient clinic.

Infants with congenital malformations, children born to HIV-infected mothers, those with a primary immunodeficiency, infants who received plasma or immunoglobulin transfusion five months before MMR vaccination until last blood collection at 18 months of age or those vaccinated for measles or varicella before the study period were all excluded.[10]

Mother and child demographic and clinical data were collected from the medical records, and the following information was collected on study inclusion: chronological age, weight, length, body mass index, and clinical complications during the first 12 months of life.[11]

At 12 months of age, before vaccination against measles, mumps and rubella virus, 4 mL of peripheral blood was collected for evaluation of humoral immunity to measles virus vaccine. At 15 months of age, before vaccination against varicella, 4 mL of peripheral blood was collected for evaluation of humoral immune response for MMR (post-vaccination dosage) and varicella-zoster virus (pre-vaccination). Finally, at 18 months of age, 4 mL of blood was collected for varicella-zoster post-vaccination antibody evaluation.

Measles antibodies were measured by indirect enzyme-linked immunosorbent assay (ELISA), as previously described.[12] Individuals with antibody levels $\geq$0.120 IU/mL were considered immune against measles.[13]

Varicella antibodies were measured by ELISA.[14] Individuals with antibody levels $\geq$0.100 IU/mL was considered immune against varicella.[15]

Statistical analysis

Numerical variables were compared using the *t*-test (normal distribution) or Mann–Whitney *U* test (non-normal distribution), and categorical variables were compared using the χ^2 or Fisher's exact test. Factors associated with post-vaccination antibody levels were analyzed by linear regression. For sample size calculations, groups of 10–20 infants were included for each variable considered in the linear regression model. The Statistical Package for the Social Sciences (SPSS) for Windows v.17.0 (*IBM SPSS Statistics, Somers, NY, USA*) was used for statistical analysis, and $p < 0.05$ was considered significant.

Results

During the study period, among the 89 infants born prematurely in follow up at the premature outpatient clinic of the Institution, 20 had received the MMR vaccine before the study entry and were excluded. Of the 69 infants included, 4 (5.8%) abandoned the study before the collection of blood samples. Therefore, 65 infants born prematurely (25–34.4 weeks of gestation) were compared to 56 infants born at full-term (Figure 1). The comparative analysis for these two groups is shown in Table 1.

Of the 65 premature infants, 24 (36.9%) were small for gestational age and 49 (75.4%) were exposed to antenatal corticosteroids. In the neonatal unit, 37 (56.9%) premature infants had respiratory distress syndrome, 17 (26.2%) had patent ductus arteriosus, 29 (44.6%) had clinical sepsis, and 25 (38.5%) had bronchopulmonary dysplasia. During hospitalization, 40 (61.5%) premature infants required mechanical ventilation, 6 (9.4%) received corticosteroids, and 31 (47.7%) received at least one red blood cell transfusion.

The rate of breastfeeding (65.5% vs. 87.5%, $p = 0.006$) was lower and duration (3.2 ± 3.7 vs. 8.9 ± 6.3 months, $p < 0.001$) shorter in premature than term infants. Approximately 15.5%

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