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Hyporesponsiveness to the infecting serotype after vaccination of children with seven-valent pneumococcal conjugate vaccine following invasive pneumococcal disease

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ABSTRACT

Antibody responses to the infecting serotype in children who are vaccinated with pneumococcal conjugate vaccine (PCV) after having invasive pneumococcal diseases (IPD) have not been fully investigated. Of 56 children diagnosed with IPD between October 2009 and April 2013 in whom the infecting serotype was confirmed, 17 who were vaccinated with PCV7 following IPD were tested to determine the geometric mean concentration of serotype-specific immunoglobulin G (IgG) and the geometric mean titers of opsonization indices (OIs) using paired sera obtained at the onset of IPD and after PCV doses following the resolution of IPD. The geometric mean concentrations of serotype-specific IgG for all PCV7 serotypes other than serotype 6B were significantly increased after the last PCV7 dose compared with those at the time of IPD onset ($P < 0.01$), as were the geometric mean titers of OIs for all PCV7 serotypes. In 14 children with IPD caused by PCV7 serotypes for whom both IgG and OI results were available, the OIs for the infecting serotype at the time of IPD onset were <8, although the IgG levels varied between from <0.2 to >5.0 μg/ml. After the last PCV7 dose, the OIs for the infecting serotype remained <8 for six (43%) of 14 children. In these six children, hyporesponsiveness to PCV7 was specific for the infecting serotype. Hyporesponsiveness was found for serotypes 6B ($n = 5$) and 23F ($n = 1$). No difference was found between the responders ($n = 8$) and the hyporesponders ($n = 6$) with regard to any clinical characteristics. Our data suggest that hyporesponsiveness to the infecting serotype may occur in children vaccinated with PCV7 following IPD.

1. Introduction

Streptococcus pneumoniae is a major worldwide cause of morbidity and mortality resulting from pneumonia, bacteremia, and meningitis [1]. Antibodies to pneumococcal capsular polysaccharide (CPS) and complement provide protection against pneumococcal strains with homologous or cross-reactive capsular serotypes [2]. The introduction in 2000 of the seven-valent pneumococcal conjugate vaccine (PCV7; Prevenar®, Pfizer) for children in the United States younger than 2 years and children aged 2–4 years in a high-risk category was effective, dramatically reducing the incidence of invasive pneumococcal disease (IPD) [3,4]. The

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lowered rate of hospitalization for childhood and adult pneumonia has been sustained during the decade since the introduction of PCV7 [5].

In Japan, PCV7 was licensed in October 2009, the Japanese government began to subsidize it for children less than 5 years of age in November 2010. PCV7 for children under 5 years of age was subsequently included in the routine immunization schedule at public expense in April 2013.

Vaccine-induced protective immunity is currently estimated by measuring the concentrations of serotype-specific immunoglobulin G (IgG) using enzyme-linked immunosorbent assay (ELISA) [6] and the opsonization index (OI) using a multiplex opsonophagocytic assay (MOPA) [7]. The World Health Organization (WHO) working group reported that antibody concentrations of 0.2–0.35 μg/ml measured with the ELISA using serum without serum absorption with 22F polysaccharide, correlated best with an OI of 8, which in turn correlated best with protective efficacy [8]. Henckaerts et al. proposed a protective threshold concentration of 0.20 μg/ml assessed with ELISA using serum absorption with 22F polysaccharide as a measure of the serotype-specific efficacy of the pneumococcal conjugate vaccine against IPD among infants less than 1 year of age [9], with an exception of 19F [10]. We recently reported that the OIs for the infecting serotypes in sera of children with IPD were almost undetectable during acute phase of IPD, although the levels of serotype-specific IgG were higher than 0.20 μg/ml [11]. Based on this finding, it was necessary for us to examine whether children with IPD could develop antibody response to the infecting serotype after vaccination with PCV7.

A previous study demonstrated that most children respond to PCV7 following resolution of IPD, but suggested that IPD caused by particular serotypes in children could result in hyporesponsiveness to the infecting serotype [12]. However, limited information is available in regards to the immune response in children vaccinated with PCV following IPD because the serotype-specific OIs have never been evaluated. We, therefore, conducted the present study to determine antibody response to PCV7 vaccine serotypes by measuring the OIs as well as the IgG levels in children vaccinated with PCV7 following IPD.

2. Materials and methods

2.1. Patients

Children under 9 years of age, who had infection caused by *S. pneumoniae*, which was isolated from normally sterile body sites such as blood or cerebrospinal fluid, were enrolled in this study when their attending doctors requested the measurement of the antipneumococcal antibodies in their sera. Fifty-six children were enrolled between October 2009 and April 2013 at 41 hospitals in Japan. All of the pneumococcal isolates were serotyped at the Department of Bacteriology I, National Institute of Infectious Diseases, by agglutination tests with rabbit antisera (Statens Serum Institute, Copenhagen, Denmark). Serotype 6C was confirmed by an in-house antiserum [13]. Because the OI for the infecting serotype was assumed to be low after the onset of IPD, we determined the antibody response after vaccination with PCV7 vaccination following the resolution of IPD. Of 56 children with IPD, 21 received PCV7 vaccination following the resolution of IPD (Fig. 1). One child who died of IPD and the other 34 children did not receive PCV7 vaccination. Paired sera collected at the onset of IPD (the first blood sample) and after PCV7 vaccination (the second blood sample) were collected from 17 children of the 21

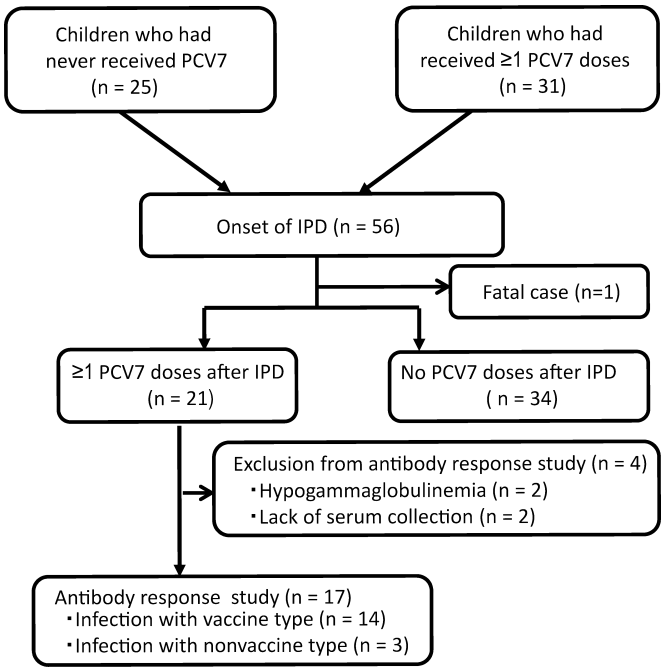

Fig. 1. Flow diagram of this study of children with invasive pneumococcal disease.

children who received PCV7 vaccination following the resolution of IPD. The other four children were excluded from this study was not collected at the time of IPD (two children) or they had comorbid hypogammaglobulinemia (two children). Fourteen of the 17 children were infected with a PCV7 serotype, and three were infected with a non-PCV7 serotype. As children received one to three doses of PCV7 after their episode of IPD, we defined the PCV7 dose before the second blood sampling as the last PCV7 dose. The median number of days (range) from IPD onset to the first blood sampling and from the last PCV7 dose to the second blood sampling was 0 (0–11) and 32 (27–120), respectively. The median number of days (range) from the IPD onset to the last PCV7 dose was 132 (15–633). Sera from children were submitted to the Research Institute for Microbial Diseases (RIMD), Osaka University, Japan, for determination of the IgG levels by ELISA and the OIs by MOPA.

Data collected from these patients included age at illness, clinical manifestations, outcome, comorbid conditions, and vaccination history. Clinical manifestations were divided into two categories: meningitis and non-meningitis. The non-meningitis categories included clinical manifestations of sepsis and sepsis with focal signs other than meningitis. The schedule of immunization with PCV7 was implemented according to a previous guideline [3]. The standard schedule is for infants aged 2–6 months: 3 doses as a primary series and the fourth (booster) dose at age 12–15 months. The catch-up schedules are for children aged ≥7 months: 2 doses as primary series and 1 dose as a booster for infants aged 7–11 months, 2 doses for children aged 12–23 months, and a single-dose for children aged ≥24 months. Furthermore, some of the children received more PCV7 doses than the age-appropriate schedules after treatment for IPD, if the parents or guardians agreed with additional booster doses of PCV7. Breakthrough infection was defined as IPD in a child who had received ≥1 PCV7 dose and for which the pneumococcal isolate was a PCV7 serotype, and vaccine failure was defined as the subset of breakthrough infection in which the patients had completed the vaccine schedule [3,14,15].