〈Original Article〉

Pneumococcal IgG levels against 13-valent pneumococcal conjugate vaccine serotypes in Japanese children with a medical history of hematopoietic neoplasms and solid tumors

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Children aged 6–18 years with a medical history of hematopoietic neoplasm and other immunocompromising conditions are at high risk for invasive pneumococcal disease (IPD). The Advisory Committee on Immunization Practices in the United States has therefore recommended that these children be immunized routinely with 13-valent pneumococcal conjugate vaccine (PCV13). Little is known, however, about the immunity of these children to pneumococci of PCV13 serotypes, except for heptavalent pneumococcal conjugate vaccine (PCV7) serotypes. Serum samples were therefore collected from Japanese children aged 5–18 years being followed up for hematological neoplasms or solid tumors, and concentrations of specific antibodies against *Streptococcus pneumoniae* PCV13 (non-PCV7) serotypes were measured. None of these children had received PCV13. Against all six serotypes, the immunoglobulin G (IgG) levels of the study patients were lower than those were of age-matched healthy controls. Children who received chemotherapy within 6 months prior to sample collection, had lower serotype-specific IgG levels than those who did not. These findings indicate that many immunocompromised children not recommended for routine vaccination owing to their age group did not have PCV13 serotype-specific IgG levels that could prevent IPD. These results suggest that the vaccination with PCV13 is necessary for children at high risk of IPD.

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Introduction

Streptococcus pneumoniae is a Gram-positive diplococcus that causes respiratory tract infections such as pneumonia, acute otitis media, and sinusitis. *S. pneumoniae* can also cause fatal invasive infections, such as sepsis, bacteremia, and bacterial meningitis, regardless of treatment with appropriate antibiotics. The heptavalent pneumococcal conjugate vaccine (PCV7), licensed and approved for universal use in the United States in 2000, was first introduced in Japan in February 2010. The approved immunization schedule has been described as a 3＋1 schedule, consisting of three doses for the primary series and one booster injection. This vaccine was introduced in April 2013 for universal use in children aged ＜5 years, resulting in a markedly reduced incidence of invasive pneumococcal disease (IPD). Following the introduction of PCV7 in Japan, the incidence of IPD-associated non-meningitis in children aged ＜5 years had decreased 56% and the incidence of meningitis had decreased 61%[1]. However, because the incidence of IPD caused by non-PCV7 serotypes increased since the introduction of PCV7, PCV7 was replaced in November 2013 by the 13-valent pneumococcal conjugate vaccine (PCV13), which covers an additional six serotypes.

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommended routine PCV13 vaccination of children aged 6–18 years who had not received the vaccine previously and who had immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leakage, or cochlear implants[2]. Similarly, some European countries recommended routine PCV13 vaccinations of these children[3]. In Japan, PCV13 is routinely administered to children aged ＜5 years and adults aged ≥65 years. Regardless of the underlying conditions, PCV13 is not licensed for children aged ≥6 years. Our previous survey described 26 children aged ≥6 years with IPD in Chiba prefecture, Japan, with 69% having underlying diseases, especially malignancy[4]. These results indicated that children in this age group, not routinely vaccinated with PCV13, were at high risk for underlying diseases of IPD. However, little is known about their immunity to PCV13 pneumococcal serotypes not present in PCV7. To assess the need for PCV13 vaccination of children aged 5–18 years not routinely recommended for PCV13 vaccination, this study measured levels of pneumococcal serotype-specific immunoglobulin G (IgG) against serotypes present in PCV13 but not in PCV7.

Materials and Methods

Surplus serum samples from routine blood examinations were collected between January and May 2015 from children aged 5–18 years who were being followed up for hematological neoplasms or solid tumors in remission at Chiba University Hospital, Japan. The patients who had previously received intravenous immunoglobulin within 6 months of the study were ex-

cluded. Serum concentrations of IgG directed against the pneumococcal serotypes 1, 3, 5, 6A, 7F, and 19A, which are present in PCV13 but not in PCV7, were measured using WHO-approved enzyme-linked immunosorbent assays[5]. An IgG level ≥0.35 μg/mL was defined as positive, in accordance with WHO recommendations[6]. Individual serotype-specific IgG levels in these children were compared with those in non PCV vaccinated healthy children (N＝100, age range: 6–19 years) previously described[7]. Patients background, such as age, sex, underlying conditions, PCV vaccine history, treatment history were extracted from the medical records.

Statistical analysis was done using StatView version 5.0 (SAS Institute Inc., Cary, North Carolina, USA). We used the Mann-Whitney U tests for comparing the geometric mean concentrations (GMCs) of IgGs against serotypes and the Fisher's exact test for comparing the rates of positive IgG levels. Differences with a p value <0.05 were considered statistically significant.

This study was approved by the research ethics committee of Chiba University (No. 1964) and written informed consent was obtained from the children and/or their legal guardians.

Results

Patient characteristics

Forty-one patients (24 boys, 17 girls; median age, 12 years) were included in this study. Their underlying diseases included leukemia (56%), lymphoma (12%), solid tumors (27%), and other hematopoietic neoplasms (5%). Nine of the 41 patients (22%) had received PCV7, and one had received the 23-valent pneumococcal polysaccharide vaccine (PPSV23), but none had received PCV13. Twelve patients (29%) had undergone chemotherapy within 6 months, and six patients (15%) had a history of hematopoietic stem cell transplantation (HSCT) (Table 1).

Serotype-specific IgG levels

Serotype-specific IgG levels are shown in Figure 1. The geometric mean concentrations (GMCs) of IgGs against serotypes 1, 3, 5, 6A, 7F, and 19A were 0.75, 0.49, 0.81, 0.67, 0.35, and 1.59 μg/mL, respectively. In comparison, the GMCs of IgGs against these six serotypes in age-matched healthy Japanese children had been reported to be 1.5, 1.39, 1.95, 2.07, 0.89, and 2.67 μg/mL, respectively[7], with the IgG levels against all six serotypes being significantly lower in the study patients than in the age-matched controls (Figure 1). When comparing among six serotypes, the GMC of IgG against serotype 7F was lower than others. In addition, lower percentages of study patients than of controls had positive IgG levels (≥0.35 μg/mL) against the six serotypes (Table 2). The serotype-specific IgG levels of study patients did not correlate with their total IgG levels.

Table 1. Patient characteristics (N: 41, Age: range, 5–18 years; median, 12 years)

		N	(%)
Sex	Male	24	(59)
Underlying diseases	Leukemia	23	(56)
	Lymphoma	5	(12)
	Solid tumor	11	(27)
	Other	2	(5)
Siblings	(+)	32	(78)
Total IgG（μg/mL） (35 patients' data)	>500	35	(85)
Vaccine history	PCV13 (-)	41	(100)
	PCV7 (-)	32	(78)
	PCV7 (+)	9*	(22)
Treatment history	Chemotherapy within 6 months	12	(29)
	History of hematopoietic stem cell transplantation	6	(15)

*four doses：1, three doses：0, two doses ：1, one dose：7

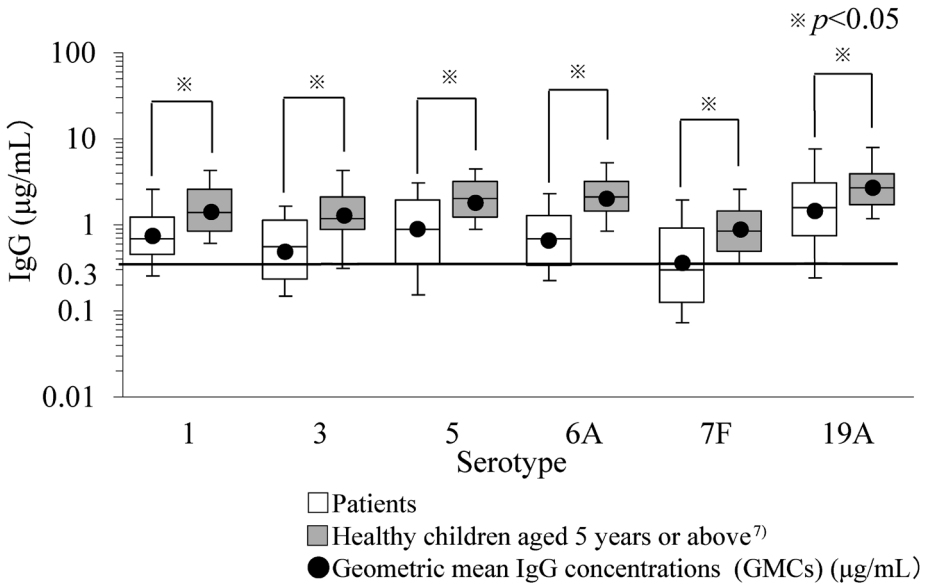
Effects of chemotherapy and transplantation on serotype-specific IgG levels

We compared of IgG levels from patients who did and did not receive chemotherapy within 6 months prior to sample collection, and who did and did not have the history of HSCT. Twelve patients received chemotherapy and their serotype-specific IgG levels could have been lower, but there were no statistically significant difference against all serotypes (Figure 2). Six children had a history of HSCT (mean time after transplant, 39 months). The serotype-specific IgG levels of them were higher than those of non-HSCTs but the number of these patients was too small to use statistical analysis (Figure 3). No other specific factors were found to influence the levels of serotype-specific IgG.

Discussion

Several studies have shown that people with immunocompromising conditions are at risk of IPD[8–11], as are children with immunocompromising conditions such as hematopoietic neoplasms[12]. Chemotherapy has a negative effect on the immune system, which may lead to the loss of specific antibodies and immunological memory against pathogens. For example, specific IgG levels against every PCV7 serotype were found to be lower in 53 children aged 8–18 years with acute

Fig. 1. Pneumococcal serotype-specific IgG levels in study patients (N＝41) and healthy children (N＝100)



The transverse line at 0.35 is the cut-off value for positive pneumococcal serotype-specific IgG level. Against all 6 serotypes, the IgG levels of the study patients were significantly lower than those of age-matched healthy Japanese children ($p<0.05$).

Table 2. Rates of positive IgG levels (%)

Serotype	1※	3※	5※	6A※	7F※	19A※
Patients	88	71	76	73	42	88
Healthy children[7)]	100	99	100	100	91	100

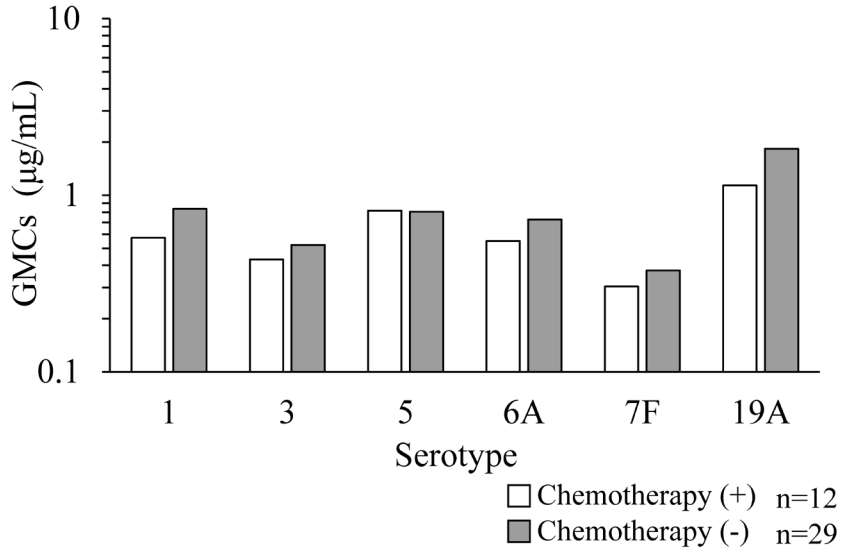
※ $p<0.05$

The percentages of positive IgG levels (≥0.35 μg/mL) of study patients and controls against the six serotypes. In all serotypes, the positive rates of the study patients were significantly lower than those of age-matched healthy Japanese children.

lymphoblastic leukemia 9 months after the completion of maintenance chemotherapy than in age-matched unvaccinated healthy controls[13)].

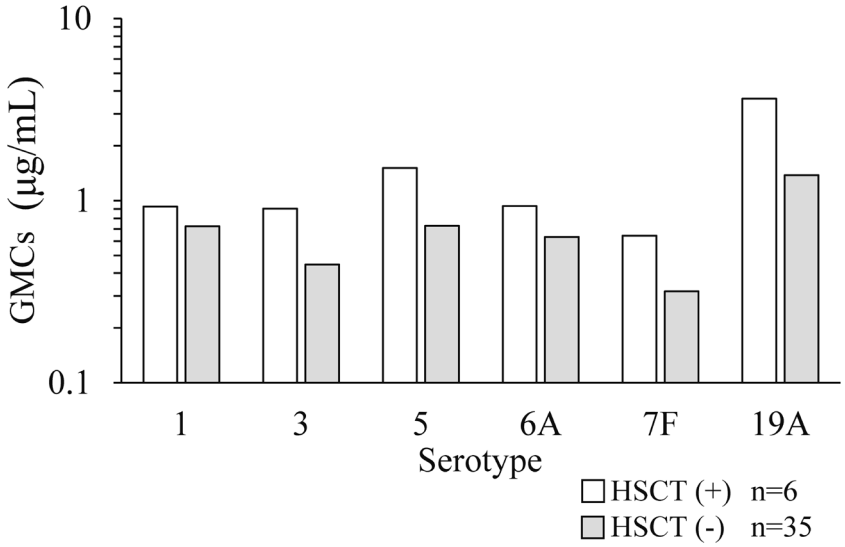
While the incidence of IPD due to PCV7 serotypes has decreased, the incidence of IPD due to PCV13 serotypes has increased, especially to serotype 19A[1)]. The immunity to PCV13 serotypes in immunocompromised children has not been clarified. A study of PCV13 serotype-specific IgG levels in 39 children with cancer aged 1–18 years within 12 months after completing chemotherapy, found that the rates of positive IgG levels were below 50% for eight of 12 serotypes[14)]. However, that study included patients previously immunized with PCV13 and did not

Fig. 2. Geometric mean concentrations (GMCs) of serotype-specific IgG in children who did and did not receive chemotherapy within 6 months



Serotype-specific IgG levels were lower in patients with (white bars) than without (gray bars) a history of chemotherapy within 6 months but there were no statistically significant difference against all serotypes.

Fig. 3. Geometric mean concentrations (GMCs) of serotype-specific IgG in children who did and did not undergo hematopoietic stem cell transplantation (HSCT)



Serotype-specific IgG levels were higher in patients with (white bars) than without (gray bars) a history of HSCT but there were no statistically significant difference against all serotypes.

clarify the interval after chemotherapy.

In our study, 62% of the patients were assessed ≥6 months after completing chemotherapy, and none had been previously immunized with PCV13. To our knowledge, this is the first study

to show that IgG levels in Japanese immunocompromised children are low against PCV13 (non-PCV7), as well as PCV7, serotypes.

Our study confirmed that the rates of positive IgG levels in children with hematological neoplasms and solid tumors who were outside recommended ages for routine PCV13 vaccination were lower than those in healthy unvaccinated children. Based on the results, PCV13 vaccinations may be important for patients with them even if their ages are outside the range recommended for routine vaccination. Other studies have reported that PCV vaccination of immunocompromised patients outside the routine age range is both safe and effective[15–19]. This study provides evidence of such PCV vaccinations.

Moreover, we found that the levels of IgG against serotype 7F were lower than those against other serotypes. We considered that this result was due to a lower frequency of natural exposure to this serotype[20] and because serotype 7F is not a common cause of IPD in Japan[21].

Humoral immunity has been reported to recover approximately 6 months after completing chemotherapy[22]. Our study found that the GMCs and the rates of positive IgG levels were lower in patients with a history of chemotherapy within 6 months before the study. These findings suggested that the ability to produce antibodies had not recovered completely in these patients.

Conditioning chemotherapy regimens before HSCT have been found to eliminate immunocompetent cells, reducing pneumococcal-specific antibody titers to below preventable levels within 6–12 months[23]. Our results showed that post-HSCT patients had higher antibody titers. However, our study included a small number of patients who had undergone HSCT, indicating a need for future studies that include larger numbers of patients.

PPSV23 has also been recommended for children aged ≥2 years who are at high risk of pneumococcal disease[2]. The ACIP has recommended that immunocompromised children receive a single PCV13 dose, followed by a dose of PPSV23 ≥8 weeks later and a second PPSV23 dose 5 years after the first PPSV23 dose[24]. Despite similar recommendations in Japan, only one patient in this study received PPSV23. People need to be made aware of immunization.

The major limitation of this study was that we did not use serotype-specific opsonophagocytic assays. To further evaluate protective immunity, opsonization activities (OPAs) should also be examined. In some cases, serotype-specific IgG levels did not correlate with the OPA results[25].

In conclusion, we measured pneumococcal serotype-specific IgG levels against PCV13 serotypes in children with hematopoietic neoplasms who were not recommended to receive routine vaccinations owing to their age. Many of these children did not have sufficient IgG concentrations to prevent IPD. This study suggested that high-risk children in Japan may require vaccination with PCV13.

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Conflicts of Interest

All other authors report no potential conflicts of interest.

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