Successful discontinuation of immunoglobulin G replacement at age 10 in a patient with immunoglobulin G2 deficiency

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Abstract

Context: Immunoglobulin G2 deficiency that persists beyond the age of 6 years is likely to be permanent.

Case report: We report on a young Japanese female, diagnosed as having immunoglobulin G2 deficiency and low anti-pneumococcal immunoglobulin G2 antibody levels when 3 years old, with a subsequent medical history of frequent respiratory infections and asthma. Monthly intravenous immunoglobulin replacement therapy was started at 4 years of age. After 8 years of age, an anti-pneumococcal immunoglobulin G2 trough level could be maintained with administration intervals longer than 6 weeks, and after 9 years and 10 months of age, therapy was discontinued. The frequency of hospital admissions was reduced by the introduction of the replacement therapy (from 8.4 times/year before the introduction to 1.1 times/year during the therapy). The patient was also able to discontinue daily medications for asthma, and serum immunoglobulin G2 was maintained at a normal level even after the cessation of replacement therapy.

Conclusion: Termination of immunoglobulin replacement therapy in a patient with a symptomatic immunoglobulin G2 deficiency is possible, even for a child older than 6 years.

Keywords

Immunoglobulin G2 subclass deficiency, specific polysaccharide antibody deficiency, anti-pneumococcal immunoglobulin G2

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Introduction

The level of serum immunoglobulin G2 (IgG2), a major component of antibodies to polysaccharide antigens, such as Streptococcus pneumoniae and Haemophilus influenzae type b, reaches adult values much later than IgG1 and IgG3, but many individuals with IgG subclass deficiencies are asymptomatic. The clinical presentations in patients with IgG deficiency include recurrent sinopulmonary infections, otitis media, and, rarely, sepsis and meningitis, but other patients have recurrent or chronic bacterial infections, usually of the respiratory tract. Also, IgG2 subclass deficiency seems to be associated with asthma and chronic obstructive pulmonary disease (COPD).

If the condition persists beyond the age of 6 years, it is likely to be permanent. Herein, we describe a girl with IgG2 deficiency who was provided with immunoglobulin replacement therapy since she was 4 years old, but therapy was no longer required beyond the age of 10 years.

Case

A young female patient 5 years and 4 months of age was referred to the Pediatric Infectious Disease Clinic at Keio University Hospital (Tokyo, Japan) for follow-up management of IgG2 deficiency. Previously, this patient had more than 30 admissions for respiratory infections with or without asthma. She received inhaled steroid and beta-stimulants, and oral or intravenous theophylline, but was not intubated nor intensive care unit (ICU)-managed. She stayed for several days to 3 weeks for each admission from 6 months...
of age until 3 years and 11 months of age, when she was diagnosed with IgG2 deficiency and specific polysaccharide antibody deficiency, due to low serum IgG2 (57.4 mg/dL, with 58.5–292.1 mg/dL representing ±1.96 standard deviation (SD) range for healthy Japanese children 2–4 years old7) and low anti-pneumococcal (PC) IgG2 (0.7 µg/mL, with 4.3 µg/mL representing an average level for healthy children 1–2 years old8). Other IgG subclasses and IgG, the patient was 9 years and 10 months old. The level of anti-
ment therapy because the anti-PC IgG2 level was being ade-
shown in Figure 1. We then considered stopping the replace-
noglobulin administration and anti-PC IgG2 trough levels is
(moving average for two previous intervals) between immu-
mental and physical stress. The relation between the intervals
age, and the frequent visits to the hospital caused the patients
because IgG2 would usually recover spontaneously at this
When the patient first visited our clinic, she was afebrile
and in apparent good health, with no remarkable findings on
physical exams (height, 114.3 cm (90–97 percentile) and body
weight, 19.5 kg (75–90 percentile) at 5 years and 4 months). She
continued receiving intravenous treatment with 5 g/dose of
immunoglobulin (polyethylene glycol treated human
immunoglobulin, currently named “Kenketsu
Venoglobulin-IH®”; Japan Blood Products Organization) for
her 19.5 kg body weight, in a regimen aiming to maintain a
minimum anti-PC IgG2 trough level of 4.3 µg/mL. We tried
to increase the length of time between administrations
because IgG2 would usually recover spontaneously at this
age, and the frequent visits to the hospital caused the patients
mental and physical stress. The relation between the intervals
(moving average for two previous intervals) between immu-
oglobulin administration and anti-PC IgG2 trough levels is
shown in Figure 1. We then considered stopping the replace-
ment therapy because the anti-PC IgG2 level was being ade-
quately maintained even at intervals longer than 6 weeks after
the age of 8 years, and the final dose was administered when
the patient was 9 years and 10 months old. The level of anti-
PC IgG2 fluctuated somewhat thereafter, but increased to
5.2 µg/mL at 14 years and 9 months of age. The most recent
evaluation, at 18 years 9 months of age, showed a spontane-
ous elevation to 11.0 µg/mL. The last data evaluated at
18 years 9 months old were as follows: IgG1, 1083 mg/dL;
IgA, 178 mg/dL; IgM, 77 mg/dL; IgG1, 617 mg/dL; IgG2,
361 mg/dL, IgG3, 26.2 mg/dL; and IgG4, 20.6 mg/dL. The
IgG2 value was the highest among those measured and was
within normal adult range (208–754 mg/dL). The total IgE
was as high as 940 U/mL. She was never immunized with either pneumococcal polysaccharide or conjugate vaccine, which had not been introduced in Japan. The frequencies of hospital admission due to respiratory problems decreased soon after the replace-
ment therapy was started (Table 1).

Discussion
Recent data from a cohort of 13 patients in a Canadian
immunology clinic suggest that a condition of low IgG2 lev-
el may completely resolve within 0.6–6 years (median:
1.5 years).1 In this cohort, one patient recovered at 10 years
of age, but this patient had recurrent diarrhea rather than
recurrent respiratory infections, had no antibiotic prophy-
laxis or immunoglobulin replacement therapy, and had no
major invasive infection during the follow-up period.2 Thus,
ours is the first detailed report of a patient with IgG2

![Figure 1. Relationship between intravenous immunoglobulin (IVIG) replacement intervals and anti-pneumococcal IgG2 levels.](image-url)
deficiency with repeated respiratory infections who recovered at an age older than had been previously reported.

We believe the diagnosis of IgG2 deficiency was appropriate as the patients fulfilled the following criteria: (1) patient ≥2 and <18 years old, (2) serum IgG ≥4.0 g/L, and (3) one or more IgG subclasses (IgG1, IgG2, and/or IgG3) below age-related normal (<−2.0 SD).6,9 Although the reported case might not be, strictly speaking, IgG2 “deficiency” because of spontaneous resolution, we referred to the case as “IgG2 deficiency” as the outcome is not included in the case definition. We used the anti-PC IgG2 as a routine serum marker of the patient’s immune state and as a diagnosis for the following reasons. Because it is the only kit available in Japan on a commercial basis, its use has been introduced in an international journal,8 and the cost of determining anti-PC IgG2 levels was much lower than that for determining IgG subclass itself (approximately 22 vs 300 GBP in Japan, with neither expense covered by insurance at that time). IgG subclass (IgG2) as a routine serum marker was favorable, but anti-PC IgG2 might reflect the total IgG2, as the increase in the IgG2 concentration was reflected by improved antibody responses to Streptococcus pneumoniae immunizations.1

In Japan, immunization more than twice with a polysaccharide vaccine was contraindicated until October 2009 because of possible adverse effects after repeated immunization. Therefore, she would have been unable to be re-immunized if she had received a dose at a younger age. Also, immunization with the polysaccharide vaccine to children (except among asplenic patients) was very uncommon. The pneumococcal conjugate vaccine was only relatively recently introduced in Japan, in April 2010, for children aged between 2 months and 9 years, and with our patient already 14 years of age, administration was considered off-label use and unnecessary. Since immunization using readily available vaccines was unavailable for our female patient, we instead relied on monitoring IgG2 and anti-PC IgG2 levels over time.

The frequency of hospital admissions decreased in our patient after the initiation of the replacement therapy. Because the frequency decreased soon after the replacement therapy was started, we speculate that this was more attributable to the therapy than to spontaneous recovery due to her growth. It is not known why our case spontaneously recovered at a relatively advanced age. Ozen et al.10 evaluated 131 children with hypogammaglobulinemia and analyzed the predictor factors for outcome. In total, 15 patients with low IgG2 were included, and it was reported that persistence of hypogammaglobulinemia beyond 5 years could occur when the patients met at least one of the following criteria: low IgM between 2 and 5 years of age, low B-cell counts, and impaired antibody response to a pneumococcal polysaccharide vaccine. Our female patient had a normal IgM level at diagnosis at 3 years of age and normal B-cell counts at 6 years 5 months of age (no data available for <6 years). We do not know whether our case would have shown a normal antibody response to pneumococcal vaccine because she was never immunized. As our patient did not meet the first two of the above criteria, a good prognosis might have been predicted.

In conclusion, the history of our patient shows that someone with IgG2 deficiency and specific polysaccharide antibody deficiency who requires immunoglobulin replacement therapy may recover even at an age beyond 6 years. Additionally, the monitoring of anti-PC IgG2 trough levels can be useful as an indicator during the follow-up of patients with IgG2 deficiency.

### Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Masayoshi Shinjoh and Takao Takahashi have received research funds from Japan Blood Products Organization (current name).

### Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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### Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article, and verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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**Table 1. Admission frequency due to respiratory problems.**

| Period                          | Prior to Immunoglobulin replacement therapy | During Immunoglobulin replacement therapy | After completion of Immunoglobulin replacement therapy |
|--------------------------------|--------------------------------------------|------------------------------------------|------------------------------------------------------|
| Patient age, duration (months) | 6 months to 4 years (1 months (43))        | 4 years 1 months to 9 years 10 months (68) | 9 years 10 months to 15 years 8 months (70)          |
| Admission frequency, times     | 30                                         | 6                                        | 2                                                    |
| Annual hospital admission frequency, times/year | 8.4                                      | 1.1                                      | 0.3                                                  |

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