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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,[1] but many individuals with IgG subclass deficiencies are asymptomatic.[2] The clinical presentations in patients with IgG deficiency include recurrent sinopulmonary infections, otitis media, and, rarely, sepsis and meningitis,[1] but other patients have recurrent or chronic bacterial infections, usually of the respiratory tract. Also, IgG2 subclass deficiency seems to be associated with asthma[3,4] and chronic obstructive pulmonary disease (COPD).[5]

If the condition persists beyond the age of 6 years, it is likely to be permanent.[1,6] 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

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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 old[7]) 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 old[8]). Other IgG subclasses and IgG, IgA, and IgM, were within normal range (IgG1, 475.4 mg/dL; IgG3, 27.7 mg/dL; IgG4, 1.2 mg/dL; IgG, 526–562 mg/dL; IgA, 36 mg/dL; and IgM, 121 mg/dL). The total IgE was as low as 120 U/mL, but there were positive reactions to dog skin and mites. The antibody responses to measles vaccination and varicella infection were normal. Concerning her respiratory infections, the specifics of any associations with pneumococcal or *Haemophilus* infections were unknown. Her growth and mental development were normal. At the age of 4 years and 1 month, intravenous immunoglobulin replacement therapy was started at a dose of 5 g/dose (body weight 16 kg) at 4-week intervals. Concomitantly, the patient took daily medications for asthma that contained no inhaled or oral steroids but contained a leukotriene receptor antagonist.

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 normal 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 immunoglobulin administration and anti-PC IgG2 trough levels is shown in Figure 1. We then considered stopping the replacement therapy because the anti-PC IgG2 level was being adequately 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 spontaneous elevation to 11.0 µg/mL. The last data evaluated at 18 years 9 months old were as follows: IgG, 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 1300 U/mL, but she no longer had allergic symptoms. Her height was 164.7 cm (90–97 percentile) and her body weight was 61.2 kg (90–97 percentile). She had become a full-time university student.

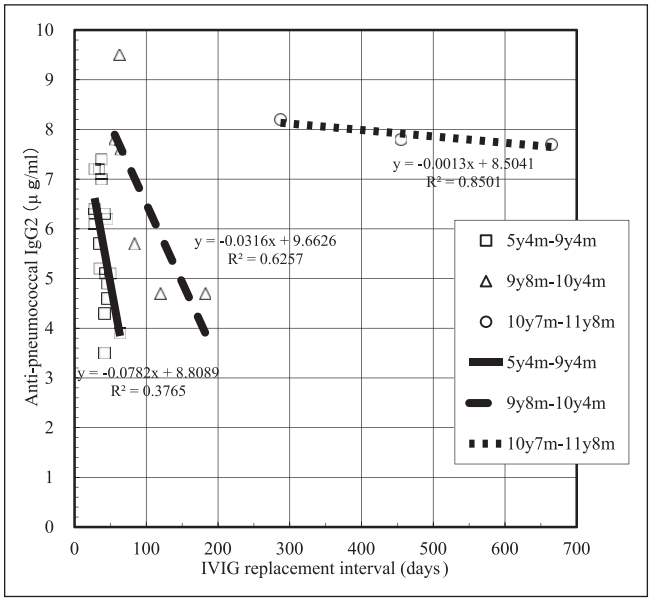

Figure 1. Relationship between intravenous immunoglobulin (IVIG) replacement intervals and anti-pneumococcal IgG2 levels.

During the follow-up period, other immunological tests such as lymphocyte subsets were normal: lymphocyte counts, 3677/µL; CD3+, 2685/µL (73% of lymphocytes); CD4+, 1692/µL (46%); CD8+, 809/µL (22%); CD19+, 625/µL (17%); and CD3-CD16+56+ cell counts, 294/µL (8%) (at 6 years 5 months of age). Lymphocyte proliferation in response to phytohemagglutinin and complements were normal. Dilation of part of the bronchial tree on chest computed tomography (CT) was transient. Daily medications for asthma were not needed after the patient turned 11 years old. Although she had been diagnosed with atopic dermatitis since 6 years of age, she recovered spontaneously at around the same period, although 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 replacement 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 levels may completely resolve within 0.6–6 years (median: 1.5 years).[3] 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 prophylaxis or immunoglobulin replacement therapy, and had no major invasive infection during the follow-up period.[3] Thus, ours is the first detailed report of a patient with IgG2

Table 1. Admission frequency due to respiratory problems.

Period	Prior to	During	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

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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