

IgG subclass deficiency and anti-pneumococcal IgG2 in Japanese children with recurrent infection

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Abstract

Immunoglobulin G and subclass levels were measured in 88 children with recurrent infection to determine risk of recurrent infection. Levels of specific IgG2 against *Streptococcus pneumoniae* showed a significant correlation with total IgG2. An IgG2 test was performed in the 88 patients with recurrent infection. In the group whose IgG2 showed less than 80 mg/dL, 3 out of 6 (50%) had levels of greater than 1 µg/mL of specific IgG2 against *S. pneumoniae*. In the group whose IgG2 levels ranged from 80 to 100 mg/dL, 4 out of 7 children showed less than significant levels of specific IgG2 against *S. pneumoniae*. On the other hand, among 15 patients whose total IgG2 levels were less than 80 mg/dL, only 6 showed recurrent infection with otitis media and/or pneumonia. These results indicate the need to measure levels of specific IgG2 against *S. pneumoniae* to determine the immunological state in children with recurrent infection.

Introduction

Immunoglobulin G is subtyped into 4 subclasses : G1, G2, G3, and G4. The concentration is in the order of G1 > G2 > G3 > G4. Immunoglobulin G subclass deficiency is an immunodeficiency disease accompanied by repeated bacterial infection¹⁻³⁾. Replacement therapy with intravenous immunoglobulin (IVIG) for IgG subclass deficiency has been covered by health insurance in Japan since 2015. Immunoglobulin G subclass deficiency does not show low total IgG values in all cases, and specific IgG responses to specific bacteria vary. Immunoglobulin G2, in particular, is important in the defense against infection with capsular bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Patients with IgG2 deficiency are vulnerable to frequent infections with pneumonia and otitis media⁴⁾⁵⁾. On the other hand, some patients show only loss of *S. pneumoniae*-specific IgG2 and normal levels of total IgG2.

These patients cannot produce specific IgG2 and show an increase in susceptibility to infection. Several genomic studies have discussed these B cell abnormalities⁶⁾⁷⁾. In Japan, the 3 indications for IVIG in IgG subclass deficiency include a serum IgG2 level of less than 80 mg/mL ; two or more occurrences of acute bronchitis or pneumonia within the past 6 months ; 4 or more occurrences of otitis media ; and identification of *S. pneumoniae* or *H. influenzae*. The purpose of this study was to investigate IgG subclass and anti-pneumococcal IgG2 in children with recurrent infection to determine the proper indication for replacement therapy using IVIG.

Study participants

A total of 88 unvaccinated patients with recurrent infection were enrolled in the study ; all were aged under 15 years, before the time for periodic inoculation with the pneumococcal vaccine. In addition, 15 patients with low concentrations of IgG2 aged 4 months to 3 years

Received October 11, 2017, Accepted June 20, 2018

Key words : *Streptococcus pneumoniae*, IgG2, IgG subclass

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who were suspected as having an immunodeficiency were also enrolled.

The study protocol was approved by the Research Ethics Committee of Tokyo Medical University (Permission number : 3844).

Materials and methods

IgG subclasses were measured by sandwich ELISA as reported by Hayashibara et al⁸⁾. Anti-pneumococcal IgG2 levels were measured by sandwich ELISA as reported by Kojima et al⁹⁾. The component vaccine of Pneumovax[®] (*S. pneumoniae* vaccine) was fixed as the antigen. The passable level of defense was appri-

mately 1-2 µg/mL⁹⁾. For the statistical analysis, a *t* test was used to compare total IgG2 with specific IgG2 for *S. pneumoniae*. *P* values that were less than 0.05 were considered to indicate statistical significance. The statistical analysis was performed with Statcel software (OMS, Saitama, Japan).

Results

Specific IgG2 levels against *S. pneumoniae* showed a significant correlation with total IgG2 in the 88 healthy unvaccinated controls (correlation ratio, 0.698), as shown in Fig. 1. Specific IgG2 levels against *S. pneumoniae* showed no correlation with age (Fig. 2). Table 1 shows

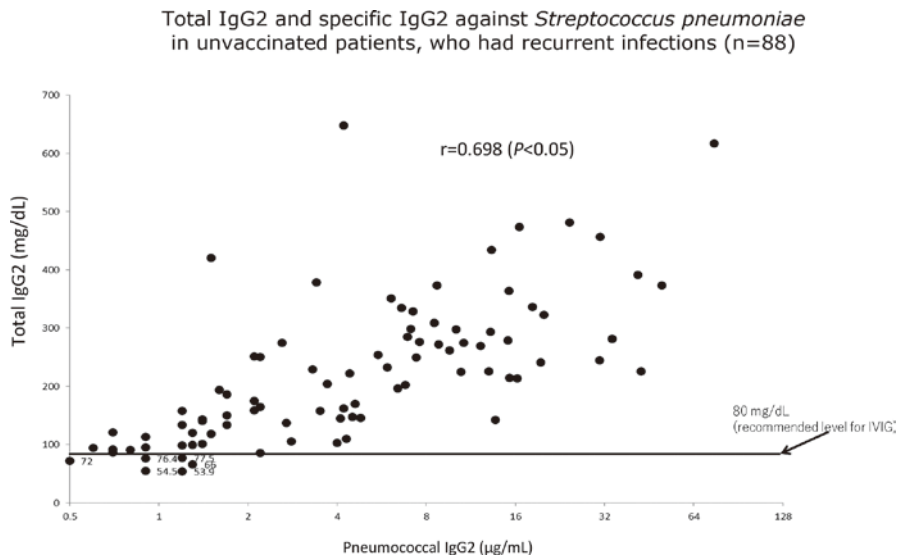


Fig. 1 Total IgG2 and specific IgG2 against *Streptococcus pneumoniae* in 88 unvaccinated patients with recurrent infection (*n* = 88).

Recurrent infection was defined as 2 or more lower respiratory infections, or 4 or more otitis media, within 6 months.

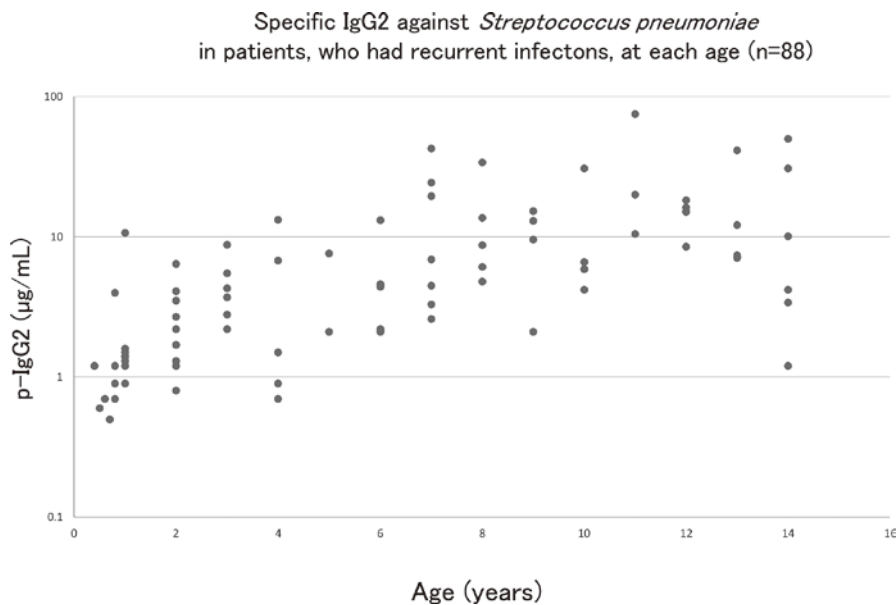


Fig. 2 Specific IgG2 against *Streptococcus pneumoniae* in patients with recurrent infection at each age (*n* = 88). Specific IgG2 against *Streptococcus pneumoniae* showed no correlation with age.

the data for those with low levels of total IgG2 of less than 100 mg/dL. In the group whose IgG2 showed levels of less than 80 mg/dL, 3 of 6 children (50%) had lev-

els of greater than 1 µg/mL of specific IgG2 against *S. pneumoniae*. On the other hand, in the group whose IgG2 levels ranged from 80 to 100 mg/dL, 4 of 7 children showed less than significant levels of specific IgG2 against *S. pneumoniae* (Table 1). There were 2 cases that showed less than 1 µg/mL of specific IgG2 against *S. pneumoniae* in the group whose total IgG2 showed levels greater than 100 mg/dL. Among 15 patients whose total IgG2 levels were less than 80 mg/dL, only 6 showed recurrent infection with otitis media and/or pneumonia (Table 2).

Table 1 Patients with low levels of total IgG2

Number	Status	Age (years, months)	p-IgG2 (µg/mL)	IgG2 (mg/dL)
1	healthy	5 m	1.2	53.9
2	healthy	9 m	0.9	54.5
3	healthy	2 y	1.3	66
4	healthy	8 m	0.5	72
5	healthy	4 y	0.9	76.4
6	healthy	10 m	1.2	77.5
7	healthy	6 y	2.2	85.8
8	healthy	10 m	0.7	86.4
9	healthy	2 y	0.8	91
10	healthy	7 m	0.7	91.5
11	healthy	6 m	0.6	94.2
12	healthy	14 y	1.2	98.4
13	healthy	1 y	1.3	99.4

Unvaccinated patients with low total IgG2 levels (< 100 mg/dL) and recurrent infections. Patients with p-IgG2 less than 1 µg/mL and those with IgG2 below 80 mg/dL are marked.

Discussion

The mechanism underlying selective IgG subclass deficiency is largely unknown in humans. Intravenous immunoglobulin is mainly recommended in addition to antibiotics and anti-viral drugs for IgG subclass deficiency¹⁰⁾. However, the present study demonstrated that this may not be appropriate in patients with recurrent disease. Some children with normal levels of total immunoglobulin and total IgG2 can have a defect in the production of specific immunoglobulin.

Although levels of specific IgG2 against *S. pneumoniae* showed a significant correlation with total IgG2 in

Table 2 Children with IgG2 < 80 mg/dL

No	Age	Otorhinolaryngology history	Disease	>4 times /6 m OMA	>2 times /6 m lower respiratory infections	Pneumococcal vaccine (times)	IgG	IgG1	IgG2	IgG3	IgG4	IgA	IgM
1	4 m	+	Emanuel syndrome	-	+(GERD)	1	223	122	50.5	16.0	6.0	10	78
2	5 m	+	Acute bronchitis, OMA	+	+	0	527	305	62.8	72.7	<3.0	64	101
3	7 m	-	Kawasaki disease suspected	-	-	3	183	228	46.4	29.2	<3.0	14	24
4	7 m	+	Pneumonia	-	+	3	276	160	31.1	13.4	<3.0	21	77
5	7 m	+	Asthmatic bronchitis	-	+	Unknown	889	505	78.0	120	7.6	60	127
6	8 m	-	Immunodeficiency suspected	-	-	3	254	143	45.8	15.7	4.5	27	26
7	8 m	-	Acute viral infections	-	-	3	583	342	43.5	34.5	9.5	18	77
8	10 m	-	Immunodeficiency suspected	-	-	3	215	137	45.6	25.6	10.1	15	58
9	1 y	-	Hypothyroidism	-	-	3	337	222	74.8	14.0	<3.0	34	72
10	1 y	+	OMA	+	-	0	693	444	63.5	83.0	5.5	38	97
11	1 y	+	Immunodeficiency suspected	+	-	3	918	609	78.8	34.3	15.1	62	77
12	1 y	-	Upper respiratory infection	-	-	Unknown	463	307	60.2	43.9	<3.0	30	98
13	1 y	-	Hypothyroidism suspected	-	-	0	688	396	74.1	52.3	<3.0	24	68
14	1 y	-	Pneumonia	-	-	Unknown	376	254	37.9	55.6	<3.0	34	50
15	2 y	+	Kawasaki disease suspected	-	-	1	399	256	72.7	10.1	<3.0	40	60

These patients were extracted from among 88 with recurrent infection based on low total IgG2 levels.

GERD, gastroesophageal reflux ; F.U.O., fever unknown origin ; OMA, otitis media acute low level

the present study, no such correlation was observed at low levels of IgG2. Moreover, only 6 out of 15 patients whose total IgG2 levels were less than 80 mg/dL showed recurrent infection with otitis media and/or pneumonia. These results suggest that specific IgG2 against *S. pneumoniae* needs to be measured to determine the immunological state of children with recurrent infection.

Pneumococcal-specific IgG2 cannot be produced in patients with deficiency in specific immunocompetence. Therefore, 80 mg/dL of IgG2 should be considered as a rough indication for treatment with IVIG.

Recurrent respiratory infection is associated with chronic pulmonary damage¹¹⁾. There is a high risk for bacterial meningitis, which might induce irreversible sequelae¹²⁾. Moreover, bronchial asthma and several autoimmune diseases are commonly associated with subsequent upper and lower respiratory infections¹³⁾. Therefore, IVIG should be started early under a precise diagnosis.

Competing financial interests

This work was not supported by any grant, and there was no conflict of interest associated with this study.

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感染を繰り返す日本人小児における IgG サブクラス欠損と IgG2 肺炎球菌抗体

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【要旨】 今回、我々は感染を繰り返した 88 人の児に対してそのリスクを比較する目的で IgG およびそのサブクラスを測定した。肺炎球菌特異的 IgG2 抗体の値は総 IgG2 と有意に相関している。しかし、総 IgG2 が 80 mg/dL 未満の群では、6 人中 3 人 (50%) が肺炎球菌特異的 IgG2 抗体は 1 µg/mL より多く、80-100 mg/dL の群では 7 人中 4 人 (57%) が低値を示した。また、15 人の総 IgG2 が 80 mg/dL 以下であった患者の中で、6 人が中耳炎や肺炎を繰り返した。この結果から、感染を繰り返す小児や総 IgG2 の低い患児において肺炎球菌特異的 IgG2 を測定する事は、重要と考えられる。

〈キーワード〉 肺炎球菌、IgG2、IgG2 サブクラス
