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Specific Antibody Deficiency in Adult Patients With IgG or IgG Subclass Deficiency

Joo-Hee Kim,[1] **Jae-Hyuk Jang**,[2] **So-Hee Lee**,[2] **Eun-Mi Yang**,[2] **Seung Hun Jang**,[1] **Ki-Suck Jung**,[1] **Hae-Sim Park**[2*]

[1]Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea
[2]Department of Allergy & Clinical Immunology, Ajou University School of Medicine, Suwon, Korea

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Correspondence to
Hae-Sim Park, MD, PhD
Department of Allergy and Clinical Immunology, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon 16499, Korea.
Tel: +82-31-219-5000
Fax: +82-31-216-6380
E-mail: hspark@ajou.ac.kr

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ORCID iDs
Joo-Hee Kim
https://orcid.org/0000-0002-1572-5149
Jae-Hyuk Jang
https://orcid.org/0000-0002-4225-7117
So-Hee Lee
https://orcid.org/0000-0001-7124-9434
Eun-Mi Yang
https://orcid.org/0000-0001-8371-3513
Seung Hun Jang
https://orcid.org/0000-0001-5457-5780
Ki-Suck Jung
https://orcid.org/0000-0002-6878-6543

ABSTRACT

Purpose: Specific antibody deficiency (SAD) involves a deficient response to a polysaccharide vaccine despite having normal immunoglobulin levels. The failure of the polysaccharide response can be observed as a component of various primary antibody deficiencies. However, only a few studies have described the clinical and immunological profiles in SAD and/or other primary immunodeficiencies (PIDs) in adults.
Methods: A total of 47 patients who had a clinical history suggestive of antibody deficiency or had already been diagnosed with various antibody deficiencies were enrolled. Polysaccharide responses to 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) were measured using the World Health Organization enzyme-linked immunosorbent assay (WHO-ELISA), and postvaccination immunoglobulin G (IgG) titers were compared to clinical and laboratory parameters.
Results: Based on the American Academy of Allergy, Asthma, and Immunology (AAAAI) criteria for the WHO-ELISA, 11 (23.4%) patients were diagnosed as having SAD. Sixteen-three percent of them had combined with other types of PID, such as IgG subclass deficiency and hypogammaglobulinemia. Postvaccination IgG titers for the serotypes 4/9V/18C correlated with IgG2 ($P = 0.012$, $P = 0.001$, and $P = 0.004$) and for 6B/9V/14 with IgG3 ($P = 0.003$, $P = 0.041$, and $P = 0.036$, respectively). The IgG3 subclass levels negatively correlated with forced expiratory volume in 1 second (FEV1, %) and FEV1/forced vital capacity ($P < 0.001$ and $P = 0.001$, respectively).
Conclusion: SAD can be diagnosed in patients with normal IgG levels as well as in those deficient in IgG or the IgG3 subclass, implicating that restricted responses *to Streptococcus pneumoniae* polysaccharide antigens commonly exist in patients with predominantly antibody deficiency.

Keywords: Adult; asthma; IgG; pneumococcal vaccines; antibodies; immunologic deficiency syndromes; infection

INTRODUCTION

Specific antibody deficiency (SAD) has been described as the inability to mount an antibody response to purified *Streptococcus pneumoniae* capsular polysaccharide antigens in the presence

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Hae-Sim Park
https://orcid.org/0000-0003-2614-0303

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of normal immunoglobulin concentrations.[1,2] The typical signs and symptoms of SAD are recurrent respiratory tract infections, such as otitis media, bronchitis, and pneumonia. SAD can be observed in patients with an otherwise intact immune system or be present with other primary immunodeficiency diseases (PIDs). Several abnormalities in the production of anti-polysaccharide antibodies have been described in patients with immunoglobulin G (IgG) subclass deficiency (IGGSD).[3,4]

IGGSD is defined as a decrease in the levels of one or more of the IgG subclasses with normal levels of IgG and IgM. Decreased or subnormal IgG2 or IgG3 levels are common in the cohorts of children and adults, and chronic airway diseases, such as asthma or allergic rhinitis, are common comorbidities in these cohorts.[5,6] As IgG antibody responses to bacterial capsular polysaccharide antigens are mostly restricted to IgG2, patients with IgG2 deficiency may be more susceptible to infections with *Hemophilus influenzae* or *S. pneumoniae*.[7] Several studies have suggested that IgG3 is important in the primary response to various infections.[8,9] IgG3 has the ability to activate subsequent host immune responses, such as complement pathways, Fcγ receptor-mediated immune responses, and antibody-dependent cellular cytotoxicity, which contribute to the elimination of viral pathogens, and some reports suggest that IgG3 has the strongest effector functions among all IgG subclasses.[10,11]

Hypogammaglobulinemia (HGG) refers to the condition of patients with decreased IgG levels but normal cellular immunity who do not fulfill the diagnostic criteria for other antibody deficiencies. Symptomatic patients with HGG experience decreased quality of life, infectious complications and increased health care costs; however, the evaluation of the reduction in IgG levels is a challenge, as the diagnosis is exclusive and sometimes transient.[12] Furthermore, little is known about the natural history and long-term prognosis of HGG.

Although predominantly antibody deficiency (PAD) disorders have been estimated to be the most commonly identified PID globally, there have been only a few studies about the prevalence and clinical presentation of SAD and/or other antibody deficiencies, such as IGGSD and HGG.[13,14] Some patients with IGGSD exhibit impaired specific antibody production, predisposing them to having more recurrent respiratory tract infections.[6] Multiplex bead-based assays for specific IgG determination to pneumococcal capsular polysaccharide (PnP) are increasingly being utilized because of their ease of use, fast turn-around time, and low cost.[2] However, the results of multiplex assays do not correlate well with the standardized methods of the World Health Organization enzyme-linked immunosorbent assay (WHO-ELISA), so multiplex assays are not reliable tools for the evaluation of antibody responses to polysaccharide antigens.

Therefore, we performed this study to diagnose SAD based on the standardized method of the WHO-ELISA in a Korean adult population. Furthermore, we explored the prevalence of SAD in patients with other antibody deficiencies, such as IGGSD and HGG, and evaluated the clinical and immunological features in patients with SAD and/or underlying other PIDs.

MATERIALS AND METHODS

Study design

Patients were enrolled when they met the following inclusion criteria: (i) age older than 18 years; (ii) medical history suggestive of antibody deficiency (including recurrent lower

and upper respiratory tract infections, otitis with or without otorrhea, and skin/soft tissue/invasive bacterial infections), so that assessment of the anti-polysaccharide antibody response was indicated for the clinical care of the patients; and (iii) diagnosed with PADs such as IGGSD or HGG. We defined 'suspected PID' cases as those who met criteria (i) and (ii) and 'confirmed PID' cases as those who met criteria (i) and (iii). The exclusion criteria were as follows: (i) vaccination with a pneumococcal vaccine in the previous 5 years and (ii) previous allergic reaction to any vaccine. The Prodiax-23® vaccine (PPV23; MSD Korea, Seoul, Korea) was administered by intramuscular injection. A blood sample was obtained to determine baseline antibody titers against serotype for 4, 6B, 9V, 14, 18C, 19F and 23F at the time of injection, and 4–6 weeks later, a second blood sample was obtained for postvaccination antibody concentrations. Demographic and clinical information was collected by a physician via a standardized case record form. Pre- and postvaccination blood was separated by centrifugation, and serum was stored at − 20°C until simultaneous analysis of specific IgG. The study was approved by the ethical committee of the hospitals (AJIRB-MED-OBS-17-317; AJIRB-BMR-KSP-20-158; Hallym-2017-I115) and written informed consent was obtained from all patients.

Antibody response to PPV23

The response to PnP was tested in the immunogenetic facility at Ajou University Medical Center (Suwon, Korea) using the third-generation WHO-ELISA (the reference serotype-specific assay).[15,16] Titers of antibodies against 7 capsular serotypes were assessed before and 4 to 6 weeks after the administration of PPV23. The results were interpreted according to the guidelines issued in 2015 by the American Academy of Allergy, Asthma & Immunology (AAAAI) Working Group.[1] Briefly, a participant was considered to have an impaired response for a single serotype if the postimmunization antibody titer was below 1.3 μg/mL (considered to be protective) and/or did not achieve a 4-fold increase (relative to the preimmunization value). A 2-fold increase was acceptable if the initial titer was already above 1.3 μg/mL. Patients were classified as having a mild, moderate, or severe severity of the SAD phenotype based on the guidelines.

Statistical analysis

Statistical analyses were performed with SPSS 25.0 (IBM Software, Chicago, IL, USA) and GraphPad Prism (v. 8.4.2; GraphPad Software, San Diego, CA, USA). Data are expressed as numbers and percentages or means ± standard deviations. The Wilcoxon matched-pairs signed-rank test was used to compare pre- and postimmunization antibody titers to each serotype. The χ^2 or Fisher's exact test of independence was used to calculate the statistical significance of the correlations between categorical variables. Correlations between continuous variables were analyzed by linear regression. *P* values of 0.05 or less were considered statistically significant.

RESULTS

Population characteristics

The baseline characteristics of the study subjects are shown in **Table 1**. A total of 47 patients were enrolled in this study. The male to female ratio was 1:3.7, and the mean age was 48.8 ± 12.0 years. The subtypes of confirmed PID were IGGSD (n = 16, 53.3%), HGG (5, 16.7%), IgM deficiency (n = 2, 6.7%), IgA deficiency (n = 1, 3.3%), and others (n = 6, 12.8%). When we compared the baseline characteristics between patients with suspected PID and those

Table 1. Baseline characteristics between patients with suspected PID and those with confirmed PID

Characteristics	Suspected PID	Confirmed PID	All	*P*-value
No. of patients	17	30	47	0.258
M/F (% male)	2/15 (11.8)	8/22 (26.7)	10/37 (21.30)	0.230
Smoker/ex/never	0/2/15	2/5/23	2/7/38	0.475
Age at enrollment (yr)	47.9 ± 12.6	51.9 ± 10.0	48.8 ± 12.0	0.258
No. of SAD	4 (23.5)	7 (23.3)	11 (23.4)	0.988
Family history of PID	0 (0.0)	2 (7.0)	2 (4.3)	0.277
Underlying diseases				
Bronchial asthma	16 (94.1)	22 (73.3)	38 (80.9)	0.163
Allergic rhinitis	9 (52.9)	24 (80.0)	33 (70.2)	0.070
Chronic rhinosinusitis	8 (47.1)	13 (43.3)	21 (44.7)	0.741
Bronchiectasis	7 (41.2)	22 (73.3)	2 (4.3)	0.029
Autoimmune diseases	2 (11.8)	3 (10.0)	5 (10.7)	0.264
Malignancy	2 (11.8)	1 (3.3)	2 (4.3)	0.311
Infectious complications				
History of recurrent URI	10 (58.8)	24 (80.0)	34 (72.3)	0.119
History of sepsis	2 (11.8)	1 (3.3)	3 (6.4)	0.256
History of pneumonia	8 (47.1)	8 (26.7)	16 (34.0)	0.156
No. of lifetime pneumonia presentations	2.0 ± 3.6	0.6 ± 1.2	1.1 ± 2.4	0.126
No. of antibiotic uses in one year	2.2 ± 2.2	1.2 ± 2.1	1.6 ± 2.2	0.141
No. of hospitalizations in 5 years	3.4 ± 8.2	4.8 ± 8.1	4.3 ± 8.1	0.569
Immunoglobulin levels				
IgG (916–1,796 mg/dL)	1,129.6 ± 362.1	1,131.1 ± 296.4	1,130.7 ± 313.3	0.579
IgA (93–365 mg/dL)	229.7 ± 97.2	216.4 ± 117.9	220.4 ± 111.0	0.443
IgM (40–260 mg/dL)	126.9 ± 45.6	116.3 ± 67.4	119.5 ± 61.3	0.376
IgG1 (405–1,010 mg/dL)	631.7 ± 288.0	624.9 ± 188.0	627.1 ± 222.9	0.605
IgG2 (169–786 mg/dL)	427.1 ± 211.2	446.8 ± 231.5	440.3 ± 222.7	0.810
IgG3 (11–83 mg/dL)	34.4 ± 21.2	21.6 ± 24.0	25.9 ± 23.7	0.020
IgG4 (3–201 mg/dL)	62.8 ± 86.4	57.7 ± 59.7	59.4 ± 68.8	0.754

Values are presented as mean ± standard deviation or number (%).
PID, primary immunodeficiency; SAD, specific antibody deficiency; URI, upper respiratory infection; Ig, immunoglobulin.

with confirmed PID, there was no significant difference regarding age or sex between the 2 groups. However, bronchiectasis was more prevalent in patients with confirmed PID ($P = 0.029$), and the mean level of the IgG3 subclass was significantly lower in patients with confirmed PID ($P = 0.020$) than with suspected PID. Most patients suffered from upper and/or lower respiratory tract infections. Sixteen patients (34.0%) manifested with 1 or more episodes of pneumonia, and 34 patients (72.3%) suffered from recurrent upper respiratory tract infections (more than 3 episodes per year). Three patients had a history of sepsis. Thirty-five patients (74.5%) experienced hospitalization more than once in 5 years due to infectious complications. As 80% of patients had asthma comorbidity, we collected lung functions and asthma severity parameters. Lung function was relatively well preserved; however, 82.3% patients with suspected PID and 63.9% with confirmed PID had moderate-to-severe asthma (**Supplementary Table S1**). None of the subjects had a history of receiving a pneumococcal polysaccharide conjugate vaccine. No serious or severe vaccine-related adverse events were reported.

PnP antibody response

The postvaccination IgG values and fold changes for the 7 serotypes are shown in **Fig. 1**. Eleven patients were diagnosed with SAD (11/47, 23.4%), including both patients with confirmed PID (7/30, 23.5%) and those with suspected PID (4/17, 23.3%) according to the WHO-ELISA (**Table 1**). Six patients had a mild phenotype, 3 patients had a moderate phenotype, and 1 patient had a severe phenotype based on the AAAAI guidelines.

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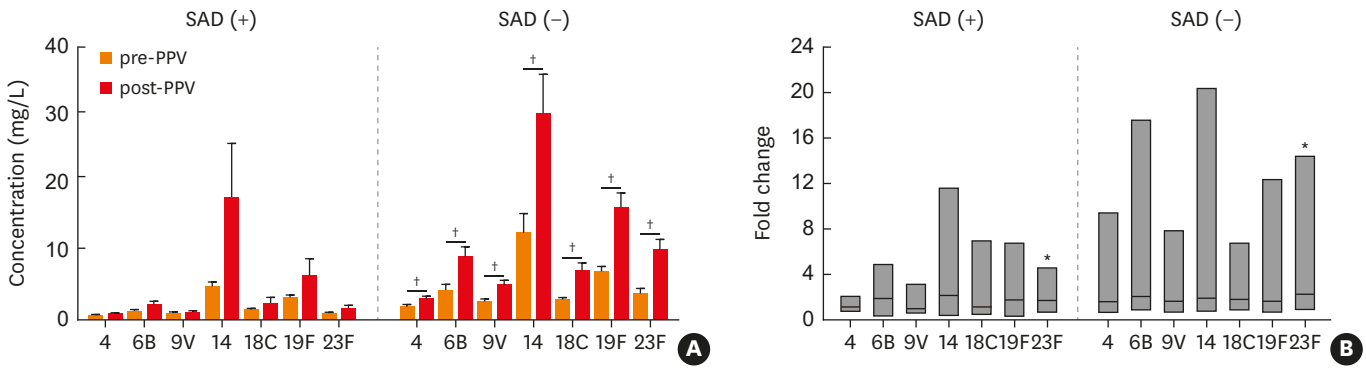

Fig. 1. Comparison of pre- and postvaccination IgG levels for the 7 serotypes (A) and fold changes (B) between patients with SAD and patients without SAD.
Ig, immunoglobulin; PPV, pneumococcal polysaccharide vaccine; SAD, specific antibody deficiency.
*$P < 0.05$ by Mann-Whitney U test; †$P < 0.001$ by Wilcoxon matched-pairs signed-rank test.

Postvaccination IgG values were not increased properly in patients with SAD, while postvaccination IgG values were increased for all 7 serotypes in those without SAD (**Fig. 1**).

Characteristics of the patients with SAD

Seven out of 11 patients with SAD had been diagnosed with other PIDs. Two of them were diagnosed with IGGSD (18.2%), 3 with HGG (27.3%), and 2 with both HGG and IGGSD (18.2%). Only 4 patients (36.4%) were diagnosed with SAD without any underlying PID (**Fig. 2**). When we compared the clinical characteristics between the patients with and without SAD, there was no difference between the 2 groups except the prevalence of IgG deficiency (**Table 2**). The percentages of non-responder to serotypes 4/6B/9V/18C/23F were higher in patients with SAD compared to those without SAD (**Table 3**).

Correlation of IgG subclasses and post-vaccination IgG for serotypes

As patients had decreased one or more IgG subclasses, significant correlations between the level of IgG subclasses and antibody titers for each serotype were observed. IgG2 level was correlated with postvaccination IgG for serotype 4 (r = 0.372, $P = 0.012$)/9V (r = 0.475, $P = 0.001$)/18C (r = 0.416, $P = 0.004$). IgG3 level was correlated with post-vaccination IgG for

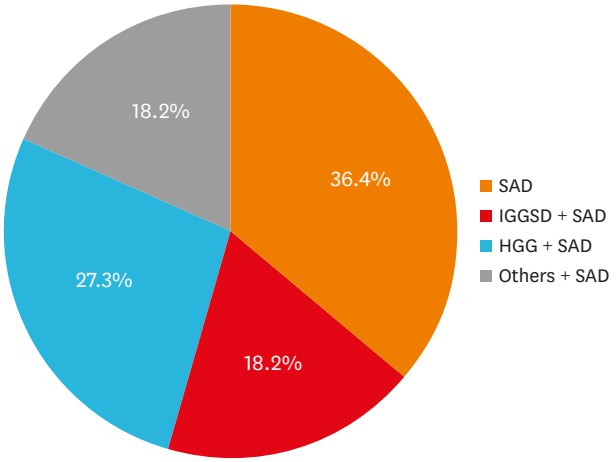

Fig. 2. The distribution of SAD in patients with/without PID.
IGGSD, immunoglobulin G subclass deficiency; HGG, hypogammaglobulinemia; SAD, specific antibody deficiency; Others, Total IgG with IgG3 subclass deficiency; PID, primary immunodeficiency disease.

Table 2. Comparison of clinical characteristics between patients with SAD and those without SAD

Characteristics	SAD+	SAD−	*P*-value
No. of patients	11	36	
M/F (% male)	3/8 (27.3)	7/29 (19.4)	0.579
Age at enrollment (yr)	51.9 ± 10.0	47.9 ± 12.6	0.335
Initial PID diagnosis			0.416
IGGSD	2 (18.2)	14 (38.9)	
HGG	3 (27.3)	2 (5.6)	
IgM deficiency	0 (0.0)	2 (5.6)	
IgA deficiency	0 (0.0)	1 (2.8)	
Others	2 (18.2)	4 (11.1)	
Suspected PID	4 (36.4)	13 (36.1)	
Infectious complications			
History of recurrent URI	9 (81.8)	25 (64.9)	0.422
History of sepsis	0 (0.0)	3 (8.3)	0.322
History of pneumonia	4 (36.3)	12 (33.3)	0.847
No. of lifetime pneumonia	1.2 ± 1.9	1.1 ± 2.6	0.776
No. of antibiotic use in a year	1.6 ± 1.9	1.6 ± 2.9	0.852
No. of hospitalization in 5 years	1.9 ± 1.7	5.1 ± 9.1	0.949
Underlying diseases			
Bronchial asthma	11 (100.0)	27 (75.0)	0.183
Allergic rhinitis	6 (54.5)	27 (75.0)	0.293
Chronic rhinosinusitis	7 (63.6)	14 (38.9)	0.329
Bronchiectasis	6 (54.5)	23 (63.9)	0.577
Autoimmune diseases	1 (9.1)	4 (11.2)	0.974
Malignancy	0 (0.0)	2 (5.6)	0.703
Immunoglobulin levels (mg/dL)			
IgG (916–1,796 mg/dL)	1,046.5 ± 341.9	1,156.2 ± 305.0	0.338
IgA (93–365 mg/dL)	230.0 ± 95.5	217.5 ± 116.5	0.759
IgM (40–260 mg/dL)	97.6 ± 52.1	126.2 ± 63.0	0.201
IgG1 (405–1,010 mg/dL)	657.0 ± 85.7	618.6 ± 249.1	0.636
IgG2 (169–786 mg/dL)	421.6 ± 239.6	445.6 ± 221.1	0.768
IgG3 (11–83 mg/dL)	26.7 ± 14.8	25.6 ± 25.8	0.906
IgG4 (3–201 mg/dL)	64.4 ± 81.6	57.9 ± 65.9	0.796
No. of patients with each Ig deficiency			
IgG	5 (45.5)	4 (11.1)	0.031
IgA	0 (0.0)	4 (11.1)	0.486
IgM	1 (9.1)	2 (5.6)	0.828
IgG1 subclass	0 (0.0)	2 (5.6)	0.677
IgG2 subclass	1 (9.1)	0 (0.0)	0.304
IgG3 subclass	3 (27.3)	15 (41.7)	0.533
IgG4 subclass	0 (0.0)	1 (2.8)	0.854

Values are presented as mean ± standard deviation or number (%).
IGGSD, immunoglobulin G subclass deficiency; HGG, hypogammaglobulinemia; PID, primary immunodeficiency disease; URI, upper respiratory infection; SAD, specific antibody deficiency; Ig, immunoglobulin.

Table 3. Nonresponders to pneumococcal serotypes among patients with (+)/without (−) SAD

Serotypes	SAD+	SAD−	All (n = 47)	*P*-value
4	9 (81.8)	6 (16.7)	15 (31.9)	< 0.0001
6B	3 (27.3)	1 (2.8)	4 (8.5)	0.035
9V	7 (63.6)	2 (5.6)	9 (19.1)	< 0.0001
14	1 (9.1)	0 (0.0)	1 (2.1)	0.234
18C	4 (36.4)	0 (0.0)	4 (8.5)	0.002
19F	1 (9.1)	0 (0.0)	1 (2.1)	0.234
23F	5 (45.5)	1 (2.8)	6 (12.8)	0.002

Values are presented as number (%).
SAD, specific antibody deficiency.

serotype 6B ($r = 0.440$, $P = 0.003$), 9V ($r = 0.305$, $P = 0.041$), and 14 ($r = 0.314$, $P = 0.036$)(**Fig. 3**). This tendency was also observed in patients with confirmed PID (**Supplementary Fig. S1**).

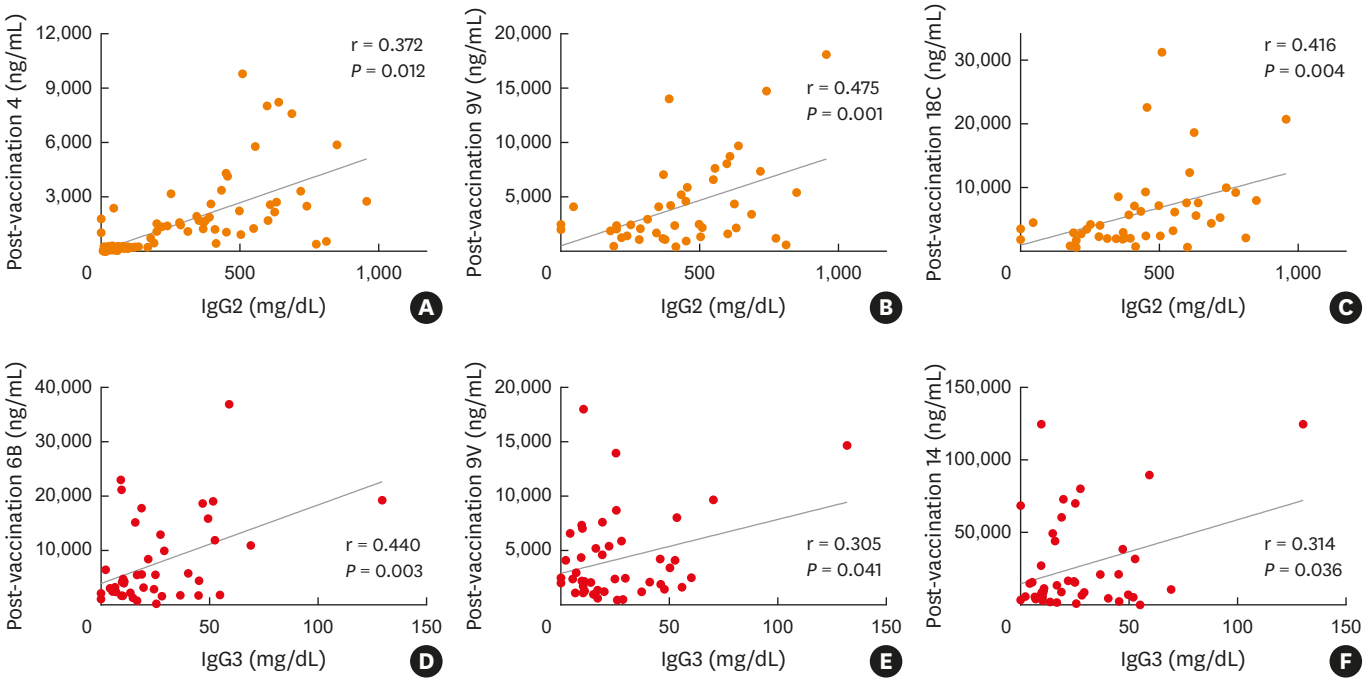

Fig. 3. Correlation between IgG2 (A–C)/IgG3 (B–D) subclass levels and postvaccination IgG levels for the serotypes in all subjects.
Ig, immunoglobulin.

Correlation of IgG subclasses/IgG and clinical parameters

When we compared IgG subclasses level with clinical parameters, we found that IgG3 subclass levels have a strong negative correlation with forced expiratory volume in 1 second (FEV1, %) and FEV1/forced vital capacity (FVC) in all subjects (r = −0.565, $P < 0.001$ for FEV1, and r = −0.532, $P = 0.001$ for FEV1/FVC, respectively; **Fig. 4**). Subgroup analysis with confirmed PID patients or SAD patients shows the inverse correlation between lgG3 levels and lung function parameters (**Supplementary Fig. S2**). The total IgG levels had a strong negative correlation with the number of lifetime pneumonia in all subjects (r = −0.473, $P = 0.001$).

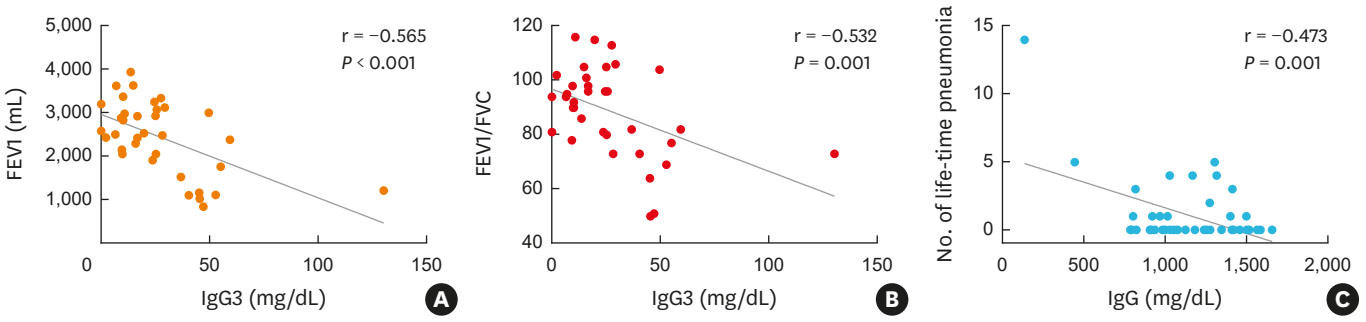

Fig. 4. Correlation between FEV1, FEV1/FVC and IgG3 subclass levels (A and B) and the correlation between the number of lifetime pneumonia presentations and IgG level (C) in the subjects.
FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Ig, immunoglobulin.

DISCUSSION

In the present study, we confirmed SAD cases among adult patients with confirmed PID or those with suspected PID using the standardized WHO-ELISA method. Two-thirds of the SAD patients had already been diagnosed with other types of PID, such as IGGSD and HGG. IgG2 or IgG3 levels correlated with postvaccination IgG titers to various tested serotypes, suggesting that IgG subclasses can play important roles in the defense mechanism against polysaccharides during bacterial infections.

Vaccine responses to PnP are important for the diagnosis and management of patients with suspected PID.[1] Several genetically defined PID, such as Wiskott–Aldrich Syndrome, ataxia telangiectasia, 22q11.2 deletion, and NEMO deficiency, are associated with impaired production of antibodies to PnP.[17,18] Furthermore, responses to PnP can be impaired in patients with other PAD, such as IGGSD and selective IgA deficiency, as shown in the previous studies.[6,19] The present study demonstrated that 63.6% of the SAD patients in adults had already been diagnosed as having other antibody deficiencies such as IgG3SCD or HGG, suggesting that antibody response to PnP is an essential step to evaluating SAD in the management of PID in adults.

PAD is a common PID of the B cell compartment. However, recent developments have shown that these conditions can also be caused by functional impairments in other immune cell lineages, including innate immune cells and T cells.[20,21] Edwards *et al.*[22] reported that 30% of PAD patients showed reduced T-cell numbers, which render patients more prone to severe infection, and Shin *et al.*[23] demonstrated that a low count of natural killer cells is associated with noninfectious complications in patients with common variable immunodeficiency (CVID). Immunophenotyping using flow cytometry found that the different extents of defects in the memory B-cell and plasma-cell subsets are associated with the subtypes of SAD.[24] These data have shown that not only B cells but also other immune cells are involved in the development of PAD, and explain why antibody deficiencies are heterogeneous groups of disorders having different clinical manifestations as well as different vulnerabilities to bacteria or viruses based on the subtypes, although details remain to be elucidated.

In this study, we found a strong positive correlation between postvaccination titers of IgG to serotypes and serum IgG2/IgG3 levels of each individual. Abnormalities in specific polysaccharide antibody production have been well described in IgG2-deficient patients, who have frequent respiratory infections.[3,7,25] As IgG2 was the most active subclass regarding binding activity to most pneumococcal serotypes, we expected a quantitative association between IgG2 and postvaccination IgG titers. However, 60% of these subjects were in IgG3 deficiency, so we compared the level of IgG3 and the postvaccination IgG titer, and found a strong correlation between IgG3 level and postvaccination IgG titers for serotypes 6B, 9V and 14. Abrahamian *et al.*[6] observed similar findings, with 6 out of 11 IgG3 deficiency patients having SAD, and the most common nonprotective serotypes were 3, 8, 9N, and 12F. Parker *et al.*[26] showed that in patients with subnormal IgG3 levels, non-responders had a reduced response to serotypes (1, 3, 8, 9, 12, 14, 19, 51 and 56). Furthermore, antibodies of the IgG3 subclass from several commercial intravenous IgG preparations had the most potent binding and opsonic activity for pneumococcal serotype 6B, which is associated with mortality in invasive pneumococcal diseases.[27,28] These observations suggest that IgG3 is involved in the immune response to produce protective antibodies against certain types of *S. pneumoniae* antigens in adult patients in this country.

The most prevalent chronic infection-related pulmonary disease diagnosed in PID patients is bronchiectasis. Other chronic respiratory complications include asthma, chronic obstructive pulmonary disease (COPD), and chronic sinusitis. A lack of adequate immune defenses leading to recurrent infections may result in a chronic inflammatory response that leads to airway hyperreactivity and remodeling and eventually to fixed obstruction.[29-31] Indeed, 80.9% of the subjects from the present study had a comorbidity of asthma, and 61.7% of them had bronchiectasis. In addition, their asthma control status was in a partly (68.4%) or uncontrolled (21.1%) state at enrollment in this study despite regular asthma treatment (**Supplementary Table S1**). Interestingly, we found strong negative correlations between lung parameters such as FEV1 (% pred.) and FEV1/FVC and the level of the IgG3 subclass. Considering the clinical manifestations, such as recurrent viral illnesses and comorbidities of asthma/bronchiectasis/chronic rhinosinusitis, of these patients, we postulate that decreased FEV1 and obstructive changes might be the consequences of inadequate responses against viral or bacterial respiratory infections. In previous studies, more frequent exacerbation and decline in lung function in patients with chronic airway diseases,[32,33] and Barton *et al.*[34,35] similarly showed that frequent or severe respiratory tract infection is the most common manifestation of undiagnosed IGGSD.

Infectious complications, especially repeated viral infections, were the most common manifestations, followed by lower respiratory tract infections, such as pneumonia, in this study. We included various PAD patients, such as those with IGGSD or HGG. Two-thirds of patients with confirmed SAD had a deficiency of total IgG or more than 1 IgG subclass. Compared to CVID patients, IGGSD or HGG patients are generally considered to be clinically milder and are often not treated with the immunodeficiency taken into consideration.[12,36] However, as shown in this study, they suffer from recurrent respiratory infections and already have complications, such as bronchiectasis and obstructive airway diseases. Dupin *et al.*[37] showed that asthma with HGG was associated with more pronounced bronchiectasis. Recently, using a pooled meta-analysis, Leitao Filho *et al.*[38] demonstrated that HGG is common in COPD patients and is associated with an increased risk of COPD hospitalization. In the present study, we found that IgG levels had a strong negative correlation with the number of lifetime pneumonia presentations ($r = -0.473$, $P = 0.001$). Through this study, we confirmed an epidemiological association between chronic airway diseases and antibody deficiency diseases. Considering that 90% of the patients from this study had asthma and that their initial manifestation was associated with respiratory infection, it is important to evaluate PAD status differentiating from chronic airway diseases, and start proper management to avoid further complications.

There are 2 limitations to this study. One is that we did not consider the memory SAD phenotype, which refers to those patients who are initially able to mount an adequate response to vaccination but lose this response after 6 or more months. The prognostic implication of the memory SAD phenotype needs to be determined, but switched memory B-cell levels were decreased in SAD patients compared to those in healthy controls, and those patients are susceptible to infectious complications, similar to the severe phenotypes of SAD.[39,40] The other is that we did not examine functional immunity in SAD patients. Adults are vulnerable to pneumococcal infections despite having generally high levels of antipneumococcus antibodies, so ELISA results may not correlate with protection in adults.[41] As opsonization is the primary *in vivo* pathway for defense against pneumococcal infections, opsonophagocytic assays (OPAs) are widely accepted as a reference method to determine the protective capacity of antipneumococcus antibodies.[42] Therefore, to precisely determine the functional capacities of protective antibodies, both quantitative and qualitative evaluations should be considered.

Nonetheless, this study has some strengths. First, this study reveals the SAD distribution in the adult population with/without underlying PAD. The majority of reported studies on the association between SAD and IGGSD have been in children, and a few studies have reported the clinical and immunological features of adult patients with SAD and/or other PIDs.[6,14] Total IgG deficiency was more prevalent in the SAD patients than in those without SAD, and HGG or IGGSD was the most common underlying antibody deficiency in the patients with SAD. Secondly, we found an interesting clinical and immunological significance for measuring the IgG3 subclass. IgG3 deficiency was the most common type of IGGSD in the present study, and IgG3 levels had a strong negative correlation with FEV1 and FEV1/FVC. Although the number of subjects was relatively small, this finding indicates that recurrent infections in patients with IgG3 deficiency having impaired immune systems lead to lung function decline and obstructive airway diseases, such as asthma, COPD, and bronchiectasis. Thirdly, there was a strong positive correlation between the concentration of the IgG2 or IgG3 subclass and postvaccination IgG titers for certain serotypes, suggesting that IgG subclass-deficient patients have an impaired ability to produce proper antibodies against *S. pneumoniae*. However, this finding needs to be validated in a larger cohort.

SAD was found in both groups of patients: patients having normal immunological profiles and those already diagnosed with PAD. Although SAD has a wide range of clinical and immunological presentations, it is more prevalent in patients with chronic airway diseases. Not only bacterial infection but also recurrent viral illness is common initial manifestations of SAD. Caution is strongly advised regarding the approach to patients who may have decreased IgG or IgG3 subclass levels. Early diagnosis and proper management are essential to avoid permanent damage, such as bronchiectasis and lung function decline, and serious infectious complications.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1

Comparison of asthma severity and lung parameters in patients with asthma among study subjects

Click here to view

Supplementary Fig. S1

Correlation between IgG2 (A~C)/IgG3 (B~D) subclass levels and postvaccination IgG levels for the serotypes in patients with PID.

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Supplementary Fig. S2

Correlation between clinical parameters and Ig levels in patients with PID (A-C) and patients with SAD (D-F).

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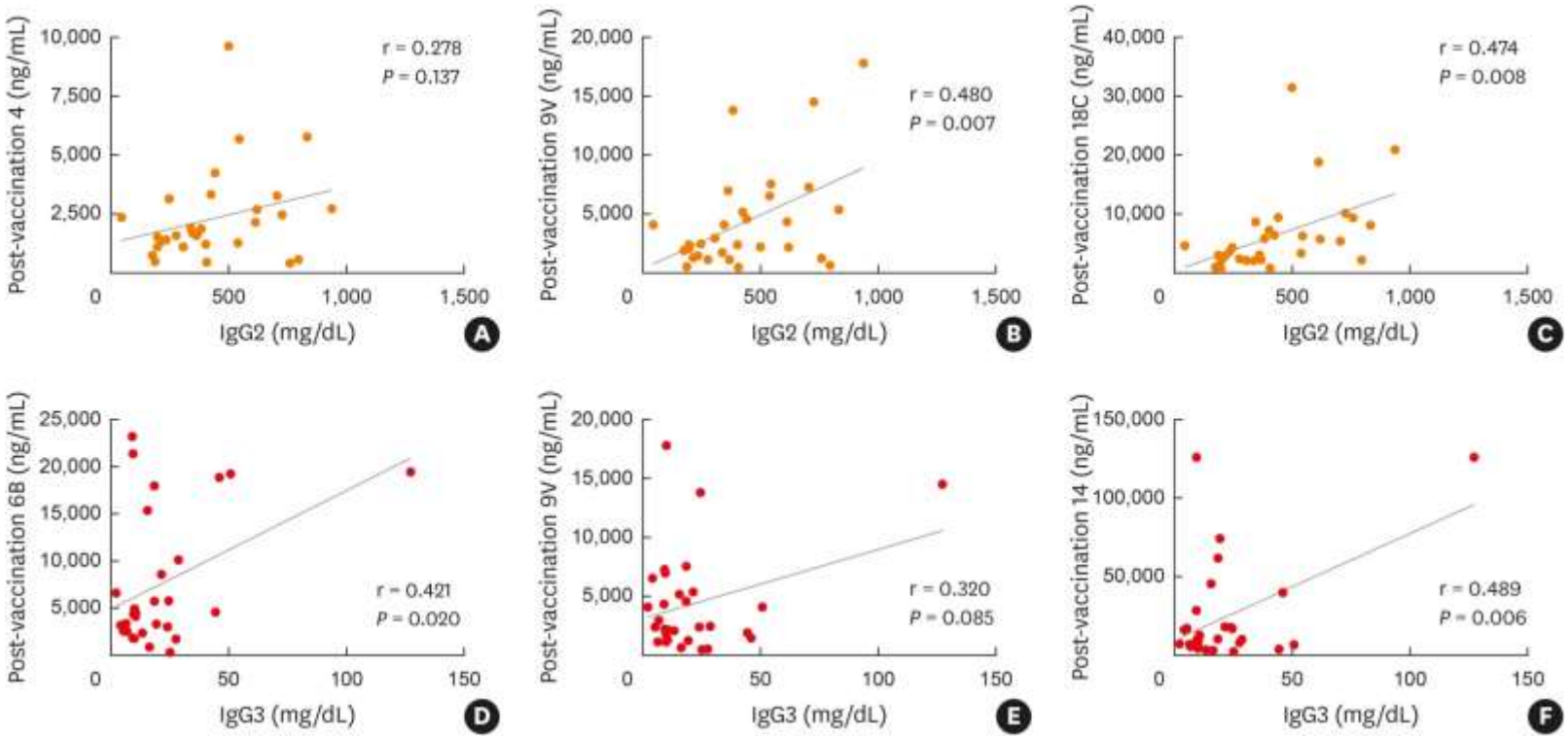

Supplementary Fig. S1. Correlation between IgG2 (A~C)/IgG3 (B~D) subclass levels and postvaccination IgG levels for the serotypes in patients with PID.

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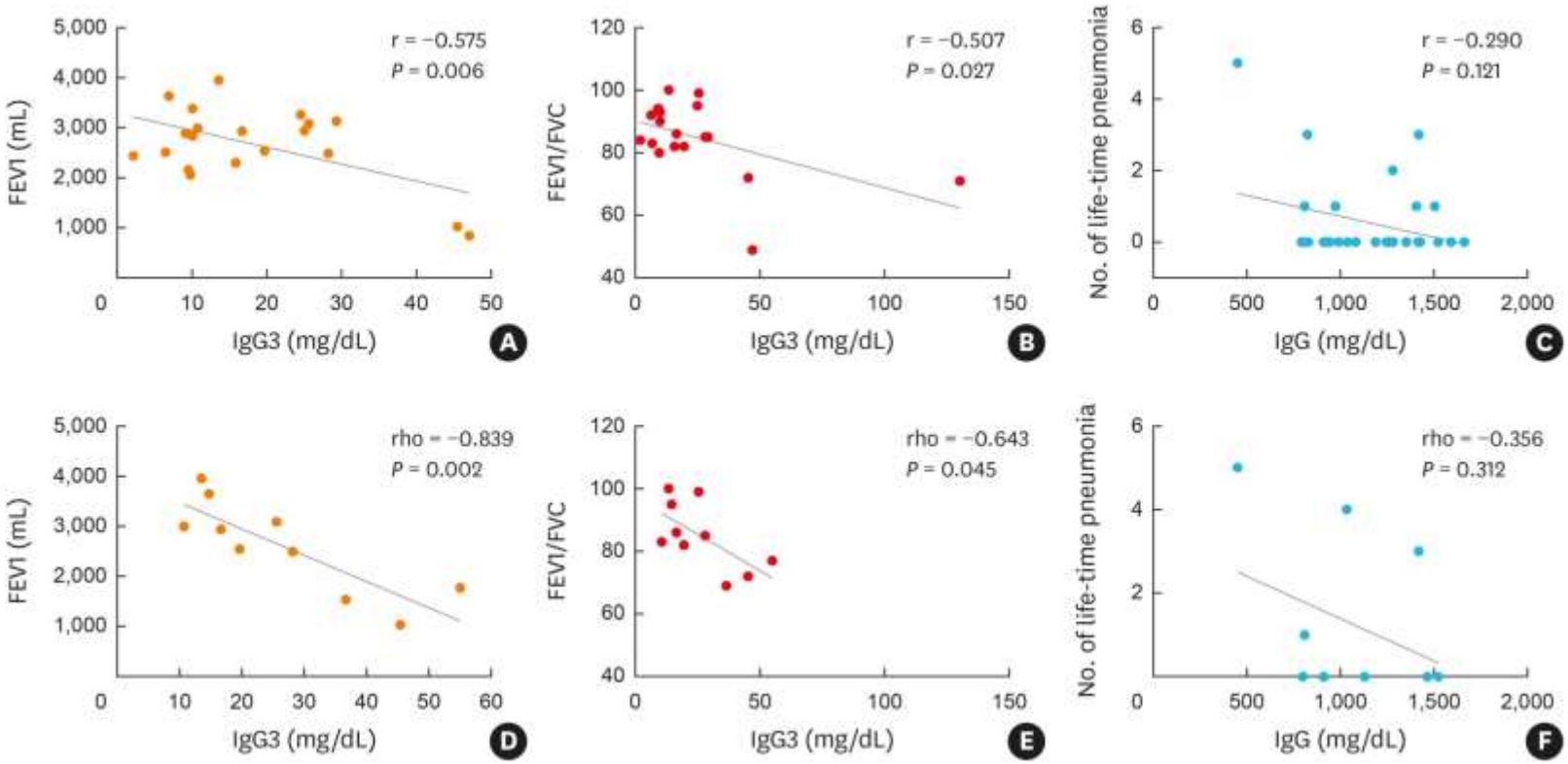

Supplementary Fig. S2. Correlation between clinical parameters and Ig levels in patients with PID (A-C) and patients with SAD (D-F).

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