

Antibody response to pneumococcal vaccination in children with chronic or recurrent rhinosinusitis

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Purpose: Although chronic and recurrent rhinosinusitis is prevalent in children, little is known about its causes. Here, we investigated the humoral immunity in children with chronic or recurrent rhinosinusitis.

Methods: We examined 16 children attending the outpatient clinic at the CHA Bundang Medical Center including 11 boys and 5 girls, aged 3–11 years (mean age, 5.6 years), who had rhinosinusitis for >3 months or >3 times per year. The complete blood count with differential and total serum concentrations of Immunoglobulin (Ig) E, IgA, IgD, IgM, IgG, and IgG subclasses (IgG₁, IgG₂, IgG₃, and IgG₄) of all children were measured. All subjects received 23-polysaccharide pneumococcal vaccination (PPV), and the levels of antibodies to 5 serologic types (4, 6B, 14, 18C, and 23F) of pneumococcal capsular polysaccharide antigens were measured before and after vaccination. Post-PPV antibody titers ≥ 0.35 $\mu\text{g/mL}$ or with a ≥ 4 -fold increase were considered as positive responses.

Results: The titers of IgG, IgA, IgD, and IgM were within normal range in all 16 children, whereas the total IgE concentration was higher than normal in 2 children. IgG₁ deficiency was observed in 1 patient and IgG₃ deficiency in 3. After PPV, 1 patient failed to respond to all 5 serologic types, 2 failed to respond to 4 serologic types, and 2 failed to respond to 3 serologic types.

Conclusion: Clinicians should consider the evaluation of humoral immune functions in children with chronic or recurrent rhinosinusitis who do not respond to prolonged antibiotic treatment.

Key words: Rhinosinusitis, Humoral immune deficiency, Polysaccharide pneumococcal vaccines

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Introduction

Rhinosinusitis, defined as an inflammation of the nose and paranasal sinuses, is one of the most common disorder in pediatric populations. Although it is difficult to estimate the incidence of rhinosinusitis in children, 5–10% of children with upper respiratory tract infections will go on to develop acute rhinosinusitis with a subset of children progressing on to chronic or recurrent state^{1,2}. The chronic or recurrent inflammatory state disrupt daily activities and impair their quality of life, especially when the symptoms are recurrent or chronic. Acute rhinosinusitis is usually infectious whereas the etiology of chronic or recurrent rhinosinusitis remains poorly defined. The general consensus is that the etiology of chronic or recurrent rhinosinusitis is multifactorial. Factors predisposing to the development of chronic or recurrent rhinosinusitis include allergy, various immune-associated disorders, defects in the mucociliary clearance system, and biofilms-associated chronic bacterial infection.

Immunoglobulin (Ig) antibody levels, the four subclasses of human IgG, have an

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important role in host defenses against bacteria and viruses. Deficiencies in IgA or IgG are considered to play an important role in the development of chronic rhinosinusitis³. Of the IgG subclass deficiencies, IgG₂ deficiency has been most closely associated with chronic/recurrent rhinosinusitis in children^{4,5}. However, IgG-subclass levels can vary with age and therefore, transitory Ig defects may occur as one ages. Additionally, the existence of serotype-specific IgG antibodies to pneumococcal bacteria may play an important role in the prevention of pyogenic infections. Furthermore, antibody response to pneumococcal vaccination (PPV) is a good measure of humoral immune function⁶. A great body of evidence have demonstrated a close association between immune function, as measured by antibody response to PPV, and recurrent infections, such as rhinosinusitis^{7,8}. To date, however, there have been no studies confirming a relationship between humoral immune function and antibody titers in a Korean subjects who had vaccination against pneumococcus. Therefore, we sought to ascertain the association between humoral immune deficiency and chronic or recurrent rhinosinusitis in Korean children by measuring antibody responses to 23-polysaccharide PPV in children with chronic or recurrent rhinosinusitis.

Materials and methods

1. Subjects

The present study involved 16 children attending the outpatient clinic at the CHA Bundang Medical Center, who had chronic or recurrent rhinosinusitis for more than 3 months or more than three times in a year at the CHA Bundang Medical Center between January and July 2007. Informed consent for participation was obtained from the guardian of each subject. Rhinosinusitis was diagnosed by patient inquiry and subsequent examination by an experienced pediatrician according to the guidelines of the American Association of Pediatrics⁹. Chronic rhinosinusitis was defined as episodes of inflammation of the paranasal sinuses with the presence of thick nasal discharge and productive cough for more than 3 months. Recurrent rhinosinusitis was defined as presence of bacterial infection of the paranasal sinuses, each lasting less than 30 days and separated by intervals of at least 10 days during which the patient is asymptomatic⁹.

2. Methods

All patients were vaccinated with *Streptococcus pneumoniae* capsular polysaccharide (Pneumo 23, Korean Vaccine Co., Seoul, Korea) in the outpatient clinic at the CHA Bundang Medical Center. Prior to vaccination, a differential complete

blood count was performed; erythrocyte sedimentation rate (ESR) was measured; and serum concentrations of total IgE, IgA, IgD, IgM, and IgG, and the IgG subclasses (i.e., IgG₁, IgG₂, IgG₃, and IgG₄) were assayed. Igs were analyzed using a BN II Nephelometer (Dade Behring, Marburg, Germany). Antibody titers to five serologic types of capsular polysaccharide (4, 6B, 14, 18C, and 23F) were measured in serum samples obtained before and 4–6 weeks after vaccination, using third-generation enzyme-linked immunosorbent assay, at the Center for Vaccine Evaluation and Study at Ewha Womans University. The five most common serologic types in Korea^{7,10,11} were selected for analysis. Antibody titers ≥ 0.35 $\mu\text{g/mL}$ after vaccination or with a ≥ 4 -fold increase were considered positive^{12,13}. Conversions of three of five antibody titers with a < 4 -fold increase were considered abnormal^{10,13}. Normal ranges for immunoglobulins were determined using data of the Mayor Medical Laboratory¹⁴, figures from Boston¹⁵, and a Korean database¹⁶.

Results

1. Clinical characteristics of chronic or recurrent rhinosinusitis in children

The present study consisted of 16 patients (11 boys and 5 girls) aged between 3 and 11 years, with a mean age of 5.6 years. The total blood cell numbers and proportion of white blood cells (WBCs) were within normal ranges in all patients, although the ESR levels of three children were higher than the reference range. All patients had normal CH50 test results (Table 1).

2. Serum immunoglobulin concentrations in patients

Total IgG, IgA, IgD, and IgM concentrations were normal in all patients, when comparing the patients' results to the test's reference values¹⁴, whereas total IgE concentrations were high in two patients. Among the IgG subclasses, all patients had normal IgG₄ concentration. One patient had an above-normal IgG₁ concentration and one a below-normal level, and one patient had an above-normal IgG₂ concentration. One patient had an above-

Table 1. Clinical characteristics of chronic or recurrent rhinosinusitis in children (n=16)*

Characteristic	Value
Male sex	11
Age (yr)	5.6 (3–11)
White blood cell (μL)	7,788 \pm 3,424
Erythrocyte sedimentation rate (mm/hr)	17 \pm 11
CH50 test	Normal

Values are presented as mean (range) or mean \pm standard deviation.

*Chronic or recurrent rhinosinusitis patients.

normal and three a below-normal IgG₃ concentration (Table 2).

3. Antibody titers before and after polysaccharide PPV

Thirteen of the 16 patients (81%) showed normal antibody conversion, >0.35 µg/mL, to all five antigens (4, 6B, 14, 18C, and 23F) after polysaccharide PPV. Of the three patients who

showed abnormal conversion, all responded to PS23F and two patients responded to PS4. Five patients (31%) did not yield a 4-fold increase; of these, two showed a <4-fold increase in three polysaccharide-specific antibodies, two showed a <4-fold increase in four antibodies, and one showed a <4-fold increase in all five antibodies (Table 3).

Table 2. Serum immunoglobulin (Ig) concentrations in patients

Patient no.	Age (yr)	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	IgD (mg/dL)	IgE (IU/mL)	IgG ₁ (g/L)	IgG ₂ (g/L)	IgG ₃ (g/L)	IgG ₄ (g/L)
1	8	1,200	125.0	163.0	<0.23	50.4	6.15	2.16	0.46	0.21
2	3	1,190	61.7	126.0	<0.23	6.7	6.70	1.15	0.26	0.25
3	6	1,010	197.0	67.0	0.86	25.1	5.11	1.75	0.26	0.20
4	9	838	90.7	127.0	1.95	51.6	6.62	4.39	0.54	0.30
5	5	1,360	107.0	139.0	2.77	151.0	7.12	2.76	0.64	0.09
6	3	1,090	144.0	114.0	2.90	112.0	5.82	1.71	0.50	0.29
7	11	1,430	290.0	278.0	0.83	207.0* [‡]	6.33	4.05	0.18 ^{†,‡}	0.29
8	3	1,000	127.0	47.0	<0.23	17.3	7.95	1.80	0.39	0.17
9	4	891	50.0	54.3	1.50	55.2	4.51	1.48	0.30	0.16
10	3	985	133.0	49.2	<0.23	31.3	7.42	2.04	0.35	0.25
11	7	1,570	126.0	117.0	<0.23	37.1	10.70* [‡]	2.16	2.30* ^{‡,§}	0.15
12	7	1,100	132.0	166.0	0.32	19.6	6.10	2.41	0.54	0.24
13	7	1,160	195.0	94.9	1.09	241.1* [‡]	5.61	8.83* ^{‡,§}	0.14 ^{†,‡,§}	0.48
14	4	750	158.0	112.0	1.15	61.4	2.98 ^{†,‡}	2.25	0.13 [†]	0.15
15	4	1,060	83.5	50.9	0.43	9.0	7.42	2.28	0.30	0.43
16	6	822	139.0	74.4	1.45		6.10	2.93	0.67	0.28

*Greater than normal. [†]Less than normal, compared with the reference range in Korea; ^{‡,§}Less than normal, compared with reported reference ranges^{14,15}.

Table 3. Titers of antibodies to antigens of the polysaccharide pneumococcal vaccine

Patient no.	PS4		PS14		PS6B		PS19F		PS23F		<4 FI
	Post* [†]	FI	Post	FI	Post	FI	Post	FI	Post	FI	
1	0.98	3.20	152.13	55.10	3.02	3.50	4.97	1.33	12.88	18.70	3
2	1.43	1.50	0.13 [†]	1.30	3.39	1.20	11.93	1.10	0.17 [†]	0.80	5
3	9.12	43.50	10.89	2.30	1.28	2.10	11.93	7.80	6.38	10.80	2
4	8.92	66.80	10.00	13.70	4.37	1.40	22.63	6.30	11.71	58.50	1
5	3.93	40.80	27.37	1.10	1.84	1.60	2.26	0.90	0.62	2.80	4
6	132.90	317.60	0.23 [†]	1.40	0.77	1.30	1.51	0.70	0.14	1.60	4
7	177.70	906.50	26.02	81.70	33.30	1.50	11.55	0.80	6.88	7.00	2
8	115.70	583.40	4.16	12.40	1.86	1.40	3.15	0.50	0.55	5.30	2
9	188.40	140.50	0.63	1.90	4.50	3.30	6.97	0.90	0.34 [†]	4.90	3
10	324.30	425.10	4.96	1.20	13.30	20.40	14.69	21.20	0.41	1.80	2
11	71.58	36.20	241.12	258.70	137.05	67.20	131.55	93.30	45.33	59.60	0
12	6.62	6.20	4.11	56.40	54.05	11.20	38.97	2.10	1.18	1.20	2
13	52.83	56.20	43.95	1.10	52.02	11.80	37.57	4.50	19.61	5.10	1
14	32.14	76.50	14.67	2.50	49.78	23.50	34.13	30.20	2.70	0.90	2
15	33.39	13.60	8.72	1.90	26.34	8.30	6.35	2.30	6.05	4.00	2
16	15.65	173.60	4.81	1.40	7.88	6.00	22.42	2.30	7.69	14.20	2

PS, polysaccharide; FI, fold increase.

*Antibody titer after polysaccharide pneumococcal vaccination. [†]Less than 0.35 µg/mL (protective threshold, >0.35 µg/mL).

Discussion

We found that one patient (6.2%) had an IgG₁ deficiency and three (18.7%) had an IgG₃ deficiency. Based on antibody titers to five pneumococcal antigens, we found that 5 of 16 patients (31%) showed abnormal humoral immune function. Taken together, 8 of 16 patients (50%) had abnormal results on immune studies, three of whom had IgG subclass deficiency and five of whom had abnormal humoral immune function.

The most important measure of humoral immune function is assessment of changes in antibody titer after vaccination⁶. We measured antibodies to five serologic types. We defined a significant change as a ≥ 4 -fold increase in at least three titers. We found that two patients (12.5%) showed no significant increase in three titers (sensitivity, 63.6%; specificity, 87.4%) and one showed no significant increase in any of the five titers (sensitivity, 72.7%; specificity, 56.8%). A previous study consisting of 307 adult patients with chronic rhinosinusitis demonstrated that 67 patients of them (21.8%) showed a humoral immune deficiency^{17,18}. Another study by Shapiro et al.¹⁹ in 61 children with refractory sinusitis showed that 34 of them (55.7%) had abnormal immune results; 11 patients had low Ig levels, 6 had low Ig levels and vaccine hyporesponsiveness, and 17 had poor vaccine response only. In line with previous studies, we found that a high proportion of our patients (5 of the 16 patients [31%]) demonstrated humoral immune deficiency. In contrast, the study by Hidalgo et al.⁶ in 78 children with recurrent infections found that only five of them (6.4%) failed to develop protective antibody levels after vaccination against pneumococcus. Another study examining 245 adult patients with chronic rhinosinusitis not responding to prolonged antibiotic treatment reported that only 22 patients (9%) showed low Ig levels after vaccination against pneumococcus¹⁸. Furthermore, it has been suggested that antibody production capacity may not have an important role in the development of chronic rhinosinusitis. Taken together, humoral immune deficiency is not a common cause of chronic rhinosinusitis and clinicians should consider other causes of chronic rhinosinusitis not responding to proper antibiotic treatment⁸.

Although previous studies have demonstrated a relationship between IgA and IgG₂ deficiencies and chronic rhinosinusitis in adults^{20,21}, we were unable to confirm these data as none of our patients showed an IgA or IgG₂ deficiency. We found that one patient (6.2%) had an IgG₁ deficiency and three (18.7%) had IgG₃ deficiencies. In line with our study, a previous study of 30 patients with chronic rhinosinusitis showed that 3, 7, 14, and 10 patients had IgG₁, IgG₂, IgG₃, and IgG₄ deficiencies, respectively.²² Another study of 307 adult patients with chronic rhinosinusitis demonstrated that 7 patients (2.2%) had IgA deficiencies, 6 (2.0%) IgG₂ deficiencies, and 55 (17.9%) IgG₃

deficiencies.¹⁷ Another study consisting of 245 patients with chronic rhinosinusitis found that 5 patients (2.0%), 10 patients (4.1%), 1 patient (0.4%), and 1 patient (0.4%) had IgG₁, IgG₂, IgG₃, and IgG₄ deficiencies, respectively, and 5 (2.0%) had a common variable immune deficiency¹⁸. A previous study comprising 27 allergic respiratory children with recurrent sinusitis reported that primary and/or secondary humoral immune deficiency is not the main cause of chronic/recurrent sinusitis⁹. A previous study consisting of 30 Korean children demonstrated that there is a close association between immune deficiency and recurrent or chronic rhinosinusitis in children²². To the best of our knowledge, there have been no studies confirming a relationship between humoral immune function and antibody titers in patients with pneumococemia. While the prevalence is not different from our results, the smaller number of patients in our study made it difficult to determine the prevalence of immunoglobulin deficiencies. Therefore, it is not clear whether IgG subclass deficiencies are clinically significant in children with chronic or recurrent rhinosinusitis²³.

The present study has limitations that need to be taken into account when considering the study and its contributions. Firstly, the present study had no control group. Secondly, it had relatively small number of subjects compared with previous studies.

In conclusion, we determined immune deficiencies in children with chronic or recurrent rhinosinusitis by quantitating immunoglobulin concentrations and measuring antibody titers to PPV and found that a substantial proportion of patients with chronic or recurrent rhinosinusitis had abnormal immune functions. Therefore, humoral immune deficiency may be considered as a cause of chronic or recurrent rhinosinusitis. Relevant treatment guidelines and long-term measurement of antibody titers may be needed in patients with recurrent or chronic rhinosinusitis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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References

1. Han M. The management of sinusitis in children. *Korean J Pediatr* 2007;50:328-34.
2. Criddle MW, Stinson A, Savliwala M, Coticchia J. Pediatric chronic rhinosinusitis: a retrospective review. *Am J Otolaryngol* 2008; 29:372-8.
3. Meyts I, Bossuyt X, Proesmans M, De B. Isolated IgG3 deficiency in children: to treat or not to treat? Case presentation and review of the literature. *Pediatr Allergy Immunol* 2006;17:544-50.
4. Soderstrom T, Soderstrom R, Avanzini A, Brandtzaeg P, Karlsson G, Hanson LA. Immunoglobulin G subclass deficiencies. *Int Arch Allergy Appl Immunol* 1987;82:476-80.
5. Shackelford PG, Polmar SH, Mayus JL, Johnson WL, Corry JM, Nahm MH. Spectrum of IgG2 subclass deficiency in children with recurrent infections: prospective study. *J Pediatr* 1986;108(5 Pt 1):647-53.
6. Hidalgo H, Moore C, Leiva LE, Sorensen RU. Preimmunization and postimmunization pneumococcal antibody titers in children with recurrent infections. *Ann Allergy Asthma Immunol* 1996;76:341-6.
7. Sorensen RU, Leiva LE, Javier FC 3rd, Sacerdote DM, Bradford N, Butler B, et al. Influence of age on the response to *Streptococcus pneumoniae* vaccine in patients with recurrent infections and normal immunoglobulin concentrations. *J Allergy Clin Immunol* 1998;102:215-21.
8. Costa Carvalho BT, Nagao AT, Arslanian C, Carneiro Sampaio MM, Naspitz CK, Sorensen RU, et al. Immunological evaluation of allergic respiratory children with recurrent sinusitis. *Pediatr Allergy Immunol* 2005;16:534-8.
9. American Academy of Pediatrics, Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics* 2001;108: 798-808.
10. Sniadack DH, Schwartz B, Lipman H, Bogaerts J, Butler JC, Dagan R, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children--implications for vaccine strategies. *Pediatr Infect Dis J* 1995;14:503-10.
11. Kim SM, Hur JK, Lee KY, Shin YK, Park SE, Ma SH, et al. Epidemiological study of pneumococcal nasal carriage and serotypes among Korean children. *Korean J Pediatr* 2004;47:611-6.
12. Siber GR, Chang I, Baker S, Fernsten P, O'Brien KL, Santosham M, et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. *Vaccine* 2007;25:3816-26.
13. Kamchaisatian W, Wanwatsuntikul W, Slesman JW, Tangsinmankong N. Validation of current joint American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma and Immunology guidelines for antibody response to the 23-valent pneumococcal vaccine using a population of HIV-infected children. *J Allergy Clin Immunol* 2006;118:1336-41.
14. Behrman RE, Kliegman R, Jenson HB. *Nelson textbook of pediatrics*. 16th ed. Philadelphia: WB Saunders Co., 2000:2202.
15. Leung DY, Sampson H, Geha R, Szeffler SJ. *Pediatric allergy principles and practice*. 6th ed. St. Louis: Mosby Co., 2003.
16. Lee YK, Kim DS, Lee KY, Lee JW, Lim HB. Normal values of IgG and IgG subclass concentrations according to age in children. *Pediatr Allergy Respir Dis* 1999;9:93-9.
17. Vanlerberghe L, Joniau S, Jorissen M. The prevalence of humoral immunodeficiency in refractory rhinosinusitis: a retrospective analysis. *B-ENT* 2006;2:161-6.
18. May A, Zielen S, von Ilberg C, Weber A. Immunoglobulin deficiency and determination of pneumococcal antibody titers in patients with therapy-refractory recurrent rhinosinusitis. *Eur Arch Otorhinolaryngol* 1999;256:445-9.
19. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. *Pediatrics* 1991;87:311-6.
20. Wise MT, Hagaman DD. An immunological approach to chronic and recurrent sinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2007;15:10-7.
21. Sethi DS, Winkelstein JA, Lederman H, Loury MC. Immunologic defects in patients with chronic recurrent sinusitis: diagnosis and management. *Otolaryngol Head Neck Surg* 1995;112:242-7.
22. Kim HK, Kim HH, Chung HR. Serum immunoglobulins in children with recurrent sinusitis. *Korean J Otolaryngol-Head Neck Surg* 1997;40:1752-6.
23. Slavin RG, Spector SL, Bernstein IL, Kaliner MA, Kennedy DW, Virant FS, et al. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol* 2005;116(6 Suppl):S13-47.