Asian pacific Journal of Allergy and Immunology (1988) 6 : 129-133

Selective IgG Subclass Deficiencies in Patients with Recurrent Sinopulmonary Infections : Report of Two Cases

Chen-Cheng Chou, Kue-Hsiung Hsieh, Yung-Zen Lin, Chen-Kai Ting and Jiu-Yao Wang

SUMMARY **Two patients with recurrent sinopulmonary infections and normal total serum immunoglobulin levels were found to have selective deficiencies in IgG subclasses. The serum of one patient contained abnormally low IgG2 and IgG4; and the other was deficient in IgG4. Both patients responded to the treatment with high dose intravenous immunoglobulin. The experiences on these two cases strongly suggest that IgG subclasses should be checked in patients with recurrent sinopulmonary infections in face of normal total immunoglobulins.**

Four subclasses of human IgG have been recognized [1] and designated IgG1, IgG2, IgG3 and IgG4. [2] The unique structural, physicochemical, genetic and functional characteristics have also been well described. [3] Selective deficiencies of one or more IgG subclasses may predispose to unusual susceptibility to recurrent pyogenic infections despite normal total IgG. In 1970, Schur *et al* [4] and Yount *et al* [5] first reported selective gamma-G globulin deficiencies in patients with recurrent pyogenic infections, however, only a limited number of reports on IgG2 or IgG2-IgG4 deficiencies and even fewer on isolated IgG4 deficiency with recurrent sinopulmonary infections have appeared in the literature up to now. [6-11] Moreover, the therapeutic strategy still needs to be established. We here report two cases of selective IgG subclass deficiency, one with IgG2-IgG4 deficiency and the other IgG4 deficiency; both of them responded to replacement therapy with high dose intravenous immunoglobulin.

CASE REPORTS

Case 1 :

A 3-year-old malnourished, underdeveloped boy had recurrent episodes of pneumonia, which required him to be hospitalized 5 times since 5 months of age. Frequent loose stool was also noted. He had no past history of adverse reaction to live vaccines and no family history of early infant death or recurrent severe infections. One month prior to admission to our hospital, he developed cough, dyspnea and intermittent fever again. Physical examination on admission revealed presence of tonsils and lymph nodes of normal size, diffuse fine moist rales on both lung fields and no eczematous skin lesions. Chest X-rays showed pneumonia and bronchiectasis of right lower lobe. *Hemophilus influenzae* was recovered from the aspirated sputum. Serum IgG2 and IgG4 were undetectable. The protracted respiratory symptoms, which were refractory to antibiotic therapy alone, were improved after adding high dose intravenous immunoglobulin (IVIG, Gamimune, Cutter, USA) at a dose of 400 mg/kg per 3 weeks. However, lobectomy of right lower lobe was performed because of bronchiectasis with persistent atelectasis. The patient has now been on regular IVIG with improved general condition and lessened frequency of respiratory infection.

Case 2 :

A 9-year-old girl had a history of repeated episodes of pneumonia since 3 years of age and chronic productive cough since the age of 5 years. She was admitted to our hospital because of worsening respiratory

From The Department of Pediatrics, College of Medicine, National Taiwan University, Taipei, Taiwan, Republic of China

Correspondence : Dr. Kue-Hsiung Hsieh, Department of Pediatrics, National Taiwan University, Hospital, No. 1, Chang-Te Street, R.O.C.

symptoms and intermittent abdominal pain with frequent loose stool in the past year. Her younger brother died of sepsis at the age of 1 year and a 7-year-old sister was living and well. Physical examination found barrel chest with diffuse fine moist rales and clubbing fingers. Radiological studies revealed multiple pneumonic patches, bronchiectasis and cloudiness over the maxillary, sphenoid and ethmoid sinuses. Sweat chloride test and serum α-1-antitrypsin level were normal. Immunological studies revealed undetectable IgG4 in her serum. The sinopulmonary symptoms and frequent loose stool were much improved after adding high dose IVIG (400 mg/Kg/3 wks) to antibiotic treatment regimen.

METHODS

Polymorphonuclear leukocyte (PMN) function : Chemotactic activity was assessed by the method of the modified Boyden's chamber.[12] Nitroblue tetrazolium test (NBT) was checked by the method of Baehner *et al.*,[13] using commercial kits (Sigma, St. Louis, MO, USA).

Enumeration of lymphocyte subpopulations: B cells with surface immunoglobulin (sIg) were enumerated by direct immunofluorescence.[14] The OKIa1$^+$ (B cell), CD3$^+$ (total T cell), CD4$^+$ (helper/inducer T cell) and CD8$^+$ (suppresor/cytotoxic T cell) cells were counted according to the instructions inserted in the monoclonal antibody packages (Orthoclone Phamaceutical Corp., Raritan, NJ).

Lymphoproliferative response to phytomitogens was performed by the method of Bradley.[15]

Determinations of serum immunoglobulins and complement : Serum IgG, IgA, IgM, C3 and C4 levels were measured by nephelometry (Beckman, Los Angeles, CA, USA). IgG subclasses were determined by single radial immunodiffusion method of Mancini,[16] using immunoplates purchased from Serotec, England. The serum immunoglobulin values of the patients were compared to those for age-matched controls reported previously.[16-18]

RESULTS

The results of immunological studies are shown in Tables 1, 2 and 3. The PMN functions serum C3, C4, IgG, IgA and IgM concentrations were normal in both cases. T-cell function in terms of T-cell subsets and lymphoproliferative responses to mitogens was normal in case 1, but impaired in case 2 as evidenced by reversed T4/T8 ratio and diminished mitogenic response. The serum IgG2 and IgG4 levels of case 1 and IgG4 level of case 2 were undetectable. The total serum IgG and IgG subclasses were measured serially

Table 1. Studies of nonspecific immunity*

Polymorphonuclear leukocytes
- a) Chemotactic activity
  - No chemoattractant : 300 cells/10 fields
  - With chemoattractant : 502 cells/10 fields
  - Ratio : 1.67 (2.4 ± 0.6)$^+$
- b) NBT test
  - Unstimulated : 50–60%
  - Stimulated : 90%
- c) Bacterial killing : Normal

Serum complement level
- C3 : 108 mg/dl (113.7 ± 13.7)$^+$
- C4 : 20.3 mg/dl (34.4 ± 12.4)$^+$

*Case 2
$^+$Numbers in parentheses represent normal values for age (mean ± 1 SD)

Table 2. Studies of humoral immunity

B cell number (% of surface Ig positive)

	IgG	IgA	IgM
Case 1	3	4	13
Case 2	11	2	7
Normal	(8 ± 3)$^+$	(3 ± 1)	(9 ± 3.5)

Serum immunoglobulin levels (mg/dl)

	IgG	IgA	IgM
Case 1	836	115	108
Normal	(892 ± 183)$^+$	(93 ± 27)	(56 ± 18)
Case 2	827	68	74
Normal	(1,320 ± 309)$^+$	(187 ± 55)	(166 ± 48)

Serum IgG subclass (mg/l)

	IgG1	IgG2	IgG3	IgG4
Case 1	8,840	ND*	400	ND*
	(3,810–8,840)‡	(700–4,430)	(170–900)	(10–1,160)
Case 2	9,460	2,460	189	ND*
	(4,220–8,020)‡	(1,130–4,800)	(150–1,330)	(10–840)
Father@	7,090	3,830	237	306
Mother@	14,600	4,540	101	127

* Not detectable. Sensitivity of immunoplates : IgG2 > 845 mg/l, IgG4 > 50.7 mg/l.
$^+$ Numbers in parentheses represent normal values for age–matched controls (Mean ± 2 SD)
‡ Range of values for age–matched controls
@ Of case 2

Table 3. Studies of cellular immunity

Total lymphocyte counts (cells/mm^3)
Case 1 : 6,985
Case 2 : 3,852

T cell subsets (%)

	CD3	CD4	CD8
Case 1	72	39	26
Case 2	74	31	53
Normal	(72.4 ± 0.8)+	(43.1 ± 4.5)	(35.1 ± 3.0)

Mitogen response

	Control	ConA		PHA		PWM	
	cpm	cpm	SI*	cpm	SI	cpm	SI
Case 1	4,508	4,533	2.02	231,426	52.3	17,188	4.79
Case 2	2,658	6,301	3.36	68,938	25.8	16,912	7.03
Normal			(42 ± 26)+		(118 ± 79)		(35.6 ± 20.5)

* SI : Stimulation index
+ Numbers in parentheses are normal vaules (Mean ± 1 SD)

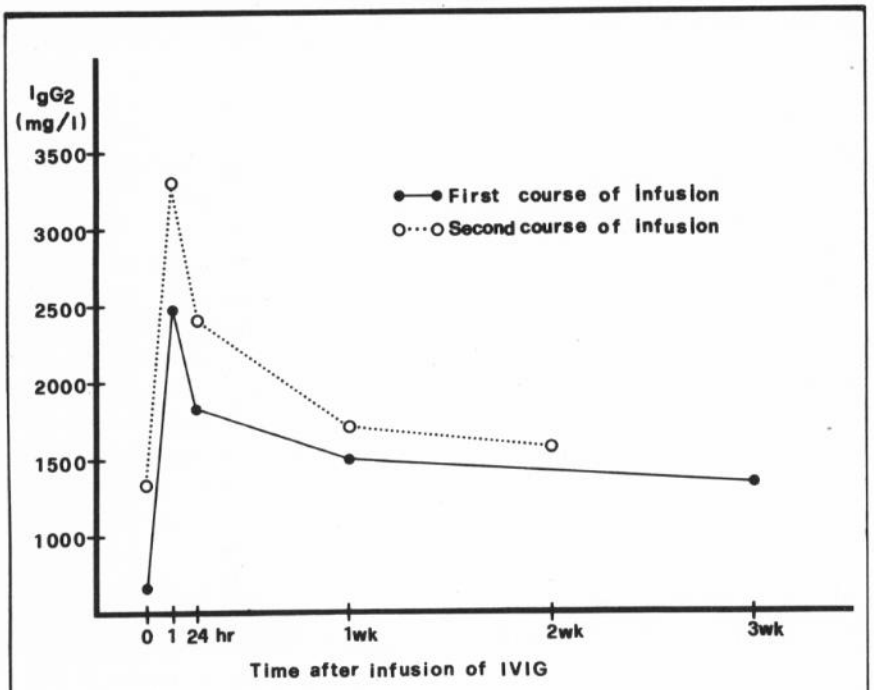

Fig. 1 The serum IgG2 level of case 2 after infusion of IVIG.

after infusion of IVIG at a dose of 400 mg/kg. The serum IgG2 level of case 1 could be maintained within normal range by using such dosage (Fig. 1), but the serum IgG4 levels of both patients were still undetectable after IVIG treatment. Through out the whole course of five infusions in case 2 and regular treatment for more than 2 years in case 1, no adverse reaction was encountered.

DISCUSSION

The recurrent sinopulmonary infection which progresses to bronchiectasis is unusual in children and needs thorough investigation for underlying congenital, anatomical or immunological etiologies.[19] Regarding immunodeficiency,the selective IgG subclass deficiency has been stressed for "idiopathic" patients whose serum total IgG levels are within the normal range. After excluding the other possible etiologies, the diagnosis of selective IgG2-IgG4 deficiency and IgG4 deficiency, respectively, in the two patients in this report were strongly suspected as evidenced by repeated inability to detect IgG2 and IgG4 in their sera.

The studies of IgG subclasses and the diagnosis of selective IgG subclass deficiency[6-11] have become possible after the availability of specific antibodies and development of sensitive methods such as single radial immunodiffusion or enzyme-linked immunosorbant assays. In 1970, Schur *et al.*[4] and Yount *et al.*[5] first reported disporportionate IgG subclass deficiency in patients with hypogammaglobulinemia and recurrent pyogenic infections. In 1974, Oxelius[6] further described recurrent severe pulmonary infection caused by *H. influenzae* in three patients in a family with combined IgG2-IgG4 deficiency but with normal amounts

of total IgG. Subsequently, a few studies reported the presence of IgG2 deficiency in a variety of diseases which always presented with more frequent and more severe respiratory tract infections, *e.g.* IgA deficiency,[7] ataxia-telangiectasia[8] and a certain portion of nonallergic[9] and allergic children.[10] Furthermore, many patients with IgG2 deficiency also had low level of IgG4. In fact, Beck *et al.*[11] and Heiner[20] reported the association of isolated deficiency of IgG4 with severe recurrent sinopulmonary infection which could progress to bronchiectasis. The clinical pictures of severe recurrent sinopulmonary infections in the presence of normal total IgG but undetectable IgG2 and IgG4 in our cases were comparable to those described in the above-mentioned reports.

However, the exact incidence of selective IgG subclass deficiency among patients with recurrent infections is still not known. Noyes *et al.*,[10] in a clinical and asthma practice reported 31 of 75 patients with recurrent upper respiratory infections were found to have IgG subclass deficiency with normal level of total IgG; Umetsu *et al.*[21] found 20 children with selective IgG deficiency and recurrent sinopulmonary infections among 2800 new patients seen in an allergy clinic over a period of 3 years. Stanley *et al.*[22] showed that 7% of their patients with chronic or recurrent respiratory infections had serum IgG2 concentration more than 3 SD below the mean of healthy subjects. Shackelford *et al.*[23] reported that 7 of 30 patients examined because of recurrent infections had IgG2 deficiency. Oxelius *et al.*[7] mentioned that 7 of 37 diseased patients with IgA deficiency had coexisting IgG2 deficiency. Heiner[20] found that in 5 of 35 patients with idiopathic bronchiectasis, the serum IgG4 was extremely low. Beck *et al.*[11] reported that of 422 normal or atopic patients, 4 cases had IgG4 deficiency with recurrent infection and 3 of them progressed to bronchiectasis. Taken together, these studies suggest that selective deficiency of IgG subclasses, especially IgG2 and IgG4, is not infrequent and more common than previously recognized.

The infections in patients with selective IgG deficiency are frequently caused by organisms with polysaccharide capsules and are relatively restricted to the IgG2 subclasses. Siber *et al.*[24] had demonstrated a correlation between IgG2 concentrations and antibody responses to polysaccharide antigens from the encapsulated bacteria, *e.g.*, *Streptococcus pneumoniae* and *Hemophilus influenzae*. The reason why patients with IgG4 deficiency are also susceptible to the capsular polysaccharide antigen remains to be elucidated. Perhaps the lack of complement fixation by antigen-antibody complexes involving IgG4 portends a unique role for this subclass in lung defense.[11] *H. influenzae* had been cultured repeatedly from the sputa of our patients and this result was consistent with previous reports.[6,10,21,24]

Regarding the pathogenesis of IgG subclass deficiency, Umetsu *et al.*[21] suggested that a lack of subclass-specific helper/inducer T cells or an excess of subclass-specific suppressor T cells may cause IgG subclass deficiency in humans. This hypothesis was based on the observation that IgG subclass isotype-specific helper and suppressor cells have been detected in animals.[25] However, IgG2 and IgG4 deficiencies tend to occur together, often in association with deficiencies of IgA and/or IgE.[20] This concomitant occurrence of IgG2, IgG4, IgE or IgA deficiencies suggests that the subclass deficiency may have broad gene deletion within the immunoglobulin heavy-chain locus on chromosome 14 or defect in the regulation of the heavy-chain gene switch.[21,26]

Although the therapeutic efficacy of intravenous gammaglobulin (IVIG) has not yet been well established,[23] it is widely accepted that immunoglobulin replacement therapy is indicated in the clinical setting of recurrent infections and IgG subclass of > 2 SD below the mean for age.[27] The goal is to bring the deficient concentration of any subclass to well within the range of normal and to maintain the concentration until the infection is controlled.[28] Both adverse local and systemic and anaphylatic reactions to immunoglobulin may occur.[29] The reaction depends on the route of administration, the type of preparation and the patient himself. Schwartz[30] reported that the overall incidence of reactions to IVIG (pH 4.25) was only 5.1 percent in a total of 232 infusions in 39 patients, with all reactions being transient and disappearing when the infusion rate was slowed. Intramuscular gammaglobulin preparations are claimed to lack IgG4, but most commercially available IVIG preparations contains appropriate concentrations of all four IgG subclasses. By giving IVIG at a dose of 400 mg/kg per 3 weeks, our patients could achieve and maintain a normal serum IgG2 level although the serum IgG4 level was still undetectable. As both of our patients had satisfactory relief of respiratory symptoms without any adverse reaction, these results support the clinical benefit of IVIG described previously.

In summary, IgG subclass deficiencies of one or more of the IgG subclasses may increase susceptibility to recurrent pyogenic infections. Even with normal total IgG, deficiency of IgG4 alone or in combination with IgG2 has been associated with recurrent infections. Gammaglobulin replacement therapy is safe in patients without IgA deficiency and has beneficial effect on most patients with IgG subclass deficiency.

References

1. Grey HM, Kunkel HG. H Chain subgroups of myeloma proteins and normal

TS γ-globulin. J Exp Med 1964; 120 : 253-66.

2. Notation for human immunoglobulin subclasses. Bull WHO 1966; 35 : 953.
3. Spiegelberd HL. Biological activities of immunoglobulins of different classes and subclasses.Adv Immunol 1974; 12 : 259-94.
4. Schur PH, Borel H, Gelfand EW, Alper CA, Rosen FS. Selective gamma-G globulin deficiencies in patients with recurrent pyogenic infections. N Engl J Med 1970; 283 : 631-4.
5. Yount WJ, Hong R, Seligmann M, Kunkel HG. Imbalance of gamma globulin subgroups and gene defects in patients with primary hypogammaglobulinemia. J Clin Invest 1970; 49 : 1957-66.
6. Oxelius VA. Chronic infections in family with hereditary deficiency of IgG2 and IgG4. Clin Exp Immunol 1974; 17 : 19-27.
7. Oxelius VA, Laurell AB, Linquist B, *et al.* IgG subclasses in selective IgA deficiency. N Engl J Med 1981; 304 : 1476-7.
8. Oxelius VA, Barkel AI, Hanson LA. IgG2 deficiency in ataxia telangiectasia. N Engl J Med 1982; 306 : 515-7.
9. Smith TF, Morris EC, Bain RP. IgG subclasses in nonallergic children with chronic chest symptoms. J Pediatr 1984; 105 : 896-900.
10. Noyes J, Woodmansee D, Chervinsky P. IgG subtype abnormalities with normal total IgG in a clinical allergy practice. Ann Allergy 1986; 57 : 273-5.
11. Beck CS, Heiner DC. Selective immunoglobulin G4 deficiency and recurrent infections of the respiratory tract. Am Rev Resp Dis 1981; 124 : 94-6.
12. Boyden S. The chemotactic effect of mixtures of antibody and antigen on polymorphonuclear leucocytes. J Exp Med 1962; 115 : 453-66.
13. Baehner RL, Nathan DG. Quantitative nitroblue tetrazolium test in chronic granulomatous disease. N Engl J Med 1968; 278 : 971-6.
14. Major GAC. Identification of B lymphocytes by surface fluorescence. In : Weir DM, ed, Handbook of experimental immunology. 3rd ed. Oxford : Blackwell Scientific Publications, 1978 : 5-7.
15. Bradley LM. Cell proliferation. In : Mischell BB and Shiigi SM, eds, Selected methods in cellular immunology. San Francisco : WH Freeman and Co., 1980 : 158-66.
16. Mancini G, Carbonara AV, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. Int J Immunochem 1965; 2 : 235-54.
17. Hsieh KH. Study of the development of humoral and cellular immunities in the human : the development of serum immunoglobulin in normal Chinese children from birth to 15 years of age. Acta Pediatr Sinica 1978; 19 : 301-9.
18. Oxelius VA. IgG subclass levels in infancy and childhood. Acta Pediatr Scand 1979; 68 : 23-7.
19. Rubin BK. The evaluation of the child with recurrent chest infections. Ped Inf Dis 1985 : 88-98.
20. Heiner DC. Significance of immunoglobulin G subclasses. Am J Med 1984; 80 : 1-6.
21. Umetsu DT, Ambrosino DM, Quinti I, Siber GR, Geha RS. Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG-subclass deficiency. N Engl J Med 1985; 313 : 1247-51.
22. Stanley PJ, Corbo G, Cole PJ. Serum IgG subclasses in chronic and recurrent respiratory infections. Clin Exp Immunol 1984; 58 : 703-8.
23. Shackelford PG, Polmar SH, Mayus JL, Johnson WL, Corry JM, Nahm MH.Spectrumof IgG2 subclass deficiency in children with recurrent infections: prospective study. J Pediatr 1986; 108 : 647-53.
24. Siber GR, Schur PH, Aisenberg AC, Weitzman SA, Schiffman G. Correlation between serum IgG2 concentrations and the antibody response to bacterial polysaccharide antigens. N Engl J Med 1980; 303 : 178-82.
25. Lowy IL, Brezin C, Neauport-Sautes C, Theze J, Fridman WH. Isotype regulation of antibody production: T-cell hybrids can be selectively induced to produce IgG1 and IgG2 subclass-specific suppressive immunoglobulin-binding factors. Proc Natl Acad Sci USA 1983; 80 :2323-7.
26. Cooper MD. B lymphocytes. new development and function. N Engl J Med 1987; 317 : 1452-6.
27. Berger M, Immunoglobulin G subclass determination in diagnosis and management of antibody deficiency syndromes. J Pediatr 1987; 110 : 325-8.
28. Heiner DC. Recognition and management of IgG subclass deficiencies. Ped Inf Dis 1987; 6 : 235-8.
29. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. N Engl J Med 1986; 314 : 560-4.
30. Schwartz RS. Overview of the biochemistry and safety of a new native intravenous gamma globulin, IVIG,pH 4.25. Am J Med 1987; 83 (suppl 4A) : 46-51.