Immunoglobulin G (IgG) subclass deficiency in Thai children

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Summary

Background: **Patients with Immunoglobulin G (IgG) subclass deficiency may suffer from recurrent infections, mainly sino-pulmonary infection.**

Objective: **To determine the epidemiology of IgG subclass deficiency in Thai children at a tertiary care hospital and to compare the differences between children who were diagnosed with IgG subclass deficiency by using low level criteria [less than 2 standard deviation (SD) of normal levels for age] and by using low percentage criteria (proportion of each IgG subclasses/total IgG).**

Methods: **The study was a descriptive study of 55 children up to 15 years old with recurrent infections diagnosed as having IgG subclass deficiency but no acquired or other primary immune deficiencies except for IgA and/or IgM deficiency.**

Result: **Isolated IgG3 subclass deficiency was the most common IgG subclass deficiency (56.4%). IgG3 subclass deficiency, either isolated or combined with other IgG subclass deficiency, was found in 85.5% of the cases. The common age of onset was between birth and five years of age. The most common presenting symptom was recurrent sinusitis (83.6%). Majority of the cases (89.3%) were diagnosed by low percentage criteria while 12.7% were diagnosed by low level criteria. All cases with low levels of IgG subclass antibodies also had low percentages. There were no statistically significant differences in the clinical manifestations and management methods between the children who were diagnosed by low level and low percentage.**

Conclusion: **IgG3 subclass deficiency was the most common IgG subclass deficiency in Thai children. The most common presenting symptom was recurrent sinusitis. Although the diagnosis could be made in the patients with recurrent upper respiratory infection by using low level criteria, but the diagnosis should be considered when the low percentage criteria are met.** ***(Asian Pac J Allergy Immunol 2011;29:332-7)***

Key words: *IgG subclass deficiency, primary immune deficiency, recurrent sinusitis*

Abbreviations

IgG	=	Immunoglobulin G
SD	=	Standard deviation
PID	=	Primary immune deficiency
IVIG	=	Intravenous immunoglobulin

Introduction

Immunoglobulin G (IgG) subclass deficiency is one of the four most common primary immune deficiency (PID) diseases in children.[1] Patients with IgG subclass deficiency may suffer from recurrent infection, mainly sino-pulmonary infection. Some patients are subclinical but some experience severe infection that can be the cause of death.[2] Cases with chronic or severe infection may need long-term

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antibiotics, intravenous immunoglobulin (IVIG) and/or hospital admission which, affects the quality of life of the patients as well as their families. They may also become a financial burden to society and the country.[2]

IgG has four subclasses (IgG1, 2, 3 and 4) according to the difference in the proteins in the heavy chain. Each IgG subclass possesses different biological activities. IgG subclass deficiency can be coincident with other primary immune deficiency, such as IgA or IgM deficiency. Each IgG subclass deficiency can be found separately or together with other IgG subclass deficiencies, especially IgG1 with IgG3 deficiency and IgG2 with IgG4 deficiency.[2] The level of IgG subclass antibodies increases with age. The normal percentages of IgG subclass 1, 2, 3 and 4 to total IgG are 60-70, 20, 5-7 and 1-3% respectively.[3] IgG subclass deficiency is suspected when the children suffer from recurrent infections, especially sino-pulmonary infection. The diagnosis should be confirmed by measuring serum IgG subclass levels. According to the widely accepted criteria, the diagnosis is made when each IgG subclass level is less than 2 standard deviations (SD) of normal range for age group.[4-5]

In our experience, most children with recurrent bacterial infection have normal levels of IgG, IgG subclasses and normal results from other immunological investigations. In some of them, IgG subclass deficiency is still the most likely diagnosis. We proposed that the diagnosis of IgG subclass deficiency should be considered if the percentages of IgG 1, 2, 3 and 4 are less than 60, 20, 5 and 1% respectively.[3]

This study was performed to determine the epidemiology of IgG subclass deficiency in Thai children at a tertiary care hospital and to compare the differences between children who were diagnosed with IgG subclass deficiency by using low level criteria (less than 2 SD of normal levels for age) and by using low percentage criteria.

Methods

This is a descriptive study of children up to15 years old with recurrent infection during the last 15 years (1993-2008). Investigations to determine the underlying causes of recurrent infection were performed. Allergic rhinoconjunctivitis, asthma and infections were treated as recommended in the international clinical practice guideline for each disease. To be diagnosed with IgG deficiency patients should have serum IgG subclass levels lower than 2 SD of the normal levels for age or lower than 60, 20, 5 and 1% of IgG1, 2, 3, 4 respectively. They should have normal total serum IgG level without any acquired or other primary immune deficiencies, except IgA and/or IgM deficiency.

IgG subclasses were measured by nephelometry, using reagents and an automated system (SIEMENS). Pre-immunization and post-immunization pneumococcal antibody titers were performed by using an ELISA test for a combination of 23 serotypes. The patients had been followed with regard to their clinical and IgG subclass profiles for at least 2-3 years. This study was approved by ethics committee, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. After receiving informed consent from parents, demographic data such as age, sex, clinical manifestations, type of IgG subclass deficiency and treatment were recorded.

Statistical analysis

Data analysis was performed using computer database and SPSS statistical software (version 11.0). Fisher's exact test was used to compare the data of the patients diagnosed by low level and low percentage criteria.

Table 1. Distribution of IgG subclass deficiency in 55 Thai children.

IgG subclass deficiency	Number of patients n (%)
Isolated IgG 3 deficiency	31 (56.4)
IgG 2, 3 deficiency	9 (16.4)
IgG 2, 4 deficiency	6 (10.9)
IgG 1, 3 deficiency	5 (9.1)
Isolated IgG 2 deficiency	1 (1.8)
Isolated IgG 4 deficiency	1 (1.8)
IgG 3, 4 deficiency	1 (1.8)
IgG 2, 3, 4 deficiency	1 (1.8)

Results

Fifty five children with recurrent infection (34 boys and 21 girls) were included in this study. Two of them were dizygotic twins (a boy and a girl). All of the cases had low percentages of IgG subclasses. Seven cases (12.7%) had IgG subclass levels lower than 2 SD of the normal level for their age, together with low percentages. Forty eight cases (87.3%) had only low percentages of IgG subclasses. There was

no significant difference between the demographic data of the patients diagnosed by low level and low percentage criteria. Isolated IgG subclass deficiency was found in 33/55 cases (60%) as shown in Table 1. The most common isolated IgG subclass deficiency was isolated IgG3 (56.4%). Forty seven out of 55 patients (85.5%) had IgG3 subclass deficiency, either isolated or combined with other IgG subclass deficiency. IgG2 together with IgG3 deficiencies and IgG2 together with IgG4 deficiencies were found in 16.4 and 10.9% of the cases respectively. Two cases also had IgA deficiency (3.6%) and one had IgM deficiency (1.8%). None of them had autoimmune diseases or malignancies. Pre-immunization and post-immunization pneumococcal antibody titers were performed in 33 out of 55 patients. The result showed that 17 patients had specific antibody deficiency (30.9% of total and 51.52% of the tests performed). The prevalence of specific antibody deficiency was not different between the groups diagniosed with low level and low percentage criteria.

The most common age of onset of IgG subclass deficiency was birth to less than 5 years of age (78.1%), followed by 5 to less than 10 years of age (20%) and 10 to 15 years of age (1.8%). The mean age of onset was 3 years and 4 months old (minimum 2 months, maximum 10 years and 11 months).

The most common age of diagnosis was 5 to less than 10 years old (47.3%), followed by less than 5 years old (43.6%) and 10 to less than 15 years old (9.1%). Mean age at diagnosis was 5 years and 9 months (minimum 2 months, maximum 14 years and 8 months). Mean duration from the onset of symptom to the diagnosis was 2 years and 5 months. The most common clinical presenting symptom was recurrent upper respiratory infections (89.1%). The most common infection was sinusitis as shown in Table 2. Thirty patients (54.5%) had co-morbid diseases at the time of diagnosis, as shown in Table 3. The most common co-morbid disease was allergic rhinitis (21.8%), followed by asthma (14.6%).

In all of the patients, recurrent infection was treated with antibiotics. Six patients were admitted for intravenous antibiotics. Forty seven patients (85.5%) had recurrent infections after antibiotic therapy and needed preventative measures for recurrent infections. The methods of prevention of recurrent infections were oral antibiotic prophylaxis (69.1%) and intravenous immunoglobulin (IVIG) 400 mg/kg/every four weeks (36.4%). Forty two of 48 patients (87.5%) diagnosed by low percentage criteria received prevention, 35 patients with antibiotic prophylaxis and 18 patients with IVIG. Five out of 7 patients (71.4%) diagnosed by low level criteria received prevention, 3 patients with antibiotic prophylaxis and 2 patients with IVIG as shown in Table 4. The patients also received treatment for co-morbidities, according to the standard treatment of each disease. There was no significant difference in antibiotic prophylaxis and IVIG usage between the group diagnosed by percentage or level criteria (p <0.05). There were 6 cases (10.9%) admitted to the hospital because of severe infection, 5 with serious sinusitis and one with secondary bacterial infection from severe atopic dermatitis. All of the cases needed intravenous antibiotics. The mean duration of admission was 11 days (4-29 days). All of the admitted cases were diagnosed by low percentage criteria.

In the 2-to-10 year follow-up, half of the cases showed normal level or percentage of IgG subclasses for age especially in the younger age group. The episodes and severity of bacterial infection decreased in most of the cases. Prophylactic antibiotic or IVIG could be stopped in more than half of the cases who need prophylaxis. The patients in this group had no frequent or serious bacterial infection although the IgG subclass levels or the percentage were still lower than normal levels for age in some of them.

Table 2. Presenting symptoms of IgG subclass deficiency

Presenting symptoms	Number of patients n* (%)
Recurrent sinusitis	46 (83.6)
Recurrent pneumonia, bronchitis, atelectasis	6 (10.9)
Recurrent otitis media	3 (5.4)
Recurrent rhinitis with positive family history of primary immunodeficiency	2 (3.6)
Recurrent skin infection	1 (1.8)
Chronic diarrhea with malabsorption	1 (1.8)

* Some children had more than one presenting symptom

Discussion

Antibody deficiency is the most common PID in Thailand (46%)[6] similar to other countries worldwide.[1]

Table 3. Co-morbidities in children with IgG subclass deficiency.

Co-morbidities	Number of patients N=30* (%)
Allergic rhinitis	12 (21.82)
Asthma	8 (14.55)
Non allergic rhinitis	7 (12.73)
Allergic conjunctivitis	3 (5.45)
Obstructive sleep apnea	2 (3.64)
Atelectasis	1 (1.82)
Nasal polyp	1 (1.82)
Cow milk protein allergy	1 (1.82)
Gastroesophageal reflux	1 (1.82)
IgM Nephropathy	1 (1.82)
β-Thal/HbE	1 (1.82)

* Some children had more than one co-morbid

Table 4. The prevention of recurrent infection for each criterion of diagnosis.

Methods of prevention	Criteria of diagnosis n* (%)		Total n* (%)
	Percentage (N=48)	Level+Percentage (N=7)	(N=55)
Antibiotic prophylaxis	35 (72.9)	3 (42.9)	38 (69.1)
Intravenous immunoglobulin	18 (37.5)	2 (28.6)	20 (36.4)
Total cases with prevention	42 (87.5)	5 (71.5)	47 (85.5)

*Some children received more than one treatment

Ig G subclass deficiency was found in 32.84% of Thai children with immunodeficiencies.[6] IgG3 subclass deficiency was the most common IgG subclass deficiency (85.5%) in our study group with recurrent infections, followed by IgG2 subclass deficiency (30.9%). This finding is supported by previous studies in children[7,8] and adults.[8,9] However, some studies have shown that IgG2 deficiency was the most prevalent IgG subclass deficiency in pediatric patients.[10-12] This also differed from the results of another previous study that showed that IgG4 deficiency was the most common IgG subclass deficiency in children and IgG3 subclass deficiency was the most common in adults.[13]

IgG2 subclass deficiency is associated with a reduced immune response to polysaccharide antigens so the patients with IgG2 subclass deficiency are prone to infections with encapsulated organisms.[10]

Whether IgG3 subclass deficiency really persists is still controversial. IgG3, comprising 4–8% of total serum IgG, is the most susceptible to proteolytic digestion. The half-life of IgG3 is much shorter (7–9 days) in comparison to the half-lives of the other IgG subclasses (21–23 days). IgG3 is also an excellent activator of the complement system and it is directed predominantly towards protein antigens.[14] Furthermore, IgG3 binds with high affinity to Fc receptors on macrophages and thus may be important in antibody-mediated phagocytosis.[15] These factors may explain why patients with isolated IgG3 deficiency present with recurrent upper respiratory tract infections. IgG3 is responsible for the primary immune response to *Moraxella catarrhalis* and the M component of *Streptococcus pyogenes*, which are the pathogens responsible for upper and lower respiratory infections.[16,17] In contrast, there was a report that patients with complete absence of IgG3 due to gene deletion in the heavy chain constant regions have no infectious complications.[8] Some authors who believe that IgG3 subclass deficiency is not the cause of recurrent bacterial infection have suggested that during bacterial infection, the IgG3 subclass is low because of its short half life.

In this study, the most common age of onset was birth to 5 years old. The majority of reported studies for IgG subclass deficiency have been in children.[1-4] It is known that IgG1 and IgG3 levels increase as children grow up and reach adult levels earlier than the IgG2 and IgG4 subclasses.[18] The IgG subclass level was reported to reach normal levels by the age of 5.[1] This is in contrast to the observation from our study that more than half of the patients still had symptoms after the age of 5 years.

A previous study suggested that the diagnosis of IgG subclass deficiency should be based on strict criteria: 1) a history of recurrent bacterial infections, primarily respiratory; 2) impaired response to immunization with protein and/or polysaccharide antigens; 3) significant reductions in serum concentrations of one or more IgG subclasses; 4) age 4 years or older. (The last criterion is controversial).[19]

In our study, all of the cases had low percentage of IgG subclasses. Twelve point seven percent of cases also had IgG subclass levels lower than 2 SD of normal level for age. There was no significant difference between the demographic data of the

patients diagnosed by low level criteria and low percentage criteria. This might be due to small number of the cases diagnosed by low level criteria. However, low percentages of IgG subclasses is a valuable criterion for screening of IgG subclass deficiency in the cases with chronic or recurrent bacterial infections.

The standard method of diagnosis of IgG subclass deficiency is the level less than 2 SD[4,5] but some papers showed that normal IgG subclass levels did not exclude IgG subclass deficiencies. In this study, we found that some of the patients with recurrent bacterial infections had normal levels for age but a low percentage of IgG subclass. We thought that it might be due to specific antibody deficiency but this was found only in 51.5% of the cases in which pneumococcal titers, pre and post vaccination, were checked. Previous studies have reported that IgG subclass deficiency might found together with specific antibody deficiency.[20,21] One study showed that 42% of IgG subclass deficiency cases had specific antibody deficiency.[21] We found that the prevalence of specific antibody deficiency was not different between the group diagnosed using low level criteria and that meeting low percentage criteria.

The most common clinical presenting symptom in our study was recurrent bacterial infection, especially infection of upper and lower respiratory tract. This is supported by previous reports.[1-5,7-8,20-21] The most common co-morbid disease in our study was allergic rhinitis (21.8%), followed by asthma (14.6%). IgG subclass deficiency has been reported to occur with co-morbidities such as asthma, allergic rhinitis and several autoimmune diseases.[9,22] Asthma has been found in 40-50% of subjects with IgG3 subclass deficiency.[23,24] One paper demonstrated IgG3 deficiency in over 33% of a cohort of 310 wheezy children below the age of 3 years.[22] IgG and IgG subclass deficiency should be considered in patients presenting with recurrent upper and lower respiratory infections, particularly in those with respiratory allergies or autoimmune diseases.[8,9]

In all of our patients, recurrent infection was treated with antibiotics. Six patients were admitted for intravenous antibiotics. Forty seven patients (85.5%) had recurrent infections after antibiotic therapy and needed preventive therapy, 69.1% with oral antibiotic prophylaxis and 36.4% with intravenous immunoglobulin (IVIG). There was no significant difference in the severity of symptoms, the rate of admission, antibiotic prophylaxis and IVIG usage between the group diagnosed by percentage criteria and by level criteria, $p > 0.05$. Prophylactic antibiotics are the first line treatment for recurrent infections.[25-27] IVIG treatment was indicated in the case that bacterial infection was serious or could not be treated with antibiotics alone or occurred frequently.[2,23,28-29] The dose should be 400–600 mg/kg/3–4 weeks intravenously or 100 mg/kg/week subcutaneously.[2]

During the 2-to-10 year follow-up period, half of the cases developed normal levels or normal percentages of IgG subclasses for age, especially in the younger age group. More than half of the cases were able to stop prophylactic antibiotics or IVIG within 3 years without frequent or serious bacterial infection, although their IgG subclass levels or percentages were lower than normal for their ages. More cases should be studied for a longer period of follow up to confirm this. A previous study suggested that although IgG subclass levels might normalize in 30 to 40% of the patients at about 6 years of age, most took longer to recover and the deficiency might never resolve in some patients with isolated IgG2 deficiencies.[7]

In conclusion, IgG3 subclass deficiency was the most common IgG subclass deficiency in Thai children at a tertiary hospital. The most common presenting symptom was recurrent sinusitis. The diagnosis can be made in patients with recurrent respiratory infections by using the criteria of IgG subclass levels lower than 2 SD of normal level for age or the percentage of IgG1, 2, 3, 4 to total IgG lower than 60, 20, 5 and 1% respectively.

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References

1. Stiehm ER. The four most common Pediatric immunodeficiencies. Journal of Immunotoxicology. 2008;5:227-34.
2. Ochs HD, Stiehm ER. Antibody deficiencies. In: Steihm ER. ed. Immunologic disorders in infants and children, 5th ed. Philadelphia: WB Saunders; 2004. p. 309-462.
3. Blaese RM, Winkelstein J. IgG subclass deficiency and specific antibody deficiency. In Towson MD, ed. Patient & Family Handbook for Primary Immunodeficiency Diseases. Immune Deficiency Foundation; 2007. p. 51-3.

4. Herrod HG. IgG subclass deficiency. Allergy Proc. 1992;13:299-302.
5. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Clin Immunol. 1999;93:190–7.
6. Benjasupattananan P, Simasathein T, Vichyanond P, Leungwedchakarn V, Visitsunthorn N, Pacharn P, et al. Clinical characteristics and outcomes of primary immunodeficiencies in Thai children: An 18-year experience from a tertiary care center. J Clin Immunol. 2009;29:357–64.
7. Karaca NE, Karadeniz C, Aksu G, Kutukculer N. Clinical and laboratory evaluation of periodically monitored Turkish children with IgG subclass deficiencies. Asian Pac J Allergy Immunol. 2009;27:43-8.
8. Oxelius VA, Hanson LA, Bjorkander J, Hammarstrom L, Sjoholm A. IgG3 deficiency: common in obstructive lung disease. Hereditary in families with immunodeficiency and autoimmune disease. Monogr Allergy. 1986;20:106–15.
9. Kim JH, Park HJ, Choi GS, Kim JE, Ye YM, Nahm DH, et al. Immunoglobulin G subclass deficiency is the major phenotype of primary immunodeficiency in a Korean adult cohort. J Korean Med Sci. 2010;25:824-8.
10. Kuijpers TW, Weening RS, Out TA. IgG subclass deficiencies and recurrent pyogenic infections, unresponsiveness against bacterial polysaccharide antigens. Allergol Immunopathol (Madr). 1992;20:28-34.
11. Chong CY, Lee TL, Ho MHK, Lee SL, Lau YL. Review of IgG subclass and IgA deficiency in a tertiary center. HK J Paediatr. 2006;11:205-9.
12. Ozkan H, Atlihan F, Genel F, Targan S, Gunvar T. IgA and/or IgG subclass deficiency in children with recurrent respiratory infections and its relationship with chronic pulmonary damage. J Investig Allergol Clin Immunol. 2005;15:69-74.
13. Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. Clin Experimental Immunol. 2009;159:344–50.
14. Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? Curr Allergy Asthma Rep. 2002;2:356–60.
15. Shackelford PG. IgG subclasses: importance in pediatric practice. Pediatr Rev. 1993;14:291–6.
16. Jefferis R, Kumararatne DS. Selective IgG subclass deficiency: quantification and clinical relevance. Clin Exp Immunol. 1990;81:357-67.
17. Kim CH, Kim DG, Park SH, Choi JH, Lee CY, Hwang YI, et al. Incidence of immunoglobulin G subclass deficiencies in patients with bronchiectasis and the clinical characteristics of patients with immunoglobulin G subclass deficiency and bronchiectasis. Tuberc Respir Dis. 2009;66:295-9.
18. Insel RA, Looney RJ. The B-lymphocyte system: fundamental immunology. In: Stiem ER, Ochs HD, Winkelstein JA. eds. Immunologic disorders in Infants and children. Philadelphia: Elsevier Saunders; 2004. p. 53-84.
19. Lawton AR. IgG subclass deficiency and the day-care generation. Pediatr Infect Dis J. 1999;18:462-6.
20. Ricardo U, Hidalgo H, Moore C, Lily E. Post-immunization pneumococcal antibody titers and IgG subclasses. Pedriatr Pulmonol. 1998;22:167-73.
21. Gross S, Blaiss MS, Herrod HG. Role of immunoglobulin subclasses and specific antibody determinations in the evaluation of recurrent infection in children. J Pediatr. 1992;121:516-22.
22. Ones U, Guler N, Somer A, Salman N, Yalcin I. Low immunoglobulin G3 levels in wheezy children. Acta Paediatr. 1998;87:368–70.
23. Soderstrom T, Soderstrom R, Enskog A. Immunoglobulin subclasses and prophylactic use of immunoglobulin in immunoglobulin G subclass deficiency. Cancer. 1991;68:1426-9.
24. de Moraes Lui C, Oliveira LC, Diogo CL, Kirschfink M, Grumach AS. Immunoglobulin G subclass concentrations and infections in children and adolescents with severe asthma. Pediatr Allergy Immunol. 2002;13:195-202.
25. American Academy of Pediatrics. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108:798-808.
26. Paradise JL. Antimicrobial prophylaxis for recurrent otitis media. Ann Otol Rhino Laryngol. 1992;101:33-6.
27. Ahuja GS, Thompson J. What role for antibiotics in otitis media and sinusitis? Postgrad Med. 1998;104:93-9,103-4.
28. Bonilla FA, Bernstein L, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005; 94:S1–60.
29. Finocchi A, Angelini F, Chini I, Di Cesare S, Cancrini C, Rossi P, et al. Evaluation of the relevance of humoral immunodeficiencies in a pediatric population affected by recurrent infections. Pediatr Allergy Immunol. 2002;13:443-7.