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CASE REPORT

IgA Deficiency: A Report of Three Cases from Thailand

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SUMMARY Selective IgA deficiency has been reported to be the most common primary immunodeficiency disease in Western countries. A markedly lower frequency of this condition has been reported in the Japanese population. While most of the IgA deficient cases are healthy, some patients develop significant recurrent sinopulmonary infections, allergic disorders and autoimmune diseases. Herein, we report three cases of IgA deficiency among Thai patients, all of whom suffered from chronic sinopulmonary infections. Two of the three patients had absolute IgA deficiency while the third had a partial IgA deficiency. The associated conditions found in these three patients were deficiencies of an IgG subclass, allergic rhinitis and lupus nephritis. The youngest child (5 years old boy with lupus nephritis) expired from *Pneumocystis carrinii* pneumonia complicated with adult respiratory distress syndrome.

IgA is the immunoglobulin which plays a key role in mucosal immunity. It is important in preventing infectious agents from penetrating through mucosal surfaces of the respiratory, gastrointestinal and genitourinary tracts. Deficiency of IgA can cause infections of sinopulmonary, gastrointestinal systems and, rarely, severe recurrent infections leading to permanent intestinal and airway damages, with or without associated autoimmune disorders. IgA deficien-cy is defined as a serum IgA level of less than 5 mg/dl.[1] Patients with partial IgA deficiency have also been recognized as those with IgA levels greater than 5 mg/dl but less than 2 standard deviations below age-adjusted mean levels.[1] IgA deficiency without deficiency of other immunoglobulins, and with normal antibody and cell-mediated immunity is defined as selective IgA deficiency.[2] The prevalence of IgA deficiency ranges from 1:223 to 1:1,000 in community populations[3] and from 1:400 to 1:3,000 among healthy blood donors.[4] Thus, it is commonly quoted to be the most common condition among all primary immunodeficiency diseases. In Asian countries, IgA deficiency has occasionally been reported from Japan,[5] Korea,[6] China,[7] Taiwan,[8] Russia,[9] India,[10] Sri Lanka,[11] Singapore,[12] Malaysia,[13] Saudi Arabia[14] and Israel.[15] However, prevalence of IgA deficiency may be lower in Asia according to a report from Japan indicating a prevalence of 1:18,500.[5] As the condition is rarely observed in Thailand, it is our objective to report three Thai children with IgA deficiency from the Pediatric Allergy and Immunology Clinic, Faculty of Medicine Siriraj Hospital with various clinical spectrums and a brief review of the literature.

CASE REPORTS

Case 1: IgA deficiency with chronic sinusitis/otitis media

A 15-year-old girl presented to a private hospital with a history of recurrent rhinorrhea since 3 years of age. She was diagnosed as having chronic sinusitis with bilateral serous otitis media. Apart from treatments with multiple courses of antibiotics and with prophylactic antibiotics, she underwent myringotomy with tympanostomy tube insertion and with antral washout of both maxillary sinuses at 6 years of age. The antral washout specimens were taken from both sinuses and were sent for bacterial cultures which yielded no growth of significant pathogen. Her skin prick test was negative to common aeroallergens in Thailand. Immunologic work ups at 6 years of age revealed

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IgG 1,087 mg/dl, IgM 181 mg/dl and IgA levels (on two different determinations) of less than 10 and 5 mg/dl. IgG subclass levels were not available at the time of her initial presentation. The diagnosis of IgA deficiency was then made. She continued to experience recurrent respiratory symptoms requiring repeated courses of antibiotics. On her last visit, at 15 years of age, she still had chronic sinusitis and a perforation of the right tympanic membrane. Immunologic studies on her last visit demonstrated a low IgA level (< 20 mg/dl) as well as levels of IgG 1,250 mg/dl, IgM 142 mg/dl, IgG_1 687 mg/dl, IgG_2 397 mg/dl, IgG_3 55 mg/dl and IgG_4 6 mg/dl (0.5% of total IgG). A diagnosis of IgA deficiency with IgG_4 deficiency was entertained.

Case 2: IgA deficiency with recurrent sinusitis/otitis media and allergic rhinitis

An 11-year-old Thai girl presented to the Siriraj Hospital with a history of chronic rhinosinusitis since 6 years of age. She was also snoring and had a breathing difficulty during sleep. On physical examination, chronic rhinosinusitis and bilateral otitis media with effusion was observed. Apart from treatment with repeated courses of oral antibiotics, she underwent myringotomy with tympanostomy tube insertion bilaterally, together with adenoidectomy at 7 years of age. Her laboratory investigations included positive skin prick test (3+) to house dust mites, IgG 2,375 mg/dl, IgM 372 mg/dl, IgA less than 5 mg/dl, IgG_1 1,380 mg/dl, IgG_2 365 mg/dl, IgG_3 76 mg/dl and IgG_4 3.5 mg/dl. The level of IgG_4 was less than 1% of her total IgG. Her ANA was positive (1:40 speckled type) but other immune profiles (Anti-DNA, RF, LE, anti-Sm, anti-RNP) were negative. The diagnosis of IgA deficiency with IgG_4 deficiency and with allergic rhinitis was made. Despite multiple courses of antibiotics and measures to control house dust mite allergens, she continued to exhibit chronic respiratory symptoms. Allergen immunotherapy with house dust mite extract was therefore initiated. She responded rapidly to the treatment with a significant resolution of her respiratory symptoms. After 2 years of allergen immunotherapy, immunoglobulin levels were repeated. Her IgA was still less than 23.5 mg/dl, IgG 2,606 mg/dl, IgM 298.6 mg/dl, IgG_1 1,720 mg/dl, IgG_2 490.7 mg/dl, IgG_3 49.2 mg/dl and IgG_4 less than 16.5 mg/dl.

Case 3: IgA deficiency with lupus nephritis

A 5 year-old Thai boy presented with a history of recurrent pneumonia and chronic otitis media since 5 months of age. He also suffered frequently recurrent superficial skin infections. He was hospitalized on several occasions during which episodes of neutropenia were established off and on, usually associated with high fever. On physical examination, he had a perforated right ear drum, but no palpable cervical lymph nodes. Laboratory studies revealed IgG 736 mg/dl, IgM 56 mg/dl, IgA 13 mg/dl, IgG_1 1,330 mg/dl, IgG_2 73.4 mg/dl (4.4% of total IgG), IgG_3 245.1 mg/dl and IgG_4 level less than 14.6 mg/dl (< 0.88% of total IgG). CD_3, CD_4, CD_8 counts and CD_4/CD_8 ratio were all normal (CD_3 3,392 cells/mm^3, CD_4 1,407 cells/mm^3, CD_8 1,685 cells/mm^3 and CD_4/CD_8 ratio = 0.84). His CD_{19} counts on two measurements were 121 (2.77% of total lymphocytes) and 220 cells/mm^3 (5.92% of total lymphocytes). Delayed type hypersensitivity reaction was positive for *Candida* and DTP. A milk precipitin test was negative. His skin prick tests to aeroallergens were negative. A diagnosis of IgA with IgG_2 and IgG_4 deficiency was made. During his admission to Siriraj Hospital, an episode of hematuria with high blood pressure, hepatomegaly and neutropenia was observed. His serum BUN, creatinine, albumin and globulin levels were normal. ANA was positive (1:160 speckled type), other autoimmune profiles including VDRL, anti-DNA, LE cell preparation and anti-SM were all negative. The C_3 level was 70.4 mg/dl and the ASO titer was less than 50 IU/ml. A bone marrow aspiration demonstrated a maturation arrest of myeloid series at the promyelocytic stage. No bacterial pathogen was isolated from blood, urine and bone marrow aspiration cultures. A renal biopsy revealed WHO class-IV diffuse glomerulonephritis. A diagnosis of lupus nephritis was made and he was started on prednisolone 2 mg/kg/day. On his last hospitalization, he developed severe pneumonia with respiratory failure. His chest X-ray showed diffuse patchy infiltration and a diagnosis of adult respiratory distress syndrome (ARDS) was made. A complete blood count showed a normal neutrophil count with a normal C_3 level (1,020 μg/ml), a negative ANA with low immunoglobulin levels (IgG 411 mg/dl, IgA 23 mg/dl and IgM 25 mg/dl). A high LDH level of 6,844 U/L was observed. He was intubated and placed on a respirator along with administration of broad spectrum antibiotics, methylprednisolone and intravenous immunoglobulin. Hemocultures revealed no growth of pathogens. Bacterial growth from tracheal suctions consisted only of normal flora. Unfortunately, he did not survive this illness. A lung necropsy was performed and demonstrated evidence of *Pneumocystis carinii* pneumonia.

DISCUSSION

IgA deficiency has been reported to be the most common primary immunodeficiency disease

in Western countries.[2,16] In the most recent studies of the immunoglobulin levels in 300 healthy Thai children, no IgA deficiency case was found.[17,18] Despite active investigation among our patients with recurrent infections, we have been able to identify only three patients with IgA deficiencies from the large Allergy/Immunology Clinic (over 6,000 outpatient visits per year). Two of these three patients reported here had an absolute IgA deficiency whereas the other had a partial IgA deficiency. Associated conditions were IgG subclass deficiencies, allergic rhinitis and lupus nephritis. Clinical characteristics of the patients are tabulated in Table 1. Report of IgA deficiency case has not been previously performed from Thailand. we provided evidence of a low prevalence of IgA deficiency in this country.

IgA deficiency is a genetically determined disease. The mode of inheritance could be either autosomal recessive[20] or autosomal dominant.[21] However, most were sporadic cases. Some patients were found to have associated chromosomal abnormalities especially of chromosome 18.[22] IgA deficiency was commonly found among family members of patients with common variable immunodeficiency (CVID).[1] These two conditions share the clinical features. Espanol *et al.*[23] reported cases of CVID diagnosed after IgA deficiencies had been detected. In our reported third case, a low number of B lymphocytes was observed preceding a progressive decline in IgG levels. He could have developed CVID although most patients with CVID had normal numbers of B lymphocytes in their peripheral blood.[24] IgA deficiency has been observed to be of transient in nature in some patients, particularly those with partial deficiency and in children under 5 years of age.[25] Besides a genetic factor, environmental factors have been identified as cause of IgA deficiency such as associations with drug therapy (phenytoin,[26] sodium valproate,[27] sulfasalazine,[28] penicillamine,[29] cyclosporin,[30] gold,[31] fenoclofenac[32] and captopril[33]) and with infections such as congenital rubella[34] and Epstein-Barr virus infections.[35] The immunopathogenesis of IgA deficiency has been linked to conditions such as inadequate or defective T helper cells,[36] IgA-specific T suppressor cells,[37] intrinsic B cell defects[36] or the presence of maternal anti-IgA antibody.[38]

Despite the fact that a majority of subjects with IgA deficiency were asymptomatic,[1] some were diagnosed because of recurrent sinopulmonary and gastrointestinal infections. Herrod[39] reported partial IgA deficiency being the most common condition seen among 74% of children with recurrent infections, moreover, this persistent partial immunoglobulin deficiency lasted for several years. Among patients with recurrent infections, deficiencies of IgG subclasses particularly IgG_2 and IgG_4 associated

Table 1 Clinical characteristics of the patients

	Case #1	Case #2	Case #3
Age (years)	15	11	5
Sex	Female	Female	Male
Age of onset of infection	3 years	6 years	5 months
Type of infections			
Chronic rhinosinusitis	+	+	-
Recurrent pneumonia	-	-	+
Otitis media	+	+	+
Associated diseases			
Allergic rhinitis	-	+	-
IgG subclass deficiency	IgG_4 deficiency	IgG_4 deficiency	IgG_2/IgG_4 deficiency
Autoimmune diseases	-	-	Lupus nephritis
Serum IgA level (mg/dl)	< 5	< 5	13
IgG subclass level (mg/dl)			
G_1	687	1,380	1,330
G_2	397	365	73.4*
G_3	55	76	245.1
G_4	6*	3.5*	< 14.6*

*Lower than normal for age in Asian children.[19]

with IgA deficiency have been found more frequently than IgA deficiency alone.[40] In this report, all three patients had associated IgG subclass deficiencies. Several IgA-deficient individuals had an increased absorption of food and bacterial antigens from the intestinal tract. This could lead to detectable amounts of these proteins in the blood, a subsequent increase in levels of specific antibodies, and the development of immune complexes in the blood.[41] Precipitating milk antibodies have been found in 50% of patients with this disorder.

In one survey of 30 IgA deficient patients, 37% were found to have associated autoimmune diseases, autoimmune phenomena or both. These conditions included SLE, rheumatoid arthritis, dermatomyositis, pernicious anemia, thyroiditis, Sjogren's syndrome, Coombs' positive hemolytic anemia, idiopathic Addison's disease and chronic active hepatitis. Rheumatoid arthritis and SLE were the most frequent conditions reported.[2] Five percent of patients with SLE were reported to have IgA deficiency.[42] It is intriguing that one of our patients (case #3, the 5 years old boy) developed SLE at a very young age. The prevalence of IgA deficiency in male SLE patients has been reported to be 9.7%.[43] Patients with autoimmune diseases, with and without selective IgA deficiency, had similar clinical presentations.[2]

IgA deficiency could also be associated with increased frequency of allergic disorders.[2] From the most recent study, 4 out of 92 asthmatic Asian children were found to have selective IgA deficiency.[12] The incidence of atopy could be as high as 55% as observed in series reported by Buckley *et al.*[16] Selective IgA deficiency has been associated with gastrointestinal disorders especially Heiner's syndrome.[44] Carcinoma (particularly adenocarcinoma of the stomach) and lymphoma have been reported to be associated with IgA deficiency as well.[45,46]

The treatment of IgA deficiency depends on the associated specific conditions and ranges from aggressive broad spectrum antibiotics in patients with recurrent sinopulmonary infections[1,2] to allergen immunotherapy in patients with certain allergic disorders. No study has investigated the role of allergen immunotherapy in patients with selective IgA deficiency together with allergic manifestations. During immunotherapy, an increase in IgG_1 and IgG_4 antibodies specific to the allergen used for immunotherapy has been detected.[47] In our second patient, IgA and IgG_4 levels remained low after allergen immunotherapy despite the fact that the patient had improved clinically. The combined deficiencies of IgA with IgG_4 could have resulted from a mutation or a deletion of genes encoding the Fc portion of IgA and nearby IgG_4 isotypes. Antibodies to IgA have been found in about 40-50% of patients with IgA deficiency. Pre-existing anti-IgA antibody could cause anaphylactic reactions whenever plasma or blood transfusions are given to these patients.[48] Immunoglobulin replacement therapy should be given with caution, using immunoglobulin preparations with low IgA concentrations (< 1 μg/ml) and should be limited to those with concomitant IgG subclass deficiencies with recurrent infections. Prior to blood transfusion, IgA deficient patients should be checked for the presence of anti-IgA antibody. If anti-IgA is detected, blood products should be washed with saline before infusion. The prognosis for patients with IgA deficiency is the same as that for associated disorders. With only three cases of IgA deficiency reported from this country during the last decade, prevalence of IgA deficiency in Thailand could have been as low as previously reported from Japan.

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