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Review of IgG Subclass and IgA Deficiency in a Tertiary Center

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Abstract We retrospectively reviewed the clinical characteristics of twenty patients with IgA and/or IgG subclass deficiency attending a tertiary centre. The median age at diagnosis was 1.21 years and the median duration of follow up was 3.83 years. The most common presenting symptom was recurrent sinopulmonary infections (45%). This was followed by refractory asthma (30%), autoimmunity (15%), and other atopic manifestations (10%). Only one out of twenty patients presented with chronic gastrointestinal disease, which contrasted with the majority of previous literature. Three patients had significant pulmonary complications including bronchiolitis obliterans, bronchiectasis and pulmonary fibrosis. The prevalence of IgA deficiency in Hong Kong Chinese population is yet to be established, though it appears not as prevalent as that in western population.

Key words Chinese; IgA deficiency; IgG subclass deficiency

Introduction

Selective IgA deficiency is the most common primary immunodeficiency and the estimated prevalence ranges from 1 in 400 to 3000 from various studies.[1-3] Most of the IgA-deficient patients are asymptomatic but some of them are susceptible of recurrent sinopulmonary infections, atopic manifestations and asthma, autoimmunity and gastrointestinal tract disease.[1,3-5] It is also known that IgA deficiency is associated with ataxia telangiectasia and chromosomal abnormalities (18q syndrome or ring chromosome 18). IgA deficient individuals with anti-IgA IgG antibodies on receipt of blood products may have anaphylactoid reaction. About 15-20% of IgA-deficient patients also have IgG subclass deficiency.[3]

Synthesis of IgG2 and IgG4 lags relative to IgG1 and IgG3 during normal development. IgG2 is the most prevalent IgG subclass deficiency in paediatric patients and it is believed that IgG2 is responsible for immune response to polysaccharides antigens, especially in the context of infection with *Streptococcus pneumoniae* and *Haemophilus influenzae*. IgG1 and IgG3 are responsible for the antibody response to protein antigens. IgG subclass deficiency may occur as an isolated single IgG subclass deficiency or in combination with other IgG subclasses. Similar to IgA deficiency, IgG subclass-deficient patients can present with recurrent sinopulmonary infections, asthma, atopy and autoimmunity.[6,7]

There is a lack of epidemiological and clinical study on IgA and IgG subclass deficiency in Hong Kong. We summarised hereto our experience in managing patients with IgA and IgG subclass deficiency in a tertiary centre.

Method

Case records of all patients with IgA and/or IgG subclass deficiency attending Paediatric Immunology Clinic at Queen Mary Hospital from July 1988 to December 2005 were retrospectively reviewed. These patients were referred

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for work up of primary immunodeficiency. Demographic, clinical presentation and absolute levels of immuno-globulins were studied. The diagnosis was made according to the age-specific references of immuno-globulins of healthy Chinese children (Appendix 1 and 2) established in our previous studies.[8,9] Selective IgA deficiency is defined as the IgA level at two standard deviations below the normal mean for age in the presence of normal serum IgG and IgM levels. IgG subclass deficiency is defined as the serum IgG subclass level at two standard deviations below the subclass normal mean for age in the presence of normal total IgG level.

Results

A total of 20 patients (Male: Female =13:7) fulfilled the diagnostic criteria was studied. The median age of at diagnosis was 1.21 years (range: 0.42 to 11.02) and the median duration of follow up was 3.83 years (range: 0.75 to 15.75 years). Eleven (55%) patients had IgG subclass deficiency, 5 (25%) had IgA deficiency and 4 (20%) with combined IgG subclass and IgA deficiency. IgG2 deficiency (9/15 patients, 60%) was the most common IgG subclass deficiency in our cohort and Table 1 enlisted the individual diagnoses and absolute levels of immunoglobulins.

The presenting symptoms with specific diagnoses of underlying immunodeficiency were summarised in Table 2. Recurrent infections accounted for the majority of patients (70%). Respiratory tract was the predilected site of infection as 9 patients (45%) had recurrent sino-pulmonary infections while the rest had infections occurring at other sites including urinary tract, orbits, gastrointestinal tract and cervical lymph nodes. Severe allergic manifestations were also common presenting problems in our cohort. Two (10%) had severe atopic eczema with allergic rhinitis and 6 had patients (30%) had severe asthma. Three patients (15%) presented with autoimmune problems, each 1 of polyarticular juvenile idiopathic arthritis, Henoch-Schonlein purpura and juvenile dermatomyositis. Only 1 patient had recurrent diarrhoea without identifiable pathogens while other chronic gastrointestinal tract disease like inflammatory bowel diseases, giardiasis, or celiac disease was not found.

Table 1 Specific diagnoses and absolute immunoglobulin levels

Patient	Sex	Age at presentation (years)	Diagnosis	Absolute value (mg/dL)						
				IgG	IgA	IgM	IgG1	IgG2	IgG3	IgG4
1	M	0.80	IgA	598	4	198	335	75	68	20
2	F	0.80	IgA	795	7	253	399	68	36	23
3	M	1.80	IgA	822	15	128	618	95	80	26
4	F	6.70	IgA	714	64	108	ND	ND	ND	ND
5	F	11.00	IgA	1,238	18	107	1,164	224	70	14
6	F	0.40	IgA+ IgG2	827	<16	118	360	60	64	18
7	M	0.80	IgA+ IgG2	976	6	81	800	69	42	39
8	M	0.80	IgA+ IgG2	597	16	89	337	30	59	4
9	M	0.60	IgA+IgG2+IgG4	504	12	73	225	16	57	0
10	M	4.40	IgG1	802	122	262	349	155	43	31
11	M	6.50	IgG1+ IgG3	579	112	78	360	210	18	11
12	F	1.10	IgG1+ IgG4	662	645	92	420	210	88	5
13	M	0.60	IgG2	688	68	82	289	64	34	15
14	M	1.00	IgG2	580	294	59	174	37	648	5
15	F	1.30	IgG2	602	22	102	291	4	22	7
16	M	3.40	IgG2	638	109	200	288	44	53	18
17	F	6.10	IgG2+ IgG4	713	92	74	722	97	89	3
18	M	0.40	IgG3	238	12	33	420	45	14	5
19	M	3.90	IgG3	1,118	104	84	448	397	0	24
20	M	5.00	IgG3	1,230	108	226	690	410	15	27
Total 20	M:F 13:7	Median 1.2								

Abbreviation: ND=not done

Table 2 Clinical presentation and specific diagnoses

Presentation	Frequency	Specific diagnosis(n)
Infection		
Recurrent sino-pulmonary	9/20	IgA(1), IgA+ IgG2(2), IgG1(1), IgG2(2), IgG3(1), IgG1+IgG3(1), IgG1+IgG4(1)
Orbital cellulitis	1/20	IgA
Cervical abscess	1/20	IgG3
Peri-anal abscess	1/20	IgG3
Recurrent diarrhoea	1/20	IgA
Allergy		
Refractory asthma	6/20	IgG1(1), IgG2(3), IgG1+IgG4(1), IgG1+IgG3(1)
Refractory eczema	2/20	IgG2+IgG4+IgA(1), IgG2 + IgA (1)
Autoimmunity		
JIA	1/20	IgG2 + IgG4
JDM	1/20	IgA
HSP	1/20	IgG2

Abbreviations: n= number of patient; JIA= Juvenile idiopathic arthritis; JDM= Juvenile dermatomyositis; HSP= Henoch Scholein purpura.
One patient can present with more than one feature.

None of our patients required regular intravenous immunoglobulin therapy or antibiotics prophylaxis. Coverage with *Pneumococcus* and *Haemophilus influenzae* vaccine was not a routine practice as it has been shown that the response was sub-optimal in patients with IgG subclass deficiency. Only 2 patients had received Pneumovax vaccine and 2 had both Hib and Pneumovax vaccines. None was given the conjugated pneumococcal vaccine. Post vaccination antibody titers however were not ascertained in these patients. The prognosis in our cohort was generally satisfactory. Only 3 had long-term complications including bronchiolitis obliterans, bronchiectasis and pulmonary fibrosis, all belonging to the group of patients presented with recurrent sinopulmonary infections.

Discussion

IgA deficiency is the most common primary immunodeficiency reported in the literature. However the prevalence was often derived from studying healthy blood donors[2,10] as most of the IgA-deficient individuals were asymptomatic. A multi-ethnic study of 33171 Chinese children found the incidence of selective IgA deficiency was 1 in 4100 (0.024%).[11]

IgA deficiency is a heterogeneous disease with variable presentations ranging from asymptomatic to recurrent sinopulmonary infections and/or gastrointestinal tract infections. Autoimmune disease, atopic manifestations and asthma can also be part of the presentation. Recurrent sinopulmonary infection was the most common reason for referral made to our center. We had one patient with recurrent gastroenteritis and it appeared to us that chronic GI manifestation was relatively few contrasting with the literature experience. However, we were limited to conclude by our small number of patients, perhaps also an element of referral bias.

Recurrent infection like most of the literature experience is the commonest presentation for IgG subclass deficiency for our group of patients. Most of them had recurrent pneumonia and sinusitis. Three patients had long-term morbidity with bronchiectasis, bronchiolitis obliterans and lung fibrosis. Atopic manifestations and asthma were also common in this group of patients. It is well documented in literature that IgG subclass deficiency is associated with bronchiectasis, recurrent chest infections and wheezing and chronic lung damage.[12-15]

Patients with combined IgA and IgG2 subclass deficiency are more prone to bacterial infections than isolated deficiency. They may have impaired antibody response to polysaccharide antigens.[16] Studies found the antibody response post 23-valent-pneumococcal vaccine was impaired in the IgG2 deficient patients comparing normal controls.[5,17,18] Thus, the newly approved conjugate-7-valent pneumococcal vaccine by the Food and Drug Administration, USA may be more helpful in preventing recurrent chest infections and hence chronic lung damage.

The prognosis in our cohort is overall satisfactory. Long

term follow up is still warranted albeit that they do not require regular therapy for their immunodeficiency as previous reports suggested and some of them might evolve into common variable immunodeficiency with panhypogammaglobulinaemia.[3]

Genetic diagnosis has become available with rapid advancement in the field. IgA-deficient patient was linked to HLA-DQ/DR locus and an extended major histocompatibility complex haplotype HLA-B8, SC01, DR3.[1] A defect in the expression of Fc-receptor of the reticuloendothelial system was identified. HLA-B8 and DR3 haplotype was found to be associated with autoimmune disorders.[18] This could partly account for the observed increase in autoimmunity. Patients with IgG subclass deficiency, a deletion of large portions of the immunoglobulin heavy chain locus on chromosome 14 could result in the decreased production of 3 or more immunoglobulins, IgG2, IgG4, IgA ± IgE.[10] Two Japanese siblings were found to have a frame shift mutations of the mRNA caused by a homozygous one-base insertion (1793insG) at the exon 4 of the C-gamma 2 gene resulted in a complete and selective IgG2 deficiency.[19] In the past, the gold standard of making diagnosis of this type of immunoglobulin immunodeficiency was based on normal reference immunoglobulin level obtained from healthy population which could be subjected to measurement and misclassification biases. The accuracy of diagnosis may be refined in the future with better definition of the underlying genetic defects.

Conclusion

Patients with IgA and IgG subclass deficiency commonly presented with recurrent infections in our center. Some patients had long-term morbidity as a result of chronic sinopulmonary infections. Poorly controlled atopic manifestations and autoimmunity can be part of the presentation. With a high index of suspicion, early diagnosis is possible. Patients may then be benefited by appropriate preventive measures such as vaccination.

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Appendix 1 Range of 3rd to 97th percentile for serum IgG subclass concentrations (mg/dL) in healthy children

Age (year)	IgG1	IgG2	IgG3	IgG4
0 to 5	170 - 1250	40 - 480	16 - 84	0 - 170
>5 to 10	350 - 1540	100 - 680	20 - 109	5 - 320
>10 to 15	480 - 1600	170 - 820	23 - 199	9 - 370

Lau YL, Jones BM, Yeung CY. Biphasic rise of serum immunoglobulins G and A and sex influence on serum immunoglobulin M in normal Chinese children. J Paediatr Child Health 1992;28:240-3.

Appendix 2 95% reference range (=/-2SD) of immunoglobulin levels in children

Age (year)	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	
			Male	Female
Cord blood	520 - 1250	0 - 5	3 - 30	3 - 30
0 - 1.5	251 - 977	<10 - 86	24 - 182	27 - 219
>1.5 - 5.5	447 - 1445	20 - 240	53 - 249	59 - 301
>5.5 - 9.5	676 - 1380	63 - 234	59 - 237	88 - 282
>9.5 - 16.5	661 - 1950	52 - 380	62 - 330	77 - 305

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