Original Article

IgA and/or IgG subclass deficiency in children with recurrent respiratory infections and its relationship with chronic pulmonary damage

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Abstract. Most patients with IgA and/or IgG subclass deficiency are asymptomatic but some may suffer from frequent mainly respiratory infections. The aim of our study was to determine the frequency of IgA and/or IgG subclass deficiencies and the rate of chronic pulmonary damage secondary to recurrent pulmonary infections in these children.

Serum IgA and IgG subclass levels were measured in 225 children aged 6 months to 6 years with recurrent sinopulmonary infections (44 with recurrent upper respiratory tract infections, 100 with recurrent pulmonary infections and 81 with recurrent bronchiolitis). In order to determine chronic pulmonary damage due to recurrent infections in patients with recurrent pulmonary infections CT scans of thorax were also obtained.

The overall frequency of antibody defects was found to be 19.1 %. IgA deficiency was observed in 9.3%, IgG subclass deficiency in 8.4% and IgA + IgG subclass deficiency in 1.4%. The prevalance of IgA and/or IgG subclass deficiency was 25% in patients with recurrent upper respiratory tract infections, 22% in patients with recurrent pulmonary infections and 12.3% in patients with recurrent bronchiolitis ($p>0.05$).

Chronic pulmonary damage in lungs was determined radiologically in 17 of 100 cases with recurrent pulmonary infection. In IgG subclass deficiencies sequel changes, although not statistically significant, were observed five times more frequently than that of IgA deficiencies. CT scans revealed pulmonary sequels in 5 of the 22 (22.7%) patients with recurrent pulmonary infections and immunodeficiency (bronchiectasis in 2 patients with IgG3 deficiency, fibrotic changes in one with IgA deficiency and in one with IgG3 deficiency, bronchiolitis obliterans in one with IgG2 +IgG3 deficiency). On the other hand, pulmonary sequels were observed in 12 patients (15.4%) with normal immunoglobulin levels. Eight of them were bronchiolitis obliterans, 2 of them were atelectasia and 1 of them was bronchiectasia.

We therefore suggest that determination of antibody levels and evaluation of pulmonary alterations is crucial in patients with recurrent sinopulmonary infections since the deficiency of antibodies is associated with a greater pulmonary damage.

Key words: Recurrent respiratory infections, IgA deficiency, IgG subclass deficiency, pulmonary damage.

Introduction

Recurrent infections, especially acute respiratory tract infections, are important cause of mortalitiy and morbidity in childhood. Approximately 4 million children die due to acute lower respiratory tract infections annualy. These infections are reported to be responsible for 28% of children deaths under five years of age. In childhood, evaluation of immune system functions is necessary if these recurrent infections have an unexpectedly severe course, do no full recovery with antibiotic treatment, need extended antibiotic therapy and become chronic [1,2].

IgA deficiency is the most common primary immunodeficiency in community. In healthy individuals, its prevalance changes between 1/600-1/800 [3]. Recently, in patients susceptible to infections who have normal IgG, IgM and IgA levels, evaluation of IgG subclass levels became current in order to explain this susceptibility. IgA and/or IgG subclass deficient individuals may be asymptomatic, or may be associated with recurrent infections, allergic diseases, autoimmune disorders or malignancies and recurrent sinopulmonary infections are the most common clinical manifestation [4-6]. Expression of these recurrent sinopulmonary infections may only be in the form of upper respiratory tract infection, or of more severe forms that end up with sequels such as bronchiectasia or obliterative bronchiolitis. In children suffering from recurrent infections frequency of IgA and/or IgG subclass deficiencies have been reported between 20 to 50% by various authors [7-10].

The aim of our study was to determine the frequency of IgA and/or IgG subclass deficiencies and the rate of chronic pulmonary damage secondary to recurrent pulmonary infections in children affected with recurrent respiratory infections.

Material and method

Two hundred twenty five subjects, (147 male and 78 female) aged 6 months to 6 years, admitted to Dr. Behçet Uz Children's Hospital between October 2001- October 2002 with recurrent sinopulmonary infections were enrolled in our study. Recurrent sinopulmonary infection was defined as the presence of ≥6 episodes of URTI or ≥3 episodes of pulmonary infections or ≥3 episodes of bronchiolitis during the previous 12 months. Patients with anatomic abnormalities of the respiratory tract, autoimmune disease, liver or kidney failure, malnutrition or cancer and those receiving corticosteroids, immunosupressants, immunostimulants, gammaglobulin or anticonvulsive drugs were excluded.

All patients were evaluated by their clinical and laboratory parameters such as age, sex, number of infections per year, type of the infections, age of onset of recurrences, number of hospitalizations, markers of infection (WBC count, ASO, C-reactive protein), chest radiography and blood levels of IgG, IgA, IgM and IgG subclass. In order to determine chronic pulmonary damage due to recurrent infections in patients with recurrent pulmonary infections computed tomography scans of the thorax were also obtained. Possible etiologic factors of recurrent infections were ruled out for all patients.

Serum IgG, IgM, IgA and IgG subclass levels were determined by immunonephelometry (BN ™ II Nephelometer, Dade-Behring Inc., Deerfied, Illinois). An IgA level <5 mg/dL was considered complete IgA deficiency. Levels >5 mg/dL but <2 SD below the age-related mean level were considered partial IgA deficiency. IgG subclass levels <2 SD below the age-related mean level were considered IgG subclass deficiency [11,12].

Low concentrations of IgG4 occur with high frequency among healthy individuals and undetectable serum levels of IgG4 have been reported in up to 15% of healthy children and 10 % of healthy adults. IgG4 levels have not been taken into consideration in many studies. Therefore IgG4 levels were neither evaluated in our study.

In accordance with their laboratory results subjects were divided into three groups: IgA deficiency (group 1), IgG subclass deficiency (group 2), and normal immunglobulin level (group 3).

The Statistical Package for Social Sciences version 6.0 (SPSS Inc., Chicago, Illinois) was used for all analyses. The comparisons between groups were made using appropriate statistical methods. Student's t-test was used for evaluating parametric double group analysis and "Fisher's Exact Test" and "Pearson Chi-square Test" were used for evaluating non-parametric double group analysis. $P < 0.05$ was considered significant.

Results

Of the 225 patients enrolled, 147 (65.3%) were males. The mean age at presentation was 43 ± 23 months (range, 6 to 72 months) and the mean age of onset of recurrent infections was 15.7 ± 14.4 months (range, 1 to 66 months). Mean number of hospitalisations was 1.1 ± 1.78 (range, 0 to 10) and in 58.7% of our patients there was no history of hospitalisation.

Among the 225 patients enrolled in the study 44 patients (19.6%) were diagnosed with recurrent URTI, 100 patients (44.4%) with recurrent pulmonary infections and 81 patients (36%) with recurrent bronchiolitis.

The overall frequency of antibody defects was found to be 19.1 % (43 patients). IgA deficiency was observed in 21 out of 225 patients (9.3%), followed by IgG subclass deficiency (19 patients, 8.4%) and IgA + IgG

Table 1. Abnormal immunoglobulin findings in patients with recurrent respiratory infections.

Abnormal immunoglobulin findings	Number of cases	%
IgA deficiency (total)	24	(10.7)
Selective IgA deficiency	21	(9.3)
Combined IgA + IgG subclass deficiency	3	(1.4)
IgG subclass deficiency (total)	19	(8.4)
IgG3 deficiency	9	(4)
IgG2 deficiency	8	(3.5)
IgG2 + IgG3 deficiency	2	(0.9)

Table 2. Distribution of cases with respect to frequency of infection.

Frequency of infection	Group I IgA deficiency		Group II IgG subclass deficiency		Group III Patients with normal Ig levels		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
12 - 24 / year	5	(20.8)	4	(21.1)	18	(9.9)	27	(12)
6 - 12 / year	16	(66.7)	13	(68.4)	96	(52.7)	125	(55.5)
4 - 6 / year	2	(8.3)	0	(0)	60	(3.3)	62	(27.5)
4 / year	1	(4.2)	2	(10.5)	8	(4.4)	11	(54.8)
Total	24	(100)	19	(100)	182	(100)	225	(100)

subclass deficiency (3 patients, 1.4%). Combined IgA and IgG subclass deficiency was shown only in three patients and these cases could not be analyzed statistically. Therefore while comparing the groups these three patients were included in IgA deficiency (Table 1). Two of these three patients had IgG3 and one of them had IgG2 deficiency.

Among the patients with IgA deficiency there was only one case with selective IgA deficiency while the rest of them were partial IgA deficiency. Among 19 patients with IgG subclass deficiency, selective IgG3 deficiency was found in 47.4% (9 patients), selective IgG2 deficiency in 42.1% (8 patients) and combined IgG2 deficiency together with IgG3 deficiency in 10.5% (2 patients).

We carried out statistical analysis of the differences between patients with IgA deficiency (group 1, n=24), IgG subclass deficiency (group 2, n=19) and normal immunglobulin levels (group 3, n=182). There were no significant differences regarding the mean age, age of onset of recurrent infections, the male/ female ratio, or mean number of hospitalisations ($p>0.05$). However, statistically significant tendency for a higher occurrence of infections per year was observed in patients with IgA and IgG subclass deficiency compared to children with normal immunoglobulin levels ($p=0.016$, $p=0.04$) (Table 2).

The prevalance of IgA and/or IgG subclass deficiency was 25% in patients with recurrent URTI, 22% in patients with recurrent pulmonary infections and 12.3% in patients with recurrent bronchiolitis. There was no significant difference in the distribution of the IgA and IgG subclass deficiency between disease groups ($p>0.05$). But there was a trend for IgG subclass deficiency in the recurrent URTI group and for IgA deficiency in the recurrent bronchiolitis group. In patients with recurrent pulmonary infections, ratios of IgA and IgG subclass deficiencies were similar (Table 3).

Table 3. Distribution of the IgA and IgG subclass deficiencies between disease groups.

Type of infection	IgA deficiency		IgG subclass deficiency		Patients with normal Ig levels	
	n	(%)	n	(%)	n	(%)
Recurrent URTI (n = 44)	4	(9.1)	7	(15.9)	33	(75)
Recurrent pulmonary infection (n = 100)	12	(12)	10	(10)	78	(78)
Recurrent bronchiolitis (n = 81)	8	(9.8)	2	(2.5)	71	(87.6)

(URTI: Upper Respiratory Tract Infection)

Table 4. Chronic pulmonary damage in patients with recurrent pulmonary infections.

Diagnosis	Normal thorax CT findings		Chronic pulmonary damage	
	n	(%)	n	(%)
Group I IgA deficiency (n = 12)	11	(91.7)	1	(8.3)
Group II IgG subclass deficiency (n = 10)	6	(60)	4	(40)
Group III Normal Ig level (n = 78)	66	(84.6)	12	(15.4)

Group I-II: p = 0.78, Group II-III: p = 0.05, Group I-III: p = 0.5

Chronic pulmonary damage in lungs was determined radiologically in 17 of 100 (17%) cases with recurrent pulmonary infection. Chronic pulmonary damage was found to be present five times more in IgG subclass deficiencies than in IgA deficiency. But this difference was not statistically significant due to the low number of cases (Table 4).

Computed tomography scans revealed pulmonary sequels in 5 of the 22 (22.7%) patients with recurrent pulmonary infections and immunodeficiency. Bronchiectasis was diagnosed in 2 patients with IgG3 deficiency. In one patient with IgA deficiency and in one with IgG3 deficiency CT scans revealed fibrotic changes. One patient with IgG2 +IgG3 deficiency had CT scan changes revealing bronchiolitis obliterans. On the other hand pulmonary sequels were observed in 12 patients (15.4%) with recurrent pulmonary infections and normal immunoglobulin levels. Eight of them were bronchiolitis obliterans, 2 of them were atelectasia and 1 of them was bronchiectasia.

Discussion

All people, especially children, come across bacteria, fungi, viruses and other parasites every day in a world full of microorganisms. Despite of this frequent everyday confrontation with microorganisms, infectious diseases are seen relatively rarely due to many systemic and local defence mechanisms of the host. Recurrent infections, especially recurrent sinopulmonary infections, are seen clinically when there is deficiency or insufficiency at any step of this cascade [2,13].

IgA deficiency is the most common primary immunodeficiency [14,15]. IgA deficiency has been

reported between 2% and 19% by authors who investigated this deficiency in recurrent infections. Kowalczyk D et al [16] investigated 6280 Polish children with recurrent infections and they found low level of immunglobulins in 287 children in which 142 (2.2%) were IgA deficiency. Gross S et al [17] evaluated 267 American children with recurrent respiratory infections and reported that 58% had a partial deficiency in one or more of the major immunoglobulin isotypes or IgG subclasses. The most common abnormality was partial IgA deficiency which was found in one third of the patients. Reports on Japanase children gave the ratio of IgA deficiency as 1/18500 [18]. This difference between communities reflects the importance of the ethnical and genetical factors in IgA deficiency.

Among our 225 patients with recurrent sinopulmonary infection IgA deficiency was determined in 10.7% of the cases. One of our IgA deficient patients had complete type of deficiency whereas the rest of them had partial type. An associated IgG subclass deficiency has been found in some patients with IgA deficiency and this has been used to explain the varied clinical manifestations related to antibody deficiency. In our study 3 of 24 patients (12.5%) with IgA deficiency had IgG subclass deficiency.

Patients with IgG subclass deficiencies suffer from infections involving respiratory tract due to encapsulated bacteria such as *Hemophilus influenzae* and *Streptococcus pneumoniae*. Decreased IgG3 levels were reported in association with chronic and recurrent infections of the lower respiratory tract and lung dysfunction. IgG subclass deficiencies have been reported to be 8% to 57% in recurrent sinopulmonary infections [19-22]. De Baets F et al [21] studied the incidence of IgG subclass deficiency in 53 children with recurrent bronchitis and found it at 57%. More than half of the cases were IgG4 deficiency and the rest of them shared IgG2 and IgG3 deficiencies equally. From our country Güneser S et al [23] reported the overall frequency of IgG subclass deficiency at 39.3 % in children with recurrent respiratory tract infections. Finocchi A et al [2] recruited 67 pediatric patients affected by recurrent infections. Thirty-seven out of 67 (55%) patients showed antibody defects; IgA deficiency 31%, IgG2 deficiency 18 %, IgG3 deficiency 15.1% and IgM deficiency 6%. As mentioned above in various studies investigating IgG subclass deficiencies, different ratios of recurrent sinopulmonary infections have been found. This variation can be attributable to differences between communities, enrolled patient groups and wheather the IgG4 levels were taken into account in the study or not.

In our study IgG subclass deficiency have been found in 19 (8.4%) of patients. Eight (42.1%) of these 19 patients had IgG2, 9 (45.4%) of them had IgG3, and 2 (10.5%) of them had both IgG2 and IgG3 deficiency. The low ratio of IgG subclass deficiency can be attributed to the exclusion of IgG4 results from our study. All patients with IgG subclass deficiency had been found to have normal total IgG levels. In case of clinical suspicion, IgG subclass levels must be evaluated even though the total IgG level is normal.

Among the groups with IgA deficiency, IgG subclass deficiency and normal immunoglobulin levels there were no significant differences with respect to mean age, sex, age of onset of recurrent infections and number of hospitalizations. But statistically significantly higher occurence of infections was observed in patients with immunodeficiency compared to children with normal immunoglobulin levels. There was a trend for IgG subclass deficiency in the recurrent URTI group and for IgA deficiency in the recurrent bronchiolitis group but these differences were not statistically significant. In patients with recurrent pulmonary infections, the ratios of IgA and IgG subclass deficiencies were similar.

The respiratory tract is affected in most cases with primary immunodeficiencies and repeated infections can lead to pulmonary alterations [24-27]. Early recognition is essential to initiate optimal therapy, to minimize the occurence and progression of lung damage. Importance of immunodeficiencies in the etiology of bronchiectasia has been emphasized by De Gracia et al [28] who reported that 48% of patients with bronchiectasia have low serum concentrations of IgG subclasses. Hill et al [29] in 89 adult patients with bronchiectasia found the overall incidence of IgG subclass deficiency to be 6%. They stated that this difference could be explained by the source and nature of the normal range used for comparison and the use of different laboratory immunoassays to estabilish normal ranges. Gomez-Carrasco JA et al [12] reported that even partial IgA deficiencies could be associated with bronchiectasia. Studies in chilhood according to the incidence of chronic pulmonary damage in immunodeficiencies is limited and very few include patients with IgA and/or IgG subclass deficiency.

In our study there were 100 patients with recurrent pulmonary infections and 17 of them had radiologically determined sequel changes in lungs. Our study revealed pulmonary sequel changes in 5 of the 22 (22.7%) patients with recurrent pulmonary infections and IgA and/or IgG subclass deficiency. Bronchiectasia was diagnosed in 2 patients with IgG3 deficiency. In IgG subclass deficiencies sequel changes, although not statistically significant, were observed five times more than that of IgA deficiencies. It was striking that all of the sequel changes were seen in IgG3 deficient cases within IgG subclass deficiencies. Our study was similar to other studies which report that chronic lung damage is mostly associated with IgG3 deficiency [30].

As a result, we determined IgA and/or IgG subclass deficiency approximately in one fifth (19.1%) of the cases with recurrent sinopulmonary infections. Our study also revealed chronic pulmonary damage in 22.7% of patients with recurrent pulmonary infections and IgA and/or IgG subclass deficiency. These changes, although

not statistically significant, were prominent in IgG subclass, particulary in IgG3 deficient patients. We therefore suggest that determination of antibody levels and evaluation for pulmonary alterations is crucial in patients with recurrent sinopulmonary infections since the deficiency of antibodies is associated with a greater pulmonary damage.

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