Prevalence of selective immunoglobulin A deficiency in healthy Turkish school children

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Immunoglobulin A (IgA) deficiency is the most common primary deficiency.

We aimed to define the prevalence of IgA deficiency among healthy school children in Turkey and the differences between geographical regions.

Blood samples were collected from 20,331 healthy school children from all regions across Turkey. The serum IgA levels were tested through nephelometric method, and all 108 samples with IgA levels lower than 5 g/L were tested through ELISA for IgG and IgM levels. All IgG and IgM values were within the normal range in all cases, and no concomitant deficiency was observed.

Our study results showed that the selective IgA deficiency incidence was 0.52% (1:188). The highest incidence, of 1:128.7, was observed in children from the Marmara region; the Black Sea Region levels (1:132.7) were lower, and the Mediterranean levels (1:365.7) were the lowest.

Key words: immunoglobulin A deficiency, incidence, childhood.

Immunoglobulin A (IgA) is the most abundant antibody isotype produced in the body. It is estimated that normal adults secrete approximately 2 g per day, an amount accounting for 60-70% of the total output of antibodies. IgA deficiency (IgAD) is the most common primary immunodeficiency. The European Society for Immunodeficiencies defines IgAD as serum IgA levels <0.07 g/L with normal IgM and IgG levels in children 4 years and over (www.esid.org)[1-3].

It is known that the dimeric form of IgA in the mucosal surface binds to microbes and toxins found in mucosal lumen, neutralizing them by blocking their entry into the host. The monomeric form of IgA in the circulation binds to the FcRα receptor on the monocytes and granulocytes; thereby, immune complexes formed by foreign antigens and IgA are cleared from the circulation by the phagocytic system without activating the complement system and without causing inflammation[4,5]. Serum IgA may also have a role in controlling the immune system through inhibition of neutrophil chemotaxis[6-8].

Although IgAD can be transient in children, in adults it is usually permanent[9,10]. The clinical features are variable. Most individuals with IgAD are asymptomatic and are identified coincidentally; yet, one-third of adult patients suffer from recurrent infections of the upper respiratory tract, gastrointestinal disorders, autoimmune disorders, and possibly allergic diseases[11, 12]. The infections are often viral and clinically mild to moderate. It is another important point that IgA-deficient individuals exposed to blood products containing IgA may develop anti-IgA antibodies that can cause anaphylactic reactions[9,13]. Based on these findings in the literature, in this study, we evaluated the prevalence of IgAD in healthy school children in Turkey and the differences between geographical regions.

Material and Methods

This study was conducted in selected schools between January 2006 and May 2008. Children in 139 schools, grades 1 to 11 (age range: 6–17 years) were invited to participate. Both urban and rural areas were included. A letter including the objectives of the study was mailed to all parents in September 2006 informing them about the content of the research. A survey and consent forms were attached to the letter. A total of 20,331 healthy school children were screened (10,450 [51.4%] boys; 9,888 [48.6%] girls); mean age: 11.6 ± 2.9 years; range: 6–17 years). Serum samples were collected from 20,331 students and stored at -80°C. The samples were tested in 2009 for IgAD. Subjects with IgAD were further tested for IgG and IgM serum levels through ELISA. Total serum IgA levels were analyzed utilizing Behring nephelometers (Dade Behring, Marburg, Germany). IgAD was defined as serum IgA levels <0.05 g/L and normal or elevated levels of serum IgG and IgM in children.

The Ethics Committee of Gazi University Faculty of Medicine approved the study protocol.

Statistics

In order to compare the prevalence determined among different groups, a chi-square test and Fisher's exact test were utilized. Differences were considered statistically significant at p values <0.05.

Results

The results obtained from a total of 20,331 screened healthy school children indicated that IgAD was detected in 108 samples (0.53%), and that the IgAD incidence is 1:188 in all screened regions. Of the 108 subjects, three tested positive for celiac disease, and one was diagnosed with familial Mediterranean fever (FMF). More elaborate data concerning patients are presented in Table I. Statistically significant differences emerged between children from the Black Sea and the Mediterranean regions (p: 0.015) and between the Marmara and the Mediterranean regions (p: 0.006). Differences between other regions were not found to be statistically significant. The data concerning all geographical regions are illustrated in Table II and Fig. 1.

Discussion

The survey of 20,331 healthy school children revealed 108 subjects with IgAD at a mean 11.6 ± 2.9 years of age, yielding a prevalence of 1:188. In general, selective IgAD is more common in Caucasians. The worldwide incidence varies depending on ethnic background, cut-off serum levels of IgA and the mean age of children. When our results are compared with other studies, we can see that the IgAD incidence in Turkey is rather close to the range in other European countries (Spain [1:163][14]), the Arabian Peninsula [1:143][15] and Canada[16]. Studies related to Israel[17], Italy[18] and Turkey (previously conducted)[19] showed the IgAD incidence to be zero [0]. However, samples of these studies were rather small, and this may have been the main reason for such findings. It is interesting, however, that the IgAD incidence is lower among Asian populations, as in China [1:2,600 to 1:5,300][20,21] and Japan [1:14,480-18.500][20,22]. Since Iran shares a border with Turkey, one may assume that geographical conditions and ethnic background may have some impact on

Table I. Data Obtained from the Survey

Data	% value
Breastfeeding (12 months)	57.9
Abdominal pain	31.8
Diarrhea	15.9
Parasitic infections	3.7
Irritability	55.1
Loss of weight	23.4
Fatigue	39.3
School performance (good/ intermediate)	57.0 / 35.5

Fig. 1. Selective IgA deficiency distribution of different geographical regions.

Table II. IgA Deficiency in Different Regions of Turkey

Regions	Tested (n)	IgA deficiency (n)/(%)	Incidence
Marmara	5536	43/0.78	1:129
Black Sea	2921	22/0.75	1:133
Central Anatolia	3011	18/0.60	1:167
Southeast Anatolia	2717	12/0.44	1:226
Western Anatolia (Aegean)	2296	10/0.44	1:230
Eastern Anatolia	1290	4/0.31	1:323
Mediterranean	2560	7/0.27	1:366

the Turkish population. However, the IgAD incidence in Iran varies between 1:450 and 1:1084. For instance, while in Bandare Turkman (Northeast Iran), the IgAD incidence is 1:450[23], it is 1:226 in Southeast Turkey. When the screened regions are compared, statistically significant differences were observed between the Mediterranean and the Black Sea samples. Similarly, significant differences also emerged between the Mediterranean and the Marmara samples. These results suggest that both ethnic background and geographical regions are important factors in determining the IgAD incidence. Consanguinity seems to depend on these two parameters.

As for clinical aspects, the incidence of parasitic infections in IgAD may be expected to be higher compared to subjects with normal IgA levels. In our study, despite the fact that the IgAD children suffered from abdominal pain and diarrhea, the parasitic infections rate (data obtained from the survey) was 3.7%, not a very high ratio compared to subjects with normal IgA levels. The gastrointestinal tract is coated with secretory IgA. It is possible that IgAD individuals may have produced secretory IgA, yet the level would not be enough to provide all-protective functions. When the levels of major immunoglobulins (IgG and IgM) are within normal limits, IgAD individuals may reveal no more infections than would individuals with normal IgA levels.

The IgA-deficient subjects were diagnosed coincidentally, and did not have any significant symptoms interfering with their normal healthy life. Yet, IgAD individuals, when needing blood products containing IgA and anti-IgA antibodies, may develop anaphylactic reactions[16, 24-27]. If necessary, IgA-deficient plasma and IgA-depleted cellular products should be separated. We also maintain that

education is of prime importance regarding the prevention of a potential anaphylactic reaction due to unscreened blood transfusion.

In conclusion, we estimate that selective IgAD does exist in healthy Turkish school children. This study, the first to be carried out with such mass screening of Turkish school children, illustrates that IgAD is a prevalent (1:188) disease in Turkey, and may go unnoticed for years due to lack of clinical data. Based on this premise, proper blood tests should be run prior to blood transfusion to keep the disease under control.

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