Research Article / Araştırma Makalesi

Retrospective Evaluation of Children with Immunoglobulin A Deficiency

İmmünglobulin A Eksikliği Olan Çocukların Retrospektif Olarak Değerlendirilmesi

[1]Halil Onur Öcal, [2]Sinem Aslan, [2]Hülya Anıl, [3]Ayben Leblebici, [2]Koray Harmancı

[1]Eskişehir Osmangazi University, Fakulte of Medicine, Department Child Health and Diseases, Eskişehir, Türkiye.
[2]Eskişehir Osmangazi University, Department of Pediatric Allergy and Immunology, Eskişehir, Türkiye.
[3]Yunus Emre State Hospital, Child Health and Diseases, Eskişehir, Türkiye.

Abstract: This study aimed to compare the clinical and immunological changes and the degree of immunoglobulin A (IgA) deficiency during the follow-up period in patients with IgA deficiency, the most common group of primary immunodeficiency. The study included 234 patients whose serum immunoglobulin levels were checked for any reason and whose IgA level was found to be below the normal level for their age when they applied to the Pediatric Allergy and Immunology outpatient clinic of Eskişehir Osmangazi University Faculty of Medicine Hospital between 2011 and 2020. The patients were divided into two groups: selective IgA deficiency and partial IgA deficiency. Patients' complaints of hospital admission, history of sibling death, diagnosis of primary immunodeficiency in the family, history of atopic dermatitis, reasons for hospitalization, history of autoimmune disease, and total immunoglobulin E (IgE) levels were examined. It was determined that the history of sibling death was higher in the group with selective IgA deficiency than in the group with partial IgA deficiency (p=0.011). In the group with partial IgA deficiency, the history of atopic dermatitis and the elevation of total IgE were found to be higher than in the group with selective IgA deficiency (respectively; p=0.012, p=0.041). Comparative examination of selective IgA and partial IgA deficiency, which we see due to disorders in the mechanisms that regulate the specialized role of IgA, is important for early diagnosis of comorbid diseases and regulation of treatment protocols.
Keywords: Immunoglobulin A deficiency, Selective IgA deficiency, Partial IgA deficiency

Özet: Bu çalışmada primer immün yetmezliğin en sık karşılaşılan grubu olan immünglobulin A (IgA) eksikliği tespit edilen hastalarda klinik ve immünolojik değişiklikler ile IgA eksikliğinin derecesinin karşılaştırılması amaçlandı. Çalışmaya 2011-2020 tarihleri arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Hastanesi Çocuk Alerji ve İmmünoloji polikliniğine başvuran ve herhangi bir nedenle bakılan serum immünglobulin düzeylerinde, IgA düzeyi yaşına göre normal seviyenin altında saptanan 234 hasta dahil edildi. Hastalar selektif IgA eksikliği ve parsiyel IgA eksikliği olarak iki gruba ayrıldı. Hastaların hastaneye başvuru şikayetleri, kardeş ölüm öyküsü, ailede primer immün yetmezlik tanısı, atopik dermatit öyküsü, hastanede yatış sebepleri, otoimmün hastalık öyküsü ve total immünglobulin E (IgE) düzeyleri incelendi. Selektif IgA eksikliği olan grupta kardeş ölüm öyküsünün parsiyel IgA eksikliği olan gruba göre daha yüksek olduğu saptandı (p=0.011). Parsiyel IgA eksikliği olan grupta ise atopik dermatit öyküsünün ve total IgE yüksekliğinin, selektif IgA eksikliği olan gruba göre daha yüksek olduğu saptandı (sırasıyla; p=0.012, p=0.041). IgA'nın özelleşmiş rolünü düzenleyen mekanizmalardaki bozukluklar nedeniyle gördüğümüz selektif IgA ve parsiyel IgA eksikliğinin karşılaştırmalı olarak incelenmesi, eşlik eden hastalıkların erken teşhisi ve tedavi protokollerinin düzenlenmesi açısından önemlidir.
Anahtar Kelimeler: İmmünglobulin A eksikliği, Selektif IgA eksikliği, Parsiyel IgA eksikliği

ORCID ID of the authors: HOÖ. 0000-0002-2313-6520, SA. 0000-0002-7052-3654, HA. 0000-0002-0889-2491, AL. 0000-0002-3941-0176, KH. 0000-0002-8494-648X

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Correspondence: Ayben LEBLEBİCİ– Yunus Emre State Hospital, Child Health and Diseases, Eskişehir, Türkiye
e-mail: aybenberal@hotmail.com

1. Introduction

IgA deficiency consists of selective IgA deficiency and partial IgA deficiency. The prevalence of selective IgA deficiency in healthy children varies between 1/300 and 1/600 (1). According to Basturk et al.'s 2011 study on 20,331 schoolchildren, the prevalence of selective IgA deficiency in our nation was determined to be 1/188 (2). Selective IgA deficiency alone is generally thought to be of limited clinical significance. It is generally known that recurrent respiratory and gastrointestinal system infections, as well as allergic and autoimmune diseases, may frequently develop in cases of low IgA. Since publications comparing selective IgA deficiency and partial IgA deficiency are limited in the literatüre, in our study aimed to determine the characteristics of patients with selective IgA deficiency and partial IgA deficiency and to compare the clinical and immunological changes observed during their follow-up.

2. Materials and Methods

The study included 234 children with low IgA who applied to the pediatric allergy and immunology outpatient clinic at the Eskişehir Osmangazi University Faculty of Medicine Hospital between 2011 and 2020. Patients were divided into two groups: selective IgA deficiency and partial IgA deficiency. Children who had IgA levels below 7 mg/dl (0.07g/L) while IgG and IgM levels were normal and other causes of hypogammaglobulinemia were excluded were included in the selective IgA deficiency group. Children whose IgM and IgG levels were normal and whose IgA levels were above 7 mg/dl but 2 standard deviations (SD) below the normal value for age were included in the partial IgA deficiency group. Ethics committee approval was received for the study (16.10.2018-16). Hospital admission complaints, sibling death history, primary immunodeficiency diagnosis in the family, reasons for hospitalization, atopic dermatitis history, and total IgE levels were examined retrospectively from the files.

For immunoglobulin levels, blood samples were centrifuged at 3000 rpm for 5 minutes and serums were separated, and the nephelometric immunometry method was measured using NFL BN II (Dade Behring, Siemens).

Data analysis was done with SPSS 21 (Statistical Package for Social Sciences) program. Values of quantitative variables were shown as mean±standard deviation or median, and values of qualitative variables were shown as frequency and percentage. The suitability of quantitative variables for normal distribution was evaluated with the Shapiro Wilk test. Comparison of two non-normally distributed groups was made with the Mann-Whitney U test. The relationship between qualitative variables was examined with Chi square analysis. Situations with $p < 0.05$ as a result of the analysis were considered significant.

3. Results

The study had 234 patients in total, 123 (52.6%) of whom were male and 111 (47.4%) of whom were female. 197 (84.2%) of these patients were evaluated as partial IgA deficiency and 37 (15.8%) as selective IgA deficiency. Of the patients with selective IgA deficiency, 22 (59.5%) were male and 15 (40.5%) were female. Of the patients evaluated as partial IgA deficiency, 101 (51.3%) were male and 96 (48.7%) were female. It was determined that both disease groups were more common in men ($p = 0.102$). The ages of the cases included in the study ranged between 4 and 16 years and the mean was 52.87±42.82 months.

When evaluated retrospectively, the reasons for admission in both groups were: 216 (92.3%) of the patients had upper respiratory tract infection (URTI), 85 (36.3%) had bronchiolitis, and 69 (29.5%) had pneumonia findings. Of 197 patients with partial IgA deficiency, 141 (72.1%) had URTI, 69 (35.5%) had bronchiolitis, and 54 (27.4%) had pneumonia. It was determined that 30 (81.1%) of 37 patients with selective IgA deficiency had URTI, 15 (40.5%) had pneumonia, and 15 (40.5%) had bronchiolitis. When both groups were compared, no significant difference was detected between complaints at hospital

admission (p=0.31, p=0.29, p=0.101, respectively).

It was learned that 89 (38%) of the 234 patients participating in the study had a history of hospitalization. The two most common reasons for hospitalization are pneumonia in 42 (47%) of the patients and bronchiolitis in 38 (43%). It was determined that 70 (35%) of the 197 patients evaluated as partial IgA deficiency and 19 (51.4%) of the patients with selective IgA deficiency had a history of hospitalization. No significant difference was detected between diagnosis groups and the presence of a history of hospitalization (p = 0.103). A history of atopic dermatitis was detected in a total of 86 (43.6%) patients, 6 (16.2%) of the patients with selective IgA deficiency and 80 (41%) of the patients with partial IgA deficiency. When the atopic dermatitis diagnosis rates were compared, a significant difference was detected between the groups (p = 0.012).

Concomitant celiac disease was found in 6 (3%) of 197 patients evaluated as partial IgA deficiency and only one (2.7%) of the patients evaluated as selective IgA deficiency in a total of 7 patients. No significant difference was detected in terms of comorbidity with celiac disease in both disease groups (p = 1.000). An accompanying autoimmune disease was detected in a total of 13 patients, 11 (5.6%) of 197 patients evaluated as partial IgA deficiency and 2 (5.4%) of 37 patients evaluated as selective IgA deficiency.

There was no significant difference between the two disease groups in terms of autoimmune disease history (p=1.000). An accompanying lymphoproliferative disease was detected in a total of 10 patients, 7 (3.6%) of the patients with partial IgA deficiency and 3 (8.3%) of the patients with selective IgA deficiency. There was no significant difference in the history of lymphoproliferative disease in either disease group (p=0.198).

Five (13.5%) of the 37 patients with a selective IgA deficiency and five (2.5%) of the 197 patients with a partial IgA deficiency had a history of sibling mortality. A history of sibling death was detected in a total of 10 (5%) of the patients participating in the study. The rate of sibling death was found to be higher in patients with selective IgA deficiency and a statistically significant difference was detected between the groups (p = 0.011).

When their family history is questioned, a family history of immunodeficiency was detected in 4 (10.8%) of 37 patients evaluated as selective IgA deficiency and in 13 (6.6%) of 197 patients evaluated as partial IgA deficiency. In both disease groups, no significant difference was detected in terms of the presence of immunodeficiency in the family (p = 0.32).

Concomitant total IgE elevation was detected in 44 (18.8%) of 234 patients included in the study. Total IgE elevation was detected in a total of 44 patients, 42 (21.3%) of the patients evaluated as partial IgA deficiency and 2 (5.4%) of the patients evaluated as selective IgA deficiency. The rate of total IgE elevation was found to be higher in patients with partial IgA deficiency and a statistically significant difference was detected between both disease groups (p = 0.041). Comparison of demographic and laboratory characteristics of the study groups are presented in Table 1.

Table 1. Comparison of demographic and laboratory characteristics of the study groups

	Total IgA Deficiency (n/%)	**Selective IgA Deficiency (n/%)**	**Partial IgA Deficiency (n/%)**	**P value**
Gender (male)	123(52.6)	22(59.5)	101(51.3)	0.102
Reason for application				
URTI	216(92.3)	30(81.1)	141(72.1)	0.31
Bronchiolitis	85(36.3)	15(40.5)	69(35.5)	0.29
Pneumonia	69(29.5)	15(40.5)	54(27.4)	0.101

Lower respiratory tract infection during hospitalization	89(38)	19(51.4)	70(35)	0.103
Atopic dermatitis	86(43.6)	6(16.2)	80(41)	**0.012**
Total IgE level	44(18.8)	2(5.4)	42(21.3)	**0.041**
Primary immunodeficiency in the family	17(8.6)	4(10.8)	13(6.6)	0.32
Sibling death history	10(5)	5(13.5)	5(2.5)	**0.011**

4. Discussion and Conclusion

Numerous studies have contributed to the literature on the clinical and immunological follow-up of patients with selective IgA deficiency, defined as a serum IgA level is <7 mg/dl, but data on partial IgA deficiency, defined as a serum IgA level is 2 SD below normal for age, are limited.

In our study, we found that male gender was predominant in both patient groups (52.6%). Aytekin et al., in a study conducted between 2006 and 2011 examining the clinical and laboratory characteristics of children aged 4 to 18 years with selective IgA deficiency, observed that 53.3% of the patients were male (3). Similarly, Arslan et al., in their 2018 study on children diagnosed with selective IgA deficiency and partial IgA deficiency, reported that 55% of the patients were male (4). Studies conducted in our country have consistently shown a higher prevalence of male gender in both groups, supporting our findings.

Patients with selective IgA deficiency can present with a heterogeneous clinical profile ranging from asymptomatic to manifestations including infections, allergy, autoimmunity, and malignancy. In a 2018 study conducted by Moschese et al. in Germany with 103 children aged 4-18, respiratory and gastrointestinal tract infections were the most common, occurring in 40-90% of the cases in both selective and partial IgA deficiency groups (1). Koenen et al., in a 2019 review, stated that sinusitis and otitis, among upper respiratory tract infections, are the most frequently identified recurrent infections in both selective and partial IgA deficiencies (5). In our study, the rate of hospital admission with URTI was high in both groups (92.3%). These results indicate a high frequency of upper respiratory tract infections not only in children with selective IgA deficiency but also in those with partial IgA deficiency. Therefore, the function and amount of IgA in mucosal immunity appear to be critical importance, especially in defense against pathogens in the respiratory system.

Allergy and autoimmune disorders may be the first and/or only symptoms of patients with selective IgA deficiency. The prevalence of allergic and autoimmune diseases increases in patients with selective IgA deficiency. In the literature, these rates are reported as 25-50% for allergic diseases and 5-30% for autoimmune diseases (1). Allergic diseases are the second most common clinical finding after recurrent infections in patients with IgA deficiency. The most common allergic diseases are asthma (6-51%), atopic dermatitis (3-49%), allergic rhinitis (3-43%), urticaria (3-24%), and food allergies (1-21%) (5). In a 2015 study by Gualdi et al. in Serbia with 102 pediatric patients diagnosed with selective IgA deficiency, the prevalence of atopic dermatitis was recorded as 57.84% (6). In the study by Moschese et al., it was found that atopic dermatitis was observed in 2.9% of children with selective IgA deficiency and in 9.7% of those with partial IgA deficiency (1). Although comparative studies on this subject are limited, the high incidence of atopic dermatitis in the group with partial IgA deficiency in our study supports the literature. The high incidence of atopic dermatitis compared to other allergic diseases can be explained by the low mean age of the children in our study group.

In one of the rare studies comparing both groups, Moschese et al. found the frequency of autoimmune diseases to be 8% in children with selective IgA deficiency and 18% in those with partial IgA deficiency (1). This rate was higher in both groups than the 3-5% rate reported in the Western general population.

The incidence of autoimmunity has been shown to be higher in the adult selective IgA population compared to the pediatric population, supporting the notion that autoimmune diseases increase with age. The high prevalence of IgA deficiency among patients initially diagnosed with autoimmune disease indicates the protective role of IgA against autoimmunity (1). The increased frequency of allergic and autoimmune diseases may result from the impaired gastrointestinal barrier due to reduced or absent IgA secretion in patients with IgA deficiency. Increased mucosal penetration may allow autoreactive antigens to cross-react with antigens that can lead to antibody formation (5). In our study, 5.6% of the patients were found to have an autoimmune disease. The low incidence of autoimmune disease in our study was associated with the short follow-up period.

The presence of a family history is one of the most important warning signs for identifying an immunodeficiency (1). Only one study in the literature compared both groups regarding family history of immunodeficiency. In this study, a family history of primary immunodeficiency was detected in 19% of the patients, with equal distribution in both groups (1). In our study, although the rate of family history of primary immunodeficiency was higher in the selective IgA deficiency group, no significant difference was detected between the two groups in terms of family history of primary immunodeficiency. However, the fact that the history of sibling death was statistically higher in the selective IgA deficiency group suggests that family history alone may not be sufficient to identify immunodeficiency. According to studies conducted in the German population, we believe that the low rate of immunodeficiency in the family in our study can be explained by the lack of primary diagnosis.

Total IgE plays a role in the pathogenesis of many allergic diseases and is an important initiator of the humoral memory response as a healthy response. Frequent infections identified in the anamnesis may guide us regarding the elevation of total IgE associated with immunodeficiency. Tekin et al., in their 2017 study on 103 patients aged between 2 and 13, observed that there was no significant difference in the total IgE levels of those with IgA deficiency compared to atopic patients with normal IgA levels (7). In a study by Gualdi et al. on 102 pediatric patients diagnosed with selective IgA deficiency, the prevalence of AD was recorded as 57.84%, while total IgE elevation was determined in only 10.17% of these patients (6). In our study, total IgE levels were higher in children with partial IgA deficiency. Although the data regarding elevated IgE in this group are contradictory in the literature, in our study we associated the high total IgE level in the partial Iga deficiency group with an increased incidence of atopic dermatitis.

One of the limitations of our study is that some of the patients were lost to follow-up over the years, and some did not accept participation in the study, resulting in a low number of patients, especially in the selective IgA deficiency group. A second limitation is that the required clinical follow-up period for lymphoproliferative and autoimmune diseases, which frequently accompany these conditions, has not been met.

In conclusion, long-term follow-up of patients with both selective IgA deficiency and partial IgA deficiency is important for detecting new diseases that may develop. According to our research, patients being monitored for recurrent infections and atopy, or who have previously been hospitalized for these reasons, should also be assessed for primary immunodeficiencies. This is because, despite being distinct disease groups, both groups are at risk for developing allergic diseases, autoimmunity, and other immune deficiencies. Given the prevalence of autosomal recessive disorders in our nation due to many consanguineous marriages, we believe that children with IgA deficiency should be closely monitored for potential immunodeficiencies in the future.

REFERENCES

1. Moschese V, Chini L, Graziani S, Sgrulletti M, Gallo V, Di Matteo G, Ferrari S, Di Cesare S, Cirillo E, Pession A, Pignata C, Specchia F. Follow-up and out come of symptomatic partial or absolute IgA deficiency in children. Europen Journal of Pediatrics (2019)178:51-69
2. Baştürk B, Sari S, Aral A, Dalgiç B. Prevalence of selective immünoglobulin A deficiency in healthy Turkish school children. Turk J Pediatr. 2011;53(4):364-8.
3. Aytekin C, Tuygun N, Gokce S, Dogu F, Ikinciogullari A, Selective IgA deficiency: clinical and laboratory features of 118 children in Turkey. J Clin Immunol 2012;32(5):961-6.
4. Arslan A. İzole IgA eksikliklerinin demografik özellikleri, klinik ve laboratuvar bulgularının incelenmesi 2018, 34:71
5. Koenen M.H, J.M. van Montfrans, Sanders E.A.M, Bogaert D, Verhagen L.M. Immunoglobulin A deficiency in children, an undervalued clinical issue. Clin Immunol 2019:209:108293.
6. Gualdi G, Lougaris V, Baronio M, Vitali M, Tampella G, Moratto D, Tanghetti P, Monari P, Calzavara-Pinton P, Plebani A, Burden of Skin Disease in Selective IgA Deficiency and Common Variable Immunodeficiency. Investig Allergol Clin Immunol 2015; Vol. 25(5): 365-384
7. Tekin M., Uzuner S., Önal H., Şiraneci R. Atopik Hastalık Tanısıyla Takipli Hastalarda İmmünglobülin A Eksikliği İnsidansı. Adıyaman Üni. Sağlık Bilimleri Derg, 2016; 2(1):176-186.

Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Ethics Committee (Decision no: 16, Date: 16.10.2018).
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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