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Original Article

Prevalence and Risk Factors of Iron Deficiency Anemia in Children with Atopic Dermatitis

Atopik Dermatitli Çocuklarda Demir Eksikliği Anemisi Sıklığı ve Risk Faktörleri

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ABSTRACT

Objective: Refraining from intake of allergic foods, chronic inflammation and immunosuppressive drug use are factors associated with anemia in atopic dermatitis (AD). In this study, we aimed to investigate the frequency of iron deficiency anemia (IDA) and comorbid risk factors affecting this frequency in children with AD.

Method: The medical records of 100 children aged 0-6 years with AD (patient group) and 100 healthy children of the same age group without AD (control group) were treated in Sivas Numune State Hospital from May 2019 to October 2019 were retrospectively analyzed.

Results: In our study, the frequency of AD in children with AD (15%) was significantly higher than in healthy children (5%) (p<0.001). Early-onset AD, increased SCORAD severity index scores, concomitant food sensitivities, especially multiple food sensitivities, asthma, skin infection, breastfeeding for more than 6 months and presence of multiple atopic conditions were associated with a higher frequency of AD in children with AD. However, hay fever, family history of atopy, exposure to cigarette smoke, large family size, consanguinity and parental socioeconomic status were not significantly associated with a higher prevalence of AD in children with AD.

Conclusion: The prevalence of AD was significantly higher in children with AD compared to healthy children. Therefore, improving clinicians' self awareness of screening and monitoring for AD in children with AD is essential to minimize the burden of AD disease. More comprehensive further studies are needed to investigate the link between IDA and AD and relevant influencing factors

Keywords: Atopic dermatitis, anemia, iron deficiency, children, risk factors

ÖZ

Amaç: Alerjik gıdalardan kaçınma, kronik enflamasyon ve immünsüpresif ilaç kullanımı atopik dermatitte (AD) anemi ile ilişkili faktörlerdir. Bu çalışmada AD'li çocuklarda demir eksikliği anemisi (DEA) sıklığını ve bu sıklığa etki eden komorbid risk faktörlerini araştırmayı amaçladık.

Yöntem: Mayıs 2019'dan Ekim 2019'a kadar Sivas Numune Devlet Hastanesi'nde 0-6 yaş arası AD'li 100 çocuk (hasta grubu) ve aynı yaş grubunda AD'si olmayan 100 sağlıklı çocuğun (kontrol grubu) tıbbi kayıtları geriye dönük olarak analiz edildi.

Bulgular: Çalışmamızda AD'li çocuklarda DEA sıklığı (%15), sağlıklı çocuklara (%5) göre anlamlı olarak yüksekti (p<0,001). AD'nin erken başlangıcı, artmış SCORAD şiddeti, eşlik eden gıda duyarlılığı, özellikle çoklu gıda duyarlılığı, astım, deri enfeksiyonu, 6 aydan uzun süre emzirme ve çoklu atopik hastalık tanısı, AD'li çocuklarda daha yüksek DEA sıklığı ile ilişkilendirildi. Oysa saman nezlesi, ailede atopi öyküsü, sigara dumanına maruz kalma, geniş aile büyüklüğü, akrabalık ve ebeveynlerin sosyoekonomik düzeyi, AD'li çocuklarda daha yüksek DEA sıklığı ile anlamlı bir şekilde bağlantılı değildi.

Sonuç: AD'li çocuklarda DEA prevalansı sağlıklı çocuklara göre anlamlı olarak yüksek bulundu. Bu nedenle, AD'li çocuklarda DEA için tarama ve izleme konusunda klinisyen farkındalığının artırılması, AD hastalık yükünün en aza indirilmesi için esastır. Gelecekte bu ilişkiyi ve etkileyen faktörleri araştırmak için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Atopik dermatit, anemi, demir eksikliği, çocuklar, risk faktörleri

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INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin conditions with increasing incidence rates in childhood. AD worsens the quality of life for both the parent and child due to allergic (food allergy, asthma, allergic rhinitis etc) and non-allergic comorbidities such as skin infections, mental health disorders, and obesity. It may be possible to improve patient outcomes and lessen the costs and burdens related to these conditions by better understanding these non-allergic comorbidities[1,2]. However, there is very little information about the links between AD and non-allergic conditions.

Iron deficiency anemia (IDA) is the most typical cause of childhood anemia and estimated to affect 20% to 25% of all preschool children worldwide, and up to 45% of children under the age of five in Turkey[3,4]. As a result, IDA is a common and important health issue affecting children under the age of five, particularly in our country.

The relationship between allergic conditions and anemia has attracted more attention in recent years. and surprisingly a strong association between anemia and allergic diseases has been detected in patients even after making adjustments for patient's confounding factors such as sex, prematurity, and obesity[5-9]. Epidemiological studies in the US[5] and Korea[6-10] have shown that children with atopic conditions, including AD,[9] wheezing, and allergic rhinitis/conjunctivitis, are up to 8 times more likely to be anemic than those without allergies. Chronic inflammation and the use of immunosuppressive drugs, in addition to food restriction, were identified as contributing factors to increased risk of anemia. Furthermore, epidemiological studies have shown a link between allergy and low iron status, suggesting that immune activation under iron-deficient conditions results in the expansion of Th2-cells rather than Th1 cells, so as to pave the way for allergic sensitization[9,11]. Therefore, we carried out a comparative case-control study among young children aged 0-6 years, to evaluate the incidence of IDA in children with and without AD in Sivas.

MATERIALS and METHODS

This case-control study included 200 pediatric patients aged 0-6 years who applied to Sivas Numune Hospital between May 1 and October 1, 2019. Our patient population included 100 children diagnosed with AD, and the control group consisted of 100 healthy children without any allergic disease. Power analysis was performed and the number of 100 cases each for the control and study groups was found to be sufficient. Retrospective analysis of the medical records, anamneses, and the results of physical exams of all pediatric patients was performed. Age, gender, socioeconomic status, personal and family histories of allergic diseases, and environmental risk factors like smoking exposure and large family sizes (more than five people living in one household) were noted. Results of the skin prick and serum-specific IgE tests were analyzed for the detection of individual sensitization patterns. The accompanying non-allergic (obesity, skin infections, etc.) and allergic (allergic rhinitis, asthma, food allergies, etc.) comorbid diseases were noted. The patients were grouped according to their age during the survey as follows: 0-2 years (infant) and 3-5 years (preschooler). The frequencies of IDA and risk factors associated with AD were analyzed and compared between the patient and the control groups.

Definition and classification of AD: The diagnostic criteria for AD proposed by Hanifin and Rajka[12] were used. Severity of AD was categorized as mild to moderate, and severe using the SCORAD (SCOring AD) index[13].

Definition and classification of IDA: Laboratory tests for hemoglobin, mean corpuscular volume, ferritin, red cell distribution width, and transferrin saturation were performed using venous blood samples. The World Health Organization guidelines were used to define and categorize IDA[14]. In IDA, erythrocyte counts, hemoglobin, hematocrit, mean erythrocyte volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, serum ferritin and iron levels decrease, while red blood cell distribution width, and levels of free erythrocyte protoporphyrin and serum soluble transferrin receptor increase[14].

Exclusion criteria: We did not include children with C-reactive protein levels above 5 mg/dL so as to eliminate active inflammation or bacterial infection in our study. Patients with congenital anomalies, syndromic patients with metabolic and genetic disorders, premature babies born at ≤35 weeks of gestation, low birth weight (LBW) babies, cases with obesity, parasitic infections, history of intensive care unit and/or hospital stay due to a recent serious infection, immunosuppressive therapy, hereditary or acquired disorders affecting hemoglobin synthesis, malnutrition, infants breastfed for less than 4 months, patients with neuromotor retardation, and other comorbid chronic diseases (kidney, cyanotic heart and lung diseases, cancer, immunodeficiency, and chronic

bowel diseases) were excluded from the study. A birth weight of <2.5 kg was considered to be LBW. Patients who had recently received iron therapy and blood transfusions as well as those who did not regularly take medications for iron prophylaxis, and those born from anemic mother were also excluded.

Statistical Analysis

The statistical analyses were performed by using IBM SPSS 22.0 statistical software package (SPSS, Inc., Chicago, IL, USA). A descriptive analysis was performed to examine the demographic features of the study population. The mean, median, standard deviation, or percentile (%) results were used to define variables including sex, age, presence of atopic diseases, use of inhalant allergens, etc. The Kruskal-Wallis or Pearson chi-square test -whichever is appropriate- was used to compare patient groups. The p-value <0.05 was regarded as the level of statistical significance. Power analysis was performed to determine the sample size.

RESULTS

Population Characteristics

The study population consisted mainly of female infants in the patient (n=104; 52%), and the control (n=96; 48%) groups with female/male ratios of 53/47, and 51/49, respectively. Median ages of the patient, and the control groups were 2.94, and 3.01 years, respectively. Children under the age of two made up the majority of cases in both the patient (62% of them) and the control (61%) groups. Any statistically significant difference was not noted between both groups in terms of demographic characteristics including gender, age, and age range at the time of study, socioeconomic status of the families, breastfeeding more than 6 months, family size, exposure to smoke and consanguinity. However, a significantly higher frequency of familial atopy was observed in the patient group (Table 1).

Comorbidities of Children with Atopic Dermatitis

According to the SCORAD scoring of severity of AD, our patients had severe (n=42; 42%), moderate (n=30; 30%), and mild (n=28; 28%) AD. The most frequent allergic comorbidities in all patients with AD were food allergy (26%), allergic rhinitis (15%), followed by asthma (7%), and urticaria (5%). Sleep disturbance (31%), IDA (15%), skin infections (5%), and immunodeficiency (2%) were the most prevalent non-allergic comorbidities (Figure 1).

Association Between Iron Deficiency Anemia and Atopic Dermatitis

The frequency of IDA was statistically higher in the group of patients with AD (15%) compared to those without (5%) (p<0.001) (Figure 2). Mean serum hemoglobin levels in the patient and control groups were 10.9 g/dL vs. 12.5 g/dL between the ages of 0-2, and 12.3 g/dL vs 13.2 g/dL between the ages of 3-5 years, respectively. In both the patient and the control groups, the frequency of IDA in children aged 0-2 years was noticeably higher than that in children aged 3-5 years. When all of the study population was considered, the mean serum hemoglobin values of the patient, and the control groups were 11.4 g/dL, and 12.8 g/dL, respectively (Table 2).

Table 1. Demographic characteristics of the study participants with (patient group) and without (control group) atopic dermatitis

Characteristics of patients	Patient group (n=100)	Control group (n=100)	p-value
Gender, female, n (%)	53 (53%)	51 (51%)	0.345
Median age during the study (year)	2.94	3.01	0.212
Age groups, n (%) 0-2 years 3-5 years	 62 (62%) 38 (38%)	 61 (61%) 39 (39%)	0.724
Low economic level, n (%)	32 (32%)	23 (23%)	0.855
Large family size, n (%),	38 (38%)	39 (39%)	0,895
Breastfeeding >6 month, n (%)	60 (60%)	64 (64%)	0.785
Exposure to smoke, n (%)	22 (22%)	32 (32%)	0.146
Family history of atopy, n (%)	49 (49%)	21 (21%)	0.025
Consanguinity, n (%)	13 (13%)	9 (9%)	0.456

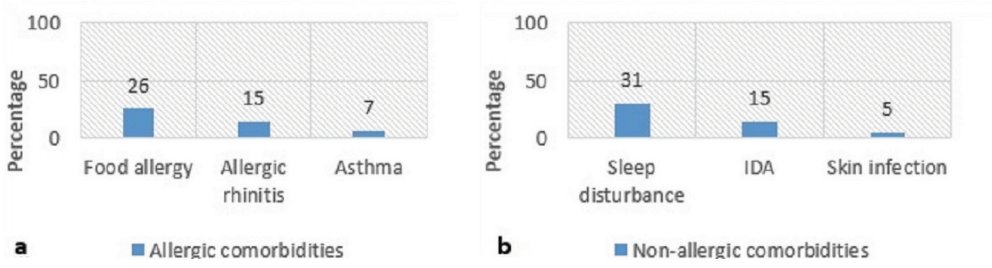

Figure 1. The three most common comorbidities of children with atopic dermatitis: a) allergic comorbidities, b) non allergic comorbidities

Iron Deficiency Anemia in Children with Atopic Dermatitis and Risk Factors

We also analysed the risk factors that may be related to the frequency of IDA in the children with AD. Gender, socioeconomic status, personal or family history of atopy, consanguinity, and large family size were not significant risk factors associated with the frequency of IDA in children with AD (the patient group) (Table 3). However, the frequency of IDA was found to be associated with the age of onset of symptoms before 2 years (early-onset AD), history of atopy except AD, having an increased SCORAD score, skin infections and breastfeeding more than 6 months (Table 3). While the median ages at the onset of AD in patients with and without IDA were 12, and 39.5 months respectively (Table 3).

There was no significant difference in terms of concomitant aeroallergen sensitization patterns between patients with AD and IDA (20.0%) and those without IDA (14.1%) (p=0.454). IDA, on the other hand, was strongly associated with food sensitization (53.3%, p=0.034) or multiple food allergen sensitization (26.7%, p=0.024). AD with and without IDA were compared in terms of concomitant allergic diseases (except AD). Patients with concomitant allergic diseases (80.0%, p<0.001), particularly asthmatics (26.7%, p<0.001) had significantly higher IDA rates. Although the patients with allergic rhinitis (20.0%) were more likely to have IDA when compared to patients without (14.1%), the correlation was not statistically significant (p=0.254). The frequency of IDA in patients with AD significantly increased with the increased number of accompanying atopic diseases (p=0.028) (Figure 3). Patients with one, and more than one atopic disease had IDA at frequencies of 26.7% and 53.3%, respectively (Figure 3).

DISCUSSION

Previous epidemiological studies have shown that people with allergic diseases are more likely to develop anemia[5-8,10,11]. In our study, children with AD had a statistically significantly higher risk of IDA compared to healthy children even after making adjustments for patient's confunding factors such as sex, prematurity, and obesity[5-8]. Our findings have shown that higher frequency of IDA in children with AD was found to be associated with non-allergic and allergic comorbid

Table 2. Distribution of Hb and IDA by age groups

Age groups	Hb g/dL (mean) ± SD	Hb g/dL min-max	Study participants with IDA n (%)
0-2 years			
Patient group	10.9±1.05	6.8-15	12 (19.3%)
Control group	12.5±1.04	7.7-17	4 (6.6%)
3-5 years			
Patient group	12.3±1.14	6.9-17	3 (7.9%)
Control group	13.2±1.02	7-18	1 (2.6%)
Total			
Patient group	11.4±1.08	6.8-17	15 (15%)
Control group	12.8±1.03	7.7-18	5 (5%)

IDA: Iron deficiency anemia, Hb: Hemoglobin, SD: Standard deviation, min-max: Minimum-maximum

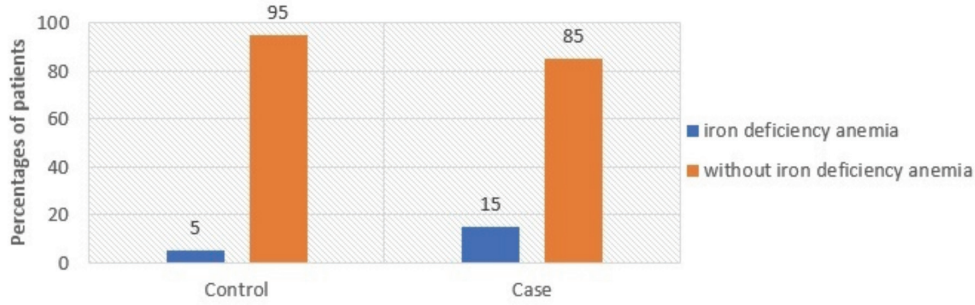

Figure 2. Distribution of iron deficiency anemia in children in the patient and control groups

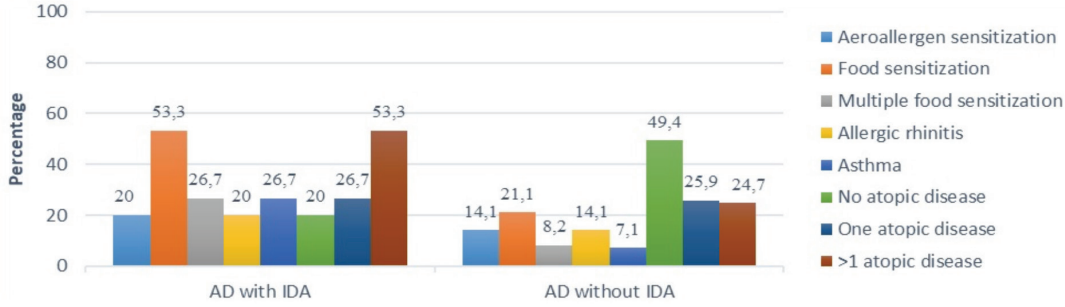

Figure 3. Association between allergic comorbidities and IDA in children with atopic dermatitis

IDA: Iron deficiency anemia

Table 3. The risk factors associated with IDA in the patients with AD

Risk factors (patient group)	AD with IDA (n=15, 100%)	AD without IDA (n=85, 100%)	p-value
Female, n (%)	8 (53.3)	45 (52.9)	0.384
Age at onset of AD, median, month (25-75 percentil)	12 (2-41)	39.5 (13.7-72)	
Early- onset AD (<2 years)	12 (80.0)	40 (47.4)	0.024
Low economic level (household income)	8 (53.3)	48 (57.6)	0.392
Education level	8 (53.3)	47 (55.3)	0.495
Large family size	5 (33.3%)	33 (38.8%)	0.358
History of atopy (except AD)	12 (80.0)	43 (50.6)	0.028
Family history of atopy	7 (46.6)	42 (49.4)	0.457
Consanguinity	6 (40.0)	28 (32.9)	0.212
Severe AD	12 (80.0)	30 (35.3)	<0.001
Skin infection	10 (66.6)	21 (24.7)	<0.001
Breastfeeding >6 months	12 (80.0)	48 (57.6)	0.036

IDA: Iron deficiency anemia, AD: Atopic dermatitis

diseases such as skin infections, asthma, food allergies with multiple food sensitization patterns, a relatively higher SCORAD score, early onset (<2 years) AD and breastfeeding for more than six months. Furthermore, we have observed that frequency of IDA increases significantly in children with AD who received diagnoses of multiple atopic diseases (allergic rhinitis, asthma, and dertmatitis etc.) as stated in previous studies[5-8]. Since AD and IDA are two of the most common medical problems affecting children under the age of five, particularly in developing countries, our findings may contribute to better understanding of the connection between these two disorders in the pediatric population of Turkey.

The underlying mechanism of AD is multidimensional and includes intricate interactions among genetic disorders, epidermal barrier deficiencies, altered immune responses, and microbiome changes. Throughout its natural course, the disease exhibits a high degree of heterogeneity, and individual trajectories are unpredictable, with a wide range of comorbid allergic and non-allergic health disorders[15-17]. IDA, on the other hand, is prevalent in both industrialized and developing nations, affecting up to 45% of children under the age of five in Turkey[4,18-20].

Despite growing interest in the relationship between anemia and atopic diseases in recent years, limited number of publications are available on this issue[5-10]. Children with atopic diseases, including AD, food allergies, allergic rhinitis, asthma are more likely to develop IDA, according to studies conducted in Japan by Yang et al.,[6] in South Korea by Rhew et al.[7,8] and in Qatar by Bener et al.[21] In line with these pediatric studies, the above-mentioned South Korean study group found a similar link between atopic diseases and IDA in the general population[7]. Furthermore, When Chang et al.[10] compared the prevalence of anemia in children with controlled asthma, they discovered that patients with uncontrolled asthma were more likely to experience anemia. The results of the present study are consistent with previously published data, revealing that IDA is more common in children with AD than in healthy children without any comorbid allergic diseases. In a 2014 study performed in Sivas, the incidence rates of IDA were 8.1%, and 3.4% in children aged 1-3 and 4-6 years, respectively[20]. According to the results of our study, the frequencies of IDA in the healthy group, and the group with AD were 6.6% vs. 19.3%, and 2.6% vs. 7.9% in the age groups of 0-2, and 3-5 years, respectively. Overall, the prevalence of IDA was statistically significantly higher in patients with AD (15%) than in control subjects without AD (5%). In line with earlier studies, our findings have also indicated that children who had more than one atopic disease had an increased frequency of IDA[5-7].

It is unclear exactly how allergic diseases increase the risk of IDA. As previously suggested in previous studies, chronic inflammation present in AD may be responsible for the increased risk of IDA in patients with allergic diseases[5-7]. Inflammatory mediators have been shown to prevent differentiation of erythrocyte, shorten half-life of erythroid cells, and suppress the response of erythropoietin to anemia leading to the development of anemia of inflammation (AI)[22]. Proinflammatory factors like ferroportin, IL-1, IL-6, and TNF-like cytokines are released as a result of the inflammatory nature of atopic diseases. These cytokines stimulate the production of hepcidin in liver, which in turn inhibits duodenal absorption, and release of iron. Ferroportin also inhibits the release of iron. Anemia is consequently caused as a result of a decrease in the iron availability required by erythroid progenitor cells[22]. Notably, both Drury et al.'s[5] and our study found that allergic rhinitis was not associated with anemia, whereas children with AD, asthma, and food allergies were more likely to develop IDA. Rhew et al.'s [7] research also showed the presence of a weaker but still statistically significant correlation between allergic rhinitis and anemia than that between other atopic diseases including asthma and AD. These findings suggest that there may be variations in the severity of inflammation in allergic diseases and systemic inflammation may exert varying effects on different atopic disease states. The increasing frequency of anemia, along with the number of allergic diseases and multiple food sensitivities, supports our theory that the inflammatory state of allergic diseases is linked to an increased risk of anemia. Additionally, the higher frequency of IDA in our study was also linked to the presence of early-onset AD, skin infection, and higher SCORAD index scores. These factors may have exacerbated the inflammatory effects of AD on outcomes and comorbidities. Skin infections that disrupt the skin barrier by lowering inflammatory threshold to haptens and irritants and activation of the innate immune system, which includes the production of inflammatory cytokines and chemokines[23]. Increased SCORAD index scores signifying severe AD were linked to increased levels of inflammatory cytokins such as IL-10, 1L-17, 1L-23[24]. As a result, the increased frequency of IDA in children with allergic comorbidities like asthma and food allergies, as well as skin infections and higher SCORAD scores and early-onset AD may be explained by the fact that these conditions enhance the impact of systemic inflammation in children with AD.

The use of systemic immunosuppressive drugs, malnutrition, obesity, and unbalanced food diet are the most frequently reported additional factors that may cause the IDA in children with AD[5,8]. Immunosuppressive medications like methotrexate, cyclosporine, or steroids were utilized as a treatment for patients with moderate to severe atopic disease. These medications may lead to hematologic disorders, anemia, or bleeding[25]. In our study, by excluding these confounding factors from our analysis, we have aimed to disregard obesity, and use of immunosuppressant drugs that can lead to anemia. In addition, children with food allergies who avoid suspected food products may suffer from a variety of nutrient deficiencies. According to studies that investigated nutritional consequences in food-allergic children, children with milk, soy, and wheat allergies were more likely to have insufficient intakes of zinc, vitamin B6 and iron[26]. In addition, the immune system may become activated due to a lack of micronutrients like iron, zinc, selenium, folate, and vitamins A, D, and C. This activation has the potential to exacerbate the situation, leading to anemia and chronic inflammation[27]. Additionally, some studies have indicated that allergies may, at a molecular level, result in iron deficiency[11]. In accordance with these studies, in our study, IDA was more frequently observed in children with AD who had food allergies, especially multiple food allergies. Therefore, nutritional interventions, such as patient or family education and developing a balanced diet, should be carefully planned to prevent unnecessary dietary restrictions.

After six months of life, breast milk is no longer sufficient to meet nutritional needs for energy and micronutrients (iron and zinc) because, five months after birth, the amount of nutrients in breast milk, including minerals, proteins, and vitamins, begins to decline. As a consequence, after four to six months of age, food intake should be initiated in combination with breastfeeding. Moreover, consuming a severely restricted range of meals or avoiding allergenic foods that are typically high in micronutrients can significantly decrease the micronutrient content of breast milk[28]. In accordance with the findings of these studies, breastfeeding for more than 6 months was linked to a greater frequency of IDA in children with AD in our study. Therefore, physicians should offer comprehensive dietary counseling to mothers breastfeeding their children with AD.

Study Limitations

There are a number of limitations concerning our study. We have not directly evaluated AI because of its similarities to IDA. Second, the use of a small sample size and lack of a large dataset drawn from national healthcare assertions prevented us from comprehensively determining the relationship between atopic disease and IDA. The amount of iron present in the foods consumed by patients can not be evaluated and analysed statistically. A strength of this study is that this is one of the first studies conducted on Turkish children regarding this topic and many confounding factors (obesity, LBW, prematurity, breastfeeding less than four months, etc.) that can influence the frequency of IDA were excluded in our study.

CONCLUSION

In our study, children with AD had a statistically significantly increased risk of IDA compared to healthy children. The presence of non-allergic and allergic comorbid diseases like skin infections, asthma, and food allergies with multiple food sensitization patterns as well as having increased SCORAD scores indicating a severe form of AD and breastfeeding for more than 6 months were found to be associated with higher frequency of IDA in children with AD. Consequently, we emphasized the importance of increasing clinicians' awareness and knowledge of IDA screening in children with AD in order to reduce disease burden, due to the elevated risk of adverse effects of IDA on development, growth, and quality of life.

Ethics

Ethics Committee Approval: The Ethics Committee of Cumhuriyet University in Sivas, Turkey, approved this study (approval number: 2019-10/36, date: 09.10.2019).

Informed Consent: All participants provided informed consent.

Author Contributions

Surgical and Medical Practices: M.S., Concept: M.S., Design: M.S., Data Collection or Processing: M.S., E.G.K., Analysis or Interpretation: M.S., E.G.K., Literature Search: M.S., E.G.K., Writing: M.S.

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