Kocaeli Med J 2019; 8; 1:29-34

Alerjik riniti olan çocuklarda alerji ve hematolojik parametreler arasında bir korelasyon var mı?

Is there any correlation between allergy and hematological parameters in children with allergic rhinitis?

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ÖZ

GİRİŞ ve AMAÇ: *Alerjik rinitte (AR) hematolojik parametrelerin önemi ile ilgili literatür bilgisi net değildir. Bu çalışmanın amacı hematolojik parametrelerin çocuklarda allerjik rinitin tanı ve şiddetiyle ilişkisini ve prediktif değerlerini değerlendirmektir.*

YÖNTEM ve GEREÇLER: *ARIA kılavuzuna göre AR tanısı alan 136 çocuğun klinik kayıtları retrospektif olarak incelendi. Çalışmaya allerjik rinit kanıtı olmayan 60 çocuk kontrol grubu olarak dahil edildi. Total immünoglobulin E düzeyleri, deri prick testleri ve tam kan sayımı değerlendirildi. AR olan çocuklar AR şiddetine göre hafif grup (grup 1) ve orta / şiddetli grup (grup 2) olarak gruplandırıldı.*

BULGULAR: *Eozinofil sayısı (EC), eozinofil yüzdesi (E%) ve eozinofil -lenfosit oranı (ELR) çalışma grubunda kontrol grubuna göre anlamlı olarak daha yüksekti (p <0,001).Cut-off değerleri, sırasıyla EC,% E ve ELR için, ≥0,34 103µL, ≥3%, ≥0,09 olarak bulunmuştur. Bu değerlerin duyarlılığı ve özgüllüğü sırasıyla, EC için % 55,9 ve % 73,3, ELR için % 73,5 ve % 71,7 ve ELR için % 61,8 ve% 73,3 bulundu. Nötrofil-lenfosit oranı (NLR) grup 2'de, grup 1'den anlamlı derecede yüksekti (p = 0,010). NLR'nin ≥1,5 prediktif değeri hastalığın şiddeti ile ilişkili olarak (duyarlılık =% 68,9; özgüllük = 63,7) bulundu.*

TARTIŞMA ve SONUÇ: *EC, E% ve ELR, AR'li çocukların duyarlılığını tanımlamak için yararlı bir belirteç olabilir. NLR ise, AR'nin şiddetinin bir göstergesi olarak faydalı olabilir ve çocuklarda hastalığın ciddiyetinin objektif ölçüsü olarak kullanılabilir.*

Anahtar Kelimeler: *Alerjik rinit, eozinofil sayısı, eozinofil lenfosit oranı, nötrofil lenfosit oranı*

ABSTRACT

INTRODUCTION: *The importance of hematological parameters in allergic rhinitis (AR) was confusing in the literature. The aim of this study was to evaluate the association and predictive value of hematological parameters with the diagnosis and severity of allergic rhinitis in children.*

METHODS: *The clinical records of 136 children who were diagnosed with AR according to the ARIA guideline were reviewed retrospectively. 60 children with no evidence of allergic rhinitis were included the study as control group. The total immunoglobulin E levels, skin prick tests and complete blood count were assessed. The children with AR were grouped as mild group (group 1) and moderate / severe group (group 2) according to severity of AR.*

RESULTS: *Eosinophil count (EC), percentage of eosinophils (E%) and also eosinophil to lymphocyte ratio (ELR) in study group was significantly higher than control group (p<0,001). Cut-off values of discrimination to sensitivity were found to be ≥0,34 103µL, ≥3%, ≥0,09 for EC, E% and ELR, respectively. Sensitivity and specificity of these values were 55,9% and 73,3% for EC, 73,5% and 71,7% for E% and 61,8% and 73,3% for ELR respectively. Neutrophil to lymohocyte ratio (NLR) in group 2 were significantly higher than group 1 (p=0,010). The predictive value of NLR was found of ≥1,5 (sensitivity=68,9%; specificity=63,7) for association with severity.*

DISCUSSION AND CONCLUSION: *EC, E% and ELR may be useful marker to define the sensitization of children with AR. NLR can be beneficial as an indicator of severity of AR and may be used an objective measure of the severity of disease in children.*

Keywords: *Allergic rhinitis, eosinophil count, eosinophil to lymphocyte ratio, neutrophil to lymphocyte ratio*

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Başvuru Tarihi: 27.10.2018
Kabul Tarihi: 11.04.2019

INTRODUCTION

Allergic rhinitis (AR) which is an Ig-E mediated type-1 hypersensitivity reaction of the nasal mucosa is the most common type of chronic disorder in pediatric population, affecting more than 40% of children (1). Due to its impact on quality of life, sleep disturbance, learning disability and economy it is a major health problem.

Diagnosis of AR is based on the correlation between clinical definition and allergic diagnostic tests such as nasal cytology, skin prick test, total Ig E, specific Ig E (sIg-E) analysis and nasal provocation tests. Among diagnostic allergic tests, the most commonly used test is skin prick test which is easy, suitable and safe method with high sensitivity to confirm sensitization of a specific allergen (70-95% specificity and 80-97% sensitivity) (2). But its allergen panel contnent is limited and it is difficult to perform for poor cooperation especially in children, severe dermographism and diffuse dermatological conditions. Also response to allergen may not be enough in patients with chronic illness and age-related hyposensitivity (2). Specific Ig E analyzes are used to confirm a mightily suspected clinical diagnosis. There is no standardization of quantitative results and specificities and sensitivities may differ between manufacturers. Also, it is more costly than skin prick test (3). Nasal provocation test evaluates the clinical effects that occur after intranasal administration of the allergen. Disadvantages of the NPT are the lack of standardized approaches to dosing and concentration of allergen extracts, and delivery systems and also the lack of a unified evaluation system, including clinical symptom scores and nasal patency measurements. It is mainly used for scientific purposes, not in clinical practice. Therefore, diagnose of AR with diagnostic tests may not always be useful due to the disadvantages of diagnostic tests and factors related to the patient.

Clinical practice guidelines on AR have clearly demonstrated the diagnostic approach of children with AR with an evidence-based documented revision and concluded that although certain diagnosis of AR without diagnostic testing is difficult, only clinical diagnosis may be sufficient (1). Symptoms of AR are rhinorrhea, nasal obstruction, nasal itching and sneezing. However, describe of these symptoms in pediatric population is inconvenient because of the high frequency of upper respiratory tract infections like non-allergic rhinitis in children and the resemblance of the symptoms of each other (1). Consequently, diagnose of AR in children based on symptoms can be quite difficult.

Complete blood count is simple, cost-effective and routinely used test in children with AR. Thus, present study aims to find the association of hematological parameters of complete blood count and AR on their diagnostic and/or predictive value.

MATERIAL AND METHODS

Patients

Children aged 3 to 10 years old with allergic rhinitis were evaluated retrospectively in the ENT department of Adana City Training and Research Hospital between April 2016 and May 2018. In patient registry files; sex, age, detailed histories of systemic disease and clinical visit notes, results of skin prick tests and complete blood cell count (CBC) of patients were appraised. Patients with asthma, adeno-tonsillar disease, immunodeficiency, autoimmune diseases, drug induced diseases, infectious diseases, cranial or genetic syndromes, vitamin D deficiency, haematological disturbance and insufficient file information were not included the study. A total number of one hundred and thirty six children with AR were included the study as study group. According to the ARIA guidelines (1), these 136 children were grouped as group 1 (mild group-45 children) and group 2 (moderate/severe-91 children) based on the severity of AR. Sixty children with no evidence of allergic disease included the study as control group.

The study was conducted and completed according to the rules outlined in the Declaration of Helsinki. Parents of children gave written informed consent for including the study. Approval of Ethics Committee of Adana City Training and Research Hospital was received for the study (Ethics Committee No / date: 207 / 19.Jun.2018).

Prick Test:

Skin prick tests have been applied with multi-test applicator on the anterior forearm. Thirty most common aeroallergens were performed using standard Alyostal ST-IR (Stallergenes SA,France) allergen extracts. The allergen panel of skin prick

test (Alyostal ST-IR, Stallergenes SA, France) were Dermatophagoides farina, Dermatophagoides pteronyssinus, Betulaceae (Betula alba, Alnus Glutinosa, Carpinus betulus, Corylus avellana), Salicacae (Populus alba, Salix caprea), mixture of 12 grasses (Lollium perenne, Dactylis glomerata, Phleum pratense, Anthoxantum odoratum, Poa pratensis, Festuca eliator, Agrostis vulgaris, Holcus lanatus, Cynodon dactylon, Avena sativa, Avena fatua, Lotus corniculatus), Oleaceae (Olea europaea, Ligustrum vulgare, Fraxinus axcelsior), Compasitae (Solidago candensis, Taraxacum oficinale, Chrysanthemum leucanthemum, Pitrak) and aspergilli mix (Aspergillus fumigatus, Aspergillus niger, Aspergillus nidulans). Before the skin prick test, parents of patients have been questioned about the using drugs (antihistamines, antitussives, corticosteroids, H2 receptor antagonists) in last 7 days. Histamine hydrochloride (10mg/ml) and physiological saline was used as positive and negative reference respectively. Skin reactions were measured 20 minutes after the application and ≥3 mm diameter of skin induration or larger than negative control was accepted as positive reaction.

Complete blood cell count

Blood samples were obtained on the day of the prick test and performed within approximately 60 minutes after blood samples with fully automated cell counter (Sysmex XN-9100TM Automated Hematology System, Kobe, Japan). Eosinophil count (103µL), percentage of eosinophils, lymphocyte count (103µL), percentage of lymphocytes, neutrophil count (103µL) and percentage of neutrophils were recorded for each patient. ELR and NLR calculations were performed by dividing the neutrophil or eosinophil count with lymphocyte count in complete blood count analysis.

Statistical Analysis

The Shapiro-Wilk test was performed to test suitability of the numerical data's normal distribution. Descriptive analyses were presented using median (minimum-maximum) for variables not distributed normally and means ± standard deviations (SD) for normally distributed variables. Mann-Whitney U test was used for group comparison of non-parametric variables. Independent Sample t test was used for parametric variables in comparison. ROC curve analysis was performed to find the cut off value for variables to predict the development of sensitivity and severity. For all that, sensitivity, specificity and area under curve were calculated. A p value of less than 0.05 was deemed statistically significant.

RESULTS

The demographic characteristics and hematological parameters as well as mean ELR and NLR values of the study group and control group were depicted in **Table 1.** No notable differences between the groups in the terms of age and sex was found (p=0,374 and p=0,278 respectively). The study group had significantly higher EC, E% and ELR than control group (p>0,05). There was no statistically significance with regard to neutrophil count, mean NLR and total Ig-E levels between the study and control groups (p>0,005).

Children with AR (study group) were grouped according to severity of AR. No noteworthy association was identified between group 1 and group 2 in the terms of age, sex, EC and ELR. However, group 2 had significantly higher neutrophil count, lymphocyte count as well as mean NLR than did group 1 (p=0,021; p=0,023 and p=0,010 respectively). The demographic characteristics and mean values of hematological variables of group 1 and group 2 are represented in **table 2.**

To investigate potential associations between diagnosis of allergic rhinitis and eosinophil count and mean ELR, we used ROC analysis. The cut-off value of the parameters association of sensitization of children was found ≥3% (AUC= 0,690; p<0,0001; sensitivity=73,5%; specificity=71,7%) for E%, ≥0,3435 103µL (AUC= 0,659; p<0,0001; sensitivity=55,9%; specificity=73,3%) for EC and ≥0,09 (AUC=0,667; p<0,0001; sensitivity=61,8%; specificity=73,3%) for ELR **(Table 3).** Furthermore, mean NLR level of ≥1,5 (AUC=0,636; p=0,0001; sensitivity=68,9%; specificity=63,7%) emerged in ROC analysis as the cut-off value for association with severity.

Table 1. Dermographic variables of the study and control groups

Variables	Study group	Control group	P value
Sex;			0,278
Boys, n/total	64/136	34/60	
Girls, n/total	72/136	26/60	
Age, mean ± SD, y	6,147 ± 2,259	5,833 ± 2,300	0,374
Total IgE, mean ± SD	80,1 ± 13	97,7 ± 11	0,075
Eosinophil, mean ± SD, 10^3µL	0,413 ± 0,301	0,279 ± 0,271	0,003
Eosinophil%, mean ± SD	4,710 ± 3,513	2,884 ± 2,366	0,000
Lymphocyte, mean ± SD, 10^3µL	4,347 ± 6,290	3,657 ± 1,445	0,403
Lymphocyte%, mean ± SD	35,691 ± 11,236	39,238 ± 10,727	0,040
Neutrophil, mean ± SD, 10^3µL	4,616 ± 1,834	4,770 ± 2,196	0,613
Neutrophil%, mean ± SD, 10^3µL	49,991 ± 11,911	49,361 ± 12,195	0,735
ELR, mean ± SD	0,139 ± 0,122	0,073 ± 0,051	0,000
NLR, mean ± SD	1,625 ± 0,906	1,427 ± 0,935	0,210

IgE, İmmunoglobulin E; ELR, Eosinophil to lymphocyte ratio; NLR, Neutrophil to lymphocyte ratio

Table 2. Dermographic variables of the mild (group1) and moderate/severe (group 2) AR

Variables	Group 1 (mild AR)	Group 2 (moderate / severe AR)	P value
Sex;			0,906
Boys, n/total	22/45	42/91	
Girls, n/total	23/45	49/91	
Age, mean ± SD, y	5,788±2,351	6,394±2,207	0,259
Total IgE, mean ± SD	82,1 ± 12	94,6 ± 10	0,063
Eosinophil, mean ± SD, 10^3µL	0,386 ± 0,294	0,468 ± 0,309	0,139
Eosinophil%, mean ± SD	4,330 ± 3,345	5,478 ± 3,752	0,073
Lymphocyte, mean ± SD, 10^3µL	3,485 ± 1,643	6,088 ± 1,548	0,023
Lymphocyte%, mean ± SD	37,736 ± 10,665	31,555 ± 11,338	0,002
Neutrophil, mean ± SD, 10^3µL	4,361 ± 1,585	5,132 ± 2,186	0,021
Neutrophil%, mean ± SD, 10^3µL	48,742 ± 11,268	52,515 ± 12,880	0,082
ELR, mean ± SD	0,127 ± 0,116	0,165 ± 0,131	0,071
NLR, mean ± SD	1,485 ± 0,739	1,909 ± 1,132	0,010

IgE, İmmunoglobulin E; ELR, Eosinophil to lymphocyte ratio; NLR, Neutrophil to lymphocyte ratio

Table 3. ROC analysis of the eosinophil to lymphocyte ratio (A), eosinophil count (B) and percentage of eosinophil (C) for association with sensitization.

Variables	Cut-off value	AUC	Sensitivity	Specificity	P value
ELR	≥ 0,09	0,667	61,8	73,3	<0,0001
Eosinophil count, 10^3µL	≥ 0,34	0,659	55,9	73,3	<0,0001
Percentage of eosinophil, %	≥ 3	0,690	73,5	71,7	<0,0001

AUC, Area Under Curve; ELR, Eosinophil to lymphocyte ratio

In the study group, children who showed sensitization to only one allergen considered to mono-sensitization group and children who showed sensitization to more than one allergen considered to poly-sensitization group. 33 children (24,3%) had mono-sensitization and 103 children (75,7%) had poly-sensitization. Group 1 had 9 children with mono-sensitization while group 2 had 24 children. No noteworthy association was identified between poly-sensitization group and mono-sensitization group in the terms of age or sex ($p>0,05$) and no remarkable association was detected between the groups according to EC, E% and mean ELR ($p= 0,085$; $p= 0,175$ and $p= 0,927$, respectively). On the other hand, mean NLR was 2,187 ± 1,123 in mono-sensitization group and 1,445 ± 0,746 in the poly-sensitization group. NLR was significantly higher in the mono-sensitization group compared to poly-sensitization group ($p<0,001$). The most common allergens were dermatophagoides farina [valid percent 79,4% (108/136)] and dermatophagoides pteronyssinus [valid percent 81,6% (111/136)]. 38 children had sensitization to mixture of grasses (valid percent 27,9%), 9 to oleaceae (valid percent 6,6%), 8 to salicae (valid percent 5,9%), 7 to aspergilli mix (valid percent 5,1%).

DISCUSSION

Eosinophilia of blood and tissue tracking exposure of the allergen is a common property of allergic disorders including AR. A number of studies have suggested that eosinophilia in blood is associated with allergen sensitization and considered to be predictors of sensitization, though not all studies conclude on the cut-off values in the clinical use (4-7). Only one study had shown that percentage of eosinophils ≥4% cut-off value (57,5% sensitivity, 72,5% specificity) was meaningful and might be used diagnosis of AR in range of 8-76 years old patients (5). Yenigün et al. (8) reported that eosinophil counts were significantly higher while lymphocyte counts were lower in children with AR and ELR could be used in the diagnosis of sensitized children. However they haven't been reported the diagnostic cut-off value of these markers. Present outcomes of our study showed that the EC, E% and ELR was associated with the sensitivity of allergens in children. Furthermore, we also demonstrated that cut-off values with discrimination to sensitivity were found to be ≥0,34 103µL, ≥3%, ≥0,09 for EC, E% and ELR, respectively. Sensitivity and specificity of these values were 55,9% sensitivity and 73,3% specificity for EC, 73,5% sensitivity and 71,7% specificity for E% and 61,8% sensitivity and 73,3% specificity for ELR. Specificity values of these parameters were found very close to each other but the sensitivity of percentage of eosinophils were higher than others.

AR is defined as a chronic allergic inflammation of the nose and described nasal symptoms of the disease. It is classified as mild or moderate / severe depending on the effects of symptoms on quality of life (2). There is still a controversy about NLR as a prognostic marker of inflammation in the literature (9). Nevertheless, Doğru et al (10) reported that NLR was associated with the severity of AR and could be useful as an indicator of inflammation marker in children with AR. Similarly, in Doğru et al (10), NLR was significantly higher in moderate / severe group than mild group in present study. Especially in preschool children, AR is evaluated concerning the severity classification on the basis of information of symptoms and the effects of symptoms on quality of life obtained by the declaration of the parents of children. NLR may be use as an indicator of inflammation and severity of AR and the conformity of family statement. Moreover, mean NLR level of ≥1,5 (AUC=0,636; p=0,0001; sensitivity=68,9%; specificity=63,7) found as a cut-off value for association with severity.

Our study exhibited that the number of poly-sensitized children was more than the number of mono-sensitized children and the most common allergen was dermatophagoides pteronyssinus and farina. In the literature there is no consensus how Ig E sensitization turn into clinical allergy. Bousquet et al (11) declared that this might be depends on multiple factors including familial history of atopy, mono- and poly-sensitization against allergen, levels of allergen sIg-E, qualitative differences in allergen sIg-E, allergen molecules with high and low allergenic activity (11). They reported that asymptomatic children might be more representative to mono-sensitization. Li et al (4) noticed that

eosinophil count and levels of serum eosinophil cationic protein were positively associated in adult AR patients regardless of the number of positive allergen. Finding of present study showed that NLR is significantly higher in mono-sensitized children compared to poly-sensitized children. This result may be due to more poly-sensitization subjects in moderate/severe group and needs further investigations. No correlations between eosinophil count and ELR found in terms of sensitization status.

LIMITATIONS OF THE STUDY

This study also had some limitations common to any single-institutional retrospective analysis. First, the study subjects were consisted of only 136 children with AR and 60 control. Second, children did not classify according the duration of symptoms like intermittent and persistent AR.

CONCLUSION

Present outcomes indicated that eosinophil count, percentage of eosinophils, and also ELR could be important marker in the diagnosis of sensitization of children with over 70% specificity and 60% sensitivity values. These inexpensive and easily accessible markers can be used to discrimination of allergic or non-allergic children. Furthermore, NLR can be beneficial as an indicator of severity of AR and may be used to confirm of the severity of disease in children.

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