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RHINOLOGY

Is neutrophil–lymphocyte ratio associated with the severity of allergic rhinitis in children?

Mahmut Dogru[1] · Muhammed Fatih Evcimik[2] · Ahmet Adnan Cirik[3]

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Abstract Neutrophil lymphocyte ratio (NLR) could be an important measure of systemic inflammation. There is a lack of knowledge about the neutrophil–lymphocyte ratio in rhinitis. We aimed to determine the relationship between the clinical parameters of allergic rhinitis and NLR in children. 438 children who were diagnosed with allergic rhinitis and followed up in our hospital were included in the study. The control group included 180 control children with no evidence of allergic disease. The immunoglobulin E levels, skin prick tests and complete blood count were measured. Mean NLR was 1.77 ± 1.67 in the study group and 1.70 ± 1.65 in the control group. Mean NLR was significantly higher in children with allergic rhinitis compared to controls ($p < 0.05$). The patients with allergic rhinitis were grouped according to the severity of AR as Group I (mild group) and Group II (moderate/severe group). No statistically significant difference was present between groups in terms of gender, age, familial atopy, exposure to smoke, the presence of asthma and/or eczema, the percentage of eosinophil, serum IgE levels, number of positive sensitivity, and sensitivity to allergens ($p > 0.05$). However, NLR was significantly higher in the moderate/severe AR compared to mild AR ($p < 0.05$). Mean NLR was statistically higher in children with allergic rhinitis compared to the control group. In addition, elevated ratio is associated with the severity of allergic rhinitis in children. Neutrophil–lymphocyte can be used as an indicator of inflammation in allergic rhinitis. But further studies are needed in this issue.

Keywords Neutrophil–lymphocyte ratio · Children · Severity · Inflammation · Allergic rhinitis · Indicator

Introduction

Rhinitis is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose. Allergic rhinitis (AR) is the most common form of non-infectious rhinitis and is associated with an IgE-mediated immune response against allergens. Allergic rhinitis is a global health problem that causes major illness and disability worldwide. In addition to nasal inflammation, there is a systemic inflammation in AR [1]. There are few studies assessing systemic inflammation in allergic rhinitis [2–5]. In that study, while high sensitivity C-reactive protein (CRP), CRP, fibrinogen, alpha1-glycoprotein, alpha1-antichymotrypsin were not statistically different in allergic rhinitis compared to controls [2–4], they were found different in terms of serum amyloid A, transferrin concentration, ceruloplasmin, alpha2-macroglobulin, hs-CRP, and ceruloplasmin oxidase activity between patients and controls [3–5].

Neutrophil lymphocyte ratio (NLR) is a test used to evaluate the systemic inflammation as it is cost effective, readily available and it could be calculated easily. NLR has been associated with some conditions, such as chronic

✉ Mahmut Dogru
mdmahmutdogru@yahoo.com

[1] Department of Pediatrics, Zeynep Kamil Woman and Children's Diseases Training and Research Hospital, Istanbul, Turkey

[2] Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Istanbul Medipol University, Istanbul, Turkey

[3] Department of Otolaryngology-Head and Neck Surgery, Umraniye Education and Research Hospital, Istanbul, Turkey

inflammation in cardiovascular diseases, hypertension, diabetes mellitus, familial mediterranean fever, hepatic cirrhosis, and malignancies and it has been suggested that NLR has a prognostic importance [6–10]. We know a little about NLR in allergic diseases. These studies were often done in asthmatics and the results are conflicting [7, 11]. There is also a systemic inflammation in AR [12]. Therefore, we believe that NLR indicating systemic inflammation is high in children with allergic rhinitis and it can be used as an indicator of inflammation in allergic rhinitis. In this study, we aimed to evaluate the NLR in children with allergic rhinitis.

Materials and methods

Four-hundred and thirty-eight children who were followed up with the diagnosis of with allergic rhinitis and/or asthma and/or eczema in pediatric allergy and Immunology clinic of Zeynep Kamil Woman and Children's Disease Training and Research Hospital were included in the study. One-hundred and eighty control children without any allergic diseases were included as the control group. Patients were evaluated retrospectively between September 2012 and September 2014.

Patients with anemia/polycythemia, leukopenia/leukocytosis, thrombocytopenia/thrombocytosis according to complete blood count analysis were excluded from the study [13]. In addition, patients who had an exacerbation of asthma, receiving systemic steroids last month, acute/chronic infection, and patients with any other systemic disease such as hepatic, renal, cardiovascular diseases, diabetes mellitus, cancer and systemic inflammatory disorders were excluded. A detailed allergic history, including the age, a familial atopy history, and exposure to smoke were recorded. Familial atopy was accepted as positive when having allergic disease in first degree relatives (parents and siblings). The diagnosis and severity of rhinitis were evaluated according to the ARIA guidelines [1]. Patients who were detected sensitivity in the skin prick tests and developing nasal symptoms after exposure to these allergens were considered as allergic rhinitis. The immunoglobulin (Ig) E levels and complete blood count were measured. The study was approved by the Zeynep Kamil Woman and Children's Diseases Training and Research Hospital Ethics committee and an oral consent was obtained from all subjects and/or their parents.

Skin prick tests

Skin prick tests were performed using the same antigens for all patients. Skin prick tests were applied on the anterior forearm. Histamine (10 mg/ml) and physiological saline were used as positive and negative references, respectively. Skin reactions were evaluated at 20th minute of the application. A positive reaction was characterized as 3 mm or greater than that of the negative control. Skin prick tests for common aeroallergens (*Dermatophagoides pteronyssinus, Dermatophagoides farinae*, grasses mix, cereals mix, trees mix, weed-mix, *Alternaria alternaria*, cockroaches, cat dander and dog dander (Stallergenes SA, 92160 Antony, France) were performed using stallerpoint (Stallergenes SA, 92160 Antony, France).

Laboratory analysis

The percentage of neutrophil and lymphocyte measurements was performed within approximately 60 min after blood sampling with Coulter LH 780 Analyzer and Coulter Hmx Hematology Analyzer (Beckman Coulter, Inc. CA, USA) with original method and reagents. Neutrophil–lymphocyte ratio was calculated by dividing the percentage of neutrophils and lymphocytes in complete blood count analysis.

Statistical analyses

Statistical Package for Social Sciences (SPSS for Windows 15.0, Chicago, USA) program was used to analyze the data. Results were given as either mean ± standard deviation (SD) or as mean ± standard deviation (median) according to the distribution. Student t test was used for the comparison of normally distributed variables. Chi square and Mann–Whitney U tests were used for non-normally distributed variables. $P < 0.05$ was considered as significant.

Results

There was no difference between the groups with regard to gender and age. Mean NLR was 1.77 ± 1.67 in the study group and 1.70 ± 1.65 in the control group. Mean NLR was significantly higher in children with allergic rhinitis compared to controls ($p < 0.05$). The demographic features and NLR of the study population are shown in Table 1.

The patients with allergic rhinitis were grouped according to the severity of AR as Group I (mild group) and Group II (moderate/severe group). No statistically significant differences were present between groups in terms of gender, age, familial atopy, exposure to smoke, the presence of asthma and/or eczema, the percentage of eosinophil, serum IgE levels, number of positive sensitivity, and sensitivity to allergens ($p > 0.05$). However, NLR was significantly higher in the moderate/severe AR compared to mild AR ($p = 0.034$) (Table 2).

Table 1 Comparison of socio-demographic features and neutrophil–lymphocyte ratio between patients with allergic rhinitis and control groups

	Study group ($n = 438$)	Control group ($n = 180$)	p
Gender (n)			
Male/female	252/186	94/86	0.247[a]
Age (years)			
Mean ± standard deviation	7.3 ± 3.5	6.8 ± 2.7	0.451[b]
Minimum–maximum (median)	2–18 (6.4)	3–16 (6)	
Neutrophil–lymphocyte ratio			
Mean ± standard deviation	**1.77 ± 1.67**	**1.70 ± 1.65**	**0.044[b]**
Minimum–maximum (median)	**0.15-15.9 (1.35)**	**0.32-10.7 (1.2)**	

Statistically significant values are in bold

[a] Chi squared

[b] Mann–Whitney U test

Table 2 Comparison of socio-demographic features, clinical and laboratory findings of the patient with mild (Group I) and moderate/severe AR (Group II)

	Group I n:132	Group II n:306	p
Gender (M/F)	82/50	170/136	0.208[b]
Age (years)[a]	6.9 ± 3.6	7.3 ± 3.8	0.127[c]
Familial atopy n (%)	52 (38.2)	148 (48.4)	0.074[b]
Exposure to smoke n (%)	58 (43.9)	151 (49.3)	0.293[b]
The presence of asthma n (%)	77 (58.3)	165 (53.9)	0.404[b]
The presence of eczema n (%)	17 (30.2)	22 (7.2)	0.068[b]
Mean neutrophil–lymphocyte ratio level[a]	**1.58 ± 1.21 (1.23)**	**1.85 ± 1.82 (1.4)**	**0.034[c]**
The percentage of eosinophil[a]	4.9 ± 3.7 (3.75)	5.1 ± 3.7 (4.3)	0.618[c]
Immunoglobulin E[a] (IU/ml)	428 ± 507 (250)	450 ± 542 (232)	0.862[c]
The number of positive sensitivity[a]	2.2 ± 1.1 (2)	2.5 ± 1.3 (2)	0.071[c]
Sensitivity to house dust mite n (%)	115 (87.1)	258 (84.3)	0.558[b]
Sensitivity to pollens n (%)	32 (24.2)	96 (31.4)	0.138[b]
Sensitivity to dander n (%)	19 (14.4)	61 (19.9)	0.180[b]
Sensitivity to *A. alternata* n (%)	6 (4.5)	16 (5.2)	0.999[b]
Sensitivity to cockroach n (%)	10. (7.6)	32 (10.6)	0.383[b]

Statistically significant values are in bold

[a] Mean ± standard deviation (median)

[b] Chi square test

[c] Mann–Whitney U test

Discussion

The main important result of our study is that NLR in children with AR is higher compared to the control. As mentioned in "Introduction", NLR increases in various diseases [6–10]. Many cells serve in allergic inflammation as well as mast cells and eosinophils. The production of neutrophils in the bone marrow increases during pathologies such as infection and inflammation and they migrate to target tissues. In the absence of infection, these short-lived terminally differentiated cells will leave the bone marrow and die in the confines of the blood stream [14]. As allergic rhinitis is also an inflammatory condition, blood neutrophils are expected to increase and migrate to the nose in patients with AR. In line with this finding, neutrophils are one of the most frequent cell in studies evaluating nasal cytology in patients with AR [15–17]. As neutrophils in the nose enter from blood, an increase in NLR is expected when blood neutrophils increase. In accordance with these findings, we found that neutrophil–lymphocyte ratio is high in children with AR.

The other important result of our study is that NLR in children with moderate/severe allergic rhinitis is significantly higher than that in children with mild AR. This result suggests that NLR level is associated with the severity of allergic rhinitis. This subject has not been studied before. Nasal inflammation was shown to be more intense in the symptomatic period. Nasal inflammation is also more in severe allergic rhinitis [15, 16]. Inflammatory cells vary according to the type of sensitivity. In the study of Gelardi

et al. [15], they evaluated nasal cytology in patients with AR caused by sensitization to grass pollen and they found that moderate-to-severe AR shows significantly increased counts of mast cells and lymphocytes or plasma cells. But in those sensitive to house dust mites, Gelardi et al. [16] detected that nasal cytology showed that the cells most commonly found in the nasal mucosa were neutrophils. During the period from October to April, a peak in the number of neutrophils and also the presence of significant numbers of eosinophils, mast cells, and lymphocytes/plasma cells were found, which show the occurrence of more intense inflammation during these months [16]. There was house dust mite sensitivity in 85 % of patients in our study. In the light of these findings, despite we could not do nasal examination, we believe in the predominance of neutrophils in the nose of our patient. There is an increase in neutrophils in the blood due to the inflammation in allergic rhinitis. As a result of this, we think that NLR in the moderate/severe allergic rhinitis is higher than mild AR. These results suggest that NLR is used as an indicator of inflammation in allergic rhinitis. We think that neutrophil–lymphocyte ratio in the blood can be used to assess the severity of allergic rhinitis when the nasal cytology could not be done. But the standard limits for neutrophil–lymphocyte ratio were not determined. To determine the standard limits of neutrophil–lymphocyte ratio, further study is needed.

There are several limited aspects of our study. Firstly, other inflammatory parameters such as nasal nitric oxide in evaluating the nasal inflammation could not be evaluated in our patients. Secondly, we could not assess nasal cytology in our patients. These investigations could not be done because our study was done retrospectively. Despite these limitations, to our knowledge, it is the first study which assesses the relationship between NLR and rhinitis in such a large population in childhood.

As a result, mean NLR was statistically higher in children with allergic rhinitis compared to the control group. In addition, NLR in children with moderate to severe rhinitis was higher than mild rhinitis. These findings suggest that neutrophil–lymphocyte ratio in children with allergic rhinitis can be used as markers of inflammation. However, there is a need for further studies evaluating the neutrophil–lymphocyte ratio with nasal cytology.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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