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RESEARCH

Neutrophil/lymphocyte ratio as an indicator of radiological disease activity in clinically stable multiple sclerosis

Klinik olarak stabil multipl sklerozda radyolojik hastalık aktivitesinin bir göstergesi olarak nötrofil/lenfosit oranı

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Abstract

Purpose: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system and the most common neurological disorder causing disability in young people. There is no sensitive and specific marker for both diagnosis and follow-up. Neutrophil to lymphocyte ratio is an easily applicable method and in this study we aimed to observe the changes in this ratio in the presence of isolated radiologic activity in MS.

Materials and Methods: We compared 20 MS active patients with no clinical attack or neurologic progression and only radiologic activity with 20 age- and sex-matched clinically and radiologically stable MS patients in terms of NLR.

Results: Mean NLR value was 2.22±0.87 in radiologically active patient group (Min 1.08-Max 4.28) and mean NLR value was 2.31±1.37 in control group (Min 0.96-Max 5.92). We observed that NLR values in patients with radiologic activity only were not significantly different from NLR values in patients with both clinical and radiologic stability.

Conclusion: Marker studies in the diagnosis and follow-up of MS continue rapidly. Prospective studies involving a much larger cohort may be instructive in order to demonstrate the association of simple, easily applicable, non-invasive, inexpensive methods such as NLR with MS disease activity.

Keywords: Neutrophil, lymphocyte, ratio, multiple sclerosis, relapse, disease activity

Öz

Amaç: Multipl Skleroz (MS), merkezi sinir sisteminin demiyelinizan bir hastalığıdır ve gençlerde engelliliğe neden olan en yaygın nörolojik bozukluktur. Hem tanı hem de takip için hassas ve spesifik bir belirteç yoktur. Nötrofil/lenfosit oranı kolay uygulanabilir bir yöntemdir ve bu çalışmada MS'de izole radyolojik aktivite varlığında bu orandaki değişiklikleri gözlemlemeyi amaçladık.

Gereç ve Yöntem: Klinik atak veya nörolojik progresyonu olmayan ve sadece radyolojik aktivitesi olan 20 aktif MS hastasını, yaş ve cinsiyet açısından eşleştirilmiş 20 klinik ve radyolojik olarak stabil MS hastasıyla NLR açısından karşılaştırdık.

Bulgular: Radyolojik olarak aktif hasta grubunda ortalama NLR değeri 2.22±0.87 (Min 1.08-Maks 4.28), kontrol grubunda ise ortalama NLR değeri 2.31±1.37 (Min 0.96-Maks 5.92) olarak bulundu. Sadece radyolojik aktivitesi olan hastalardaki NLR değerlerinin hem klinik hem de radyolojik stabilitesi olan hastalardaki NLR değerlerinden anlamlı derecede farklı olmadığını gözlemledik.

Sonuç: MS'in tanı ve takibinde belirteç çalışmaları hızla devam etmektedir. NLR gibi basit, kolay uygulanabilir, non-invaziv, ucuz yöntemlerin MS hastalık aktivitesi ile ilişkisini ortaya koymak için çok daha geniş kohortu içeren prospektif çalışmalar yol gösterici olabilir.

Anahtar kelimeler: Nötrofil lenfosit oranı, multipl skleroz, relaps, hastalık aktivitesi

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INTRODUCTION

Multiple Sclerosis (MS) is a chronic, demyelinating disease of the central nervous system. It is 2-3 times more common in women than men, frequently affects the 20-40 age group, and is the most common disabling neurological disorder in young people [1]. Although the initiating factor is still not known, epigenetic factors and an autoimmune background are thought to be responsible[1-6].

Objective markers lack in the diagnosis, follow-up and evaluation of response to treatment in MS. An attack or neurologic deterioration and plaques in specific areas showing temporal distribution and spatial distribution on Magnetic Resonance Imaging are the basic diagnostic criteria [7, 8]. While most patients have attacks and remissions, a small proportion shows progressive neurologic complaints independent of attacks. Nevertheless, there are no definitive diagnostic markers for the typing of the disease or progression. Several tests including Expanded Disability Status Scale (EDSS), 25-step test, 9-hole test, or smart phone applications reported by patients during follow-up are used in the clinical setting, with limited efficacy, particularly in detecting progression [11]. The expanded disability status scale (EDSS) is the most commonly used scale in patients with MS. EDSS is a very effective method in reflecting disability, determining the degree of the disease, for evaluating treatment change, or possible progressive process [12]. Widespread neuroaxonal damage occurs in progression independent of relapse activity (PIRA) patients [13].

Since inflammation is present at almost every stage of MS [9, 10], the neurofilament light chain has been introduced as a marker of follow-up of the patients [14]. However, it requires an invasive procedure, significance level in Cerebrospinal fluid has not been standardized and costly [15].

In case of insufficient response, the treatment is modified based on clinical and radiologic activity. Since disease-modifying therapies are highly effective, an early and effective treatment plan is crucial. Another important point is the detection of insufficient response to treatment in the absence of clinical signs. Although it is still unclear whether the radiologic activity alone is sufficient for altering the ongoing treatment, it can prompt the clinician for a closer follow-up to clinical deterioration.

T cell subgroups (Th17, CD4(+), CD25(+) regulator T cells = T reg, natural killer cells), B cells, dendritic cells, microglia, and monocytes are involved in the immunopathogenesis of MS [16]. The presence and cellular intensity of inflammation varies at different stages of the disease. It has been suggested neutrophil/lymphocyte ratio (NLR) changes due to the increase in the number of cells involved during inflammation [17]. This ratio can be calculated both from the absolute number of neutrophils and lymphocytes, and from their relative number. NLR is easy to perform, Complete Blood Count (CBC) being one of the standard blood tests routinely performed in any hospital. Nevertheless, although theoretically plausible, this ratio has not been fully accepted as a direct indicator of inflammation due to the complexity of the inflammation process [17]. On the other hand, it is unknown whether the NLR is involved or a surrogate of the inflammatory process at many stages of MS.

Although radiologic activity is considered an MS disease activity, it does not always correlate with clinical activity. In some patients, radiologic activity may be observed despite the absence of any clinical complaints, symptoms or signs. In these cases, it will be possible to say that disease activity continues. In such a case, it would be correct to define a marker of disease activity that is independent of clinical assessment. As explained above, there is no easily accessible and applicable marker of disease activity at many stages of MS. Therefore, we aimed to investigate whether NLR could be a marker of disease activity in MS patients with radiologic activity without any clinical activity. From this point of view, we wanted to emphasize that the N/L ratio may also be significant for different markers for MS patients in the literature.

MATERIALS AND METHODS

Study design and sample

The patients admitted to the Gülhane Training and Research Hospital Neurology outpatient clinic between May 2022 and December 2022 for follow-up with a diagnosis of MS according to the 2017 Mc Donald diagnostic criteria were retrospectively analyzed. Patients were taken from patient data registered in the hospital system and diagnosed by specialized neurologists.

Inclusion criteria were using interferons and glatiramer acetate treatments for at least 1 year, not taking steroids in the last 3 months, absence of a

clinical attack in the last 3 months, and any neurological progression. Patients with any chronic disease, taking regular medication, taking steroid treatment within the last one month, pregnancy, fingolimod, ocrelizumab, cladribine, natalizumab and dimethyl fumarate therapies using patients, were excluded from the study. Patients under treatments of fingolimod, ocrelizumab, cladribine, natalizumab and dimethyl fumarate therapies were excluded because of these drugs affect directly NLR via their effects on T cells. Individuals with blood transfusion, surgery or major trauma in the last three months and smokers were also excluded. During laboratory analyses patients with elevated white blood cell counts (The complete blood count performed at Gülhane Training and Research Hospital utilized laboratory reference values. Upper limit reference value for white blood cells was 9750/μl) and sedimentation values above 20 mm in complete blood tests in which NLR was evaluated were also excluded from the study.

Measures

In these patients, clinical activity was considered as the presence of an attack and progression. A clinical episode in MS was defined as the appearance of a new neurological symptom or worsening of an old symptom lasting at least 24 hours without fever or infection. The radiologic activity was considered as the presence of a contrast-enhancing lesion or T2 new lesion.

For progression evaluation, no change in EDSS scores in the last two visits was accepted [17]. Contrast-enhanced cranial and/or cervical MR images were analyzed which had been performed during routine follow-ups.

NLR was calculated by dividing the neutrophil count by the lymphocyte count in the whole blood test during the follow-up examination. Two groups were created according to disease activity. The first group (named as active patient group) consisted of patients with radiological activity in the absence of clinically activity of MS. And second group (named as control group) consisted of patients without radiological and clinically activity of MS.

Accordingly, we compared 20 age- and gender-matched, radiologically active MS patients (active patient group) with no clinical progression or attack but with contrast-enhancing lesions on control MRI and 20 patients with clinically and radiologically completely controlled MS (Control) in terms of NLR.

Statistical analysis

SPSS 22 statistical program was used in the evaluation of statistical analyses. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the distribution of continuous variables. For continuous variables with a non-normal distribution, the Mann-Whitney U test was employed to examine between-group differences in NLR values, neutrophil count, and lymphocyte count. The Mann-Whitney U test was also used to compare NLR values between genders and age groups within both the overall study population and the subgroups. The statistical significance level was accepted as $p<0.05$ in all analyses.

RESULTS

For this study totally 378 patients with MS diagnosis and admitted to our outpatient clinic for routine follow-ups were screened retrospectively. Twenty MS patients with only radiologic activity without clinical attack or progression and 20 MS patients without both clinical and radiologic activity who met the inclusion and exclusion criteria were accepted for the study. Totally 40 patients are analyzed whether NLR rates are an indicator of radiologic activity.

The mean age was 29.8 ± 2.73 (Min 18 - Max 51) in both groups. Both groups consisted of 15 women and 5 men.

Mean NLR value was 2.26±1.13 in entire study population (Min 0.96-Max 5.92). Mean neutrophil count was 4.82±2.44 (Min 1.76-Max 11.73) and lymphocyte was 2.17±0.55 (Min 1.20-Max 3.30). Mean neutrophil count was 5.27±2.55 (Min 2.57-Max 11.73) and lymphocyte was 2.35±0.48 (Min 1.40-Max 3.20) and NLR value was 2.22±0.87 in radiologically active patient group (Min 1.08-Max 4.28). Mean neutrophil count was 4.37±2.30 (Min 1.76-Max 9.75) and lymphocyte was 1.99±0.56 (Min 1.20-Max 3.30) and NLR value was 2.31±1.37 in control group (Min 0.96-Max 5.92).

There was no statistically significant difference between the groups in terms of NLR values (p: 0.745, mean 2.22 ± 0.19)

According to Mann Whitney U test results, in terms of NLR medians, there is no statistically significant

difference between genders (entire study population), between gender in both groups and between under and over median age distribution (In active patient group) (Table 1).

Table 1. Median analyses of Neutrophil Lymphocyte Ratio

Median Age	n		Mean	Std Dev	Median	Min	Maks	P value
<24 age	20		2.16	1.058	1.76	1.08	5.29	0.372
≥24 age	20		2.37	1.224	1.91	0.96	5.93	
	Gender	n						
Patient	Female	15	2.17	0.795	1.86	1.09	3.67	0.896
	Male	5	2.41	1.157	1.75	1.53	4.29	
Control	Female	15	2.48	1.501	1.83	0.96	5.93	0.570
	Male	5	1.78	0.758	1.82	1.08	2.93	
	n							
Female	30		2.33	1.191	1.85	0.96	5.93	0.585
Male	10		2.09	0.98	1.79	1.08	4.29	
	n							
Patient	20		2.23	0.871	1.85	1.09	4.29	0.745
Control	20		2.31	1.371	1.83	0.96	5.93	

*Neutrophil Lymphocyte Ratio

DISCUSSION

In this study, we evaluated the role of NLR as a potential marker of radiological activity in MS patients without clinical activity. Our findings indicate that NLR cannot be used as a marker for radiological activity in these patients.

There is not any marker for MS diagnosis up to now. The significance of both clinical and MRI findings in the diagnosis of MS is undeniable. Both are required at the diagnostic stage [8]. At the diagnostic stage or in the anamnesis, the presence of a clinical attack or progression in neurological complaints, and radiologically, plaques showing temporal and spatial changes with certain criteria on MRI are required. There must also be no other disease or condition that would better explain them. In addition to the diagnosis of the disease, we also evaluate both (Clinical and radiological activity) in the follow-up of response to treatment. MS is a disease for which there is no definitive cure. As in many other chronic diseases, the agents used in the treatment of MS are expected to keep the disease under control. In other words, absence of clinical attack or progression and absence of radiologic disease activity (no new plaques, no increase in total plaque volume, no atrophy) are the main target of treatment strategies. Despite all these, approximately half of the patients transition to the secondary progressive phase within 10 years [19]. Preventing or at least delaying the transition to the secondary progressive phase is another treatment goal. However, sometimes the significance of the presence of clinical activity or radiologic activity alone is controversial. Clinically, the presence of attacks is very important. However, not all attacks are the same. For example, a spinal or brainstem attack has a very high risk of sequelae, while a sensory attack has a low risk of sequelae. For this reason, it is also controversial to prescribe treatment for every attack. Sometimes patients are unable to describe their attacks for sociocultural reasons or due to their level of education. They may associate their attacks with other clinical conditions (such as a tendency to attribute numbness or weakness in their feet to a herniated disc or numbness in their arms to a herniated cervical disc) and therefore do not express their attacks. Psychological conditions such as depressive or psychotic episodes are also difficult to identify as episodes. Considering that cognitive impairment is also seen in this disease, the information received should be scrutinized very carefully.

Progression is a difficult issue to assess and de-subjectivize. Even during the pandemic period, a life away from movement impaired the mobility of patients, leading to a false progression in EDSS values. The psychological state of the patients greatly influences the objective assessment [20]. Tests such as the 9-hole test or the 25-step walk test, which we use

in disease follow-up, may vary with the emotional state of the patient. Cognitive functions, sexual complaints or sleep disorders may also be overlooked. Even if these issues are questioned, it is difficult for every center to do so in the same way. Likewise, even if interrogations are carried out, problems arise because there are no objective scales for evaluation. Therefore, objective markers are needed.

The main pathologic factor in MS is inflammation. The content of this inflammation varies according to the type of disease or the presence of progression. The main cells causing chronic inflammation are macrophages, lymphocytes, and plasma cells [21]. Through chemokines and cytokines, neutrophils and macrophages migrate to the region in acute inflammation [22].

Systemic inflammation can be detected by many biochemical and hematologic tests. Both the number and the proportions of cells evaluated in the complete blood count have attracted attention and many different studies have been conducted on these issues. They are very simple to conduct and evaluate. In addition, their biggest advantage is that they can be evaluated on the basis of a complete blood count, which can be performed in any health institution without the need for any other test. However, because these cells are so general, it is difficult to expect them to be specific or sensitive to any disease.

It has been suggested that NLR is an easier and cheaper method to determine systemic inflammation in various diseases compared to specific tests [23]. Previous studies have reported that NLR may be associated with disease activity in autoimmune diseases such as inflammatory bowel disease, Sjögren's Syndrome, Rheumatoid Arthritis and Ankylosing Spondylitis [24-27].

In addition, in a study conducted on stroke patients, it was observed that NLR above 5 was associated with poor prognosis and high NLR was associated with hemorrhagic transformation and 3-month mortality after stroke [28].

In a very recent study by Huang et al. in 641 MS patients, they observed that high NLR was associated with 2-year relapse [29]. In addition to NLR, monocyte/lymphocyte ratio was also found to be associated with 2-year relapse. In this way, it has been reported that NLR and MLR can be used as disease activity markers. These results suggest that high NLR indicates an underlying and ongoing inflammatory process.

It has been reported that NLR can be used as a simple and useful tool in the follow-up of Alzheimer's disease, a slowly progressive neurodegenerative disease without exacerbations such as MS [30]. NLR was also found to be high in patients with Parkinson's disease, another neurodegenerative disease effecting central nervous system like MS[31].

We excluded some patients using several MS treatments just like fingolimod ocrelizumab, natalizumab or dimethyl fumarate because of their direct effects on NLR. In experimental autoimmune encephalitis models, an increase in the number of peripheral and central neutrophil cells was observed at the onset of neurologic symptoms [32]. Suppression of neutrophils may inhibit inflammation by preventing disruption of the blood-brain barrier. This hypothesis is supported by the positive effects on MS of various drugs that have an effect on blood cell counts [29].

Thus, NLR was not disease-specific in any of the studies. It cannot be considered a diagnostic marker. It may be considered an indicator of the severity of the underlying inflammation. However, inflammation is not the same in every disease. NLR can be a very general indicator of inflammation. It fails to detect local inflammation.

Although NLR is effective in indicating systemic inflammation, it may be insufficient to reflect a disease that affects only the central nervous system, such as MS. In our study, we tried to evaluate inflammation not reflected in the clinic. The presence of a contrast-enhancing lesion suggests the presence of inflammation in that region and an impaired blood-brain barrier. Perhaps the severity of inflammation was so low that it did not cause clinical complaints and did not cause a significant change in NLR. On the other hand, the limited number of patients was also influenced by the difficulty in creating the same comparison groups due to too many variables for inflammation.

One of the biggest gaps in MS is the lack of markers. Unfortunately, despite all the studies, both specific and sensitive markers have not been found yet. There is also a lack of markers for detecting progression and predicting poor prognosis. Studies on markers that are inexpensive, easily applicable, objective as well as sensitive and specific are ongoing.

The study has some limitations. Many diseases and parameters that may affect NLR were excluded from the study. Therefore, study population was small. We cannot include many of the patients we encounter in real life in this study. We accept this as one of the biggest limitations of our study. Another limitation of our study is that due to the small number of participants, it did not allow for subgroup analysis such as disease duration, treatments, presence of progression or disability.

Since the study was retrospective, it was not possible to work with a single radiologist. But all MRI scans were performed at the center where the patients were taken.

The positive point of our study was both groups were matched exactly in terms of age and gender. In addition, all kinds of diseases and treatments (including MS treatments) that may affect NLR were excluded from the study, and only the NLR effect was observed.

Main goal in MS treatment is taking disease activity under control both radiologically and clinically. Radiological activity without any clinical activity is very important in terms of patient follow-up and treatment regulation. If treatment changes are delayed, this can lead to disability. So, there is a need for much larger studies on any markers that can detect or predict the disease activity before disability occurs. NLR studies available for subgroup analyzes as a marker of MS disease activity can provide useful information in future.

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