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Evaluation of Peripheral Inflammatory Activity in Different Types of Dementia

Farklı Demans Tiplerinde Periferik İnflamatuar Aktivitenin Değerlendirilmesi

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ABSTRACT

Aim: Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by pathophysiological processes involving neuroinflammation, neurodegeneration, and synaptic dysfunction. Vascular dementia (VaD) stands as the second most prevalent form among all dementia types, sharing common pathophysiological mechanisms with AD, such as vascular oxidative stress and chronic inflammation. The neutrophil-to-lymphocyte ratio (NLR) is considered a simple, noninvasive, and widely available clinical marker of inflammation. The aim of this study is to investigate the potential differences between these two different types of dementia in terms of NLR values.

Materials and Methods: The data of patients diagnosed with AD or VaD and healthy controls who applied to a University Hospital Neurology outpatient clinic were retrospectively examined, and the groups were analyzed with statistical methods in terms of NLR levels.

Results: A total of 39 AD, 32 VaD, and 30 healthy controls were enrolled in the study. Hemogram analyses revealed significantly elevated NLR values in both the AD and VaD groups compared to the healthy control group ($p = .001$, $p = .001$, respectively). AD and VaD groups demonstrated no significant difference in NLR ($p = .787$). Additionally, as a result of regression analyses, it was determined that age and NLR were independent variables associated with the presence of dementia.

Conclusions: NLR values are at higher levels in AD and VaD patient groups compared to healthy controls. Our results support the role of peripheral inflammation in the pathogenesis of VaD, as in AD. Additional studies are needed on potential inflammatory biomarkers of VaD.

Keywords: Alzheimer's disease, Vascular dementia, NLR, Neuroinflammation

ÖZ

Amaç: Alzheimer hastalığı (AH), nöroinflamasyon, nörodejenerasyon ve sinaptik işlev bozukluğu gibi karmaşık patofizyolojik süreçlerle karakterize kronik bir nörodejeneratif hastalıktır. Vasküler demans (VaD), tüm demans türleri arasında ikinci en yaygın form olup, vasküler oksidatif stres ve kronik inflamasyon gibi AH ile ortak patofizyolojik mekanizmalara sahiptir. Nötrofil-lenfosit oranı (NLR), inflamasyonun basit, invaziv olmayan ve yaygın olarak kullanılabilen bir klinik belirleyicisi olarak kabul edilmektedir. Bu çalışmanın amacı, NLR değerleri açısından, bu iki farklı demans tipi arasındaki potansiyel farkları araştırmaktır.

Hastalar ve Yöntem: Bir Üniversite Hastanesi Nöroloji polikliniğine başvuran, AH veya VaD tanısı alan hastaların ve sağlıklı kontrollerin verileri retrospektif olarak incelenerek, gruplar NLR düzeyleri açısından istatistiksel yöntemlerle analiz edilmiştir.

Bulgular: Çalışmaya toplamda 39 AH hastası, 32 VaD hastası ve 30 sağlıklı kontrol dahil edildi. Hemogram analizleri, AH ve VaD gruplarında NLR değerlerinin sağlıklı kontrol grubuna kıyasla anlamlı bir şekilde yüksek olduğunu ortaya koydu (sırasıyla $p = .001$, $p = .001$). AH ve VaD grupları arasında NLR'de anlamlı bir fark saptanmadı ($p = .787$). Ayrıca, regresyon analizleri sonucunda, yaş ve NLR'nin demans varlığı ile ilişkili bağımsız değişkenler olduğu belirlendi.

Sonuç: NLR değerleri, AH ve VaD hasta gruplarında sağlıklı kontrollere göre yüksek seviyelerdedir. Sonuçlarımız, VaD patogenezinde de, AH'de olduğu gibi periferik inflamasyonun rolünü desteklemektedir. VaD'nin potansiyel inflamatuar biyobelirteçleri konusunda ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Alzheimer Hastalığı, Vasküler Demans, NLR, Nöroinflamasyon

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by impairment in cognitive functions, especially memory, and deterioration in daily living activities, as well as neuropsychiatric symptoms and behavioral changes. Amyloid plaques and neurofibrillary tangles are pathologic hallmarks of the disease [1, 2]. There are certain complex pathophysiological processes involving neuroinflammation, neurodegeneration, and synaptic dysfunction in AD [1]. Activated astrocytes and microglia have an important role in chronic neuroinflammation that facilitates neuronal death and the accumulation of intracellular beta-amyloid plaques and intraneuronal neurofibrillary tangles, resulting in both the onset and progression of the disease [2-6]. In addition, it seems that inflammation reaches beyond the confines of the central nervous system (CNS), as various indicators of systemic inflammation have been observed to elevate throughout the progression of the disease in AD [3, 7-9].

Vascular dementia (VaD) emerges as the second most widespread manifestation among all dementia types, manifesting through cognitive impairment, functional deterioration, behavioral disturbances, and neurological symptoms arising as sequelae to cerebrovascular disease (CVD). There are shared pathophysiological mechanisms with AD including vascular oxidative stress and chronic inflammation, serving as pivotal pathogenic elements contributing to neurovascular dysfunction [10-13].

Circulating peripheral cells such as leukocytes, lymphocytes, and neutrophils are widely used in the literature as markers of systemic inflammation [8, 9, 14, 15]. The Neutrophil-to-Lymphocyte Ratio (NLR), calculated by dividing the neutrophil count by the number of lymphocytes in the complete blood count, is recognized as one of the simple, non-invasive, cost-effective, and widely available clinical markers of peripheral inflammation. It combines information from two leukocyte subtypes and eliminates the disadvantages of absolute leukocyte values, which are affected by factors such as infection and dehydration. NLR has demonstrated associations with a spectrum of health conditions, encompassing cerebrovascular and cardiovascular diseases, Diabetes Mellitus, Hypertension, as well as various malignancies [5, 14, 16]. Furthermore, multiple studies have indicated an elevation in NLR values among individuals with AD when compared to the general population. [4, 5, 8, 15, 17, 18]. Moreover, elevated NLR level was observed in the Mild Cognitive Impairment (MCI) group in comparison to the healthy control cohort [5, 8, 19]. To the best of our knowledge, NLR, as an inflammatory marker has not been comprehensively examined in the context of vascular dementia. In a recent study, NLR levels were examined in AD and VaD types, the NLR level was found to be significantly higher in AD patients than the VaD patients [20]. It is unknown whether NLR levels in the VaD group differ from healthy individuals.

This study aims to evaluate the potential differences and diagnostic use of Neutrophil-Lymphocyte Ratio (NLR), as a well-defined inflammatory marker, in Alzheimer's disease (AD), vascular dementia (VaD), and healthy individuals.

Material-Method

We retrospectively collected the data of patients aged >65 years diagnosed with AD or VaD, and healthy controls, who had been admitted to Gazi University Faculty of Medicine, Department of Neurology outpatient clinic between January 2022 and June 2023.

Individuals with a confirmed diagnosis of probable AD, following the National Institute on Aging and Alzheimer’s Association (NIA-AA) criteria, and those diagnosed with VaD based on the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria following thorough clinical assessment and subsequent diagnostic evaluation, were included for further analysis in this study [12, 21].

Patients with diagnoses of malignancy, renal, hepatic, or chronic heart failure, coronary artery disease, connective tissue disease, hematological disease, infectious diseases, endocrine disorders, or autoimmune conditions that could potentially influence routine blood parameters were excluded from the study.

The control group in our study consisted of healthy volunteers aged over 65 years who did not have memory complaints, any comorbidities that may affect routine blood parameters, whose cognitive tests were normal, who were examined in our outpatient clinic for other reasons, and who were given blood samples.

We retrospectively collected all demographic, clinical, neuroimaging, and laboratory data from the hospital database system. Age, gender, education, disease duration, results of clinical and neuropsychological examinations, and the scores of the Mini-Mental State Examination (MMSE) test were recorded for each patient.

Complete blood count data studied from samples taken following overnight fasting routinely collected into EDTA tubes and then subjected to automated hematological analysis (Unicel® DxH800 automatic hematology analyzer) were recorded. Neutrophil and Lymphocyte counts and NLR, were analyzed in AD, VaD, and healthy control groups.

This retrospective study adhered to the ethical principles outlined in the Helsinki Declaration, and the study protocol received approval from the Ethics Committee of Gazi University Faculty of Medicine (2023/878).

Statistical analyses

The statistical analysis was carried out using the IBM SPSS 20 package program. The normality of numeric data was assessed using the Shapiro-Wilk test and presented as mean ± SD or median (min-max) where appropriate. Categorical variables were expressed as percentages. For pairwise comparisons, the Student's t-test or Mann-Whitney U test was employed based on the normality of the data. In cases where there were more than two groups, One-Way ANOVA or Kruskal-Wallis variance analysis was applied. Categorical variables underwent evaluation through the Chi-Square test. Simple correlations were performed using the Spearman test. To identify independent associates of dementia presence, a logistic regression model was employed. A two-tailed p-value of <0.05 was considered statistically significant.

Results

In total, 39 AD patients (17 men; mean age, 72.41 ±1.31 years), 32 VaD patients (17 men; mean age, 77.56 ±1.48 years), and 30 healthy controls (15 men; mean age, 68.53±2.10 years) were included in our study. The gender distribution and education level were similar among the three study groups; but the mean age was older among patients with VaD when compared to AD and healthy control groups (p=.037 and p=.001, respectively). There was no difference in age between AD and HC groups (p=.665).

Demographic characteristics and laboratory parameters of the study population are presented in Table 1.

Table -1. Baseline characteristics and hemogram parameters of the study population

	AD	VaD	HC	P
Age [years (mean±SD)]	72.41 ±1.31	77.56 ±1.48[a,b]	68.53±2.10	.001 *
Sex (F% vs M%)	56% vs 44%	47% vs 53%	%50 vs %50	.713
Education (<=8 years vs > 8 years)	51% vs 49%	66% vs 34%	%60 vs %40	.465
MMSE score	16.92 ± .61	17.53 ±.75	28.40±.27[c,d]	.000*
WBC (10 9/L)	7.23 ± .33	7.46 ±.31	7.00±.33	.654
NEU (10 9/L)	4.52 ± .26	4.75 ±.26	3.94±.24	.138
LYM (10 9/L)	1.86 ± .11	1.95 ±.12	2.23 ± .10	.07
NLR (Neutrophil/ Lymphocyte Ratio)	2.81±.28	2.71±.22	1.81±.11[e,f]	.001*

*p < 0.05

a p=.001 (VaD vs HC), b p=.037 (VaD vs AD), c p= .001 (AD vs HC), d p= .001 (VaD vs HC),

e p=.001 (AD vs HC), f p =.001 (VaD vs HC)

Regarding the patients with dementia, MMSE scores were similar in both AD and VaD groups (16.92 ± .61 for AD vs 17.53 ±.75 for VaD, p=.624); however, disease duration was longer in patients with AD (3.51±.13 years for AD, 3.09±.16 years for VaD, p=.022).

In Hemogram analyses, WBC, NEU, and LYM counts were similar among the three study groups (p= .654, p=.139, p=.07, respectively). Nevertheless, the NLR value demonstrated a significant difference between patients and controls, which was 2.81±.28 for AD patients, 2.71±.22 for VaD patients, and 1.81±.11 for

healthy controls (p=.001). Pairwise comparisons revealed no difference between patients with AD and VaD in terms of NLR (p=.787).

No significant correlation was demonstrated between NLR and age, regarding the whole study population or patients with dementia (p=0.087 and p=0.170 respectively).

Both univariate and multivariate regression analyses showed that age and NLR were independently associated with the presence of dementia (Table 2).

Table-2 Regression analysis for the independent associates of dementia presence

	Univariate analysis			Multivariate analysis		
	Exp (B)	(%95 CI)	p	Exp (B)	(%95 CI)	p
Age	1.063	1.012-1.117	**0.015***	1.056	1.000-1.115	**0.048***
Sex	1.316	0.501-3.457	0.577	1.015	0.350-2.941	0.978
Education	0.433	0.164-1.142	0.091	0.721	0.246-2.111	0.551
NLR	3.120	1.504-6.470	**0.002***	2.994	1.383-6.478	**0.005***

Discussion

In our current investigation, it emerged that individuals diagnosed with AD or VaD exhibited heightened NLR levels in comparison to the healthy control group. There was no significant difference in NLR levels between the AD and VaD patient groups. Moreover, our findings highlighted the predictive capacity of NLR in indicating the presence of AD or VaD.

Our observations concerning AD align with a multitude of studies indicating elevated NLR levels in AD patients compared to healthy controls. This consistency lends support to the significant involvement of chronic inflammation in the pathogenesis of AD [4, 5, 7, 9, 14, 17, 18]. Also, our study reflected the importance of NLR as a peripheral inflammatory marker in the VaD group as well as in the AD group.

Activation of inflammatory markers in the peripheral circulation triggered by neuroinflammation has been the subject of much AD research. NLR is one of the most frequently studied peripheral inflammatory markers in the AD literature [5, 15, 17, 18]. First, Kuyumcu et. al found that the patients with AD have elevated NLR in comparison with healthy controls and NLR was strongly predictive for diagnosis of AD and the association between NLR-AD was independent of well-known confounders like age, gender, etc. [17]. The following studies about NLR showed similar results in AD and MCI groups [5, 8, 15, 18, 19, 22]. Similarly, our results demonstrated an independent association between NLR and the presence of dementia.

Neutrophils, considered pivotal inflammatory cells, may increase in numbers stimulated by certain inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin-9 (IL-9), both implicated in the pathogenesis of AD [9, 23]. Elevated neutrophil counts, prompt T-cell activation and release of TNF-a. The chronic release of TNF-a by microglia is implicated in the accumulation of amyloid-beta (Ab) and phosphorylated tau (p-tau) [5, 25]. Furthermore, the activation of neutrophils plays a contributory role in the worsening of neurodegenerative diseases by causing damage to the blood–brain barrier (BBB). The increased migration of peripheral neutrophils and lymphocytes into the central nervous system, coupled with heightened neutrophil production in circulation, results in a substantial elevation of the peripheral NLR in patients diagnosed with AD and MCI [5, 23, 25-27].

Vascular oxidative stress and inflammation stand out as pivotal pathogenic factors contributing to neurovascular dysfunction and underlie many deleterious effects observed in VaD [10]. Inflammation serves as a central process linking various cardiovascular risk factors to both vascular and neuronal damage. Plasma levels of inflammatory proteins, including α1-antichymotrypsin, C-reactive protein, and IL-6, have been noted to rise years before the onset of VaD [25, 28]. Platelet and related inflammatory markers, such as Mean Platelet Volume (MPV) and Platelet-to-Lymphocyte Ratio (PLR), have been evaluated in several VaD studies. However, research on the role of NLR as an inflammatory marker in VaD cases remains limited. A recent study by Bulut et al. assessed NLR in VaD, revealing significantly higher levels in the AD group compared to the VaD group [20]. In contrast, our study found no significant difference between VaD and AD patients in terms of NLR, with both groups exhibiting higher NLR values than healthy controls. To the best of our knowledge, this is the first study that evaluated NLR in the VaD group

and healthy controls and showed that NLR values are significantly elevated in VaD compared to healthy controls. Our findings lend support to the involvement of peripheral inflammation in the pathogenesis of VaD, similar to AD. Prior studies have proposed that the elevated NLR observed in Alzheimer's disease might be a consequence of aging [15]. Based on this, our findings that the higher mean age in the VaD group compared to the controls may be thought as another potential reason for the higher NLR levels in VaD. However, our analyses did not detect any correlation between age and NLR levels, both in assessments involving all participants and within the dementia patient groups. Consequently, the elevated NLR levels observed in the VaD group are more likely attributable to the role of inflammation in the pathogenesis of VaD.

Limitations

Several limitations exist in the current study. Firstly, the relatively small sample size may hinder the generalizability of the findings. Secondly, the retrospective design of the study precludes the availability of follow-up data, thereby limiting our ability to predict subsequent clinical implications based on the observed results. Another limitation of our study is that the traditional inflammatory markers like CRP, TNF alpha, and interleukins, have not been assessed. However, the main objective of the current study was the prediction of dementia through a simple and inexpensive method like a routine hemogram.

Conclusion

In summary, our study concludes that individuals with Vascular Dementia (VaD) exhibit elevated Neutrophil-to-Lymphocyte Ratio (NLR) levels, highlighting the involvement of inflammatory pathophysiology, akin to Alzheimer's disease (AD). Future investigations with larger populations and longitudinal follow-up are essential to validate our findings and explore the pathophysiological and clinical significance of alterations in peripheral blood cells for the management of VaD.

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