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Association between MPV and Cerebral Vascular Ischemic Burden in Mild to Moderate Alzheimers's Disease

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ABSTRACT

Objective: Vascular pathologies and chronic neuroinflammation play an important role in Alzheimer's Disease (AD). Increased platelet activity, which underlies the pathophysiology of atherosclerosis and systemic inflammation, has been reported several times of AD. However, the relationship between this increase and neuroimaging correlates has not been studied yet. This study aims to evaluate the relationship between mean platelet volume (MPV), as a reliable indicator of platelet activity, and vascular ischemic burden in neuroimaging of AD. **Materials and Methods:** Medical records of mild-moderate AD cases diagnosed in our dementia outpatient clinic between 2021-2022 were retrospectively reviewed. Patients were classified as having "mild" or "severe" vascular ischemic burden on MRI. Clinical findings and platelet markers (Platelet-PLT, Platelet Distribution Width-PDW, Mean Platelet Volume-MPV) were compared between the groups. Multivariate regression was applied for potential confounders regarding vascular ischemic burden. **Results:** Out of 59 patients, 36 had 'mild' and 23 had 'severe' ischemic burden. Demographic and clinical features were similar; however, MPV was significantly higher in the group with severe ischemia (p=0.013). Multivariate analysis revealed an independent association between MPV and ischemic burden. An MPV value of ≥8.7 fL had a sensitivity of 69.6% and a specificity of 61% for severe burden. **Conclusion:** Our results highlight the role of platelet activation in the vascular pathogenesis of AD. During the early evaluation of AD, increased MPV can serve as a marker to determine the high-risk group in terms of cerebral ischemic burden. This might enable close monitoring and timely management of high-risk patients regarding the development of vascular morbidities.

Keywords: Alzheimer's Disease, Mean Platelet Volume, MPV, Vascular Ischemic Burden, Inflammation.

Hafif-Orta Evre Alzheimer Hastalığında MPV'nin Serebral Vasküler İskemik Yükle İlişkisi

ÖZ

Amaç: Alzheimer Hastalığı'nın (AH) temelinde, vasküler patolojiler ve kronik nöroinflamasyon önemli yer tutmaktadır. Ateroskleroz ve sistemik inflamasyon patofizyolojisinde kritik rol oynayan trombosit aktivitesinin de, AH'de arttığı çok kez bildirilmiştir. Ancak bu artışın, hastalıktaki nörogörüntüleme korelatlarıyla ilişkisi henüz incelenmemiştir. Bu çalışmada amaç, trombosit aktivitesinin göstergesi olan ortalama trombosit hacminin (MPV), AH nörogörüntülemesindeki vasküler iskemik yükle ilişkisini değerlendirmektir. **Gereç ve Yöntem:** 2021-2022 yılları arasında demans polikliniğimizde tanı alan hafif-orta evre AH olgularının kayıtları retrospektif incelendi. Hastalar MRG'deki iskemik yüke göre "ağır" veya "hafif" olarak sınıflandırıldı ve klinik bulgular ile platelet belirteçleri (Platelet-PLT, Platelet Dağılım Genişliği-PDW, Ortalama Trombosit Hacmi-MPV) gruplar arasında karşılaştırıldı. Vasküler yükle ilişkili potansiyel değişkenlere yönelik çoklu regresyon analizi uygulandı. **Bulgular:** İncelenen 59 hastanın 36'sı MRG'de 'hafif', 23'ü 'ağır' vasküler iskemik yüke sahipti. Gruplar demografik ve klinik yönden benzerken; MPV ağır iskemik yükü olan grupta anlamlı yüksekti (p=0.013). Çoklu regresyonda, MPV ve iskemik yük arasında bağımsız ilişki gözlendi. ≥8.7 fL MPV değerinin ağır serebral iskemik yük varlığı açısından %69,6 duyarlılığa ve %61 özgüllüğe sahip olduğu görüldü. **Sonuç**: Bulgularımız AH vasküler patogenezinde trombosit aktivasyonunun rolünü vurgulamaktadır. Artmış MPV AH'nın erken dönem değerlendirmesinde, serebral iskemik yük açısından yüksek riskli grubun belirlenmesinde bir belirteç olarak kullanılabilir. Bu erken tespit; vasküler morbiditeler açısından yakın takibe ve korunma/tedavi stratejilerini zamanında planlamaya olanak sağlayacaktır.

Anahtar Kelimeler: Alzheimer Hastalığı, Ortalama Trombosit Hacmi, MPV, Vasküler İskemik Yük, Inflamasyon.

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INTRODUCTION

Alzheimer's disease (AD) is a chronic, heterogeneous neurodegenerative disease characterized by complex pathological processes involving neuroinflammation, neurodegeneration, and synaptic dysfunction. Among individuals over 65, vascular diseases are also accounted for significant risk factors that take part in the pathophysiology and cause a remarkable predisposition (De la Torre JC, 2010; Elman-Shina K et al., 2022). The possible link between such vascular disorders and AD is likely based on cerebral hypoperfusion and tissue ischemia, triggering neurodegeneration through a chronic neuroinflammatory response. Chronic inflammation facilitates neuronal death and consequently paves the way for the accumulation of amyloid plaques and neurofibrillary tangles, which result in both the onset and progression of the disease (Elman-Shina K et al., 2022; Custodio N et al., 2017; Snowdon DA et al., 1997). Furthermore, background inflammation in AD seems to extend far beyond the central nervous system (CNS), as numerous markers reflecting systemic inflammation have been demonstrated to increase during the disease course (Chen SH et al., 2017; Casoli T et al., 2010; Dong X et al., 2019). Out of them, platelets and related indices were found to be reliable indicators of the presence and severity of disease, according to the recent literature.

Many studies have shown significant alterations in terms of the number and activity of the platelets, which play a critical role in the pathophysiology of systemic inflammation and atherosclerosis result (Casoli T et al., 2010, Sevush S et al., 1998; Talib LL et al., 2012). Mean Platelet Volume (MPV), one of the most studied platelet-related indices, represents the average size of platelets in peripheral blood and provides notable information regarding their activity and functional status. It is easily accessible from routine hemogram studies and the elevation, which is known to be compatible with increased platelet activity and vascular inflammation, has been accepted as an inflammatory biomarker in the setting of several diseases (Slavka G et al., 2011; Korniluk A et al., 2019). Nonetheless, contradictory results regarding MPV were reported for patients with Mild Cognitive Impairment (MCI) or AD. While some authors reported an increase in MPV for this group compared to controls; some others suggested a decrease (Chen SH et al., 2017; Wang RT et al.,2013).

In this study, we aimed to evaluate the relationship between Mean Platelet Volume (MPV) and cerebral vascular ischemic burden on neuroimaging among patients with mild to moderate Alzheimer's disease who have no overt diagnosis of cardiac and/or cerebrovascular disease. Early identification (e.g., during the initial visits) of patients with severe burdens is essential since they could benefit from close monitoring to prevent the development of definite vascular accidents.

To the best of our knowledge, no similar study exists in the literature that evaluates the relationship between MPV alterations and neuroimaging correlates of cerebral ischemic burden in AD.

MATERIALS AND METHODS

Patients

Medical records of patients admitted to the outpatient clinic of dementia and neurocognitive disorders in the Neurology Department of Gazi University Research and Training Hospital between January 2021 and May 2022 were retrospectively reviewed. The patients with a final diagnosis of mild-moderate AD, according to National Institute on Aging and Alzheimer's Association (NIA-AA) criteria after clinical assessment and consequent diagnostic workup, were subjected to further analysis. Individuals with an already diagnosis of malignancy, active infection, an additional neurodegenerative disorder, definite cardio-cerebrovascular diseases (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, and atrial fibrillation, heart failure, stroke) and autoimmune diseases, as well as the patients receiving any medication that could potentially affect hemogram parameters, were excluded (Benjamin EJ et al., 2018). Age, gender, and comorbid illnesses; results of clinical and neuropsychological examinations both including the structured interview with the patients and the family and neurological examinations; the scores of the Montreal Cognitive Assessment (MoCA) test; hemogram parameters and cranial MRI findings were recorded. The grade of the vascular ischemic burden on cranial MRI was classified according to the scoring system identified by Fazekas et al. (Fazekas F et al., 1987).

Laboratory

Venous blood samples for complete blood count were taken from all patients on the same morning with the first visit to the outpatient clinic following overnight fasting. The samples were collected into EDTA tubes and then subjected to an automatic hematological analysis (Unicel® DxH800 automated hematology analyzer). Platelet count and platelet-related markers, including mean platelet volume (MPV) and platelet distribution width (PDW), were recorded for each patient.

Magnetic resonance imaging

All patients underwent a standardized Cranial Magnetic Resonance Imaging (MRI) study under the dementia protocol following a detailed history and neurological and mental examination for dementia symptoms (MRI; 3-Tesla Magneton Aera; Siemens, Erlangen, Germany). The sections were examined in detail by an expert neuroradiologist, and the vascular burden with microangiopathic ischemic features observed in the T2 and FLAIR sequences were scored based on the scoring system described by Fazekas et al. [Fazekas 0: No lesion or single punctate lesion (subcortical hyperintensities), Fazekas 1: Multiple punctate lesions, Fazekas 2: Confluent lesions

(bridging), Fazekas 3: Diffuse confluent lesions]. Regarding this study, patients with a Fazekas score of 0 to 1 were referred to as having 'mild ischemic burden' and patients with a score of 2 to 3 as 'severe ischemic burden'.

Statistical analysis

The statistical analysis was conducted via IBM SPSS 20 software package (SPSS, Inc., Chicago, Illinois, USA). The normality of numeric data was assessed by the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean (±SD), and skewed parameters were presented as median (min-max). Categorical variables were expressed as percentages (%) and evaluated with the Chi-square test. Demographic features, rate of comorbid diseases, Montreal Cognitive Assessment (MoCA) scores and hemogram results were compared between groups of patients who have neuroimaging findings compatible with either 'mild ischemic burden (Fazekas Stage 0-1)' or 'severe ischemic burden (Fazekas Stage 2-3)'. Pairwise comparisons regarding continuous variables were performed via independent sample's t-test or Mann-Whitney U test according to the normality. A logistic regression model was applied of analyze potential variables associated with vascular ischemic burden in neuroimaging. A two-tailed p-value of < 0.05 was considered statistically significant.

Ethical considerations

This retrospective research was conducted under the ethical standards of the Helsinki Declaration, and the study protocol was approved by the Ethics Committee of Gazi University Faculty of Medicine (2023 / 878).

RESULTS

Fifty-nine eligible patients with a diagnosis of mild to moderate Alzheimer's Disease who have accessible neuroimaging and laboratory data were included. Out of this 59, 34 (58%) were female and 25 (42%) were male. The mean age of the entire cohort was 73.2±7.9 years. The most common comorbidities were hypertension (HT) and diabetes mellitus (DM) which were referred to as cardiovascular (CV) risk factors. Among the entire cohort, 71% of the patients (n:42) had a positive history of hypertension, out of whom 52% had coexistent DM. The baseline demographic characteristics of the study population are summarized in Table 1.

Table 1. Baseline demographic and clinical characteristics of the study population (n=59).

Variable	
Age [years (mean ± SD)]	73.2±7.9
Gender	
Female [n (%)]	36 (61%)
Male [n (%)]	23 (39%)
Education	
None [n (%)]	7 (12%)
Primary [n (%)]	27 (46%)
High school and college [n (%)]	25 (42%)
Cardiovascular risk	42 (71%)

61% (n:36) of the patients had cranial MRI findings compatible with 'mild ischemic burden', and 39% (n:23) had features of 'severe ischemic burden'. The two groups were similar in terms of age, gender, education, CV risk, and Montreal Cognitive Assessment scores (MoCA) (p:0>05). Platelet count and platelet distribution width either did not demonstrate a significant difference between the two (p:0.18 and p:0.76, respectively). However, mean platelet volume (MPV) was shown to be significantly higher in the group with 'severe ischemic burden' (p:0.01) (Table 2).

Table 2. Pairwise comparisons between groups according to fazekas stage (mild vs severe) (n=59).

	Mild Stage [Fazekas 0-1] (n:36)	**Severe Stage [Fazekas 2-3] (n:23)**	**p**
Age [years (mean±SD)]	72±8.4	75±6.9	0.15
Sex [F (%) vs M (%)]	71% vs 29%	48% vs 52%	0.08
ED. (E0 vs E1 vs E2 %)	14% vs 42% vs 44%	9% vs 52% vs 39%	0.69
Positive history for CV risk [% (n)]	72% (n:26)	70% (n:16)	0.70
MOCA score	16.3±4.6	16.8±5.2	0.78
PLT (10^3/µl)	248.2±66.8	220.9±58.1	0.18
MPV (fL)	8.6±0.98	9.3±1.1	**0.01***
PDW (%)	16.5±1.6	16.3±1.7	0.76

Univariate and multivariate regression analyses for potential confounders regarding cerebral vascular ischemic burden revealed a significant association between MPV increase and advanced Stage of Fazekas. The relationship was independent of age, gender, and comorbid CV risk factors (Table 3).

A ROC curve analysis. Demonstrated that MPV values >8.7 fL had a sensitivity of 69.6% and a specificity of 61% for 'severe ischemic burden' in the setting of mild to moderate AD (AUC: 0.680, 95% CI: 0.542-0.818, p<0.021*) (Figure 1).

Table 3. Evaluation of covariates with potential influence on fazekas stage (n=59).

Variable	Univariate Analysis			Multivariate Analysis		
	Exp(B)	95% CI	p value	Exp(B)	95% CI	p
Age	1.05	0.98-1.13	0.15	1.07	0.99-1.16	0.08
Sex	0.39	0.13-1.13	0.08	0.33	0.10-1.1.	0.07
CV risk	1.14	0.36-3.59	0.83	1.59	0.41-6.17	0.50
MPV	1.93	1.11-3.37	**0.02***	2.32	1.21-4.46	**0.01***

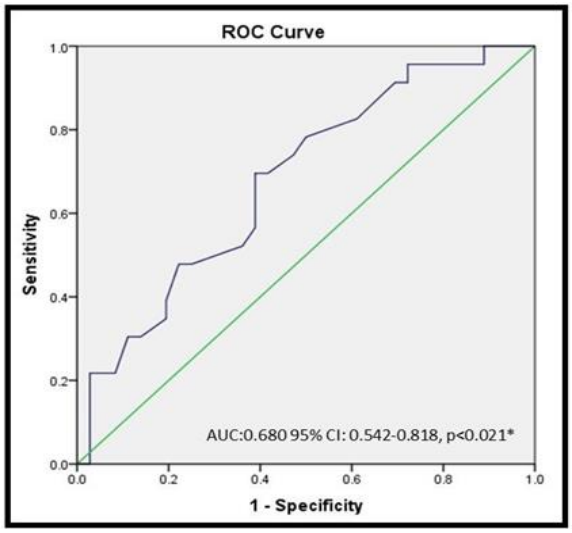

Figure 1. ROC curve analysis.

DISCUSSION

The current study's results demonstrated a significant relationship between MPV and cerebral ischemic burden in patients with mild to moderate AD who have similar demographic and clinical characteristics. MPV, accepted as a reliable marker of systemic inflammation, was found to be increased in patients with advanced MRI findings, as in the ones with mild features. To the best of our knowledge, this is the first study in the literature, searching for the relationship between MPV and neuroimaging correlates of vascular ischemic burden in AD.

In addition to typical pathological marks like senile plaques and neurofibrillary tangles, there is plenty of evidence regarding the ongoing inflammatory process in AD, which include enhanced aggregation of activated microglia, astrocytes around the postcapillary venules, and adhering leucocytes inside. Because neuroinflammation promotes the activation of the peripheral immune system, many inflammatory markers in circulation have been the subject of relevant research in AD. Platelets and their relative indices cover a remarkable proportion of these studies (Chen SH et al.,2017). Platelets have a prominent pro-inflammatory role and act as an important source of circulating amyloid-beta (a-ß) (Li QX et al.,1998; Talib LL et al., 2012). In activation, they adhere to leukocytes and endothelium with the aid of adhesion molecules and pave the way for the secretion of inflammatory mediators like interleukins and chemokines. Some other changes regarding the levels of enzymatic components inside, like cyclooxygenase-2 (COX-2) and phospholipase A2, which take part in the synthesis of inflammatory mediators, were also reported in the last decades (Krzystanek E et al.,2007; Bermejo P et al., 2008).

As an important platelet-derived parameter, mean platelet volume (MPV) is easily obtained from routine hemogram studies and represents the measure of average platelet size. The normal range varies between 7.5-12.0 fL; under physiological conditions, the ratio of large platelets / total platelets is not expected to exceed 0.2-5.0% (Korniluk A et al., 2019). Increasing MPV is an outcome of enhanced platelet aggregation, synthesis, and release of thromboxane TXA2 and β-thrombomodulin (Choi DH et al.,2016). In many pathological conditions that develop on the background systemic inflammation, such as cardiovascular and peripheral arterial diseases and cerebrovascular accidents, MPV increase was demonstrated to be a steady accompaniment reflecting overall vascular mortality (Slavka G et al., 2011; Korniluk A et al.,2019; Greisenegger S et al., 2004; B; Lance MD et al., 2012; Tohgi H et al.,1991). Its prognostic value was confirmed in acute ischemic stroke either (Greisenegger S et al., 2004). Taken together, MPV elevation in AD is not surprising due to the neuroinflammatory framework of the disease (Huang LT et al., 2022).

However, some few reports exist in the literature, that argue the opposite. Wang et al. examined platelet markers in Mild Cognitive Impairment (MCI), AD, and healthy controls in 2013. They reported a significant decrescent in MPV and PDW levels among patients with AD as to MCI and controls. The authors suggested a correlation between the grade of cognitive impairment and a decrease in MPV in that

study (Wang RT et al.,2013). One year later, the same group published similar results in a slightly different cohort consisting of two other dementia groups (AD and VaD) and controls; and again stated decreased values of MPV and PDW among dementia patients when compared to controls (Liang QC et al., 2014). However, the authors could not clarify the definite mechanism underlying this diminishment. They proposed a possible association between hematopoietic disorders and the onset/progression of AD and suggested that dysregulation in bone marrow cells, including megakaryocytes, may be responsible for this reduction.

In contrast, most of the papers in the literature, which are relevant to this issue, disclosed concordant findings with the current study. For instance, Chen et al. demonstrated high MPV values in 92 AD patients compared to 84 age, sex-matched controls (Chen SH et al., 2017). The results of another research from Dong et al. were similar to our findings, which reported an average MPV value of 8.78 fL among 57 patients with MCI, which was significantly higher than the mean (8.40 fL) of 59 controls (Dong X et al., 2019). Guzel et al. found increased levels of MPV among 38 patients with AD as to 29 controls, and further analysis revealed that the values of MPV in patients with moderate to severe AD were also higher than the ones with mild disease. The authors also introduced a negative correlation between MPV and MMSE in patients with AD (Guzel S et al., 2013). Yesil et al. identified an average MPV value of 8.46 fL among 126 patients with AD, while it was 8.17 for controls and significantly lower than the patient group (Prodan CI et al., 2011).

There are some limitations to the current study. First, the sample size is relatively small, making it difficult to generalize the findings. Second, the absence of follow-up data due to the retrospective design disables to presume the subsequent clinical implications of the observed results. On the other side, homogenous subgroups of patients in terms of demographic and clinical characteristics during pairwise comparisons, as well as persistent retrieval of a consistent relationship between elevated MPV and vascular burden after adjustment for all potential confounders, strengthen the reliability of our results.

CONCLUSIONS

The current study's findings support the role of platelet activation in the vascular pathogenesis of AD and indicate an independent association between MPV and ischemic vascular burden on neuroimaging. Early identification of patients with the high ischemic burden on initial evaluation is essential since completion of the diagnostic workup, particularly neuroimaging of the patients with cognitive complaints, AD could take some time; and this subset of patients might be more prone to cardio-cerebrovascular consequences. In such circumstances, an MPV value of >8.7 fL could serve as a marker for the physician to choose the right population that would benefit from close monitoring of prevent vascular morbidities.

Conflict of Interest

The author declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contributions

Plan, design: EEA; **Material, methods and data collection:** EEA, MU; **Data analysis and comments:** EEA, MU; **Writing and corrections:** EEA.

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