Turkish Journal of Medical Sciences

Volume 44 | Number 6 Article 23

1-1-2014

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TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2014) 44: 1060-1066

doi:10.3906/sag-1212-5

The increase of mean platelet volume in patients with Alzheimer disease

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Received: 02.12.2012 • **Accepted:** 01.10.2013 • **Published Online:** 24.10.2014 • **Printed:** 21.11.2014

Background/aim: Vascular risk factors play an important role in the progression of Alzheimer disease (AD). Mean platelet volume (MPV) is a determinant of platelet functionality and increased MPV is associated with an increased risk of vascular inflammation. Here we aimed to examine whether MPV could be used as a marker of vascular damage in AD and to discuss the relation between MPV and other vascular risk factors.

Materials and methods: A total of 109 outpatients with AD and 81 healthy controls were included in this study. Diagnosis of AD was made according to defined criteria. The Turkish version of the Mini Mental State Examination (MMSE) was used for cognitive assessment. According to the test results, patients were divided into 2 subgroups, mild (MMSE ≥ 18) and moderate (MMSE < 18), and their MPV levels were compared.

Results: MPV levels were higher in the AD group. There was no statistically significant difference between the moderate group and the mild group according to MPV values.

Conclusion: Increased MPV in patients with AD may point to platelet dysfunction. MPV is an indicator of increased in vivo platelet activation. Hence, platelets could be the link between vascular risk factors and AD. The assessment of MPV in patients with AD may help identify the patients that could benefit from additional antiplatelet therapy.

Key words: Alzheimer disease, dementia, cognitive decline, mean platelet volume, platelet activation, vascular risk factors

1. Introduction

Alzheimer disease (AD) is the most common form of dementia and is characterized by progressive cognitive decline. Multiple risk factors, including hypertension, diabetes mellitus, high serum homocysteine, atrial fibrillation, atherosclerosis, high serum cholesterol, and thrombogenic factors, are described for the pathogenesis of AD. Several studies have shown that vascular risk factors, atherosclerosis, and increased platelet activity play an important role in the progression of dementia in AD. In addition, AD and vascular dementia share many similar risk factors and cannot be distinguished clinically. This situation may support the role of vascular pathogenesis in AD (1–3).

AD is characterized by the abnormal progressive accumulation of amyloid-β (Aβ) in the brain's parenchyma and microvascular areas. Amyloid plaques consist of insoluble deposits of Aβ, which originate from the amyloid precursor protein (APP). This protein is expressed in the central nervous system. In a healthy brain, these protein fragments are broken down and eliminated. In patients with AD, these fragments accumulate as insoluble plaques. Several peripheral tissues produce APP normally. Platelets are an important source of APP in the blood and involve similar concentrations of APP isoforms as are found in the brain (4,5). Many studies have shown that APP and Aβ are stored in platelets and released into circulation with platelet activation (2).

Mean platelet volume (MPV), the average size of platelets in blood, is obtained from a routine blood count. Therefore, MPV measurement is an easily applicable and low-cost method for the assessment of platelet activity. MPV is positively correlated with increased in vivo platelet activity (6–10). MPV increases in vascular disease and in the presence of risk factors (e.g., hypertension, diabetes mellitus, hyperlipidemia) for vascular diseases (6–11). Increased MPV values were reported in cardiovascular disease and thromboembolic disorders (12). In addition,

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MPV was measured in acute ischemic stroke patients and was found to be associated with prognosis (13–15). Increased platelet activity and atherosclerosis contribute to the progression of dementia in AD (1). Many significant changes in levels and enzymatic activities of platelets in AD have been demonstrated in several studies. Mediators secreted by platelets contribute to the vascular events that result in vascular inflammation and atherosclerosis (16). In this study, we aimed to examine whether there is a difference in the MPV level in patients with AD compared to healthy controls and to discuss the relation between MPV and other vascular risk factors.

2. Materials and methods

2.1. Study population and procedures

Patients diagnosed with AD were collected consecutively from January 2009 until July 2012 in the Department of Neurology at University Hospital. Data were obtained by clinical interview, laboratory exams, physical and neurological examination, and computed tomography or magnetic resonance imaging. One hundred and nine patients met the established diagnostic criteria of probable AD (17,18). The Turkish version of the Mini Mental State Examination (MMSE) was used to screen for cognitive impairment (19,20). The MMSE is also used to follow the course of cognitive change in an individual over time, so it is an effective tool for the evaluation of response to treatment. The maximum score is 30, and while high points can never fully rule out dementia, higher scores indicate better cognitive performance.

Patients with AD were divided into 2 subgroups for mild (MMSE ≥ 18 points, 78 patients) and moderate (MMSE < 18 points, 31 patients) cognitive impairment. The control group consisted of 81 subjects, matched for age and sex, without dementia, stroke, or hematologic disease (21).

Laboratory exams included complete blood count, chemical profile, thyroid function test, and vitamin B12. Participants who were active smokers or heavy drinkers, who had cancer or abnormal liver or thyroid function tests, or who were receiving antiplatelet or anticoagulant therapy were excluded. The study protocol was approved by the Ethics Committee of Fatih University. The aims and procedures of the investigation were explained and a consent form was provided by all participants. For patients who were incapable of providing informed consent on their own behalf, consent was obtained from relatives.

2.2. Biochemical and complete blood count analysis

After 12 h of fasting, blood samples were obtained in the early morning (between 0900 and 1000 hours), and the samples were analyzed at 1300 hours. Ten milliliters of blood was drawn from the antecubital vein. The first 3 mL of blood was used for the complete blood count and was drawn into a vacutainer tube containing 0.04 mL of 7.5% K3 salt of ethylenediaminetetraacetic acid. The remaining 7 mL of blood was drawn into a vacutainer tube without anticoagulant and was left for 20 min before centrifugation. Blood tubes were centrifuged for 10 min at 1500 × *g* and were processed within 30 min. Complete blood counts were done with a CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, IL, USA). Serum concentrations of cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and glucose were evaluated by the enzymatic dry chemistry method using a Reflotron apparatus. Low-density lipoprotein (LDL) cholesterol values were evaluated according to the Friedewald formula. Serum concentrations of free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and vitamin B12 were measured by chemiluminescent assay using a Roche Elecsys 2010 analyzer (Cobas, Mannheim, Germany) with original kits.

2.3. Statistical analyses

Statistical analyses were performed using SPSS 15. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Descriptive analyses were presented using medians and interquartile ranges for the nonnormally distributed variables and frequencies and percentages for the ordinal variables. The Student t-test was used to compare normally distributed variables between the AD and control groups. The Mann–Whitney U test was used to compare nonnormally distributed variables between the AD and control groups. The chi-square test was used to compare the proportions of patients with diabetes and hypertension in the groups. $P < 0.05$ was considered to show a statistically significant result.

3. Results

One hundred and nine patients diagnosed with AD and 81 healthy controls, making a total of 190 individuals, were included in this study. Seventy patients (64.2%) were female and 39 (35.8%) were male in the Alzheimer's group, while in the control group 56 (69.1%) were female and 25 (30.9%) were male. Demographic and clinical characteristics of individuals participating in the study are shown in Table 1.

The average MPV was 8.54 ± 1.07 fL in the AD group and 7.86 ± 0.74 fL in the control group. The mean difference of 0.68 fL (confidence interval: 0.42–0.95) that was calculated according to the control group was statistically significant. MPV was significantly different between the AD and control groups ($P < 0.001$) (Figure 1).

Table 1. Demographic and clinical characteristics of patients.

Demographic and clinical characteristics	Group	Mean ± SD	Min–max
Age (years)	Alzheimer	76.74 ± 8.99	49–96
	Control	75.32 ± 8.42	56–92
Duration of disease (years)	Alzheimer	2.65 ± 2.07	0–12
MMSE score	Alzheimer	19.27 ± 4.87	5–29

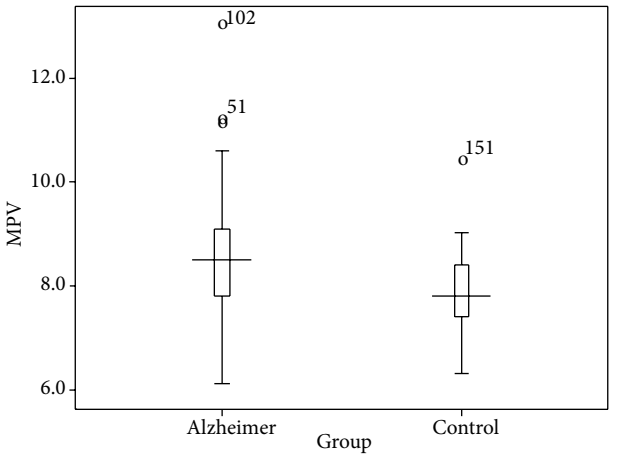

Figure 1. Comparison of intergroup MPV values by box plot chart.

The blood results are shown in Tables 2 and 3. The average platelet count was 229.05 ± 61.789/mm^3 in the AD group and 263.10 ± 65.239/mm^3 in the control group. Platelet count was significantly different between the AD and control groups (P < 0.001) (Figure 2).

The average hematocrit value was 40.33 ± 4.07% in the AD group and 41.75 ± 3.76% in the control group. The mean difference of 1.42 (confidence interval: –2.56 to –0.3) that was calculated according to the control group was statistically significant. Hematocrit value was significantly different between the AD and control groups (P < 0.05).

The median hemoglobin level was 13.60 g/dL (interquartile range: 2) in the AD group and 14.00 g/dL (interquartile range: 1) in the control group. The 0.40 g/dL difference was statistically significant. Hemoglobin value was significantly different between the AD and control groups (P < 0.05).

The mean total cholesterol value showing the lipid profile was 197.71 ± 42.22 mg/dL in the AD group and 212.60 ± 37.49 mg/dL in the control group. The mean difference of 14.90 mg/dL (confidence interval: –26.35 to –3.44) that was calculated according to the control group was statistically significant. Total cholesterol value was significantly different between the AD and control groups (P = 0.001).

The median triglyceride level was 114.00 mg/dL (interquartile range: 69) in the AD group and 133.00 mg/dL (interquartile range: 1) in the control group. The 19 mg/

Table 2. The blood results of patients.

	Group	Mean ± SD	t	P
Platelet count (×10^3/mm^3)	Alzheimer	229.05 ± 61.789	–3.66	0.000*
	Control	263.10 ± 65.239		
MPV (fL)	Alzheimer	8.54 ± 1.07	4.94	0.000*
	Control	7.86 ± 0.74		
Hematocrit (%)	Alzheimer	40.33 ± 4.07	-2.43	0.016$^{\mu}$
	Control	41.75 ± 3.76		
Total cholesterol (mg/dL)	Alzheimer	197.71 ± 42.22	–2.52	0.013$^{\mu}$
	Control	212.60 ± 37.49		
LDL (mg/dL)	Alzheimer	118.49 ± 38.56	–1.69	0.092
	Control	127.75 ± 35.53		

Student t-test. *: P < 0.01, $^{\mu}$: P < 0.05

Table 3. Further blood results of patients.

	Group	Median (interquartile range)	Z	P
Hb (g/dL)	Alzheimer	13.60 (2)	−2.70	0.007*
	Control	14.00 (1)		
Triglyceride (mg/dL)	Alzheimer	114.00 (69)	−2.22	0.026[µ]
	Control	133.00 (96)		
VLDL (mg/dL)	Alzheimer	26.00 (16)	−1.73	0.084
	Control	28.00 (19)		
HDL (mg/dL)	Alzheimer	52.00 (20)	−0.49	0.621
	Control	52.00 (25)		

Mann–Whitney U test. *: $P < 0.05$, [µ]: $P < 0.01$.

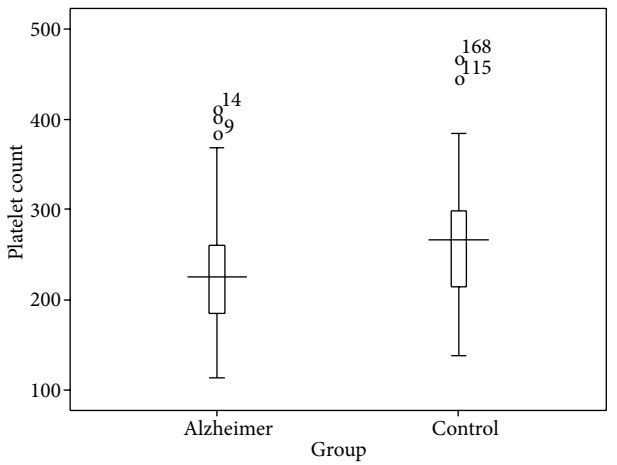

Figure 2. Comparison of intergroup platelet count by box plot chart.

dL difference was statistically significant. Triglyceride value was significantly different between the AD and control groups ($P < 0.05$). LDL, very low-density lipoprotein (VLDL), and HDL values were not significantly different between the AD and control groups ($P > 0.05$).

The rates of diabetes and hypertension were not statistically different between the AD and control groups ($P > 0.05$) (Table 4).

Of the patients with AD, 31 (28.4%) had an MMSE score below 18 and were placed in the 'moderate' group, while 78 (71.6%) had an MMSE score of 18 or above and were placed in the 'mild' group. The mean MMSE score of patients in the moderate group was 13.26 ± 3.15, and it was 21.65 ± 3.02 in the mild group.

The value of MPV was not statistically significant between the moderate group (<18) and the mild group (≥18) in patients with AD ($P > 0.05$).

Table 4. Frequencies of diabetes and hypertension in groups.

		Diabetes		χ^2	P
		Yes	No		
Group	Alzheimer	31 (28.4%)	78 (71.6%)	0.00	1.000
	Control	23 (24.7%)	58 (75.3%)		
	Total	54 (28.4%)	136 (71.6%)		
		Hypertension			
		Yes	No		
Group	Alzheimer	72 (66.1%)	37 (33.9%)	1.48	0.224
	Control	61 (75.3%)	20 (24.7%)		
	Total	133 (70%)	57 (30%)		

Chi-square test.

The values of total cholesterol, triglyceride, LDL, VLDL, and HDL showing lipid profile were not statistically significant between MMSE scores as grouped into a moderate group (<18) and mild group (≥18) in patients with AD ($P > 0.05$).

4. Discussion

In this study, we found that MPV was significantly higher in patients with AD compared to controls.

MPV is a parameter showing platelet activation and function. Although many methods are used for demonstrating platelet reactivity, an easily accessible and low-cost method is MPV measurement. There is a positive correlation between MPV and increased platelet activity. Platelets may differ in size and enzymatic activity in the blood. Larger platelets are more active and they express more GPIIb-IIIa and P-selectin, which are found on platelets. These surface proteins' roles in the platelets are activation, aggregation, and endothelial adherence (22,23). Aggregating platelets contribute to vasoconstriction and lead to hypoperfusion of the brain. Reduced cerebral blood was shown by transcranial Doppler ultrasound at an early phase of AD by Claassen et al. (24). Thus, platelet-mediated cerebral hypoperfusion can trigger pathology in AD and cause neuronal energy deficiency.

AD is associated with the progressive deposition of Aβ in the cerebral parenchyma and microvascular areas. Aβ, a major component of amyloid plaques, originates from APP via a proteolytic process. APP is also expressed in peripheral tissues. Platelets are the most important peripheral source of APP. APP and Aβ are stored in platelets and released into circulation with platelet activation (2). The relation between APP metabolism in platelets and AD is still unclear. Platelets and neurons have numerous similar features; both of them store and release neurotransmitters and express similar proteins, such as NMDA receptors. These features of platelets support their usefulness in studying the pathogenetic process in AD (25). Yesil et al. reported that increased MPV indicated a vascular risk in AD. (26). Prodan et al. followed patients with AD for 2 years and reported a linear correlation between the initial coated platelet levels and AD progression. They evaluated the disease progression with repeated MMSE administration (27). In our study, we evaluated the relation between MPV and MMSE only at the first visit, and we did not include patients who were diagnosed with mild cognitive impairment (MCI). In addition, when the patients with AD were divided into 2 subgroups, MPV was not statistically significantly different between the moderate group (<18) and the mild group (≥18). Borroni et al. reported that an abnormal pattern of APP in platelets might contribute to endothelial damage through vascular deposition of Aβ and trigger cerebrovascular pathology in AD (2). Padovani et al. reported that patients with AD had a reduced platelet/APP ratio (between the 130 kDa and 106–110 kDa immunoreactivity bands with western blot analysis) when compared with controls. In addition, reduction of the platelet/APP ratio correlated with disease severity (28). In this study, when the AD and control groups are compared, it is seen that elevated MPV may be an indicator of increased APP in platelets and also in the brain, triggered by the same stimuli.

Several epidemiologic studies showed that vascular risk factors such as hypertension, atherosclerosis, and diabetes mellitus also play important roles in the progression of AD (29,30). In our study, the rates of diabetes and hypertension were not statistically different in the 2 groups, but hemoglobin, haematocrit, and cholesterol values were significantly higher in the controls. Elevated hemoglobin, haematocrit, and cholesterol levels contribute to increased blood viscosity. While the traditional view agrees that an increased blood viscosity has a constantly negative impact on tissue perfusion, and therefore should be considered as a risk factor, some researchers argue that small increases in viscosity actually have vasodilatory effects, potentially improving tissue perfusion (31,32). In our study, lower MPV levels in controls may indicate that there is less vascular injury and better tissue perfusion.

There are several limitations of our study. First, patients with MCI were not included in the study, and thus we could not evaluate the relation between levels of MPV in patients with MCI and AD. Second, platelet activity can be influenced by multiple drugs. Although we excluded patients who used antiplatelet drugs, different drugs (e.g., statins) other than platelet inhibitors also might influence platelet functions and activity (33). In addition, assessment of the relation between the APP ratio in platelets and MPV might open new horizons for the role of MPV in AD etiology.

In conclusion, increased MPV in patients with AD may point to a platelet dysfunction. MPV is an indicator of increased in vivo platelet activation. Hence, it can be thought that platelets could be the link between the vascular risk factors and AD. The assessment of MPV in patients with AD may help identify the patients that could benefit from additional antiplatelet therapy.

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