Mean Platelet Volume Is Associated with Early Neurological Deterioration in Patients with Branch Atheromatous Disease: Involvement of Platelet Activation

Satoru Oji, MD, Dembo Tomohisa, MD, Wataru Hara, MD, Takashi Tajima, MD, Masato Suzuki, MD, Akane Saito, MD, Norihito Yoshida, MD, and Kyoichi Nomura, MD

Background: The most attentive clinical problem in patients with branch atheromatous disease (BAD) is early neurological deterioration (END). Although the platelet activation (PA) is involved in pathogenesis, the relationship between PA and END has remained unclear. We investigated clinical data including mean platelet volume (MPV, fL) as a marker for PA to identify clinically useful biomarkers for END. *Methods:* A total of 64 patients with BAD were investigated retrospectively, and divided into 2 groups based on whether neurologic symptoms deteriorated or not: BAD with and without END (END and non-END). The END was defined as patients with point increase of 1 or greater in the National Institutes of Health Stroke Scale (NIHSS); non-END was defined as those without such increase. Clinical features such as NIHSS, modified Rankin scale (mRS), laboratory data including MPV, lesion size (LS, mm) on admission, and treatments were compared between the 2 groups. *Results:* Of 64 patients, 17 cases had an END. The median values of NIHSS, mRS, MPV, and LS on admission were significantly greater in END than in non-END ($P < .05$, respectively). There was no correlation of MPV with NIHSS, mRS and LS, respectively. The median values of MPV were significantly higher in END than in non-END and control ($P < .05$, respectively). A receiver operating characteristic curve indicated a value of 10.1 as cutoff level for MPV to discriminate between END and non-END. *Conclusions:* High MPV values on admission may be an independent biomarker for END. Physicians should pay more careful attention to END in BAD showing MPV values higher than 10.1 on admission.
Key Words: Branch atheromatous disease—early neurological deterioration—mean platelet volume—glycoprotein IIb/IIIa—platelet activation.

Introduction

Branch atheromatous disease (BAD) is a form of ischemic stroke characterized by unique findings on magnetic resonance imaging (MRI) and progressive motor deficit in the early phase.[1-4] The pathogenesis of BAD has been reported to be associated with vascular factors such as stenosis at the origin of a deep penetrating artery with a microatheroma or a junctional plaque, and clotting factors including activated platelets.[1,5-8] In daily practice, the most attentive clinical problem in patients with BAD is early neurological deterioration (END), consequently developing severe neurological sequelae. Previous studies have

From the Saitama Medical Center, Saitama Medical University Kawagoe, Saitama, Japan.

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Address correspondence to Satoru Oji, MD, Saitama Medical Center, Saitama Medical University Kawagoe, Saitama, Japan. E-mail: osatoru@saitama-med.ac.jp.

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shown that END was associated with clinical factors such as older age at onset,[9,10] female sex,[9] severe neurological deficit indicated by the National Institutes of Health Stroke Scale (NIHSS) or modified Rankin scale (mRS),[9,11,12] pontine ischemic lesion site,[9,11] low-density lipoprotein (LDL),[9,13] a history of diabetes mellitus (DM),[9,11,13] and larger lesion size (LS).[14] However, the relationship between platelet activation and such deterioration has remained unclear. Meanwhile, the mean platelet volume (MPV) is known to be a simple marker, which is increased during activation of platelets.[15-17] Platelets of larger size have been demonstrated to have higher levels of glycoprotein IIb/IIIa (GPIIb/IIIa) expression on the surface of the platelet than smaller ones, which are receptors of fibrinogen.[17-19] In the present study, we investigated clinical features, laboratory data, and treatment, including MPV as a marker for platelet activation to identify clinically useful biomarkers for END in patients with acute BAD.

Patients and Methods

Patients

We retrospectively investigated 64 consecutive patients with BAD admitted to the Department of Neurology, Saitama Medical Center, Saitama Medical University from April 2014 to March 2017. Patients were divided into 2 groups, depending on whether neurological symptoms deteriorated during hospitalization or not: BAD with and without END (END and non-END, respectively). The END was defined as patients who had increases in NIHSS of more than 1 point on motor items during hospitalization,[5] whereas the non-END as those without such increases. The diagnosis of BAD was made according to the earlier description concerning MRI findings as follows: (1) infarct lesions measuring more than 15 mm in diameter on an axial slice with territorial artery stenosis less than 50%; (2) lesions in 3 or more axial slices at a slice thickness of 5 mm in the lenticulostriate artery (LSA) territory; and (3) lesions unilaterally located in the pontine and extending to the ventral pontine surface.[4,12-14] Patients who were admitted more than 72 hours after onset were excluded from this study.

Clinical Features, Laboratory Data, and Treatment

Clinical features, laboratory data, and treatment were compared between the 2 groups. Clinical features included age at onset,[9,10] sex,[9] neurological disability assessed by NIHSS and mRS on admission,[11,12] lesion site in the vascular territory of the LSA and pontine paramedian artery,[9,11] past illness such as DM,[9,11,13] hypertension,[6,9] and dyslipidemia,[9,13] smoking history,[20] transient ischemic attack history prior to admission,[11] atrial fibrillation,[21] hemodynamics on admission (systolic and diastolic blood pressure [mm Hg], heart rate [per minute]),[9] time from onset to treatment (hour),[9] and period of hospitalization (day).[3] Laboratory data on admission included platelet count (/mm^3),[15] mean platelet volume (MPV, fL),[15,22-24] platelet distribution width (%),[23] hematocrit (%), activated partial thromboplastin time (second), international normalized ratio of prothrombin time, D-dimer (ng/mL), fibrinogen (mg/dL), thrombin–antithrombin complex (ng/mL) within 24 hours after admission, estimated glomerular filtration rate (L/min/1.73 m^2),[25] liver function such as aspartate transaminase (IU/L) and alanine transaminase (IU/L),[26] C-reactive protein (mg/dL),[20] blood glucose (mg/dL), HbA1c (%),[9] LDL (mg/dL),[9,13] pulse wave velocity (cm/s),[27] ankle brachial pressure index,[28] size of ischemic lesion (mm),[14] and the frequency of asymptomatic small vessel features such as leukoaraiosis and microbleeding on MRI.[12,29] Treatment evaluation included the frequency of treatment with edaravone, argatroban,[30] ozagrel sodium, low-molecular-weight dextran, argatroban–edaravone–cilostazol cocktail treatment,[31] recombinant tissue-type plasminogen activator,[32,33] and the oral antiplatelet drug (APD) including aspirin, clopidogrel, or oral cilostazol used on the first hospital day.[34,35] All drugs were administered in standard dosage for treatment use. Past history of DM, hypertension, or dyslipidemia was defined as follows: patients with HbA1c higher than 6.2% or receiving hypoglycemic agents, patients receiving antihypertensive drugs, and patients with LDL higher than 139 mg/dL or receiving statins on admission, respectively. Laboratory data were automatically measured using the XN-9000 Hematology Analyzer (SYSMEX Corporation, Kobe, Japan). Size of ischemic lesion was evaluated by measuring the maximum diameter in ischemic lesion on an axial slice. Ethics approval for the present study, which conformed to the provisions of the Declaration of Helsinki, was granted by the ethics committee of Saitama Medical Center (No. 1734). All patients gave informed consent for their participation in this study.

Statistical Analysis

We compared data from the clinical features, laboratory data, and treatment between the END and non-END using the Mann–Whitney *U* test, chi-square test, or Fisher's exact test. The differences among END, non-END, and control group were analyzed by Kruskal–Wallis test, followed by post hoc analysis using Dunn's test. The changes in clinical features, laboratory data of each patient were evaluated with Wilcoxon signed-rank test. The correlation between 2 variables was examined by Spearman's rank-order correlation coefficient. The control group consisted of 25 patients with nonvascular disease, including 11 patients with Parkinson disease, 2 corticobasal degeneration, 2 multiple system atrophy, 2 idiopathic trigeminal neuralgia, 2 lumbar disk herniation, 2 migraine, 1 normal pressure hydrocephalus, 1 Alzheimer's disease, 1 Meige's syndrome, and 1 benign paroxysmal positional vertigo. The optimal cutoff values that discriminated