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Decreased mean platelet volume and platelet distribution width are associated with mild cognitive impairment and Alzheimer's disease

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ABSTRACT

Neuroinflammation is a critical driving force underlying mild cognitive impairment (MCI) and Alzheimer's disease (AD) pathologies. Activated platelets play an important role in neuroinflammation and have been implicated in AD pathogenic mechanisms. Mean platelet volume (MPV), a marker of platelet activation, is involved in the pathophysiology of a variety of pro-inflammatory diseases. However, little research has been conducted to investigate the relationship between platelet indices and MCI and AD pathogenesis. In this cross-sectional study, we investigated the levels of platelet count, MPV and platelet distribution width (PDW) in 120 AD patients, 120 MCI patients, and 120 non-demented controls. Our study showed that MPV and PDW were significantly lower in patients with AD as compared with either MCI or controls. Moreover, MCI patients had lower MPV and PDW values compared with the controls ($P < 0.001$). In addition, there is a positive correlation between mini-mental state examination (MMSE) and MPV and PDW, after adjusting age, gender, and body mass index ($r = 0.576$, $P < 0.001$ for MPV; $r = 0.465$, $P < 0.001$ for PDW, respectively). Multivariate analysis showed that MPV and PDW were significantly associated with MMSE ($\beta = 0.462$; $P < 0.001$ for MPV; $\beta = 0.245$; $P < 0.001$ for PDW; respectively). In conclusion, MPV and PDW were decreased in MCI and AD patients. Further prospective research is warranted to determine the potential clinical application of MPV and PDW as biomarkers in the early diagnosis of AD.

1. Introduction

Alzheimer's disease (AD), the most common form of irreversible dementia, is placing considerable burden on the patients, their families, and the society. So far, there is no curative treatment for AD. Mild cognitive impairment (MCI) is considered an early stage of AD.

A growing body of evidence has suggested that neuroinflammation plays a critical role in the development of AD (Agostinho et al., 2010). Moreover, treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced risk of developing AD (McGeer et al., 1996). Platelets play an important role in neuroinflammation (Horstman et al., 2010). In addition, activated platelets could result in an excessive amyloid-β (Aβ) production (Li et al., 1998). Amyloid precursor protein (APP) has similar concentrations in platelets and brain (Bush et al., 1990). Platelets release more than 90% of circulating APP and contain all the enzymatic machinery to its processing (Li et al., 1994). Therefore, platelet is an ideal model to study AD pathogenetic mechanisms. Some reports showed that platelet APP has been identified as a new diagnostic marker for AD patients (Borroni et al., 2010; Mukaetova-Ladinska et al., 2012). Furthermore, platelet beta-secretase activity and platelet GSK-3β activity are also found to be enhanced in AD patients and correlated with markers of the intracerebral pathology (Forlenza et al., 2005; Johnston et al., 2008; Forlenza et al., 2011). Mean platelet volume (MPV), the most commonly used measure of platelet size, is an indicator of activated platelets and is available in clinical practice. Furthermore, MPV levels are associated with different disease conditions. MPV levels were elevated in diabetes, cardiovascular disease, peripheral artery disease and cerebrovascular disease (Papanas et al., 2004; Muscari et al., 2009; Berger et al., 2010; Chu et al., 2010) and decreased in rheumatoid arthritis and ulcerative colitis (Yuksel et al., 2009; Yazici et al., 2010). Platelet distribution width (PDW), another platelet indice, indicates variation in platelet size and may be useful to distinguish hypoproductive thrombocytopenia (aplastic anemia) and hyperproductive thrombocytopenia (idiopathic thrombocytopenic purpura) (Kaito et al., 2005). However, PDW has not been studied completely.

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Recent studies have demonstrated that activated platelets play a pro-inflammatory role in the proteolytic processing of APP into Aβ by ADAMS17 and in the deposition of these proteins (Skovronsky et al., 2001; Evin et al., 2003). Moreover, some studies have showed the important role of MPV as a marker of inflammation, disease activity and efficacy of anti-inflammatory treatment in several chronic inflammatory disorders (Gasparyan et al., 2011). However, aspirin use in AD might pose an increased risk of intracerebral hemorrhage (Bentham et al., 2008; Thoonsen et al., 2010). Therefore, clarifying the exact role of activated platelet in AD is of great clinical importance.

The aim of this study is to evaluate the differences of MPV and PDW in MCI and AD patients.

2. Materials and methods

2.1. Participants

The study involved 120 AD patients (mean age 72.8 ± 3.6 years, range 65–80 years), 120 subjects with MCI (mean age 72.9 ± 3.5 years, range 66–84 years), and 120 non-demented controls (mean age 73.7 ± 4.2 years, range 64–82 years) from January 2009 to June 2012. The patients were recruited from clinic and the controls were recruited from the check-up center in our hospital. We selected the age and gender matched controls with similar educational levels. All of the subjects gave written informed consent to participate in the study. The study protocol was approved by the Ethics Committee of the Second Hospital of Harbin Medical University, China.

2.2. Clinical examination

All the subjects underwent a clinical investigation including medical history, and physical, neurological, and psychiatric examinations, laboratory tests, and an MRI scan of the brain. Blood pressure was determined using a mercury-gravity sphygmomanometer in a sitting position after a 15-min rest. Body weight was measured in light clothing, without shoes, to the nearest 0.5 kg. Height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2).

2.3. Biochemical measurements

Clinical data including medical history, smoking status and medication use were recorded for each participant. Fasting venous blood samples were collected in the morning after an 8-h fast. The values included total serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and fasting plasma glucose (FPG). The assays were performed at the Laboratory of Analytical Biochemistry at the Second Hospital of Harbin Medical University, Harbin, using a biochemical analyzer (MODULAR ANALYTICS, Roche, Mannheim, German) using standard methods. Platelet count, MPV and PDW were determined with an autoanalyzer (Sysmex XE-2100, Kobe, Japan). The whole blood samples were collected in EDTA-containing tubes and all samples were processed within 30 min after blood collection.

2.4. Diagnosis and exclusion criteria

Global cognitive function was assessed by the mini-mental state examination (MMSE). General inclusion/exclusion criteria are as follows: (1) Normal subjects: MMSE scores between 24 and 30, clinical dementia rating (CDR) of 0, non-MCI, and non-demented. (2) MCI subjects: MMSE scores between 24 and 30, memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and non-demented (Winblad et al., 2004). (3) Probable AD: fulfill the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria. Diabetes mellitus was defined as fasting serum glucose was ≥7.0 mmol/L or nonfasting serum glucose was ≥11.1 mmol/L or as taking prescription medications. For the controls or the patients with impaired fasting glucose, DM was diagnosed if a 2-h post-glucose level after a 75-g oral glucose tolerance test ≥ 11.1 mmol/L. Hypertension was diagnosed if systolic blood pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg, or as antihypertensive treatment. Two readings were taken, with a 5-min interval between measurements. The mean of the two readings was recorded. CAD (coronary atherosclerotic heart disease) was defined as the occurrence of a nonfatal myocardial infarction, a percutaneous coronary angioplasty, other forms of acute or chronic ischemic heart disease. The Modification of Diet in Renal Disease (MDRD) equation was used to estimate glomerular filtration rate (eGFR). MDRD equation was: $eGFR = 186.3 \times (SCr)^{-1.154} \times (age)^{-0.203}$(×0.742 if female).

Exclusion criteria for this study included diabetes mellitus, hypertension, depression, psychiatric diseases, chronic alcoholism, tumor, infection, hematological disorders, autoimmune diseases, chronic liver and kidney diseases, atrial fibrillation, abnormal vitamin B_{12} or thyroid function tests, stroke (Hachinski et al., 2006), Parkinson's disease, and medical treatment with anticoagulant, statins, and clopidogrel.

2.5. Statistical analysis

The SPSS statistical software package version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. All data was expressed as means ± SD or median (IQR) or percentage. The Chi-square test was used for all categorical variables, while one-way ANOVA or Kruskal–Wallis H test was used for continuous variables. Correlations between MMSE score and platelet indices were tested by partial correlation adjusted for age, gender and BMI. Multivariate analysis was performed using linear regression model to determine the relationships between MMSE and various clinical variables including age, gender, BMI, platelet, MPV, and PDW. A P value of <0.05 was considered to be statistically significant.

3. Results

The clinical characteristics of the control, MCI and AD subjects are showed in Table 1. One-way ANOVA analysis indicated a significant group difference in BMI, MPV, PDW and MMSE levels ($P < 0.001$). There were no significant differences in age, gender, FPG, TC, TG, HDL, LDL, creatinine, eGFR, platelet, CAD, smoking status and aspirin use between the three groups.

The correlation coefficients between MMSE and age, gender, levels of education were −0.123 ($P = 0.020$), −0.069 ($P = 0.190$), 0.108 ($P = 0.041$), respectively. After adjusting for age, gender, and BMI, the partial correlation coefficients between MMSE and platelet, MPV, and PDW were 0.084 ($P = 0.111$), 0.576 ($P < 0.001$), 0.465 ($P < 0.001$), respectively. The positive correlations between MMSE score and platelet indices after adjustment for age, gender and BMI are presented in Figs. 1 and 2.

A two-sided Pearson chi-square test was used to analyze the MPV and PDW levels as a correlate of control subjects, MCI, and AD patients (see Table 2). The results showed a significant difference of MPV levels in different group (for control group vs. MCI group,