Observational Study

Medicine®

OPEN

Altered peripheral profile of blood cells in Alzheimer disease

A hospital-based case-control study

Si-Han Chen, MD, Xian-Le Bu, MD, PhD, Wang-Sheng Jin, MD, Lin-Lin Shen, MD, Jun Wang, MD, Zheng-Qian Zhuang, MD, Tao Zhang, MD, PhD, Fan Zeng, MD, PhD, Xiu-Qing Yao, MD, PhD, Hua-Dong Zhou, MD, PhD, Yan-Jiang Wang, MD, PhD*

Abstract

Alzheimer disease (AD) has been made a global priority for its multifactorial pathogenesis and lack of disease-modifying therapies. We sought to investigate the changes of profile of blood routine in AD and its correlation with the disease severity.

In all, 92 AD patients and 84 age and sex-matched normal controls were enrolled and their profiles of blood routine were evaluated.

Alzheimer disease patients had increased levels of mean corpuscular hemoglobin, mean corpuscular volume, red cell distribution width-standard deviation, mean platelet volume,and decreased levels of platelet distribution width, red blood cell, hematocrit, hemoglobin, lymphocyte, and basophil compared with normal controls.

Alterations in quantity and quality of blood cells may be involved in the pathogenesis of AD and contribute to the disease progression.

Abbreviations: AD = Alzheimer disease, HCT = hematocrit, HGB = hemoglobin, LYM = lymphocyte, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MPV = mean platelet volume, NC = normal control, PDW = platelet distribution width, RBC = red blood cell, RDW-SD = red cell distribution width-standard deviation.

Keywords: Alzheimer disease, blood cell profile, case-control study, immunity

1. Introduction

Alzheimer disease (AD), a growing global public health challenge and the most frequent cause of dementia, is characterized by extracellular deposition of misfolded amyloid-β (Aβ) protein and intracellular formations of hyperphosphorylated neurofibrillary tangles (NFTs).[1] Over the past decades, a lot of efforts have been made to explore the pathogenesis of AD, but the exact mechanisms underlying AD remained largely unknown. Accumulating evidence suggests that immunosenescence, a term delineating the growing age-associated changes in immune competence, contributes to AD pathogenesis. This notion is supported by experiments on APPswe/PSENldE9 transgenic animals, which indicated that functional immune system is not only required for enhanced Aβ clearance and improved cognition, but may also be implied for therapeutic methods.[2] Previous studies have observed biochemical property alterations in lymphocytes of AD and mild cognition decline (MCI) patients, including substantial oxidative stress, mitochondrial dysfunction, and cell cycle dysfunction. These biochemical alterations presented in lymphocytes of AD and MCI seem to influence their physiological immune functions.[3] Simultaneously, lines of evidence have showed the level of hemoglobin, mean cell hemoglobin concentrations, packed cell volume and higher erythrocyte sedimentation rates, red cell distribution width (RDW) were decreased in AD patients, indicating a strong association between AD and anemia.[4] In addition, blood platelets have been reported to be implicated in AD with expression of high levels of amyloid precursor protein (APP) and their activation status potentially affecting the pathogenesis of AD.[5]

These findings suggest that peripheral blood cells might be involved in the pathogenesis of AD, and would be of potential importance for the management of the disease. In the present study, we sought to analyze the change of blood routine profile of AD, and its relation with disease severity in a cohort of Chinese AD patients.

2. Materials and methods

2.1. Study population

In general, 92 AD patients and 84 age and sex-matched normal controls (NCs) were recruited from Chongqing Daping Hospital between November in 2011 and January in 2016. All participants were ethic Han Chinese. The clinical assessment and diagnosis of AD dementia were performed following the protocol described in our previous studies.[6,7] In brief, the demographic data, medical

Editor: Chaur-Jong Hu.

Funding: This study was supported by National Natural Science Foundation of China (Grant number 81625007).

The authors have no conflicts of interest to disclose.

Department of Neurology and Center for Clinical Neuroscience, Daping Hospital, Third Military Medical University, Yuzhong District, Chongqing, China.

* Correspondence: Yan-Jiang Wang, MD, PhD, at Department of Neurology and Center for Clinical Neuroscience, Daping Hospital and Institute of Field Surgery, Third Military Medical University, 10 Changjiang Branch Road, Yuzhong district, Chongqing, China (e-mail: yanjiang_wang@tmmu.edu.cn).

Medicine (2017) 96:21(e6843)

Received: 24 January 2017 / Received in final form: 11 April 2017 / Accepted: 12 April 2017

http://dx.doi.org/10.1097/MD.0000000000006843

history, and cognitive and functional status were collected and assessed using formal questionnaire and neuropsychological battery, including Minimum Mental State Examination (MMSE) and Activities of Daily Living (ADL), which were validated previously in Chinese older people.[8,9] The subjects with abnormal performance in MMSE assessment were further scheduled for neuropsychological tests, including Clinical Dementia Rating (CDR)[10] and Hachinski Ischemic Score (HIS) for assessing significant vascular disease.[11]Subjects with potential dementia were further subjected to cranial computed tomography (CT) or magnetic resonance image (MRI). These procedures were administered by experienced neurologists. Dementia was diagnosed based on criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV. Diagnosis of probable AD was made according to the criteria of National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA). The severity of dementia was classified as mild (CDR score = 1), moderate (CDR score = 2), and severe dementia (CDR = 3). The subjects were not eligible if they had a family history of dementia; had a concomitant neurologic disorder potentially affecting cognitive function (eg, severe Parkinson disease); were in a state of obvious infection or inflammation potentially affecting the indices of blood routine; had severe cardiac, pulmonary, hepatic, renal diseases, or any kinds of tumor; had any potent hematopathies including leukaemia, malnourished anemia, aplastic anemia, hemolytic anemia, hemorrhagic anemia, platelet disorders, and so on; and declined to participate in the study. This study was approved by the Ethic Committee of the Daping Hospital. Written consents for blood collection were obtained from all participants or their legal representatives.

2.2. Blood sampling and collection of indices of blood routine

Fasting blood was sampled between 08:00 and 09:00 to avoid the variation related to a possible circadian rhythm effect. To avoid the possible effects of drugs on indices of blood routine, fasting blood of participants were sampled within 2 hours after they were admitted to hospital. Blood samples were centrifuged within 2 hours after collection, and stored at −80°C until use. Indices of blood routine in AD and NC including red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), RDW-standard deviation (RDW-SD), lymphocyte (LYM), neutrophil (NEU), eosinophilia (EOS), basophil (BASO), monocyte (MONO), white blood cell (WBC), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), platelet distribution width (PDW), mean platelet volume (MPV), ratio of lymphocyte/white blood cell (LYM/WBC), neutrophil/white blood cell (NEU/WBC), and monocyte/white blood cell (MONO/WBC) were collected and analyzed.

2.3. Clinical assessment

The medical history was collected from medical records and current medication from a formal questionnaire. The data included prior head trauma and surgery, prior gas poisoning, schizophrenia, hypothyroidism, coronary heart diseases, atrial fibrillation, cardiac vascular disease (CVD) defined by history, presence of focal neurological signs or brain imaging including strategic or multiple lesions, or diffuse white matter lesions, or transient ischemic attack (TIA), chronic obstructive pulmonary disease, chronic hepatitis, chronic renal insufficiency, hypertension, diabetes mellitus, hypercholesterolemia, Parkinson disease, and regular use of relative medications.

Table 1

Demographic data of subjects.

	AD patients (n = 92)	NCs (n = 84)	*P*
Age, y [mean (SD)]	69.95 (10.63)	70.6 (5.39)	.785
Male, n (%)	46 (50.55%)	39 (46.42%)	.301
MMSE, mean (SD)	15.09 (4.56)	29.08 (1.00)	<.0001
CDR, mean (SD)	1.84 (0.73)	0	<.0001
ADL, mean (SD)	44.34 (12.10)	20.18 (0.60)	<.0001
AD course, y (SD)	2.16 (1.27)		
Hypertension, n (%)	14 (15.05%)	12 (14.28%)	.862
Diabetes mellitus, n (%)	10 (10.75%)	6 (7.14%)	.390
Hyperlipidemia, n (%)	9 (9.67%)	7 (8.33%)	.738
Medication, n (%)			
AD	27 (29.35%)		
Hypertension	9 (64%)	9 (75%)	.555
Diabetes mellitus	6 (60%)	3 (50%)	.696
Hyperlipidemia	4 (44.44%)	2 (28.57%)	.515

Data are expressed as the means (standard deviation) *P* value, 2 independent *t* tests, Mann–Whitney *U* test, or chi-square test as appropriate.

AD = Alzheimer disease, ADL = Activities of Daily Living, MMSE = Mental State Examination, NC = normal control, SD = standard deviation.

Blood samples were collected for measuring folic acid, vitamin B 12 (VB12), hemogram, fasting glucose, thyroxin, creatinine, uric acid, transaminase, and total cholesterol. Besides, all participants were subjected to blood pressure measurement and electrocardiogram, chest radiography (X-ray), and abdominal ultrasound. Diagnosis of diseases including anemia, hypothyroidism, hypertension, diabetes mellitus, hypercholesterolemia, obesity, coronary heart diseases, atrial fibrillation, CVD, chronic renal insufficiency, and chronic hepatitis were based on International Classification of Diseases, tenth Revision (ICD-10).

2.4. Clinical medication

Medication for AD included donepezil, galantamine, and memantine. Medicines for hypertension included diuretics, beta receptor blocker, calcium antagonist, and angiotensin-converting enzyme inhibitors. Medicines for diabetes mellitus included sulfonylureas, metformin, α-glucosidase inhibitor, and euglycemic agent. Medicines for hyperlipidemia included statins, fibrates, and nicotinic acid. Among them, sulfonylurea is an insulin secretagogue and may have a potential impact on peripheral blood cell. Statins, clopidogrel, and angiotensin-converting enzyme inhibitor may influence indices associated with platelets.

2.5. Statistical analysis

The differences in demographic characteristics and blood routine indexes between groups were assessed by 2 independent *t* tests, Mann–Whitney *U* test, or chi-square test. Pearson correlation analysis was used to analyze the association of indices of blood cell with MMSE and ADL score. Specifically, 1-way analysis of variance (ANOVA) was utilized to investigate the correlation between indices of blood cell and AD severity. The data were expressed as the mean ± standard deviation (SD)for numerical variables, or as the number (%) for categorical variables. All hypothesis testing was 2-sided and $P < .05$ was defined as

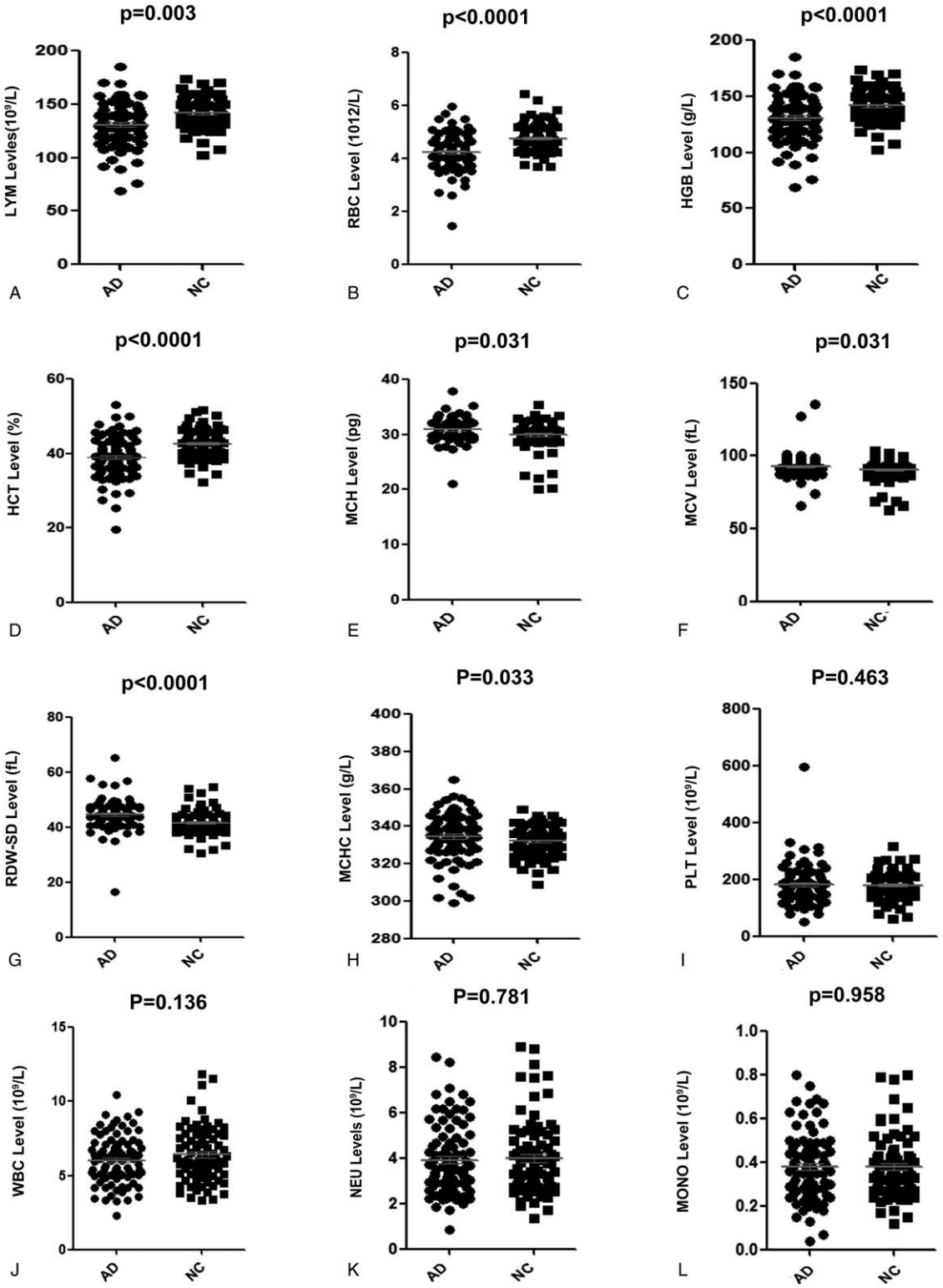

Figure 1. Comparison of indices of blood cells between AD patients (n = 92) and NCs (normal control) (n = 84). HCT (A), HGB (B), LYM (C), MCH (D), MCHC (E), MCV (F), MONO (G), NEU (H), RBC (I), RDW-SD (J), WBC (K), PLT (L) levels in AD patients and NCs. HCT = hematocrit, HGB = hemoglobin, LYM = lymphocyte, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MONO = monocyte, NEU = neutrophil, RBC = red blood cell, RDW-SD = red cell distribution width-standard deviation, WBC = white blood cell. Data are expressed as mean ± SE (standard error).

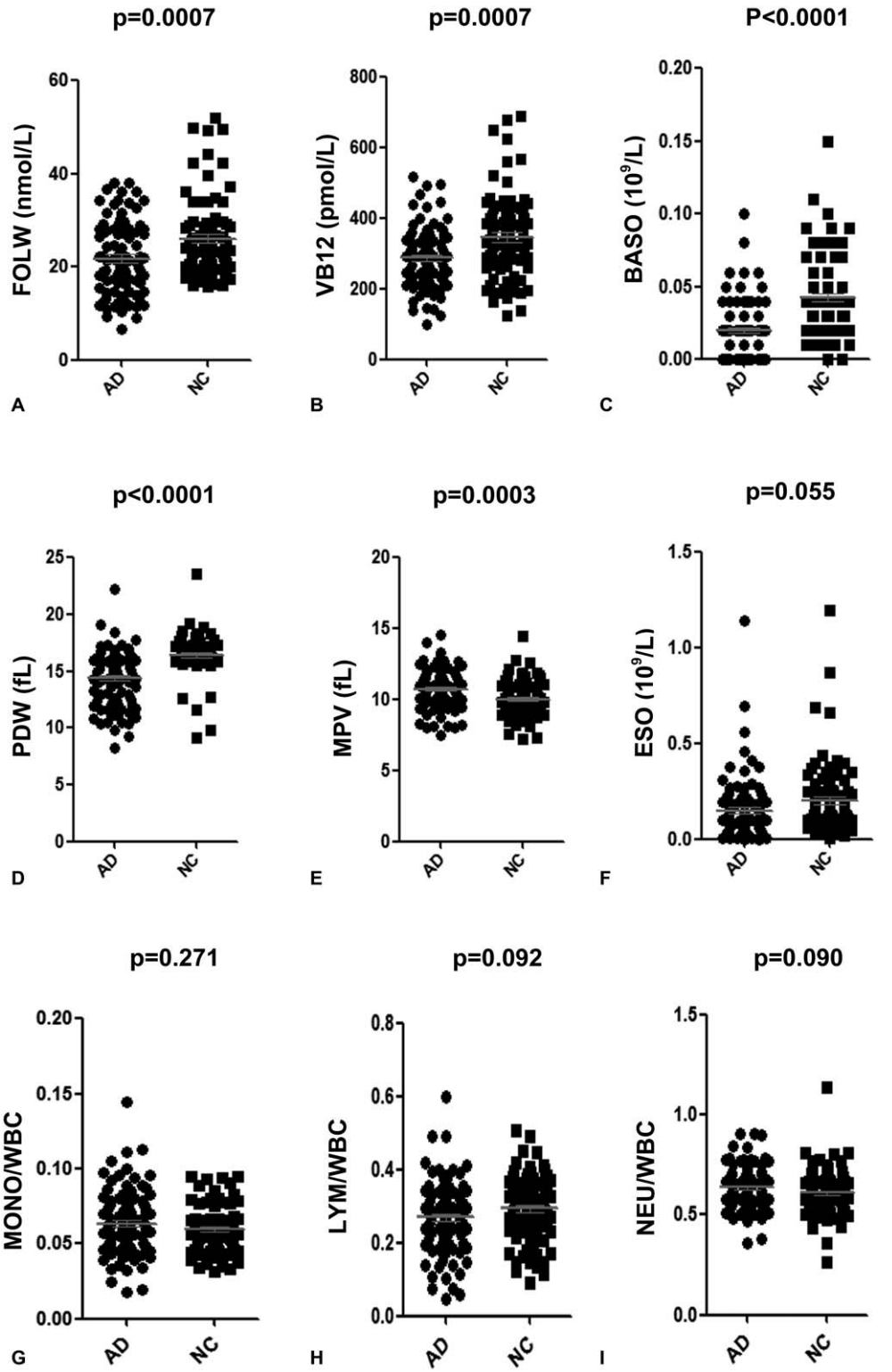

Figure 2. The levels of FOLW (A), VB12 (B), BASO (C),PDW (D), MPV (E), ESO (F), and ratio of MONO (G), LYM (H), NEU (I) to WBC in AD patients (n = 92) and NCs (normal controls) (n = 84). BASO = basophil, ESO = eosinophilia, FOLW = folic acid, LYM = lymphocyte, MONO = monocyte, MPV = mean platelet volume, NEU = neutrophil, PDW = platelet distribution width, VB12 = vitamin B12, WBC = white blood cell. Data are expressed as mean ± SE (standard error).

statistically significant. Computations were carried out with GraphPad Prism Version 5.0and SPSS Version 20.0.

3. Results

3.1. The demographic characteristics of study population

As shown in Table 1, the mean age was 69.95 ± 10.63 years for the AD patients and 70.6 ± 5.39 years for NCs, and the MMSE score (15.09 ± 4.56 vs 29.08 ± 1.00; $P < .0001$), ADL score (44.34 ± 12.10 vs 20.18 ± 0.60; $P < .0001$), and CDR score (1.84 ± 0.73 vs 0; $P < .0001$) of AD patients and NCs were assessed. The mean disease course of AD patients was 2.16 ± 1.27 years. Among them, 27 patients were defined as mild dementia, 48 patients were defined as moderate dementia, and 16 patients were defined as severe dementia. There were no significant differences in sex, comorbidities including hypertension, hyperlipidemia, diabetes mellitus, and medications between the 2 groups. There was no significant difference in patients taking sulfonylureas (83.33% vs 100%; $P = .667$), statins (44.44% vs 42.86%; $P = .949$), clopidogrel (85.71% vs 91.67%; $P = .636$), and angiotensin-converting enzyme inhibitor (92.86% vs 100%; $P = .345$) between AD patients and NCs.

3.2. Comparison of blood cell profiles, plasma folic acid, VB12 between AD patients and NCs

The AD patients had lower levels of LYM ($1.55 \pm 0.57 \times 10^9$/L vs $1.80 \pm 0.57 \times 10^9$/L; $P = .003$) (Fig. 1A) compared with that of NCs. In addition, AD patients had lower levels of RBC ($4.20 \pm 0.67 \times 10^{12}$/L vs $4.75 \pm 0.50 \times 10^{12}$/L; $P < .0001$), HGB (130.83 ± 19.29 vs 141.70 ± 13.52 g/L; $P < .0001$), HCT (39.00 ± 5.37% vs 42.66 ± 3.71%; $P < .0001$), and higher levels of MCH (31.65 ± 6.71 vs 29.97 ± 2.61 pg; $P = .031$), MCV (92.60 ± 7.70 fL vs 90.19 ± 6.94 fL; $P = .034$), RDW-SD (44.69 ± 5.42 fL vs 41.60 ± 4.19 fL; $P < .0001$), MCHC (334.51 ± 12.25 vs 332.05 ± 7.84 g/L; $P = .033$) than NCs (Fig. 1 B–H). However, there were no significant differences in levels of PLT, WBC, NEU, MONO, and BASO between AD patients and NCs (Fig. 1 I–L). Besides, AD patients had lower levels of FOLW (21.88 ± 8.03 vs 26.00 ± 8.36; $P = .0007$), VB12 (290.28 ± 86.42 vs 345.75 ± 119.38; $P = .0007$), BASO (0.02 ± 0.02 vs 0.04 ± 0.03; $P < .0001$), PDW (14.38 ± 2.47 vs 16.39 ± 1.73; $P = < .0001$), and higher level of MPV (10.74 ± 1.35 vs 10.03 ± 1.23; $P = .0003$) than NCs. However, there was no statistical significance in the level of ESO and the ratio of MONO, LYM, and NEU to leukocyte, respectively (Fig. 2A–I).

3.3. Correlation between blood cell profiles, plasma folic acid, VB12, and MMSE score

Pearson correlation analysis was used to investigate the correlation of scores of MMSE with indices of peripheral blood. No significant correlations were revealed between scores of MMSE and WBC, MONO, NEU, LYM, PLT, RBC, PDW, MPV, ESO, BASO, HCV, HGB, MCH, MCHC, MCV, RDW-SD, FOLW, VB12, MONO/WBC, NEU/WBC, and LYM/WBC (Table 2).

3.4. Correlation between blood cell profiles, plasma folic acid, VB12, and ADL score

Pearson correlation analysis was used to investigate the correlation of scores of ADL with indices of peripheral blood. There were no significant correlations between ADL scores and WBC, MONO, NEU, LYM, PLT, PDW, MPV, ESO, BASO, RBC, HCV, HGB, MCH, MCHC, MCV, RDW-SD, MONO/WBC, FOLW, VB12, NEU/WBC, and LYM/WBC (Table 3).

Table 2

Correlations between scores of MMSE and indices of peripheral blood in AD patients.

Variables	Coefficient	Standard error	P
WBC	−0.024	1.596	.823
MONO	0	0.148	.998
NEU	−0.058	1.502	.581
LYM	0.142	0.571	.178
PDW	−0.042	0.258	.693
MPV	0.095	0.141	.368
PLT	−0.048	69.571	.648
ESO	−0.127	0.017	.228
BASO	0.088	0.002	.403
RBC	0.143	0.674	.174
HCV	0.114	5.342	.277
HGB	0.115	47.345	.273
MCH	−0.19	6.784	.68
MCHC	0.089	148.043	.398
MCV	−0.133	9.208	.204
RDW-SD	−0.157	5.387	.134
FOLW	0.152	0.817	.148
VB12	0.056	8.836	.597
MONO/WBC	0.005	0.0218	.96
NEU/WBC	−0.077	0.107	.465
LYM/WBC	0.144	0.107	.172

BASO = basophil, ESO = eosinophilia, FOLW = folic acid, HCT = hematocrit, HGB = hemoglobin, LYM = lymphocyte, LYM/WBC = lymphocyte/white blood cell, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MMSE = Mini-Mental State Examination, MONO = monocyte, MONO/WBC = monocyte/white blood cell, MPV = mean platelet volume, NEU = neutrophil, NEU/WBC = neutrophil/white blood cell, PDW = platelet distribution width, PLT = platelet, RBC = red blood cell, RDW-SD = red cell distribution width-standard deviation, VB12 = vitamin B12, WBC = white blood cell.

3.5. Comparison of indices of blood cell by AD severity

One-way analysis of variance was used to investigate the correlation between indices of blood cell and AD severity. We found that patients with mild dementia had higher RBC count (4.46 ± 0.59 vs 3.96 ± 0.76; $P = .019$) than patients with severe dementia. Patients with moderate dementia had lower PLT count (163.38 ± 50.64 vs 209.69 ± 113.50; $P = .02$) than patients with severe dementia. We did not find significant differences in other indices of blood cell among various degree of AD.

4. Discussion

In the present study, we found that AD patients had lower levels of LYM, BASO, and PDW, and higher level of MPV. In the meantime, changed indices of erythrocyte were observed in AD patients, including lower levels of RBC, HGB, HCT, FOLW, and VB12, and higher levels of MCH, MCV, and MCHC compared with those of NCs. Thereinto, patients with mild dementia had higher RBC count than patients with severe dementia. Patients with moderate dementia had lower PLT count than patients with severe dementia.

The decreased number of lymphocytes and basophils in AD were consistent with a previous study.[12] There were 3 aspects for the mechanisms related to the decreased lymphocyte count in AD patients compared with NCs: the changes in maturational environment caused by advanced impairments of thymic

Table 3

Correlations between score of ADL and indices of peripheral blood in AD patients.

Variables	Coefficient	Standard error	*P*
WBC	−0.031	1.596	.771
MONO	0.03	0.148	.758
NEU	−0.015	1.502	.890
LYM	−0.169	0.571	.107
PLT	0.026	69.571	.808
PDW	0.009	0.258	.932
MPV	−0.079	0.141	.452
ESO	0.165	0.017	.116
BASO	−0.018	0.002	.865
RBC	−0.149	0.674	.157
HCV	−0.106	5.342	.314
HGB	−0.115	47.345	.273
MCH	−0.156	6.784	.138
MCHC	−0.012	148.043	.908
MCV	−0.093	9.208	.376
RDW-SD	0.137	5.387	.194
FOLW	−0.113	0.817	.282
VB12	−0.041	8.836	.695
MONO/WBC	0.073	0.0218	.492
NEU/WBC	−0.055	0.107	.604
LYM/WBC	−0.143	0.107	.173

BASO = basophil, ESO = eosinophilia, FOLW = folic acid, HCT = hematocrit, HGB = hemoglobin, LYM = lymphocyte, LYM/WBC = lymphocyte/white blood cell, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MMSE = Mini-Mental State Examination, MONO = monocyte, MONO/WBC = monocyte/white blood cell, MPV = mean platelet volume, NEU = neutrophil, NEU/WBC = neutrophil/white blood cell, PDW = platelet distribution width, PLT = platelet, RBC = red blood cell, RDW-SD = red cell distribution width-standard deviation, VB12 = vitamin B12, WBC = white blood cell.

functions in AD patients may hamper the differentiation of lymphocytes[13]; AD patients showed elevated susceptibility to apoptotic death caused by reactive oxygen species (ROS) and deficiency in antioxidants or antioxidant enzymes[14–17]; the entry of peripheral lymphocytes into the brain was induced by elevated neuroinflammation, production of inflammatory mediators, and facilitated by increased permeability of blood-brain barrier (BBB) in AD.[18–22] The decreased lymphocyte count in AD suggests aberrant immunity which plays a critical role in the pathogenesis of AD.

In regard to basophil, it contains histamine and express the high affinity IgE receptor FcεRIα.[23–25] And increased serum and brain concentrations of histamine, which has anti-inflammatory character and acts as a neurotransmitter in central nervous system (CNS), has been found in AD patients. However, the influence of AD on the number and function of basophils has remained elusive.[26]

As to platelets, we found that AD patients had lower level of PDW and higher level of MPV than NCs. Previous studies have demonstrated that PDW was decreased in AD patients, which was in line with our study. However, results about MPV were inconsistent among different studies.[27–30] Increased levels of MPV may be indication of platelet activation, which may contribute to vasoconstriction and hypoperfusion of brain,[29,30] and lead to release of more Aβ into circulation, as platelet are the most important source of Aβ in the periphery.[31]

We found that AD patients had higher levels of MCH, MCV, and RDW-SD, and lower levels of RBC count, HCT, HGB than NCs. Several mechanisms might be underlying these changes of RBC. The changes of RBC profiles of AD in our study could be resulted from the relative lower levels of folic acid and VB12 concentrations in AD patients compared with NCs. Folic acid and VB12 are essential for DNA synthesis and cell division of red blood cell, and deficiency of folic acid and VB12 causes anemia with increased MCV, MCH, and decreased HGB.[32] In addition, a previous study also showed that AD patients had significantly lower HGB, MCHC, and HCT, which are related to the disturbed metabolism of iron in AD.[4]

Besides, we found that RBC counts significantly lower in AD patients than in NCs, and patients with mild dementia had higher RBC count than patients with severe dementia. As is well-known, brain oxygen supply mainly derived fromoxygen carried by RBC. Decreased RBC count may cause hypoxia which could promote Aβ production and neurodegeneration in the brain.[33–35] Meanwhile, brain-derived Aβ can also mitigate deformality and impair oxygen delivery capacity of RBC.[36–38] Taken together, reduced count and abnormal quality of RBC might not only be the result of AD, but can also contribute to the pathogenesis of AD. In this regard, recovery of RBC number and quality, such as by supplementation of folic acid and VB12, correction of aberrant iron metabolism, is essential to prevent or treat AD.[4,39–41]

Monocytes have been suggested to play critical roles in the pathogenesis of AD.[42] However, we did not find any significant discrepancy between AD patients and NCs. Given that, we can assume that the role of monocyte played in pathogenesis of AD is mainly determined by its functions rather than its quantity. Previous studies have confirmed the defective phagocytosis of Aβof monocytes in AD, and enrichment of levels of functionally normal monocytes resulted in substantial remission of disease progression in animal models of AD.[43–45]

There are several limitations in our present study. Some chronic comorbidities are important confounding factors which may affect the blood cell profiles of patients, thus cause bias of the results of our study. Even though we included common comorbidities including hypertension, hyperlipidemia, diabetes mellitus, and the relevant medications which were comparable between the 2 groups, it is still difficult to completely rule out the potential influence of other comorbidities on the profile of peripheral blood routine. In addition, although we have found differences in parameters associated with WBC and RBC between AD patients and NCs, it remains unclear whether these changes are causes or results of AD.

5. Conclusions

In summary, there are significant changes of peripheral blood cell profiles in AD patients, suggesting that alterations in quantity and quality of blood cells may be involved in the pathogenesis of AD and contribute to the disease progression. Future studies are needed to confirm our findings in other populations, and to further investigate the pathophysiological and clinical significance of these changes of blood cells in the pathogenesis and management of AD.

Acknowledgments

The authors are grateful to AD patients and NC participants in this study for providing blood samples to be applied for our research.

References

[1] Apostolova LG. Alzheimer disease. Continuum (Minneapolis, Minn) 2016;22:419–34.
[2] Gendelman HE, Mosley RL. A perspective on roles played by innate and adaptive immunity in the pathobiology of neurodegenerative disorders. J Neuroimmune Pharmacol 2015;10:645–50.

[3] Wojda U. Alzheimer's disease lymphocytes: potential for biomarkers? Biomarkers Med 2016;10:1–4.
[4] Faux NG, Rembach A, Wiley J, et al. An anemia of Alzheimer's disease. Mol Psychiatry 2014;19:1227–34.
[5] Gowert NS, Donner L, Chatterjee M, et al. Blood platelets in the progression of Alzheimer's disease. PloS One 2014;9:e90523.
[6] Li J, Wang YJ, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. Neurology 2011; 76:1485–91.
[7] Zeng F, Zou HQ, Zhou HD, et al. The relationship between single nucleotide polymorphisms of the NTRK2 gene and sporadic Alzheimer's disease in the Chinese Han population. Neurosci Lett 2013;550:55–9.
[8] Zhou H, Deng J, Li J, et al. Study of the relationship between cigarette smoking, alcohol drinking and cognitive impairment among elderly people in China. Age Ageing 2003;32:205–10.
[9] Zhou DH, Wang JY, Li J, et al. Study on frequency and predictors of dementia after ischemic stroke: the Chongqing stroke study. J Neurol 2004;251:421–7.
[10] O'Bryant SE, Lacritz LH, Hall J, et al. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 2010;67:746–9.
[11] Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke: Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37: 2220–41.
[12] Shad KF, Aghazadeh Y, Ahmad S, et al. Peripheral markers of Alzheimer's disease: surveillance of white blood cells. Synapse (New York, NY) 2013;67:541–3.
[13] Licastro F, Savorani G, Sarti G, et al. Zinc and thymic hormone-dependent immunity in normal ageing and in patients with senile dementia of the Alzheimer type. J Neuroimmunol 1990;27:201–8.
[14] Ponce DP, Salech F, SanMartin CD, et al. Increased susceptibility to oxidative death of lymphocytes from Alzheimer patients correlates with dementia severity. Curr Alzheimer Res 2014;11:892–8.
[15] Moslemnezhad A, Mahjoub S, Moghadasi M. Altered plasma marker of oxidative DNA damage and total antioxidant capacity in patients with Alzheimer's disease. Caspian J Intern Med 2016;7:88–92.
[16] Wang X, Wang W, Li L, et al. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta 2014;1842: 1240–7.
[17] Zhao Y, Zhao B. Oxidative stress and the pathogenesis of Alzheimer's disease. Oxidat Med Cell Longevity 2013;2013:316523.
[18] Britschgi M, Wyss-Coray T. Systemic and acquired immune responses in Alzheimer's disease. Int Rev Neurobiol 2007;82:205–33.
[19] Kook SY, Seok Hong H, Moon M, et al. Disruption of blood-brain barrier in Alzheimer disease pathogenesis. Tissue Barriers 2013;1: e23993.
[20] Bonotis K, Krikki E, Holeva V, et al. Systemic immune aberrations in Alzheimer's disease patients. J Neuroimmunol 2008;193:183–7.
[21] Man SM, Ma YR, Shang DS, et al. Peripheral T cells overexpress MIP-1alpha to enhance its transendothelial migration in Alzheimer's disease. Neurobiol Aging 2007;28:485–96.
[22] Liu YJ, Guo DW, Tian L, et al. Peripheral T cells derived from Alzheimer's disease patients overexpress CXCR2 contributing to its transendothelial migration, which is microglial TNF-alpha-dependent. Neurobiol Aging 2010;31:175–88.
[23] Schroeder JT. Basophils beyond effector cells of allergic inflammation. Adv Immunol 2009;101:123–61.
[24] Siracusa MC, Comeau MR, Artis D. New insights into basophil biology: initiators, regulators, and effectors of type 2 inflammation. Ann N Y Acad Sci 2011;1217:166–77.
[25] Schroeder JT. Basophils: emerging roles in the pathogenesis of allergic disease. Immunol Rev 2011;242:144–60.
[26] Song C, Vandewoude M, Stevens W, et al. Alterations in immune functions during normal aging and Alzheimer's disease. Psychiatry Res 1999;85:71–80.
[27] Wang RT, Jin D, Li Y, et al. Decreased mean platelet volume and platelet distribution width are associated with mild cognitive impairment and Alzheimer's disease. J Psychiatric Res 2013;47:644–9.
[28] Liang QC, Jin D, Li Y, et al. Mean platelet volume and platelet distribution width in vascular dementia and Alzheimer's disease. Platelets 2014;25:433–8.
[29] Yesil Y, Kuyumcu ME, Cankurtaran M, et al. Increased mean platelet volume (MPV) indicating the vascular risk in Alzheimer's disease (AD). Arch Gerontol Geriatr 2012;55:257–60.
[30] Koc ER, Uzar E, Cirak Y, et al. The increase of mean platelet volume in patients with Alzheimer disease. Turk J Med Sci 2014;44: 1060–6.
[31] Borroni B, Akkawi N, Martini G, et al. Microvascular damage and platelet abnormalities in early Alzheimer's disease. J Neurol Sci 2002; 203–4. 189-193.
[32] Chan LN, Mike LA. The science and practice of micronutrient supplementations in nutritional anemia: an evidence-based review. JPEN 2014;38:656–72.
[33] Peers C, Dallas ML, Boycott HE, et al. Hypoxia and neurodegeneration. Ann N Y Acad Sci 2009;1177:169–77.
[34] Babiloni C, Del Percio C, Lizio R, et al. A review of the effects of hypoxia, sleep deprivation and transcranial magnetic stimulation on EEG activity in humans: challenges for drug discovery for Alzheimer's disease. Curr Alzheimer Res 2014;11:501–18.
[35] Salminen A, Kauppinen A, Kaarniranta K. Hypoxia/ischemia activate processing of amyloid precursor protein: impact of vascular dysfunction in the pathogenesis of Alzheimer's disease. J Neurochem 2017;140: 536–49.
[36] Jayakumar R, Kusiak JW, Chrest FJ, et al. Red cell perturbations by amyloid beta-protein. Biochim Biophys Acta 2003;1622:20–8.
[37] Mohanty JG, Eckley DM, Williamson JD, et al. Do red blood cell-beta-amyloid interactions alter oxygen delivery in Alzheimer's disease? Adv Exp Med Biol 2008;614:29–35.
[38] Lan J, Liu J, Zhao Z, et al. The peripheral blood of Abeta binding RBC as a biomarker for diagnosis of Alzheimer's disease. Age Ageing 2015;44: 458–64.
[39] Zhang M, Xu W, Huang G, et al. Folic acid inhibits amyloid beta-peptide production through modulating DNA methyltransferase activity in N2a-APP cells. Mediators Inflamm 2015;16:25002–13.
[40] Liu H, Li W, Zhao S, et al. Folic acid attenuates the effects of amyloid beta oligomers on DNA methylation in neuronal cells. Eur J Nutr 2016;55:1849–62.
[41] Chen H, Liu S, Ji L, et al. Folic acid supplementation mitigates Alzheimer's disease by reducing inflammation: a randomized controlled trial 2016;2016:5912146.
[42] Gu BJ, Huang X, Ou A, et al. Innate phagocytosis by peripheral blood monocytes is altered in Alzheimer's disease. Acta Neuropathol 2016; 132:377–89.
[43] Fiala M, Lin J, Ringman J, et al. Ineffective phagocytosis of amyloid-beta by macrophages of Alzheimer's disease patients. J Alzheimers Dis 2005;7:221–32. [discussion 255–262].
[44] Darlington D, Li S, Hou H, et al. Human umbilical cord blood-derived monocytes improve cognitive deficits and reduce amyloid-beta pathology in PSAPP mice. Cell Transplant 2015;24:2237–50.
[45] Gu BJ, Huang X, Ou A, et al. Innate phagocytosis by peripheral blood monocytes is altered in Alzheimer's disease. Acta Neuropathol 2016;132:377–89.