Altered peripheral profile of blood cells in Alzheimer disease
A hospital-based case-control study

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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, hemoglobin, lymphocyte. 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).

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 APPswPSEN1ΔE9 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.

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.

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.

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.

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 ethnic Han Chinese. The clinical assessment and diagnosis of AD dementia were performed following the protocol described in our previous studies. In brief, the demographic data, medical
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. The subjects with abnormal performance in MMSE assessment were further scheduled for neuropsychological tests, including Clinical Dementia Rating (CDR) and Hachinski Ischemic Score (HIS) for assessing significant vascular disease. 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 (e.g., 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 leukemia, 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 $-80^\circ C$ 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, cardic 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.

Blood samples were collected for measuring folic acid, vitamin B$12$ (VB$12$), 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 sulfonylurea, metformin, a-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 as appropriate. AD=Alzheimer disease, ADL=Activities of Daily Living, MMSE=Mental State Examination, NC=normal control, SD=standard deviation.

| 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 (6.00) | <.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) $t$ value, 2 independent $t$ tests, or chi-square test as appropriate. AD=Alzheimer disease, ADL=Activities of Daily Living, MMSE=Mental State Examination, NC=normal control, SD=standard deviation.
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 5.0 and 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 ± 6.06; 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

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 ± 0.47 × 10^9/L vs 1.80 ± 0.57 × 10^9/L; P = .003) (Fig. 1A) compared with that of NCs. In addition, AD patients had lower levels of RBC (4.20 ± 0.67 × 10^12/L vs 4.75 ± 0.50 × 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-4).

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

| 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 | .223 |
| MONO | 0 | 0.148 | .908 |
| 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 | 0.697 | .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 | 14.043 | .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 = eosinophil, 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.

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).

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 (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.

The decreased number of lymphocytes and basophils in AD were consistent with a previous study. 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

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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 basophils, 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 hyperperfusion 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 PDW-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 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.[34]

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 from oxygen 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.[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 Aβ by 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.

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