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# Correlations of vascular cognitive impairment with brain-derived neurotrophic factor and trace elements

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## ABSTRACT

**Background:** Cognitive impairment has become one of the major public health problems due to population aging and the increased morbidity associated with stroke. In this study, we aimed to analyze the correlations of vascular cognitive impairment (VCI) with brain-derived neurotrophic factor (BDNF) and trace elements.

**Methods:** Between January 2022 and January 2024, a total of 206 subjects were included in the study, of which 103 were VCI patients treated in our hospital (a cognitive impairment group), and 103 were volunteers undergoing physical examination (a control group). Comparisons were conducted on the levels of BDNF and trace elements (Cu, Fe, Zn, Ca, Mg, Se, As, and Al) between the two groups.

**Results:** In comparison with the control group, the cognitive impairment group had significantly reduced levels of BDNF, Cu, Fe and Zn ($p<0.05$), a significantly raised Al level ($p<0.05$), and decreases in the total score of Mini-Mental State Examination (MMSE) and corrected total score of Montreal Cognitive Assessment (MoCA) ($p<0.05$). The total score of MMSE and corrected total score of MoCA were positively correlated with the levels of BDNF, Cu, Fe, and Zn ($p<0.05$) and negatively correlated with the Al level in both groups ($p<0.05$). BDNF <5.39 μg/L, Cu <10.87 μmol/L, Fe <5.97 μmol/L, Zn <77.32 μmol/L, and Al >0.72 μmol/L were risk factors for VCI.

**Conclusions:** VCI patients have significantly lower levels of BDNF and trace elements (Cu, Fe, and Zn) and a significantly higher Al level than those of healthy populations. Excessively low levels of BDNF and trace elements (Cu, Fe, and Zn) and an overly high level of harmful element Al are risk factors for VCI.

**Keywords:** brain, cognitive impairment, correlation, neurotrophic factor, trace element

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## INTRODUCTION

Cognitive impairment has become one of the major public health problems due to population aging and the increased morbidity associated with stroke. As one of the leading causes of disability, vascular cognitive impairment (VCI) is an ischemic cerebrovascular disease mainly characterized by inability of the brain to process, manage, and feed back external information in an effective manner, resulting in a decline in cognitive function [1]. VCI is a cognitive impairment syndrome of various degrees attributed to stroke or cerebrovascular injury due to cerebrovascular disease and its risk factors. Based on the severity of impairment, VCI can be classified into mild VCI and severe VCI or vascular dementia [2]. Currently, targeted drugs for the treatment of VCI are still unavailable in clinical practice. The contradiction between high prevalence rate and inefficient treatment methods makes VCI an urgent problem to be addressed [3].

Brain-derived neurotrophic factor (BDNF), as a member of the neurotrophic protein family, is primarily released by hippocampal cells and the cerebral cortex, which supports the development, differentiation, survival and repair of various neurons and works as a vital player in the development and functional maintenance of the brain. Besides, BDNF is a crucial neurotrophic factor in the central nervous system [4]. BDNF can modulate glycolipid metabolism, inflammation, and immune responses, and has a close association with the development and progression of diverse neuropsychiatric diseases, as well as the development of cognitive impairment [5]. Trace elements in the human body account for

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lower than 0.01% of the body weight, which, however, bind to proteins and other biomacromolecules to participate in the modulation of the nervous system and play a significant role in maintaining body balance. A correlation is present between the imbalance of trace elements in the brain and the development of cognitive impairment. For instance, Hsu et al. reported that Cu exposure was a key to the progression of vascular damage and cognitive decline [6]. Sun et al. found that Zn deficiency resulted in neurodegenerative diseases, sleep disorders, and mental disorders [7].

Currently, the serum level of most trace elements has been proven to be associated with Alzheimer's disease, but the correlations of VCI with BDNF and trace element levels have rarely been reported. In view of this, the correlations of VCI with BDNF and trace element levels were explored in the present study, aiming to provide ideas for clinical treatment.

## METHODS

### Study subjects

This study was approved by the ethics committee of our hospital (approval No. WTCMH202201003). A cognitive impairment group (103 VCI patients treated in our hospital from January 2022 to January 2024) and a control group (103 healthy volunteers without VCI receiving physical examination in our hospital in the same period) were set up. In the cognitive impairment group, there were 59 males (57.28%) and 44 females (42.72%) aged 62-83 years old, with (70.68±4.29) years old on average. The body mass index ranged from 20.1 kg/m2 to 26.6 kg/m2, with a mean of (23.04±2.57) kg/m2. As to disease status, there were 53 cases (51.46%) of hypertension, 39 cases (37.86%) of glucose abnormality and 26 cases (25.24%) of heart disease. The duration of education was 0-15 years, with an average of (10.73±2.54) years. The control group consisted of 57 males (55.34%) and 46 females (44.66%) aged 61-84 years old, with a mean of (70.52±4.41) years old. The body mass index was 20.2-26.8 kg/m2, with (23.25±2.51) kg/m2 on average. In terms of disease status, there were 52 (50.49%), 37 (35.92%), and 27 cases (26.21%) of hypertension, glucose abnormality, and heart disease, respectively. The duration of education ranged from 0 years to 15 years, with an average of (10.65±2.68) years. The general data showed no statistically significant differences between the two groups (P>0.05).

Aβ42 level in the serum was measured to identify and exclude Alzheimer's disease pathology. Meanwhile, neuropsychological testing and clinical history reviews were performed to distinguish Alzheimer's disease-related cognitive profiles from VCI. MRI scans, including structural and advanced imaging sequences, were also utilized to identify vascular changes and exclude other neurodegenerative or cerebrovascular conditions. MRI scans were performed using a 3.0 Tesla scanner (Siemens MAGNETOM Trio, Germany). The imaging protocol was standardized for all subjects to ensure consistency.

### Inclusion and exclusion criteria

The inclusion criteria for the cognitive impairment group were as follows: (1) patients meeting the diagnostic criteria for VCI [8]; (2) those with the first episode and the disease time of ≤14 d to minimize the variability related to disease progression and treatment history; (3) those with good compliance and cooperation in examinations as required to ensure accurate collection of data and successful administration of cognitive assessments; (4) those with stable vital signs.

The following inclusion criteria were employed for the control group: (1) volunteers with a living background similar to that of patients in the cognitive impairment group to enhance the comparability between groups; (2) those with stable vital signs; (3) those with good compliance and cooperation in examinations as required.

The exclusion criteria involved: (1) patients with severe aphasia or difficulty in normal communication to ensure that cognitive evaluations were based on clear and effective communication; (2) those without imaging data; (3) those with systemic diseases (endocrine diseases, liver dysfunction, etc.) to eliminate confounding variables; (4) those undergoing major surgery in the past year to minimize confounding factors related to recent major health events; (5) those taking psychotropic drugs in the past six months; (6) those with severe infectious diseases or hematological diseases to prevents such conditions from confounding the relationship between VCI and cognitive impairment.

### Determination of trace element levels

Fasting blood (5 mL) was collected from each subject in the morning, followed by centrifugation for separation of the serum. Next, the separated serum was sub-packaged, diluted, and mixed on an oscillator for 1 min. Trace elements Cu, Fe, Zn, Ca, Mg, Se, As, and Al were quantified using CONTRAA800 atomic absorption spectrometer (Analytik Jena, Germany). Calibration curves were established with high linearity ($R^2 \geq 0.999$) and low limits of detection and quantification for each element. Precision was maintained with intra-assay coefficients of variation (CVs) ≤3% and inter-assay CVs ≤5%, while accuracy was confirmed through recovery rates of 95-105%. The atomic absorption spectrometry method relied on the absorption of specific wavelengths of light by free atoms in the flame, allowing

precise measurement of each trace element. Additionally, quality control measures, including calibration verification, procedural blanks, and sample replicates, were strictly followed to ensure reliable and accurate results.

### Examination of BDNF levels

Fasting blood samples were collected from subjects using serum separator tubes (BD, USA) to obtain the serum. The blood samples were centrifuged at 3,000 rpm for 15 minutes at 4°C, and the resulting serum was carefully collected and aliquoted. All samples were stored at -80°C until analysis to ensure the stability of BDNF. Serum BDNF levels were measured using a double-antibody enzyme-linked immunosorbent assay kit (Abcam, USA) following the manufacturer's protocol. The assay had a sensitivity of 1.5 pg/mL, with intra-assay CVs ≤5% and inter-assay CVs ≤8%, ensuring high precision and reliability. Measurements were conducted using ELx800 microplate reader (BioTek Instruments, USA) at an absorbance wavelength of 450 nm with a reference wavelength of 570 nm. Each sample was analyzed in duplicate to confirm accuracy, and quality control standards provided with the kit were included in each run to monitor assay performance.

### Mental status assessment

All cognitive assessments were administered by two trained and independent clinical psychologists who were blinded to the participants' group assignments to prevent bias. The mental status of subjects was assessed with two scales. One was the Mini-Mental State Examination (MMSE) scale consisting of 30 items in total, covering visuospatial execution (1 point) [9], writing (1 point), reading instruction (1 point), three-step instruction (3 points), retelling (1 point), naming (2 points), recalling ability (3 points), attention and calculation power (5 points), memory (3 points) and orientation (10 points). The total score was 30 points, and a total score ≤25 points suggested cognitive impairment.

The other was the Montreal Cognitive Assessment (MoCA) scale composed of orientation (6 points) [10], delayed recall (5 points), abstract thinking (2 points), language (3 points), attention and calculation power (6 points), visual space and execution (5 points), and naming (3 points). The total score was 30 points, which, however, should be added with 1 point to correct educational bias when the duration of education was less than 12 years. A (corrected) total score ≤25 points was considered cognitive impairment.

### Statistical analysis

SPSS 20.0 software (IBM Inc., USA) was adopted for analysis of data. All the data followed a Gaussian (normal) distribution, as verified using the Shapiro-Wilk test. Count data (gender, underlying disease, etc.) were expressed as [n (%)] and compared by the chi-square test. Measurement data like levels of trace elements Cu, Fe, Zn, Ca, Mg, Se, As and Al, BDNF level, MMSE score and MoCA score were expressed as mean ± standard deviation (mean ± s) and examined by the t-test. Pearson analysis was conducted to figure out the correlations of trace element and BDNF levels with MMSE and MoCA scores. Logistic regression analysis was implemented to identify the risk factors for VCI. $p<0.05$ denoted that the difference was of statistical significance.

## RESULTS

### Serum levels of BDNF and trace elements

The levels of BDNF, Cu, Fe, and Zn were significantly lower in the cognitive impairment group than those in the control group ($p<0.05$), while the Al level was significantly higher in the cognitive impairment group than that in the control group ($p<0.05$) (Table 1).

### MMSE and MoCA scores

In comparison with the control group, the cognitive impairment group had decreases in the total scores of MMSE and MoCA as well as corrected total score of MoCA ($p<0.05$) (Table 2 and Table 3).

### The correlations of BDNF, Cu, Fe, and Zn levels with total score of MMSE and corrected total score of MoCA

The total score of MMSE and corrected total score of MoCA had positive correlations with the levels of BDNF, Cu, Fe, and Zn ($p<0.05$) and a negative correlation with the Al level in both groups ($p<0.05$) (Table 4).

**Table 1. Levels of trace elements and BDNF (mean ± s)**

| | BDNF (μg/L) | Cu (μmol/L) | Fe (μmol/L) | Zn (μmol/L) | Ca (μmol/L) | Mg (μmol/L) | Se (μmol/L) | As (μmol/L) | Al (μmol/L) |
|---|---|---|---|---|---|---|---|---|---|
| VCI group (n=103) | 4.86 ±1.21 | 9.27 ±3.04 | 5.68 ±1.84 | 74.98 ±15.17 | 2.14 ±0.68 | 1.64 ±0.35 | 1.56 ±0.51 | 6.14 ±2.03 | 0.76 ±0.21 |
| Control group (n=103) | 5.91 ±1.34 | 12.46 ±4.06 | 6.25 ±2.07 | 79.65 ±15.89 | 2.13 ±0.69 | 1.63 ±0.31 | 1.47 ±0.47 | 5.96 ±1.92 | 0.68 ±0.22 |
| t | 5.902 | 6.383 | 2.089 | 2.157 | 0.105 | 0.217 | 1.317 | 0.654 | 2.670 |
| *p* value | <0.001 | <0.001 | 0.038 | 0.032 | 0.917 | 0.828 | 0.189 | 0.514 | 0.008 |

Abbreviations: BDNP- brain-derived neurotrophic factor, VCI- vascular cognitive impairment.

Table 2. MMSE scores (mean ± s)

| Item | Cognitive impairment group (n=103) | Control group (n=103) | t | *p* value |
|---|---|---|---|---|
| Orientation | 8.54±1.46 | 9.68±0.32 | 7.741 | <0.001 |
| Memory | 2.56±0.44 | 3.00±0.00 | 10.149 | <0.001 |
| Attention and calculation power | 4.01±0.37 | 4.38±0.34 | 7.473 | <0.001 |
| Recalling ability | 1.93±0.61 | 2.59±0.41 | 9.114 | <0.001 |
| Naming | 1.97±0.03 | 2.00±0.00 | 10.149 | <0.001 |
| Retelling | 0.92±0.08 | 1.00±0.00 | 10.149 | <0.001 |
| Three-step instruction | 2.36±0.64 | 3.00±0.00 | 10.149 | <0.001 |
| Reading instruction | 0.86±0.14 | 0.93±0.07 | 4.539 | <0.001 |
| Writing | 0.88±0.12 | 0.94±0.06 | 4.539 | <0.001 |
| Visuospatial execution | 0.84±0.16 | 0.92±0.08 | 4.539 | <0.001 |
| Total score | 24.87±3.91 | 28.44±1.56 | 8.607 | <0.001 |

Abbreviations: MMSE- Mini-Mental State Examination.

Table 3. MoCA scores (mean ± s)

| Item | Cognitive impairment group (n=103) | Control group (n=103) | t | *p* value |
|---|---|---|---|---|
| Orientation | 4.98±1.02 | 5.73±0.27 | 7.214 | <0.001 |
| Delayed recall | 2.41±0.79 | 3.52±1.13 | 8.171 | <0.001 |
| Abstract thinking | 0.99±0.32 | 1.52±0.48 | 9.324 | <0.001 |
| Language | 1.82±0.58 | 2.51±0.49 | 9.223 | <0.001 |
| Attention and calculation power | 4.18±1.34 | 5.41±0.59 | 8.526 | <0.001 |
| Visual space and execution | 3.54±1.18 | 4.71±0.29 | 9.772 | <0.001 |
| Naming | 2.04±0.61 | 2.58±0.42 | 7.400 | <0.001 |
| Total score | 20.96±5.28 | 25.98±1.67 | 8.747 | <0.001 |
| Corrected total score | 21.54±5.18 | 26.31±1.53 | 8.963 | <0.001 |

Abbreviations: MoCA- Montreal Cognitive Assessment.

Table 4. Correlations of BDNF and trace element levels with MMSE and MoCA scores

| Item | Total score of MMSE | | Corrected total score of MoCA | |
|---|---|---|---|---|
| | r | *p* value | r | *p* value |
| BDNF | 0.794 | <0.001 | 0.815 | <0.001 |
| Cu | 0.752 | <0.001 | 0.774 | <0.001 |
| Fe | 0.662 | 0.013 | 0.692 | 0.005 |
| Zn | 0.654 | 0.015 | 0.671 | 0.008 |
| Al | -0.704 | 0.003 | -0.726 | <0.001 |

Abbreviations: BDNF- brain-derived neurotrophic factor, MMSE- Mini-Mental State Examination, MoCA- Montreal Cognitive Assessment.

### Results of logistic regression analysis

The multivariate logistic regression analysis was conducted with the presence of vascular cognitive impairment (0 = no, 1 = yes) as the dependent variable and BDNF [0= >5.39 μg/L (mean in subjects), 1= <5.39 μg/L (mean in subjects)], Cu [0= >10.87 μmol/L (mean in subjects), 1= <10.87 μmol/L (mean in subjects)], Fe [0= >5.97 μmol/L (mean in subjects), 1= <5.97 μmol/L (mean in subjects)], Zn [0= >77.32 μmol/L (mean in subjects), 1= <77.32 μmol/L], and Al [0= <0.72 μmol/L (mean in subjects), 1= >0.72 μmol/L (mean in subjects)] as the independent variables. The analysis revealed that BDNF <5.39 μg/L, Cu <10.87 μmol/L, Fe <5.97 μmol/L, Zn <77.32 μmol/L, and Al >0.72 μmol/L were all independent risk factors for vascular cognitive impairment (Table 5).

## DISCUSSION

VCI is a common cognitive impairment disease, and its incidence rate is positively correlated with age. VCI is concerning to the global medical system and threatens patient brain health and safety [11]. BDNF has close relationships to the activity of nerve growth, with extensive distribution in intracerebral tissues such as the cortex, amygdala, and hippocampus [12]. BDNF can activate the receptor tropomyosin-related kinase B to promote the regeneration of neurons and the proliferation and differentiation of synapses in the nervous system, thereby facilitating the formation of neurons [13]. Trace elements can participate in oxidation resistance, neurotransmitter synthesis, physiological function of nerve cells and other activities by maintaining the state of enzyme system. The destroyed balance of trace elements easily results in various pathological damages [14].

In the present study, the levels of BDNF, Cu, Fe, Zn, and Al were significantly lower in the cognitive impairment group than those in the control group, which may be attributed to the following reasons. First, BDNF is capable of effectively suppressing the neuronal apoptosis pathway, which, in the case of cerebral ischemia and hypoxia injury, can protect nerves, promoting the regeneration of nerve cells, enabling the recovery of nerve cells in some ischemic areas, and improving the neurological

**Table 5. Results of multivariate logistic regression analysis between BDNF and trace element levels and VCI**

| Item | β | Standard error | Wald χ2 | Odds ratio | 95% confidence interval | *p* value |
|---|---|---|---|---|---|---|
| BDNF | -1.542 | 0.513 | 9.035 | 0.214 | 0.078–0.585 | 0.003 |
| Cu | -1.631 | 0.625 | 6.810 | 0.196 | 0.057–0.666 | 0.009 |
| Fe | -1.414 | 0.683 | 4.286 | 0.243 | 0.064–0.927 | 0.039 |
| Zn | -1.357 | 0.639 | 4.510 | 0.257 | 0.074–0.901 | 0.034 |
| Al | 1.374 | 0.508 | 7.316 | 3.951 | 1.460–10.694 | 0.007 |

Abbreviations: BDNF- brain-derived neurotrophic factor, VCI- vascular cognitive impairment.

function of patients [15]. Second, as a crucial component of various enzymes in cells, Cu can participate in cellular oxidative stress. A decrease in the Cu level affects the activity of superoxide dismutase, thus weakening the antioxidant capacity of tissues, triggering oxidative stress responses, and resulting in neurotoxicity. As a result, cognitive impairment occurs [16]. Third, Fe deposition in the brain is associated with the severity of oxidative injury therein. Besides, Fe is a vital component of hemoglobin and cytochrome oxidase, and a reduction in its level leads to the inhibition of enzyme system such as galactosidase, resulting in neurological impairment [17]. Fourthly, Zn can effectively relieve oxidative stress responses of the brain and remove peroxides and free radicals. In the case of a drop in the Zn level, the activity of DNA polymerase is attenuated, giving rise to difficulties in repairing the damaged area [18]. Fifthly, Al is not an essential trace element in the human body, and excessively high Al level accelerates the transcription of amyloid precursor protein genes and the generation of amyloid β-protein, enabling the accumulation of amyloid β-protein to induce VCI [19].

Moreover, VCI can be screened using MMSE and MoCA scales. The results of the present study revealed that these scores were significantly lower in the cognitive impairment group than those in the control group. In addition, the total score of MMSE and corrected total score of MoCA were positively correlated with the levels of BDNF, Cu, Fe, and Zn, but negatively correlated with the Al level. The results of logistic regression analysis demonstrated that overly low levels of BDNF, Cu, Fe, and Zn and an excessively high Al level were risk factors for VCI. Thus, most VCI patients have low levels of BDNF, Cu, Fe, and Zn, and a high Al level. Reducing exposure to harmful metals such as Al, enhancing the intake of trace elements such as Cu, Fe, and Zn, and improving the BDNF level can effectively prevent VCI and contribute to early identification [20].

Nevertheless, this study is limited. The relatively small sample size may limit the generalizability and statistical power of our findings. Measurement limitations, such as variability in serum biomarker levels due to factors like diet and diurnal rhythms, may influence the results despite rigorous protocols. Furthermore, residual confounding factors, including lifestyle and genetic predispositions, may have affected the observed relationships. Hence, it is crucial to address these limitations in future studies to enhance the understanding and validity of the biochemical factors involved in VCI.

## CONCLUSION

In conclusion, the levels of BDNF and trace elements (Cu, Fe, and Zn) are significantly lower in VCI patients than in healthy people, whereas the Al level shows a contrary trend. The levels of Cu, Fe, and Zn are positively correlated with the total score of MMSE and corrected total score of MoCA, while the Al level is negatively correlated with such scores. Excessively low BDNF and trace element (Cu, Fe, and Zn) levels together with overly high level of harmful element (Al) are risk factors for VCI. These findings highlight the importance of a multifaceted approach targeting both neurotrophic support and mineral balance to develop effective interventions for VCI patients. Future clinical trials should explore these strategies to validate their efficacy and establish evidence-based treatments aimed at preserving cognitive function and improving the quality of life in individuals with VCI.

## ABBREVIATIONS

BDNF- brain-derived neurotrophic factor

MMSE- Mini-Mental State Examination

MoCA- Montreal Cognitive Assessment

MRI- magnetic resonance imaging

VCI- vascular cognitive impairment

## AUTHORS' CONTRIBUTION

RG: study design and data analysis.

CL: study design and data collection.

HZ: data analysis and drafting the manuscript.

## CONFLICT OF INTEREST

None to declare.

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