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Serum alkaline phosphatase is related to cognitive impairment in patients with subcortical ischemic vascular disease.

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Abstract

Background: The aim of the present study was to assess the relationship between serum levels of Alkaline Phosphatase (ALP) and cognitive impairments in patients with Subcortical Ischemic Vascular Disease (SIVD).

Methods: This study included 235 patients who were assigned to a mild-cognitive-impairment group or a vascular-dementia group according to the severity of their cognitive impairments. The incidences of multiple lacunar infarctions and leukoaraiosis were confirmed using Magnetic Resonance Imaging (MRI) scans. Serum ALP was measured with an enzymatic method; the Mini-mental State Examination (MMSE) and the Cambridge Cognitive Examination-Chinese version (CAMCOG-C) were used to assess neuropsychological status; and a logistic regression was performed to explore the associations between ALP levels and cognitive impairments.

Results: ALP levels were higher in the vascular-dementia group than in the control group (82.7 ± 15.06 vs. 68.4 ± 14.8, respectively), and scores on the MMSE and CAMCOG-C were significantly lower in the vascular-dementia than in the mild-cognitive-impairment group. Additionally, ALP levels were negatively correlated with MMSE and CAMCOG-C scores (r=-0.364 and r=-0.297, respectively). The incidences of lacunar infarction and leukoaraiosis were higher in the vascular-dementia group than in the mild-cognitive-impairment group (73.9% *vs.* 60.0% and 80.0% *vs.* 64.2%, respectively), and the logistic regression revealed that ALP levels were positively associated with cognitive impairments after adjusting for potential confounding factors (Odds Ratio (OR): 1.57, 95% Confidence Interval (CI): 1.14-2.17). Furthermore, the risk of cognitive impairments increased by 57% per unit of ALP change.

Keywords: Alkaline phosphatase, Brain ischemic, Dementia, Vascular.

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Introduction

Subcortical Ischemic Vascular Disease (SIVD), which is primarily the result of pathological changes in ischemic cerebral small vessels, is second to only Alzheimer's disease in terms of disorders that lead to cognitive impairments in elderly individuals [1]. SIVD can be categorized as Subcortical Vascular Dementia (SVaD) or Subcortical Vascular Mild Cognitive Impairment (SVMCI) according to the severity of the impairments [2,3]. SIVD patients typically exhibit characteristics of multiple lacunar cerebral infarction and/or extensive cerebral white matter lesions; accordingly, the diagnostic criteria for SIVD initially proposed by Erkiniunit were based on imaging scans. Additionally, the lacunar state, subcortical arteriosclerotic encephalopathy, and ischemic dementia due to damage in various important neural locations are considered to define subtypes of SIVD.

As the development of novel technologies accelerates, an increasing number of studies have reported the widespread prevalence of ischemic cerebral vascular disease in the general population. For example, one study found that 20-40% of elderly subjects in a community population were diagnosed with ischemic cerebral vascular disease, and another showed that the rate of cognitive impairments caused by ischemic cerebral vascular disease ranges from 36% to 67%. The Honolulu Asian Aging Research Center conducted a 5 y follow-up study of Japanese-American individuals and found that 23% of vascular dementia cases were caused by a macroangiopathy, half of which were due to small vessel disease and 16% of which were due to mixed vascular lesions [4]. The cognitive impairments suffered by SIVD patients proceed more rapidly than those in other patients with the same type of stroke, which results in a poorer quality of life and worse outcomes for patients with SIVD.

Several inflammatory factors have been associated with cognitive impairments in SIVD patients, including soluble intercellular adhesion molecule-1 and insulin-like growth factor-1 [5,6]. Alkaline Phosphatase (ALP) is a type of metalloenzyme encoded by a multi-gene family that is widely distributed in prokaryotic organisms and advanced eukaryotic cells [7]. Non-tissue specific ALP is expressed in various organs, including the liver, kidneys, and bone, and plays an important role in clinical diagnoses. For example, ALP levels are associated with the outcomes and prognoses of patients with cardiovascular disease and peripheral artery disease [8-10], and there is an association between ALP levels and lacunar infarctions. However, few studies have investigated the association between ALP and cognitive function in patients with SIVD. Thus, the present study aimed to assess the relationships between ALP levels and cognitive impairments in patients with SIVD.

Materials and Methods

Study population

Using the guidelines of the Chinese Cerebral Small Vessel Disease, we recruited 235 SIVD patients (140 males and 95 females, mean age: 69.9 y) from Zhengzhou Central Hospital Affiliated to Zhengzhou University for the present study between July 2015 and July 2016. The study participants were divided into a mild-cognitive-impairment group and a vascular-dementia group based on the severity of cognitive impairments. This study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Zhengzhou University.

Criteria for cognitive impairment

A diagnosis of mild cognitive impairment was based on the following criteria, which are revised versions of those developed by Frisoni [11]: (1) fulfilment of the diagnostic criteria for SIVD, (2) mild cognitive impairments that were confirmed by family members or a caregiver, (3) a score of 0.5 on the Clinical Dementia Rating scale in the absence of dementia, (4) cognitive impairments with a limited influence on complex functions and social activities, and (5) a score<26 on the activities of daily living scale. A diagnosis of severe cognitive impairment was based on the following criteria, which are revised versions of those developed by Roman [2]: (1) a diagnosis corresponding to the criteria for vascular dementia criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [12], (2) a score on the Clinical Dementia Rating scale between 1 and 2 points, (3) one or more symptoms of small vessel disease (parkinsonian signs, small-step gait, unsteadiness, unilateral incoordination, arm drift, central facial weakness, and/or reflex asymmetry), and (4) magnetic resonance imaging (MRI) scans indicating at least five lacunar infarction sites under the subcortex and/or diffuse demyelination. All cranial MRI scans were performed using a 3.0 T GE Signa MRI system (GE Company; USA). Based on MRI T2 scans using Fluid-Attenuated Inversion Recovery (FLAIR), the study population was categorized into groups with lacunar infarctions or leukoaraiosis. Additionally, four levels were defined according to the criteria developed by Whalund [13]: 0 (no white matter lesions), 1 (focal lesion), 2 (fusion lesions), and 3 (diffuse lesions).

Patients with the following diseases or syndromes were excluded from the present study: Parkinson's disease, dementia with Lewy bodies and/or other cognitive impairments, cerebral tumor, trauma, stroke, severe infectious diseases or surgery within the previous 3 w, severe liver or renal function injuries, autoimmune diseases, metabolic syndrome, and hematological and/or bone diseases.

Data collection

General information about the patients, including age, sex, educational level, history of hypertension, history of diabetes, history of heart diseases (e.g., coronary artery atherosclerosis or arrhythmia), smoking, alcohol, and history of liver and renal diseases, was collected using a standard questionnaire. Fasting blood samples were obtained from all participants early in the morning *via* the antecubital vein, and an automatic biochemical analyzer (Swedish Modular DPP AYL-5-001) was used to determine the levels of the following biochemical indices: serum ALP, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), creatinine, Blood Urea Nitrogen (BUN), Fasting Blood Glucose (FBG), triglyceride, total cholesterol, High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C). The Mini-mental State Examination (MMSE) and the Cambridge Cognitive Examination-Chinese version (CAMCOG-C) were administered to evaluate neuropsychological status [14,15]; the CAMCOG-C includes scales assessing orientation, language (expression and understanding), memory (remote, recent, learning), attention, praxis, calculation, abstract thinking, and perception.

Statistical analysis

Continuous data are expressed as means ± standard errors or medians (quartile: Q25-Q75) according to the Kolmogorov-Smirnov test, and either t-tests or Mann-Whitney U tests were used to determine differences between two groups. Categorical data are expressed as percentages, and Chi-square tests were used to determine differences between two groups. Additionally, Spearman's correlation coefficient and logistic regression analyses were performed to explore associations between ALP levels and cognitive function. All statistical analyses were performed using SPSS 19.0 software (SPSS Inc.; Chicago, Illinois, USA), and P values<0.05 were considered to indicate statistical significance.

Results

Comparisons of general characteristics

Table 1 presents the general characteristics of the two study groups, which did not significantly differ in terms of age or sex

(P=0.629 and P=0.687, respectively). Compared with those in the control group, patients in the vascular-dementia group had a lower educational level (P=0.000) and were more likely to smoke (P=0.000) and have hypertension (P=0.000). Additionally, the ALP and BUN levels of the vascular-dementia group were higher than those of the control group (P=0.000 and P=0.000, respectively); no significant differences were observed with respect to the other parameters (P>0.05). The incidences of lacunar infarction and leukoaraiosis were higher in the vascular-dementia group than in the mild-cognitive-impairment group (73.9% *vs.* 60.0%, P=0.023; 80.0% *vs.* 64.2%, P=0.007).

Evaluation of neuropsychological scores

Table 2 shows the results of the analyses of the MMSE and CAMCOG-C scores. The total scores of the vascular-dementia group on the MMSE and CAMCOG-C were significantly lower than those of the control group (P<0.05), with similar findings observed for each sub-item score (P<0.05), including orientation, language, memory, attention, praxis, calculation, abstract thinking, and perception. The correlation analysis revealed that ALP levels were negatively correlated with scores on the MMSE and CAMCOG-C (r=-0.364, P=0.000 and r=-0.297, P=0.000, respectively) and several sub-items, including orientation (r=-0.201, P=0.002), language (r=-0.249, P=0.000), memory (r=-0.265, P=0.000), attention (r=-0.274, P=0.000), praxis (r=-0.189, P=0.005), calculation (r=-0.232, P=0.000), abstract thinking (r=-0.209, P=0.002), and perception (r=-0.154, P=0.020).

Multivariate analysis

A logistic regression analysis was performed to explore associations between ALP levels and cognitive impairments. ALP was positively associated with cognitive impairments after adjusting for potential confounding factors (Table 3), and the risk of cognitive impairments increased by 57% per unit of ALP change (Odds Ratio (OR): 1.57, 95% Confidence Interval (CI): 1.14-2.17). Additionally, hypertension (OR: 1.96, 95% CI: 1.09-3.55) and smoking (OR: 1.52, 95% CI: 1.29-8.43) were associated with an increased risk of cognitive impairments, whereas educational level was negatively correlated with the risk of cognitive impairments (OR: 0.75, 95% CI: 0.62-0.92).

Table 1. *Comparisons of general characteristics between controls and cases.*

Parameters	Control group (n=120)	Case group (n=115)	Z/t/χ2	P value
Age (y)	69.7 ± 8.01	70.2 ± 7.82	-0.484	0.629
Male (n, %)	73 (60.8)	67 (58.3)	0.161	0.687
Education, M (Q25-Q75)	11.0 (10.0-14.0)	7.0 (5.75-12.0)	45.351	0
Smoking (n, %)	25 (20.8)	49 (42.6)	12.907	0
Alcohol (n, %)	18 (15.0)	25 (21.7)	1.784	0.182
Hypertension (n, %)	50 (41.7)	80 (69.6)	18.492	0
FBG, mmol/L	5.3 ± 3.4	5.7 ± 3.3	-0.915	0.361
ALP, U/L	68.4 ± 14.8	82.7 ± 15.1	-7.323	0
ALT, U/L, M (Q25-Q75)	17.0 (125-24.6)	18.0 (14.3-22.81)	0.779	0.662
AST, U/L, M (Q25-Q75)	18.0 (16-23)	21 (16-25)	1.021	0.587
BUN, umol/L,M (Q25-Q75)	5.2 (4.5-6.5)	6.5 (5.0-8.1)	16.524	0
Creatinine, umol/L	70.3 ± 1.87	70.6 ± 2.01	-1.185	0.237
Triglyceride, umol/L	1.3 ± 0.9	1.4 ± 1.1	-0.764	0.456
Total cholesterol, umol/L	4.6 ± 1.1	4.7 ± 0.8	-0.781	0.436
HDL-C, umol/L	2.9 ± 0.9	2.8 ± 0.8	0.899	0.369
LDL-C, umol/L	1.3 ± 0.3	1.3 ± 0.4	0.435	0.664
Imaging test				
Lacunar infarction	72 (60.0)	85 (73.9)	5.126	0.023
Leukoaraiosis	77 (64.2)	92 (80.0)	7.289	0.007

Table 2. *Comparisons of cognitive function scores between controls and cases.*

Parameters	Controls	Cases	Z value	P value
MMSE	25 (25-26)	17 (12,21)	178.226	0

CAMCOG-C	81.5 (76.8-88.0)	59.5 (48.0-69.5)	146.684	0
Orientation	9 (9-10)	6 (5-8)	120.601	0
Language	24.0 (23.0-26)	18.0 (16.3-22.5)	103.547	0
Expression	8 (8-9)	7 (5-8)	89.126	0
Understanding	16 (15-18)	12 (11-13)	90.621	0
Memory	21 (16-23)	12 (9-15)	118.442	0
Remote memory	5 (3-5)	3 (2-4)	65.023	0
Recent memory	3 (2-4)	2 (1-3)	69.585	0
Learning memory	13 (11-14)	9 (7-11)	121.084	0
Attention	6 (5-7)	3 (2-4)	104.223	0
Praxis	8 (7-10)	5 (4-7)	87.408	0
Calculation	2 (2-2)	2 (1-2)	50.03	0
Abstract thinking	5.0 (1.0-7.0)	3.0 (0.3-5.0)	80.434	0
Perception	7 (6-8)	6 (5-9)	48.001	0

Table 3. *Logistics regression analysis of cognitive function impairment in SIVD.*

Parameters	B	Wald	OR	95% CI	P
Hypertension	0.675	4.976	1.96	1.09-3.55	0.026
Smoking	0.417	6.228	1.52	1.29-8.43	0.013
Education	-0.282	7.722	0.75	0.62-0.92	0.005
ALP	0.453	0.163	1.57	1.14-2.17	0.006
Constant	-0.184	7.051	-	-	0.008

Discussion

Although the pathogenesis of SIVD currently remains unclear, several common factors, including hypertension, diabetes, hyperlipidemia, and serum bilirubin and uric acid levels, have been associated with this disorder [16]. Furthermore, after vascular calcification theory recently attracted widespread attention, ALP became a focus of research because it is a regulator of vascular calcification. The present study found that ALP levels were higher in the vascular-dementia group than in the mild-cognitive-impairment group; thus, ALP could be a predictor of the severity of cognitive impairments in patients with SIVD.

ALP has been associated with the outcomes and prognoses of patients with cardiovascular disease and peripheral artery disease [8-10], and a study of 2029 acute stroke patients found that the mortality risk of patients with ALP levels>97 U/L was almost three times greater than that of those with ALP levels<57 U/L [17]. This difference is likely related to vascular smooth muscle calcification, which results in arteriosclerosis and precedes a series of brain impairments, including ischemic cerebral stroke, leukodystrophy, and intracranial hemorrhage. Furthermore, using Western blot analysis, Lomashvili found that the ALP levels in the aortic wall are significantly higher in uremic rats than in control rats [18]. Bos measured calcification volume in the coronary artery, arcus aortae, and internal (external) carotid artery using computed tomography and found that the volume of leukoaraiosis increased with the vascular calcification volume [19]. Taken together, these findings suggest that vascular calcification is involved in the processes of cerebral vascular diseases and that ALP is associated with vascular calcification. Therefore, it is reasonable to assume that ALP is related to cerebral vascular diseases. In the present study, the population was divided into two groups, and the incidences of lacunar infarction and leukoaraiosis were higher in the group with high ALP levels than in the group with low ALP levels. This finding suggests that ALP plays an important role in the development of cerebral small vessel disease.

Currently, the underlying mechanisms and effects of ALP on cognitive impairments in patients with SIVD remain unclear. In the present study, the population was divided into a mild-cognitive-impairment group and a vascular-dementia group based on the severity of cognitive impairment. ALP levels were higher in the vascular-dementia group than in the mild-cognitive-impairment group, and a correlation analysis indicated that ALP was negatively correlated with scores on the MMSE and COMCOG-C; these associations remained significant after adjusting for potential cofounding factors. Thus, ALP may induce cerebral small vascular disturbances and negatively influence cognitive function. Vidal reported that leukoaraiosis volume increases and cognitive function decreases as vascular calcification increases, which supports the idea that vascular calcification damages cognitive function *via* the modulation of leukoaraiosis [20]. Yan found that the severity of cerebral white matter injury was negatively associated with MMSE scores and that high levels of ALP could increase the volume of leukoaraiosis [21]. The present results are consistent with these findings and suggest that ALP, as a calcification regulator, was associated with cognitive impairments and leukoaraiosis in patients with SIVD.

The mechanisms underlying the effects of ALP on cognitive impairment may be partly explained by the following variables. First, vascular calcification may be involved as the overexpression of ALP could decrease extracellular pyrophosphate/endogenous hydroxyapatite levels and induce vascular calcification and artery stiffness, which would lead to atherosclerosis and cerebral vascular disease [18]. Second, the collagen precipitating theory has been proposed in this regard: ALP could cause collagen precipitation and microvascular thickening, which would lead to chronic ischemia in brain tissues [22]. Third, inflammatory mechanisms may play a role in this phenomenon insofar as ALP levels would elevate when an organism suffers a severe infection, such as septicemia. ALP levels reflect the inflammatory status of an organism, including high-sensitivity C-Reactive Protein (hs-CRP) levels [9]. It has been suggested that hs-CRP levels are associated with cerebral small vascular diseases and may represent an independent predictor of these diseases [23]. Therefore, the dual measurements of ALP and hs-CRP could be an important for assessing the presence of cerebral small vascular diseases.

Limitations

First, because the present study used a cross-sectional design, it was impossible to establish direct cause-and-effects relationship between ALP levels and cognitive impairments; thus, prospective studies are required to confirm the observed associations. Second, the present study population included only SIVD patients and did not include participants without SIVD. Third, drug use was not assessed in the present study, which is important because patients with a vascular disease are more likely to take drugs, such as statins, that can increase ALP levels. Finally, it is difficult to distinguish senile dementia from cerebral small vessel disease in its early stages.

Conclusion

In conclusion, the present study found a significant positive relationship between ALP levels and cognitive impairments in SIVD patients. These findings may prove clinically useful for the detection of possible cognitive impairments in the early stages of the disease, but further prospective studies will be required to confirm the cause-and-effect relationships involving these variables.

Conflict of Interest

There is no interest conflict.

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References

1. Roh JH, Lee JH. Recent updates on subcortical ischemic vascular dementia. J Stroke 2014; 16: 18-26.
2. Roman GC, Erkinjuntti T, Wallin A. Subcortical ischaemic vascular dementia. Lancet Neurol 2002; 1: 426-436.
3. Chui HC. Subcortical ischemic vascular dementia. Neurol Clin 2007; 25: 717-740, vi.
4. Ross GW, Petrovitch H, White LR, Masaki KH, Li CY. Characterization of risk factors for vascular dementia: the Honolulu-Asia aging study. Neurology 1999; 53: 337-343.
5. Volcik KA, Ballantyne CM, Hoogeveen R, Folsom AR, Boerwinkle E. Intercellular adhesion molecule-1 G241R polymorphism predicts risk of incident ischemic stroke: Atherosclerosis Risk in Communities study. Stroke 2010; 41: 1038-1040.
6. Umran RM, Al-Tahir M, Jagdish D, Chouthai N. Insulin-like growth factor-1 levels in term newborns with hypoxic-ischemic encephalopathy. Am J Perinatol 2016; 33: 640-645.
7. Buchet R, Millan JL, Magne D. Multisystemic functions of alkaline phosphatases. Methods Mol Biol 2013; 1053: 27-51.
8. Sahin I, Karabulut A, Gungor B, Avci II, Okuyan E. Correlation between the serum alkaline phosphatase level and the severity of coronary artery disease. Coron Artery Dis 2014; 25: 349-352.
9. Kim J, Song TJ, Song D. Serum alkaline phosphatase and phosphate in cerebral atherosclerosis and functional outcomes after cerebral infarction. Stroke 2013; 44: 3547-3549.
10. Cheung BM, Ong KL, Wong LY. Elevated serum alkaline phosphatase and peripheral arterial disease in the United States National Health and Nutrition Examination Survey 1999-2004. Int J Cardiol 2009; 135: 156-161.
11. Frisoni GB, Galluzzi S, Bresciani L. Mild cognitive impairment with subcortical vascular features: clinical characteristics and outcome. J Neurol 2002; 249: 1423-1432.
12. Battle DE. Diagnostic and Statistical Manual of Mental Disorders (DSM). Codas 2013; 25: 191-192.
13. Wahlund LO, Barkhof F, Fazekas F. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32: 1318-1322.
14. Santana I, Duro D, Lemos R. Mini-mental state examination: screening and diagnosis of cognitive decline, using new normative data. Acta Med Port 2016; 29: 240-248.
15. Heinik J, Werner P, Mendel A. The Cambridge Cognitive Examination (CAMCOG): validation of the Hebrew version in elderly demented patients. Int J Geriatr Psych 1999; 14: 1006-1013.
16. Zhou X, Wang L, Liu H, Sun ZW. Association between serum bilirubin and uric acid and cognitive impairment. Chin J Neuro 2014; 47: 305-310.
17. Ryu WS, Lee SH, Kim CK. Increased serum alkaline phosphatase as a predictor of long-term mortality after stroke. Neurology 2010; 75: 1995-2002.
18. Lomashvili KA, Garg P, Narisawa S. Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. Kidney Int 2008; 73: 1024-1030.
19. Bos D, Ikram MA, Elias-Smale SE. Calcification in major vessel beds relates to vascular brain disease. Arterioscler Thromb Vasc Biol 2011; 31: 2331-2337.
20. Vidal JS, Sigurdsson S, Jonsdottir MK, Eiriksdottir G, Thorgeirsson G. Coronary artery calcium, brain function and structure: the AGES-Reykjavik Study. Stroke 2010; 41: 891-897.
21. Yan T, Yu JR, Zhang YP. Analysis on correlation of white matter lesion and lacunar infarction with vascular cognitive impairment. Int J Clin Exp Med 2015; 8: 14119-14122.
22. Brown WR, Moody DM, Thore CR. Microvascular changes in the white mater in dementia. J Neurol Sci 2009; 283: 28-31.
23. Mitaki S, Nagai A, Oguro H, Yamaguchi S. C-reactive protein levels are associated with cerebral small vessel-related lesions. Acta Neurol Scand 2016; 133: 68-74.

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