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Research Article

The Predictive Value of Serum Alkaline Phosphatase Level on the Degree of Neurological Impairment in Patients with Acute Cerebral Infarction

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Abstract

Objective: To analyze the correlation between the changes of ALP level and the degree of neurological impairment in patients with acute cerebral infarction.

Methods: A total of 267 patients with acute cerebral infarction were selected as the cerebral infarction group, 181 elderly patients who were matched age and gender in the same period with the cerebral infarction group were selected as the control group by the physical examination. All the selected patients were tested for serum ALP, ALT, AST, Cr, BUN,TG, TC, LDL - C and HDL - C after eight hours on an empty stomach. In the 72nd hour of the patient's course of cerebral infarction, the degree of neurological impairment was assessed using NIHSS score. The relationship between serum ALP level and NIHSS score was analyzed.

Results: According to NIHSS score, the patients with score of 5~15 were Group A , patients with score of 15~20 were Group B and score of 21~42 were Group C. Pearson correlation analysis showed that the serum ALP level of the three groups was positively correlated with NIHSS score. Multivariate regression analysis results showed that the high serum ALP level of the risk of cerebral infarction is a low serum ALP level 1.58 times.

Conclusions Serum ALP level was increased in patients with acute cerebral infarction and was closely related to the degree of neurological impairment. Perhaps the serum ALP level may be used as a serum marker to predict the degree of neurological impairment in patients.

Key words: alkaline phosphatase; cerebral infarction; degree of neurological impairment

Introduction

Alkaline phosphatase (ALP) is a group of zinc-containing glycoproteins, which covers six types of isoenzymes and can dephosphorylate corresponding substrates. ALP1, ALP2 and ALP6 stem from the liver, ALP3 stems from bone cells, ALP4 is produced by the placenta and cancer cells, and ALP5 is produced in the intestinal villi epithelium and fibroblasts. The serum ALPs are mainly from the liver and bone, and widely distributed in visceral organs of the human body. High clinical ALP level is commonly used in the diagnosis and differential diagnosis of bones and liver and gallbladder diseases. Low ALP index can be detected in chronic nephritis, anemia and thyroid dysfunction. Lee [1] et al. conducted a study of 1,011 participants with normal nervous system, and the result showed that ALP level is positively correlated with asymptomatic lacunar infarction and white matter high signal intensity. In order to further investigate the relationship between ALP and acute cerebral infarction, especially the degree of nervous functional defects, the change in serum ALP level of patients with acute cerebral infarction was studied, and the study is as follows.

Objects and Methods

1. Objects

A total of 267 cases of patients with acute cerebral infarction, aged over 60 and admitted to medical care department for personnel and neurology department of Yantaishan Hospital from January 2012 to December 2013 were selected as the cerebral infarction group, with the average age of (66.91±3.41), and with 253 male patients and 14 female patients. The subtype [2] of the patients was determined by the Oxfordshire Community Stroke Project classification method. The result showed that 122 cases had complete anterior circulation infarct (45.7%), 17 cases had partial anterior circulation infarct (6.4%), 63 cases had posterior circulation infarct (23.6%), and 65 cases had lacunar infarct (24.3%). Meanwhile, 181 cases of patients aged over 60, undergone physical examination, with corresponding gender, and with no abnormalities detected in Philips Brilliance 128-row volume CT brain scanning in corresponding period

were selected from the physical examination department, and set as the control group, with the average age of (67.07±3.46), and with169 male patients and12 female patients. The inclusion criteria for cerebral infarction group are as follows: (1) the patients all conformed to the diagnostic criteria formulated by the Fourth National Cerebrovascular Disease Academic Conference as well as China Acute Ischemic Stroke Diagnosis and Treatment Guideline 2014 [3-4]; (2) the patients were definitely diagnosed by Philips Brilliance 128-row volume CT brain scanning; (3) in acute phase of cerebral infarction, the course of disease was no greater than 24h. The exclusion criteria are as follows: (1) patients with infectious disease, hepatobiliary or kidney disease, autoimmune disease, malignant tumor, blood or skeleton system disease were excluded; (2) patients with an operation history over the past month were excluded. The informed consent was signed by the patients or the family members entrusted by the patients.

2. Methods

1. History collection: the patients' medical history covers gender, age, the history of hypertension, diabetes, coronary heart disease, auricular fibrillation and diseases in hepatorenal system, blood system and skeletal system, smoking history (more than 1 cigarettes per day, for successive or cumulative 6 months) and alcohol intake history (≥ 20g/d).
2. Check items: all the included patients were kept fasting for 8h during 24h after admission to hospital. Backman DXC800 automatic analyzer was used to measure related indexes of the patients, including serum ALP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), blood urea nitrogen (BUN), triacylglycerol (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and Philips Brilliance 128-row volume CT brain scanning was conducted.
3. Neurological function deficit score: the degree of neurological function deficit of patients in cerebral infarction group at 72h of the disease course was evaluated by the National Institutes of Health Stroke Scale (NIHSS). According to the NIHSS score, 45 cases scored 5-15 (NIHSS score of 10.32±3.11) were included into Group A, 119 cases scored 15-20 were included into Group B (NIHSS score of 17.61±4.03), and 103 cases scored 21-42 were included into Group C (NIHSS score of 27.19±5.08).

3. Statistical methods

The SPSS 21.0 software was used for statistical analysis, the measurement data was denoted by ($\bar{X} \pm S$), and Kruskal-Wallis test was used for comparison among groups; the enumeration data was denoted by percent or ratio, and chi-square test was adopted; the correlation between ALP and other risk factors of cerebral infarction was analyzed by Pearson correlation analysis, and binary logistic regression was used to analyze the influencing factors of cerebral infarction. P<0.05 indicated that the difference was statistically significant.

Result

1. Comparison of serum ALP level and general data between the two groups

The difference in average age [(66.91±3.41) in infarction group, (67.07±3.46) in control group] gender [253 males (94.8%) in infarction group, 169 males (93.4%) in control group], and the ratios of hypertension [184 cases (68.9%) in infarction group, 122 cases (67.4%) in control group], type 2 diabetes mellitus[73 cases (27.3%) in infarction group, 48 cases (26.5%) in control group], coronary heart disease [191 cases (71.5%) in infarction group, 127 cases (70.2%) in control group], smoking [25 cases (9.4%) in infarction group, 18 cases (9.9%) in control group] and drinking [87 cases (32.6%) in infarction group, and 61 cases (33.7%) in control group] between infarction group and control group was not statistically significant, see Table 1. The difference in ALT, AST, BUN and Cr between infarction group and control group was not statistically significant, the serum levels of ALP, TG, TC and LDL-C in infarction group were higher than those in control group (t = 33.64, 5.07, 5.62, 14.38, P = 0.00, 0.00, 0.00, 0.00), the level of HDL-C was lower than that in control group (t = -9.21, P = 0.00), and patients in both groups had no history of atrial fibrillation, see Table 2.

Table 1: Two groups of clinical data were compared ($\bar{x} \pm s$)

Group	Hypertension Cases (%)	Type 2 diabetes mellitus Cases (%)	Coronary heart disease Cases (%)	Smoking Cases (%)	Drinking Cases (%)
Infarction group	184(68.9)	73(27.3)	191(71.5)	25(9.4)	87(32.6)
Control group	122(67.4)	48(26.5)	127(70.2)	18(9.9)	61(33.7)
χ^2 value	0.06	0.04	0.10	0.04	0.06
P value	0.80	0.85	0.75	0.84	0.81

Table 2: Two groups of serum ALP level were compared with general data ($\bar{x} \pm s$)

Group	Cases	Age (yrs)	Male (%)	TC (mmol/L)	TG (mmol/L)
Infarction group	267	66.91±3.41	94.8	6.48±0.46	3.95±0.80
Control group	181	67.07±3.46	93.4	6.24±0.44	3.55±0.86
t or χ^2 value		-0.50	0.37	5.62	5.07
P value		0.62	0.54	0.00	0.00
Group	Cases	LDL-C(mmol/L)	HDL-C(mmol/L)	BUN(mmol/L)	Cr(μmol/L)
Infarction group	267	4.44±0.41	1.11±0.17	5.94±0.39	78.62±4.63
Control group	181	3.81±0.51	1.30±0.26	5.93±0.39	78.30±4.25
t or χ^2 value		14.38	-9.21	0.14	0.73
P value		0.00	0.00	0.89	0.46

Group	Cases	ALP(U/L)	AST(U/L)	ALT(U/L)	
Infarction group	267	90.78±9.92	22.02±2.49	17.82±2.31	
Control group	181	65.36±2.67	21.61±2.77	17.65±2.50	
t or χ^2 value		33.64	1.66	0.75	
P value		0.00	0.10	0.45	

2. Comparison of serum ALP level between cerebral infarction patients with different NIHSS scores

The average age of patients in Group A, Group B and Group C was respectively (68.42±3.22), (66.68±3.48) and (66.50±3.27), and the difference was not statistically significant (H =4.79, *P* =0.07). The difference in serum ALP level between the three groups was statistically significant (H =224.90, *P* =0.00), see Table 3. The results of Pearson correlation analysis showed that there was a positive correlation between serum ALP level and NIHSS score of patients in the three groups (r =0.92, *P* =0.00).

Table 3: Comparison of serum ALP level and general data in three groups

Group	**Male Cases (%)**	**Hypertension Cases (%)**	**Type 2 diabetes mellitus Cases (%)**	**Coronary heart disease Cases (%)**
Group A	41(91.1)	28(64.4)	9(20.0)	29(64.4)
Group B	115(96.6)	83(69.7)	32(26.9)	85(71.4)
Group C	97(94.2)	73(70.9)	32(31.1)	77(74.8)
H or χ^2 value	2.12	1.16	1.95	1.64
P value	0.35	0.56	0.38	0.44
Group	Male Cases (%)	Drinking Cases (%)	Smoking Cases (%)	ALP (U/L)
Group A	41(91.1)	21(46.7)	2(4.4)	77.4±10.1
Group B	115(96.6)	37(31.1)	11(9.2)	90.2±11.5
Group C	97(94.2)	29(28.2)	12(11.7)	95.9±10.4
H or χ^2 value	2.12	5.10	1.92	224.90
P value	0.35	0.08	0.38	0.00

3. Binary logistic regression analysis of influencing factors of cerebral infarction

After the age, gender, history of hypertension, diabetes, heart disease, smoking and drinking and the levels of ALT, AST, Cr, BUN, TG, TC, HDL-C and LDL-C were corrected, the results showed that serum ALP level is the influencing factor of cerebral infarction, the risk of being attacked by cerebral infarction for patients with high ALP level (>86 U/L) is 1 .58 times that for those with low ALP level(<67 U/L) (OR =1.58, 95%*CI*: 1.26~2.02), hypertension (OR=1.17, 95%*CI*: 1.05~1.69) and LDL-C (OR =2.26, 95%*CI*: 1.77~2.81) are also risk factors for cerebral infarction, but HDL-C (OR =0.27, 95%*CI*: 0.09~0.64) is a protective factor.

Discussion

After activated by Mg^{2+}, ALP can catalyze the dephosphorylation and hydrolysis of various phosphate monoesters, ATP and pyrophosphoric compounds. Inorganic pyrophosphate is an effective angiosteosis inhibitor. In recent years, research showed that ALP can accelerate the hydrolysis of inorganic pyrophosphate and reduce the level of inorganic pyrophosphate, thereby participating in the process of accelerating angiosteosis[5]. Angiosteosis is a common pathophysiological manifestation of atherosclerosis, hypertension, diabetic angiopathies, vascular injuries, chronic kidney disease and aging, it increases the possibility of thrombosis and plaque rupture and it is not only an important risk factor of the high incidence and mortality of cardiovascular and cerebrovascular diseases, but also an important symbol of cerebral apoplexy, atheromatous cardiovascular events and peripheral vascular diseases. Angiosteosis is an independent risk factor of cardiovascular and cerebrovascular events as well as one of the main phenotypes of vascular senescence [6]. Zhu Mengen et al. [7] used the qualitative test of ALP activity in vascular smooth muscle cells to evaluate the severity of calcification, and pointed out that clinically controlling the risk factors of angiosteosis is of great significance for alleviating angiosteosis process, relieving the angiosteosis rate and delaying the progress, and is a key measure for preventing and intervening angiosteosis. Angiosteosis can occur in tunica media vasorum and tunica elastica interna. Johnson et al. [8] proposed that angiosteosis is an ectopic osteogenesis activity in vascular wall mediated by cells and regulated by various cytokines. The vascular smooth muscle cells of patients with atherosclerosis secrete type I, type III and type V collagens, thus causing thickening and blocking of the blood vessel wall. Type I collagen can accelerate the transformation of monocytes to macrophages, thereby resulting in the increase of lipid intake and the synthesis of metalloproteinase. After bonded with low density lipoprotein, type I collagen can promote the oxidative modification of low density lipoprotein, accelerate plaque formation, tuberoses and calcium intrusion and increase ALP activity, thus accelerating angiosteosis [9-10]. Higgins et al. [11] held that serum ALP level is related to hypertension, angiosteosis, inflammation, glucose metabolic disorders and insulin resistance, and participates in atherosclerosis. The study conducted by Tonelli et al. [12] showed that ALP level is a prognostic factor of myocardial infarction and peripheral

vascular diseases. During angiosteosis, endothelial cells, mesenchymal cells and hematopoietic stem cells interact with each other, react to mechanical stimulation, inflammation and metabolism, and activate the signals of bone morphogenesis. The interaction between these factors in the arterial wall can lead to angiosteosis.

Wu Youli et al. [13] have studied subcortical ischemic vascular disease. After the confounding factors were controlled, it was found that serum ALP level increased with aggravated cognitive impairment of subcortical ischemic vascular disease. After various vascular risk factors were corrected, the multiple regression analysis showed that the serum ALP level in patients with subcortical ischemic vascular disease increased significantly, the increase amount was positively correlated with the cognitive impairment of subcortical ischemic vascular disease, and it is especially true for patients with severe leukoaraiosis. Ryu et al. [14-15] studied 1,082 subjects with healthy nervous system and pointed out that high-level ALP is correlated with high signal intensity of the white matter; for cerebral small-vessel diseases, serum ALP level has joint effect with C-reactive protein, and the two are positively correlated with the high signal intensity of the white matter. The analysis of 2,029 patients showed that the increased level of ALP is an independent predictor of death caused by acute ischemia or hemorrhagic stroke. In 2016, Zhou Xia et al. [16] studied the changes in serum ALP level of patients with acute cerebral infarction, and found that serum ALP level is closely related to the area of cerebral infarction and the degree of neurological deficit. Xu Xiaolin et al. [17] made 90d of short-term prognosis, follow-up visit and investigation on 210 patients with acute cerebral infarction, and proposed that acute-phase ALP level is an independent risk factor for 90d-prognosis of patients with cerebral infarction. Kim et al.[18] made investigation on the ALP level of 1,034 patients with first-episode cerebral infarction within 3 months, and found that high-level ALP is an independent predictor of long-term functional prognosis. Perticone et al. [19] found though study that serum ALP level is positively correlated with the occurrence risk of vascular endothelial dysfunction and negatively correlated with endothelium dependent vasodilatation. Webber et al. [20] found in the American national health and nutrition survey that ALP level is closely related to age, waistline, blood pressure, exercise, ethyl alcohol and TG, and significantly correlated with the incidence of cardiovascular diseases, hypertension, hypercholesterolemia and diabetes.

The results of this study showed that the serum ALP level in cerebral infarction group was significantly higher than that in control group, serum ALP level is an influencing factor of cerebral infarction occurrence, and the difference in general factors such as gender, age, hypertension, type 2 diabetes, coronary heart disease, drinking and smoking between the two groups was not statistically significant; the levels of TG, TC and LDL-C in cerebral infarction group were higher than those in control group, the level of HDL-C was lower than that in control group, hypertension and LDL-C were risk factors of cerebral infarction occurrence, while HDL-C is a protective factor. The study conducted by Fan Liwei et al. [21] proved that the level of HDL with antioxidant ability, endothelial cell protective effect and anti-endothelial cell apoptosis function will decrease with age, and the decrease is especially obvious in females. Wang Yan, Zhang Ying et al. [22-23] respectively proposed that lipid metabolism disorder is an independent risk factor of poor early prognosis of patients with acute cerebral infarction, and hypertension control is an important measure to improve the long-term life quality of patients with first-episode ischemic cerebral infarction and hemi-limb dysfunction. NIHSS score is widely used to assess the severity degree of ischemic cerebral infarction [24], high NIHSS score means a large area of cerebral infarction and severe neurological deficit, and suggests the possibility of aorta stenosis or occlusion. Park et al. [25] made tertiles classification [<63U/L, (63-78) U/L, >78U/L] on ALP level of 1,636 patients who had coronary heart disease and adopted drug eluting stent, and studied the predictive value. The results showed that high serum ALP level is an independent predictor of patient mortality, myocardial infarction and stent thrombosis, and ALP level can predict the occurrence risk of coronary artery calcification.

To sum up, this study suggests that serum ALP level is an influencing factor of the occurrence of cerebral infarction. The occurrence risk of cerebral infarction when ALP>86 U/L is 1.58 times that when ALP<67 U/L; the correlation analysis result showed that there is a positive correlation between NIHSS score and serum ALP level of cerebral infarction patients, indicating that the degree of neurological deficit of the patients is aggravated with the increase in serum ALP level. This suggests that the change in serum ALP level of patients with acute cerebral infarction may be a serum marker for the prediction on the degree of neurological deficit. Monitoring serum ALP level is beneficial to evaluate the change in patients' condition and the prognosis.

Declarations

Funding

This study does not need any fund support, and all the work is completed within the normal work content and time. The data used in the study is also easy to access.

Conflicts of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of this manuscript.

Ethics approval and consent to participate

We declare that all human participants, human material, and human data, have been approved by Yantaishan Hospital Ethics Committee and Yantai Medical Ethics Committee (the reference number: 2008027) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We have to state that specific national laws have been observed, too. The informed consent of all subjects and/or their legal guardians has been obtained for all procedures performed in this study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

Conceptualization : Ji-ming Zou, Xiao-yu Li, Chao Han.
Data curation : Xiao-yu Li.
Investigation : Ji-ming Zou.
Methodology : Ji-ming Zou, Chao Han.
Writing – original draft: Ji-ming Zou, Xiao-yu Li.
Writing – review & editing: Ji-ming Zou, Xiao-yu Li, Chao Han.

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Consent for publication （Not Applicable）

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