eNeurologicalSci 20 (2020) 100253

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Letter to the Editor

Increased serum alkaline phosphatase and early neurological deterioration in patients with atherothrombotic brain infarction attributable to intracranial atherosclerosis

ARTICLE INFO

Keywords:
Alkaline phosphatase
Early neurological deterioration
Intracranial atherosclerosis

ABSTRACT

Objective: The purpose of this study was to determine whether increased alkaline phosphatase (ALP) was associated with early neurological deterioration (END) in patients with atherothrombotic brain infarction (ATBI) attributable to intracranial atherosclerosis (ICAS) or not.

Methods: We analyzed data derived from 70 patients (47 men; mean age, 72.4 ± 12.8 years) with symptomatic ICAS who were admitted within 3 days of ATBI onset between April 2013 and December 2018. We defined END as an increase of ≥2 in the National Institutes of Health Stroke Scale scores during the first 72 h of hospitalization.

Results: Eleven (15.7%) patients had END. Serum ALP levels on admission were significantly higher among patients with, than without END (median [interquartile range], 296 [233–338] vs. 216 [187–262] U/L, $p = .0081$).

Conclusion: Increased serum ALP levels on admission may be able to predict developing END in patients with symptomatic ICAS.

1. Introduction

The effects of alkaline phosphatase (ALP) in patients with cardiovascular disease have recently been highlighted. Epidemiological studies have demonstrated that elevated ALP was associated with the presence of atherosclerosis in the coronary and peripheral arteries, increased cardiovascular events, and increased mortality rates [1,2]. High serum ALP levels were also associated with functional outcomes and mortality after acute stroke [3,4]. We previously found that high serum ALP level on admission was a predictor of subsequent ischemic stroke events in patients with transient ischemic attack (TIA) attributable to intracranial atherosclerosis (ICAS) [5]. Lee et al. reported that ICAS was associated with early neurological deterioration (END) in patients with acute ischemic stroke [6]. Therefore, it is clinically important to clarify predictors of END in patients with symptomatic ICAS. The purpose of this study was to determine whether increased ALP was associated with END in patients with atherothrombotic brain infarction (ATBI) attributable to ICAS or not.

2. Materials and methods

2.1. Patient selection

We selected 70 patients (47 men; mean age, 72.4 ± 12.8 years) with ATBI caused by ICAS who were admitted within 3 days of onset between April 2013 and December 2018. ATBI was diagnosed according to the TOAST (Trial of Org 10,172 in Acute Stroke Treatment) classification [7]. We defined significant ICAS as ≥50% stenosis or occlusion of the intracranial arteries detected by magnetic resonance angiography (MRA). Affected intracranial vessels included the internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), vertebral artery (VA), basilar artery (BA), and posterior cerebral artery (PCA). Patients with confirmed cervicocephalic artery disease other than atherosclerosis (including dissection and cerebral angiitis) and potential sources of cardioembolism, such as atrial fibrillation, were excluded. The study protocol was approved by the Institution's ethics committee.

2.2. Patients' characteristics

We collected the following demographic and clinical characteristics of the patients from medical records: sex, age, prior ischemic stroke, prior ischemic heart disease, hypertension (blood pressure ≥ 140/90 mmHg or under antihypertensive medication), diabetes mellitus (fasting blood glucose ≥126 mg/dL, positive 75-g oral glucose tolerance test findings, or under insulin or oral hypoglycemic agents), and dyslipidemia (serum low-density lipoprotein cholesterol [LDL-Chol] ≥ 140 mg/dL, high-density lipoprotein cholesterol [HDL-Chol] < 40 mg/dL, triglycerides [TG] ≥ 150 mg/dL, or under antidyslipidemic medication), and current cigarette smoking.

2.3. Blood tests

Peripheral venous blood samples were obtained on admission. Tests included hematocrit, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase (ALP), LDL-Chol, HDL-Chol, TG, glucose, hemoglobin A1c, C-reactive protein, and D-dimer. We calculated estimated glomerular filtration rates using the formula of the Japanese Society of Nephrology [8].

2.4. Clinical outcomes

The outcome measure of the study was END defined as an increase

https://doi.org/10.1016/j.ensci.2020.100253
Received 1 April 2020; Received in revised form 21 June 2020; Accepted 30 June 2020
Available online 06 July 2020

in National Institutes of Health Stroke Scale (NIHSS) scores of ≥2 during the first 72 h of hospitalization.

2.5. Statistical analysis

Data were statistically analyzed using JMP® 12 software (SAS Institute Inc., Cary, NC, USA). Continuous variables were expressed as means ± standard deviation (age and blood pressure on admission), or as medians with interquartile ranges (IQR) (blood findings and NIHSS scores). Categorical data were summarized as ratios (%). Differences between patients with and without END were analyzed using Student *t*-tests and Mann-Whitney *U* tests for continuous values and Pearson chi-squared and Fisher exact tests for categorical variables as appropriate. Values with $p < .05$ were considered as being statistically significant.

3. Results

Forty-six patients had symptomatic ICAS in the MCA, 12 in the ICA, 8 in the BA, and 4 in the PCA. Among 11 (15.7%) patients with END, follow-up MRI showed increased numbers of infarctions in five patients, enlarged infarctions in two, and both increased and enlarged infarctions in four. Infarcts in all 11 patients were located in the territory of arteries with occlusive lesions that were responsible for the neurological symptoms of the qualifying ATBI.

Table 1 compares the characteristics of patients with and without END. Serum ALP levels on admission were significantly higher among patients with, than without END (as shown in Table 1 and Fig. 1). Serum ALP level was an independent predictor of END (odds ratio: 1.0120, 95% confidence interval: 1.0027–1.0235, $p = .0109$) after adjusting for age, sex and baseline NIHSS.

When symptomatic ICAS was divided into stenosis and occlusion, 7 of 58 patients with stenosis had END and 4 of 12 patients with occlusion had END. Serum ALP levels on admission were significantly higher among patients with, than without END (median [interquartile range], 313 [280–338] vs. 216 [187.5–261.75] U/L, $p = .0008$) in cases with stenosis. On the other hand, there was no difference in serum ALP levels on admission between patients with and without END (median [interquartile range], 224.5 [165.5–327.75] vs. 215 [125–270] U/L, $p = .7055$) in cases with occlusion.

Table 1
Characteristics of patients with and without early neurological deterioration.

	Early neurological deterioration		
	With	Without	p
	(*n* = 11)	(*n* = 59)	
Background characteristics			
Male, n (%)	6 (54.6)	41 (69.5)	0.4853
Age, years, mean (SD)	75.1 (14.6)	71.9 (12.5)	0.4576
History of			
Ischemic stroke, n (%)	2 (18.2)	7 (11.9)	0.6249
Ischemic heart disease, n (%)	0 (0.0)	8 (13.6)	0.3400
Hypertension, n (%)	9 (81.8)	39 (66.1)	0.4825
Diabetes mellitus, n (%)	5 (45.5)	20 (33.9)	0.5056
Dyslipidemia, n (%)	5 (45.5)	23 (39.0)	0.7447
Current smoking, n (%)	2 (18.2)	18 (30.5)	0.4935
Premorbid			
Antiplatelet agents, n (%)	2 (18.2)	13 (22.0)	1.0000
Antihypertensive agents, n (%)	7 (63.6)	33 (55.9)	0.7472
Hypoglycemic agents, n (%)	5 (45.5)	14 (23.7)	0.1548
Statin, n (%)	4 (36.4)	14 (23.7)	0.4561
NIHSS, median (IQR)	3 (2–6)	3 (1–5)	0.6950
SBP on admission, mmHg, mean (SD)	171.6 (33.9)	164.1 (28.7)	0.4421
DBP on admission, mmHg, mean (SD)	88.5 (20.1)	87.8 (15.5)	0.8837
Blood test findings, median (IQR)			
Hematocrit, %	41.4 (36.1–42.8)	41.2 (38.3–43.9)	0.3492
Aspartate aminotransferase, U/L	19 (14–23)	18 (16–23)	0.9161
Alanine aminotransferase, U/L	12 (8–36)	15 (10 − 21)	0.6567
γ-glutamyl transpeptidase, U/L	29 (17–45)	24.5 (17–33)	0.7605
Lactate dehydrogenase, U/L	194 (180–256)	192 (168–210)	0.2867
Alkaline phosphatase, U/L	296 (233–338)	216 (187–262)	0.0081
eGFR	70.2 (58.8–78.7)	62.6 (53.3–70.6)	0.1175
LDL-cholesterol, mg/dL	103 (88–134)	125 (93–145)	0.2485
HDL-cholesterol, mg/dL	42 (38–54)	42 (37–54)	0.8844
Triglyceride, mg/dL	122 (56–165)	117 (80.5–211)	0.4790
Glucose, mg/dL	136 (117–158)	124 (104–163)	0.3492
Hemoglobin A1c, %	6.25 (5.775–7.425)	6.05 (5.7–6.625)	0.4364
CRP, mg/dL	0.37 (0.08–2.24)	0.18 (0.06–0.34)	0.1011
D-dimer, ng/mL	1 (0.7–3.6)	0.8 (0.6–1.2)	0.2131

SD indicates standard deviation; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein.

4. Discussion

This study showed an association between increased serum ALP levels and END in patients with ATBI attributable to ICAS. Zhong et al. identified a graded relationship between serum ALP levels and risk of early death in patients with acute ischemic stroke [9]. In the China National Stroke Registry, high serum ALP levels were correlated with increased risk of all-cause mortality, stroke recurrence, composite end point, and poor functional outcomes in patients with stroke and preserved kidney function [10]. The activity of ALP serves as a molecular marker of vascular calcification, which plays significant roles in the process of atherosclerosis and leads to increased vascular stiffness as well as reduced vascular compliance [10]. Furthermore, ALP has also been considered to represent a surrogate marker of systemic inflammation, malnutrition, and metabolic syndrome, which might result in worsened clinical outcomes among patients with stroke [3].

Notably, ALP is induced by oxidative stress in vascular tissue and bone. An autopsy study has revealed that the intracranial arteries were susceptible to oxidative stress and are predisposed to respond with accelerated atherogenesis when antioxidant protection is decreased [11]. In our study, follow-up MRI showed increased number of infarction in 9 patients of 11 patients with END. When symptomatic ICAS was divided into stenosis and occlusion, serum ALP levels on admission were significantly higher among patients with, than without END in cases with stenosis. On the other hand, there was no difference in serum ALP levels on admission between patients with and without END in cases with occlusion. These findings of our study suggested that ENDs were mainly attributable to artery-to-artery re-embolism from the vulnerable plaque of symptomatic ICAS, not hemodynamic mechanism due to occlusion, and that increased ALP levels served as a surrogate marker of plaque instability in symptomatic ICAS. However, in contrast to our findings, two studies did not find an association between increased serum ALP and either the presence or the severity of intracranial arterial stenosis [3,12]. Larger studies are needed to confirm the present findings.

This study has several limitations. The sample size was too small to avoid type 1 and type 2 errors. We retrospectively analyzed data derived only from inpatients with symptomatic ICAS, which might have led to selection bias, and the study proceeded at a single center. Therefore, the present findings require confirmation by large multicenter studies to determine whether they can be generalized.

In conclusion, increased serum ALP levels on admission may be able to predict developing END in patients with symptomatic ICAS. The results of this study suggest that aggressive therapeutic strategies in the

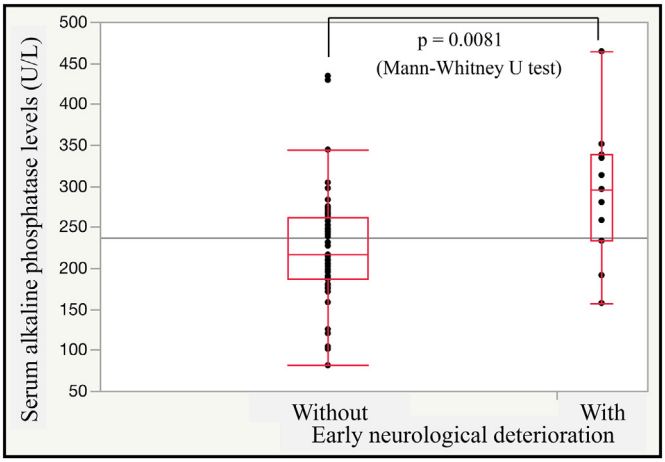

Fig. 1. Serum alkaline phosphatase levels on admission between patients with and without early neurological deterioration. Boxes represent interquartile range; Lines in boxes, median values; Whiskers, 10th and 90th percentiles.

hyper acute phase of stroke are necessary to avoid END if serum ALP level is elevated in patients with symptomatic ICAS.

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