Clinica Chimica Acta 433 (2014) 174–178

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Prognostic significance of plasma copeptin detection compared with multiple biomarkers in intracerebral hemorrhage

Wen-Hua Yu [a,1], Wen-Hong Wang [b,1], Xiao-Qiao Dong [a,*], Quan Du [a], Ding-Bo Yang [a], Yong-Feng Shen [a], Hao Wang [a], Zu-Yong Zhang [a], Qiang Zhu [a], Zhi-Hao Che [a], Qun-Jie Liu [a], Li Jiang [a], Yuan-Feng Du [a]

[a] Department of Neurosurgery, The First People's Hospital of Hangzhou, Nanjing Medical University, 261 Huansha Road, Hangzhou 310006, China
[b] Department of Neurosurgery, The Affiliated Zhongda Hospital of Southeast University, 87 Dingjiaqiao Road, Nanjing, 210009, China

ARTICLE INFO

Article history:
Received 26 February 2014
Received in revised form 11 March 2014
Accepted 13 March 2014
Available online 20 March 2014

Keywords:
Intracerebral hemorrhage
Prognosis
Copeptin
Biomarkers

ABSTRACT

Background: Higher plasma copeptin concentrations have been associated with poor clinical outcomes after intracerebral hemorrhage. This study was designed to compare plasma concentrations of copeptin and other biomarkers like myelin basic protein, glial fibrillary astrocyte protein, S100B, neuron-specific enolase, phosphorylated axonal neurofilament subunit H, tau and ubiquitin carboxyl-terminal hydrolase L1 for analysis of their prognostic prediction.
Methods: We measured plasma concentrations of these biomarkers in 118 healthy controls and in 118 acute patients with a comparison analysis for their prediction of 6-month mortality and unfavorable outcome (modified Rankin Scale score > 2).
Results: Plasma concentrations of these biomarkers were statistically significantly higher in all patients than in healthy controls, in non-survivors than in survivors and in patients with unfavorable outcome than with favorable outcome. Areas under receiver operating characteristic curves of plasma concentrations of these biomarkers were similar to those of the National Institute of Health Stroke Scale score for prognostic prediction. Plasma copeptin concentration statistically significantly improved the prognostic predictive value of the National Institute of Health Stroke Scale score, but other biomarkers did not.
Conclusions: Copeptin may help in the prediction of long-term clinical outcomes after intracerebral hemorrhage.

1. Introduction

Intracerebral hemorrhage (ICH) is associated with high mortality and poor clinical outcomes [1]. After ICH, the early prediction of death or disability is of great interest [2]. During the last decade, neurobiochemical markers in ICH patients have attracted increased attention [3]. Hemorrhagic injury to the central nervous system causes cellular activation and disintegration, leading to the release of cell-type-specific proteins such as myelin basic protein (MBP), glial fibrillary astrocyte protein (GFAP), the calcium-binding protein S100B, neuron-specific enolase (NSE), phosphorylated axonal neurofilament subunit H (pNF-H), tau protein and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1). These damage biomarkers are released into the cerebrospinal fluid and escapes into the circulation after ICH-induced disruption of the blood–brain barrier. Therefore, measurable amounts of these damage biomarkers are present in blood and reflect cerebral pathological changes and independently predict death or disability of ICH [4–15].

Vasopressin is a key regulator of body fluid homeostasis [16]. The co-secreted protein copeptin serves as a surrogate for vasopressin release [17,18]. Copeptin is known to have prognostic value in a variety of diseases including ischemic stroke, ICH, traumatic brain injury and aneurysmal subarachnoid hemorrhage [19–23]. However, to our best knowledge, there is a paucity of available data in the literature on the comparisons between copeptin and other biomarkers including NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 for the prediction of long-term clinical outcome in patients with ICH. We measured in this study the plasma concentrations of copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 in acute ICH with a comparison analysis for their prediction of 6-month mortality and poor functional outcome.

2. Materials and methods

2.1. Study population

This study prospectively included these patients with acute spontaneous basal ganglia hemorrhage admitted to the emergency room at The First People's Hospital of Hangzhou within 6 h from symptoms onset between January 2010 and January 2013, and excluded those patients under

* Corresponding author. Tel.: +86 571 56006971; fax: +86 571 56005600.
E-mail address: dxqhyy@163.com (X.-Q. Dong).
[1] Wen-Hua Yu and Wen-Hong Wang contributed equally to this work.

http://dx.doi.org/10.1016/j.cca.2014.03.014
0009-8981/

Table 1
The change of plasma biomarkers levels in patients with intracerebral hemorrhage compared with healthy controls.

Variables	Patients	Healthy controls	*P* value
Copeptin (pg/ml)	2500.7 ± 832.9	388.6 ± 134.5	<0.001
NSE (ng/ml)	14.4 ± 5.7	3.3 ± 1.1	<0.001
S100B (pg/ml)	493.6 ± 230.5	46.8 ± 16.7	<0.001
MBP (μg/ml)	13.8 ± 4.9	2.8 ± 1.1	<0.001
GFAP (pg/ml)	10.3 ± 3.9	1.9 ± 0.7	<0.001
Tau (pg/ml)	230.3 ± 102.7	10.8 ± 8.7	<0.001
pNF-H (pg/ml)	753.2 ± 191.1	17.6 ± 15.8	<0.001
UCH-L1 (pg/ml)	2270.6 ± 1295.2	203.6 ± 64.9	<0.001

Intergroup comparisons were analyzed using *t* test. NSE indicates neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1.

Table 2
The change of plasma biomarkers levels in non-survivors compared with survivors.

Variables	Non-survivors	Survivors	*P* value
Copeptin (pg/ml)	3183.9 ± 897.9	2188.6 ± 580.7	<0.001
NSE (ng/ml)	18.5 ± 5.3	12.5 ± 4.9	<0.001
S100B (pg/ml)	646.5 ± 186.2	423.7 ± 215.2	<0.001
MBP (μg/ml)	17.6 ± 6.1	12.1 ± 3.0	<0.001
GFAP (pg/ml)	13.2 ± 3.8	8.9 ± 3.1	<0.001
Tau (pg/ml)	299.1 ± 75.7	198.8 ± 98.2	<0.001
pNF-H (pg/ml)	889.6 ± 147.1	690.9 ± 176.5	<0.001
UCH-L1 (pg/ml)	3042.2 ± 1356.9	1918.2 ± 1106.3	<0.001

Intergroup comparisons were analyzed using student's *t* test. NSE indicates neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1.

use of antiplatelet or anticoagulant medication, with existing previous neurological disease and head trauma, with presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart disease and chronic lung disease, undergoing a surgical procedure, having unavailable biomarkers measurements and with missing of follow-up. Healthy individuals were evaluated as controls if they presented to our hospital and had blood collected as part of medical examination on January 2013. The study was conducted in accordance with the guidelines approved by the Human Research Ethics Committee at The First People's Hospital of Hangzhou. Written informed consent was obtained from study populations or family members.

2.2. Clinical and radiological assessment

On arrival at the emergency department, a detailed history of vascular risk factors, concomitant medication, body temperature, heart rate, respiratory rate, and blood pressure were taken. The National Institute of Health Stroke Scale (NIHSS) score was assessed. All computed tomographic scans were performed according to the Neuroradiology Department protocol. The investigators who read them were blinded to clinical information. Hematoma volume was measured according to the previously reported formula $A \times B \times C \times 0.5$ [24]. The presence of intraventricular extension of hematoma was also recorded on initial computed tomographic scan. The endpoint of this study was 6-month mortality and unfavorable outcome (modified Rankin Scale score > 2).

2.3. Immunoassay methods

Venous blood was drawn for patients on admission and for healthy controls at study entry. The blood samples were immediately placed into sterile EDTA test tubes and centrifuged at 3000 ×*g* for 30 min at 4° to collect plasma. Plasma was stored at −70 °C until assayed. The plasma concentrations of copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 were analyzed by enzyme-linked immunosorbent assay using commercial kits (Phoenix Pharmaceuticals) in accordance with the manufactures' instructions. The individual carrying out the assays was completely blinded to the clinical information.

2.4. Statistical analysis

Statistical analysis was done using the SPSS 19.0 statistical package (SPSS Inc.) and MedCalc 9.6.4.0 (MedCalc Software). The categorical variables are presented as counts (percentage), and the continuous variables are presented as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Statistical significance for intergroup differences was assessed by χ^2 or Fisher exact test for categorical variables, and by Student's *t*, Mann–Whitney *U* test for continuous variables. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of plasma copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 concentrations that optimally predicted the 6-month mortality and unfavorable outcome with calculated area under curve (AUC). A combined logistic-regression model was configured to estimate the additive benefit of copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 to NIHSS score. Comparisons of AUCs were performed using *z* test. A *P* value < 0.05 was considered significant.

3. Results

3.1. Study population's characteristics

One hundred and eighteen patients were enrolled, including 72 men and 46 women. The mean age was 64.1 ± 9.1 years (range, 48–79 years). 103 patients (87.3%) had hypertension. Thirty patients (25.4%) had diabetes mellitus. The mean admission time was 2.8 ± 1.2 h (range, 0.5–6 h). The median NIHSS score was 15 (range, 5–23). The median ICH volume was 30 ml (range, 5–60 ml). 42 patients (35.6%) had the presence of intraventricular extension of hematoma. The mean systolic arterial pressure was 169.9 ± 28.3 mm Hg (range, 110–235 mm Hg). The mean diastolic arterial pressure was 90.9 ± 11.7 mm Hg (range, 64–124 mm Hg). The mean plasma-sampling time was 4.5 ± 1.7 h (range, 1.0–9.0). 118 controls were enrolled,

Table 3
Comparisons of AUCs for the prediction of 6-month mortality after intracerebral hemorrhage.

Variables	AUC	95% CI	Criterion	Sensitivity	Specificity	*P* value
NIHSS score	0.849	0.772–0.908	>15	81.1%	74.1%	Ref.
Copeptin	0.829	0.749–0.892	>2518.2 pg/ml	78.4%	74.1%	NS
NSE	0.792	0.708–0.861	>14.5 ng/ml	78.4%	66.7%	NS
S100B	0.813	0.731–0.879	>470.7 pg/ml	83.8%	72.8%	N
MBP	0.787	0.702–0.857	>13.3 μg/ml	75.7%	70.4%	NS
GFAP	0.805	0.722–0.872	>11.7 pg/ml	67.6%	87.7%	NS
Tau	0.794	0.710–0.863	>240.2 pg/ml	86.5%	69.1%	NS
pNF-H	0.803	0.720–0.871	>816.3 pg/ml	73.0%	75.3%	NS
UCH-L1	0.770	0.683–0.842	>2039.9 pg/ml	70.3%	75.3%	NS

Comparisons of AUCs for the prediction of 6-month mortality after intracerebral hemorrhage were based on receiver operating characteristic curves and analyzed using *z* test. NIHSS indicates National Institutes of Health Stroke Scale; AUC, area under curve; NSE, neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; Ref., reference.