Journal of the Neurological Sciences 359 (2015) 298–304

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Serum caspase-cleaved cytokeratin-18 levels and outcomes after aneurysmal subarachnoid hemorrhage

Zi-Gang Yuan, Jian-Li Wang *, Guo-Liang Jin, Xue-Bin Yu, Jin-Quan Li, Tian-Lun Qiu, Rong-Xiao Dai

Department of Neurosurgery, Shaoxing People's Hospital, Shaoxing Hospital of Zhejiang University, 568 Zhongxing North Road, Shaoxing 312000, Zhejiang Province, China

ARTICLE INFO

Article history:
Received 25 September 2015
Received in revised form 3 November 2015
Accepted 11 November 2015
Available online 12 November 2015

Keywords:
Caspase-cleaved cytokeratin-18
Subarachnoid hemorrhage
Aneurysm
Prognosis
Biomarker
Mortality
Functional outcome

ABSTRACT

Objective: Cell apoptosis is involved in acute brain injury after aneurysmal subarachnoid hemorrhage (aSAH). The protein cytokeratin-18 (CK-18) is cleaved by the action of caspases during apoptosis, and the resulting fragments are released into the blood as caspase-cleaved CK (CCCK)-18. Our study examined the relationship between circulating CCCK-18 levels and long-term clinical outcomes among aSAH patients.
Methods: We recruited 128 aSAH patients and 128 controls (matched on age and sex). Serum was collected at admission to the emergency department. Unfavorable outcome was defined as the Glasgow Outcome Score scores of 1–3. After a 6-month follow-up period, outcomes were assessed using a logistic regression analyses. The prognostic predictive values were evaluated according to receiver operating curves analysis.
Results: aSAH patients had higher plasma CCCK-18 levels compared to controls (235.1 ± 86.8 U/L vs. 25.6 ± 23.4 U/L, $P < 0.001$). CCCK-18 was independently associated with World Federation of Neurological Surgeons (WFNS) scores ($t = 4.460$, $P < 0.001$) and modified Fisher scores ($t = 3.781$, $P < 0.001$). Furthermore, CCCK-18 levels were markedly higher among patients with an unfavorable outcome and among non-survivors. CCCK-18 was yet identified as an independent prognostic predictor for mortality (odds ratio, 5.769; 95% confidence interval, 1.196–27.832; $P = 0.029$) and unfavorable outcome (odds ratio, 4.909; 95% confidence interval, 1.521–15.838; $P = 0.008$), as well as had similar predictive values for them compared with WFNS scores and modified Fisher scores.
Conclusions: High circulating CCCK-18 levels were associated with injury severity and a poor clinical outcome after aSAH and CCCK-18 had the potential to be a good prognostic biomarker for aSAH.
© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Patients with aneurysmal subarachnoid hemorrhage (aSAH) account for a considerable group of patients admitted to an emergency department [1,2]. Because it affects a younger population, the proportion of the potential of years of life lost with aSAH is equivalent to that of the patients with ischemic stroke and intracerebral hemorrhage [3,4]. Brain injury begins early after aSAH [5]. An early activation of endothelial and parenchymal cell apoptosis and neuronal necrosis after SAH has been demonstrated [6]. Cytokeratin-18 (CK-18) is a protein of the intermediate filament group present in most epithelial and parenchymal cells [7]. During apoptosis, CK-18 is cleaved at various sites by the action of caspases, and the resulting fragments, called caspase-cleaved CK (CCCK)-18, are released into the blood [8]. Circulating CCCK-18 levels have been studied in patients with apoptosis-related diseases [9–15]. Moreover, circulating CCCK-18 was identified to be a superior marker as compared to creatine kinase and troponin T, for detection of myocardial damage in patients with acute myocardial infarction [16]. Elevated CCCK-18 levels in tumor cytosol can predict the poor survival in patients with breast cancer [17]. Recently, it is confirmed that serum CCCK-18 levels are associated with 30-day mortality after severe traumatic brain injury [18], suggesting that CCCK-18 could be used as a prognostic biomarker in patients with acute brain injury. However, they have not been explored in aSAH patients. Thus, the aim of this study was to determine whether there is an association between serum CCCK-18 levels and long-term clinical outcomes including mortality and functional outcome as well as whether such levels could be used as a biomarker to predict outcomes in aSAH patients.

2. Methods

2.1. Study population

In this prospective and observatory study, consecutive aSAH patients were enrolled at the Shaoxing People's Hospital between June 2011 and June 2014. Patients were initially assessed based on the following inclusion criteria: the first-ever non-traumatic SAH, the clinical history of

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; AUC, area under curve; CCCK-18, caspase-cleaved cytokeratin-18; CI, confidence interval; CT, computerized tomography; ELISA, enzyme-linked immunosorbent assay; GCS, Glasgow coma scale; GOS, Glasgow outcome scale; ROC, receiver operating characteristic; WFNS, World Federation of Neurological Surgeons.

* Corresponding author.
E-mail address: sxwjlszg@163.com (J.-L. Wang).

http://dx.doi.org/10.1016/j.jns.2015.11.020
0022-510X/© 2015 Elsevier B.V. All rights reserved.

SAH within the last 24 h before admission, the single intracranial aneurysms confirmed by computerized tomography (CT) angiography with or without digital subtraction angiography and the treatment through clipping or coiling within the 48 h after admission. Exclusion criteria included rebleeding after admission, suspected pseudoaneurysm, less than 18 years of age, a history of traumatic injuries, recent (within 1 month) infectious diseases, previous neurological diseases like intracerebral hemorrhage and ischemic stroke, previous use of antiplatelet or anticoagulant medication, and other prior systemic diseases such as uremia, liver cirrhosis, malignancy, chronic heart disease, chronic lung disease, diabetes mellitus and hypertension. We also excluded those patients with unavailable biomarker measurements, refusal of participation and loss of follow-up. Healthy controls were recruited from the same hospital as well as were age- and gender- matched to the aSAH patients. This study was approved by the ethic committee of the Shaoxing People's Hospital and the relatives of all patients and the controls signed consent forms.

2.2. Assessment

Recorded data included age, gender, aneurysm distribution, mode of aneurysm treatment including clipping or coiling, hydrocephalus, symptomatic cerebral vasospasm, World Federation of Neurological Surgeons (WFNS) grade [19] and modified Fisher grade [20]. Symptomatic cerebral vasospasm was defined as the development of new focal neurological signs, deterioration in level of consciousness, or the appearance of new infarction on CT when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening (e.g. hydrocephalus, seizures, metabolic derangement, infection, or oversedation) had been excluded [21,22].

2.3. Outcome

The clinical endpoint was death and unfavorable outcome within 6-months after SAH. The functional outcome was defined by Glasgow outcome scale (GOS) score. GOS was defined as follows: 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery. Unfavorable outcome was defined as Glasgow outcome scale score of 1–3 [23]. For follow-up, we used structure telephone interviews performed by 1 doctor, blinded to clinical information.

2.4. Sampling and laboratory analysis

Samples were collected from the patients at admission to the emergency department and from the healthy controls at study entry and were stored at −70 °C until measurement. Serum CCCK-18 concentrations were analyzed in duplicate by enzyme-linked immunosorbent assay (ELISA) using M30 Apoptosense ELISA (PEVIVA AB, Bromma, Sweden) in accordance with the manufactures' instructions. Samples were all processed by the same laboratory technician using the same equipment and blinded to all clinical data. The detection limit for the assay was 25 U/L. Thus, all values less than 25 U/L were regarded as zero.

2.5. Statistical analysis

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0 (MedCalc Software, Mariakerke, Belgium) were used to analyze data. Serum CCCK-18 concentrations were analyzed in duplicate in this study and their mean values were accepted for the statistical analysis. The normality of data distribution was assessed by the Kolmogorov–Smirnov test or Shapiro–Wilk test. The categorical variables are presented as frequency and percentage. And the continuous variables are presented as mean ± standard deviation or median (percentile 25–75). For comparison of data between two groups, the significances of inter-group differences were assessed using chi-square test or Fisher exact test for categorical data as well as Student *t* test or Mann–Whitney U test for continuous variables. Bivariate correlations were analyzed by Spearman's correlation coefficient or Pearson's correlation coefficient and then followed by a multivariate linear regression. A logistic regression model was used to identify independent predictors with respect to 6-month mortality and unfavorable outcome. Cutoff values of serum CCCK-18 levels were obtained automatically from receiver operating characteristic (ROC) curves with optimal prognostic predictive sensitivities and specificities. Bonferroni correction was used for the multiple testing. The variables, that univariate analyses revealed to be associated with poor prognosis, were incorporated into multivariate model. All *P* values lower 0.05 were considered statistically significant.

3. Results

3.1. Patients characteristics

During the study period, 174 patients were initially assessed. 46 patients were excluded because of the reasons in Fig. 1. Eventually, 128 aSAH patients were included in this study. The original 174 patients were composed of 99 (56.9%) males and 75 (43.1%) females, and have a mean age of 42.1 ± 10.9 years (range: 22–70 years); the excluded 46 patients, with a mean age of 43.2 ± 12.1 years (range: 22–68 years), included 26 (56.5%) males and 20 (43.5%) females; this group of the eligible 128 aSAH patients consisted of 73 (57.0%) males and 55 (43.0%) females, as well as was aged 41.6 ± 11.6 years (range: 23–70 years). There were no significant differences in gender and age among the three groups.

In addition, among this group of the eligible aSAH patients, the admission median WFNS score was 3 (2–3) (range: 1–5) and the admission median Fisher score was 3 (2–3) (range: 2–5). Aneurysmal location is as follows: 35 (27.3%) aneurysms were located at posterior communication artery; 21 (16.4%) aneurysms, internal carotid artery; 31 (24.3%) aneurysms, anterior communication artery; 21 (16.4%) aneurysms, middle cerebral artery; 14 (10.9%) aneurysms, anterior cerebral artery; 5 (3.9%) aneurysms, posterior cerebral artery; 1 (0.8%) aneurysms, vertebral artery. In terms of modes of treatment, 82 (64.1%) patients underwent clipping and 46 (35.9%) patients obtained endovascular coiling. Among these patients, 28 (21.9%) patients had acute hydrocephalus; 17 (13.3%) patients, intraventricular hemorrhage; 37 (28.9%) patients, symptomatic cerebral vasospasm; 31 (24.2%) patients, accepted external ventricular drain. The mean admission time was 10.1 ± 4.1 h (range: 1.0–23.0 h); the mean plasma-sampling time, 12.7 ± 4.7 h (range: 1.5–25.5 h); the mean systolic blood pressure, 146.2 ± 25.9 mmHg (range: 90–200 mmHg); the mean diastolic blood pressure, 89.4 ± 14.2 mmHg (range: 50–120 mmHg); the mean blood glucose level, 12.3 ± 4.6 mmol/L (range: 2.5–23.4 mmol/L); the mean plasma C-reactive protein level, 14.3 ± 3.9 mg/L (range: 4.5–24.4 mg/L).

3.2. The change of serum CCCK-18 levels in aSAH patients

The admission CCCK-18 levels were significantly elevated in all patients (235.1 ± 86.8 U/L) compared with healthy controls (25.6 ± 23.4 U/L, $P < 0.001$). The results of sub-population analysis for CCCK-18 concentrations at admission showed that the patients with an unfavorable outcome revealed markedly higher CCCK-18 concentrations ($P < 0.001$). The values in the patients with an unfavorable outcome were 288.0 ± 75.2 U/L compared to 212.7 ± 81.8 U/L in the patients with a favorable outcome. Similar result was found in non-survivors and survivor of the patients with aSAH (310.1 ± 85.1 U/L vs. 222.8 ± 81.0 U/L, $P < 0.001$). These comparisons were depicted in Fig. 2.

3.3. Correlation analysis

Just shown in Table 1, CCCK-18 levels were highly associated with WFNS scores, Modified Fisher scores, acute hydrocephalus,

Download English Version:

https://daneshyari.com/en/article/8275549

Download Persian Version:

https://daneshyari.com/article/8275549

Daneshyari.com