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Serum neuron specific enolase level as a predictor of prognosis in acute ischemic stroke patients after intravenous thrombolysis

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ABSTRACT

Objective: Serum neuron specific enolase (NSE) concentrations are significantly correlated with stroke severity and clinical outcome in ischemic stroke patients. We aimed to determine whether the serum levels of neuron specific enolase in acute ischemic stroke (AIS) patients after intravenous thrombolysis are associated with stroke severity, and indicative of favorable outcome.

Methods: We prospectively analyzed the serum neuron specific enolase levels with for 67 subjects with AIS patients treated with intravenous recombinant tissue type plasminogen activator (rtPA) within 4.5 h from symptom onset. Neurologic deficit was assessed by the National Institutes of Health Stroke Scale. Clinical outcome was assessed after 90 days according to the modified Rankin Scale.

Results: Neuron specific enolase levels correlated with National Institutes of Health Stroke Scale score 24 h after rtPA bolus ($R = 0.342$, $p = 0.005$). Regarding the 67 included patients, 32 (47.8%) reached favorable outcome. They had a lower NIHSS score on admission ($p = 0.000$) and at 24 h after rtPA bolus ($p = 0.000$), and had lower levels of neuron specific enolase ($p = 0.006$). But only NIHSS score at 24 h after rtPA bolus rather than neuron specific enolase level was an independent predictor for favorable outcome.

Conclusion: We found that after treatment with intravenous rtPA therapy, lower serum neuron specific enolase levels were associated with favorable outcome, which may be confounded by the link to NIHSS score.

1. Introduction

Intravenous thrombolytic therapy with recombinant tissue type plasminogen activator (rtPA) improves clinical outcome after acute ischemic stroke within 4.5 h after symptom onset [1,2]. Previous studies have shown that severe stroke indicated by higher NIHSS score and larger infarct volume is a prognostic factor for unfavorable clinical outcome in patients with acute ischemic stroke treated with intravenous rtPA [3,4]. However, reperfusion of ischemic penumbral tissue has been considered as a good surrogate end point in response to intravenous rtPA in previous studies [5,6].

Despite advances in research during the past decades, predictors of clinical outcome represented by clinical data and advanced imaging characteristics remain inconclusive. Recently, neuro-biochemical markers have brought further insights to identify of stroke patients with severe neurological deficit and to predict clinical outcome after rtPA therapy. Neuron specific enolase (NSE) is the marker of brain damage that has been studied most often and mainly used for traumatic brain injury [7], stroke [8], and hypoxic encephalopathy [9]. NSE is the γγ-isoenzyme of the glycolytic enzyme enolase found mainly in the cytoplasm of neurons and cells of neuroendocrine origin [10]. When the plasma membrane is impaired functionally or structurally, NSE is released from damaged neurons [7–11].

Numerous studies focusing on NSE have been performed in acute ischemic stroke. Experimental studies that the NSE level increased in the middle cerebral artery occluded models and correlated positively with the volume of infarcted tissue [10]. Accordingly, clinical studies reported increased NSE serum levels in ischemic stroke patients and concluded that increased NSE concentrations are significantly correlated with volumes of infarcted brain areas, severity in acute ischemic stroke measured by NIHSS score, and poor functional outcome [10,12–14]. Previous studies have demonstrated that as the cells in the ischemic penumbra underwent necrosis, NSE levels changed dynamically after symptom onset [15]. In addition, lower NSE levels are associated with clinical–diffusion mismatch [16], a surrogate of salvageable ischemic tissue, which may be more likely to benefit from rtPA.

Thus, we aimed to determine the association of serum levels of neuron specific enolase 24 h after intravenous thrombolysis in acute ischemic stroke patients with functional outcome.

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2. Methods

2.1. Participants

This was a prospective study targeting consecutive patients with acute ischemic stroke treated with rtPA within the first 4.5 h after symptom onset between August 2013 and June 2015. Stroke onset was defined as the last time the patient was known to be without any neurological deficit. Inclusion and exclusion criteria for intravenous rtPA were used in accordance with those used in the ECASS III [1]. Eligible patients received 0.9 mg of alteplase (Actilyse, Boehringer Ingelheim, Ingelheim am Rhein, Germany) per kilogram, administered intravenously (with an upper limit of 90 mg). Informed consent was obtained from all patients or their next of kin. The study protocol was approved by the local ethics committee.

2.2. Measures

2.2.1. Demographic and medical history

On arrival to the emergency department, patients underwent standard neurological examinations, electrocardiogram, blood chemistry, and non-contrast computed tomography (CT). The following clinical data were collected from all patients: 1) patient age and gender; 2) degrees of neurological deficit evaluated by NIHSS score before and 24 h after rtPA infusion; 3) risk factors of stroke including history of hypertension (HTN), and diabetes mellitus (DM), and atrial fibrillation (AF); 4) laboratory parameters including glucose level, HbA1C before rtPA infusion; 5) modified Rankin Scale at 90 days evaluated by certified investigators after rtPA therapy; 6) intracranial hemorrhage at 24 h and mortality at 90 days.

2.2.2. Clinical assessment

The modified Rankin scale (mRS) was used to assess clinical outcome at 90 days. Outcome was dichotomized, favorable and unfavorable outcomes at 90 days after therapy were defined as a modified Rankin Scale of 0–1 and 2–6, respectively. And poor outcome with dependency in daily living was defined as a mRS score of 3–6. All patients underwent a CT scan at 24 h or whenever a neurological worsening occurred to evaluate the presence of intracranial hemorrhage (ICH). CT scans were reviewed by a neuroradiologist with extensive experience in acute stroke who was blinded to clinical details and laboratory data. Symptomatic intracranial hemorrhage was defined as any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in NIHSS score, or that led to death and that was identified as the predominant cause of the neurologic deterioration [1].

2.2.3. Laboratory test

All patients had baseline blood samples drawn in the emergency room, to determine baseline glucose levels and HbA1C. Neuron-specific enolase (NSE) levels were measured at 24 h after rtPA infusion. Blood samples, obtained from all patients, were collected in chemistry test tubes. After centrifugation, serum samples were separated, and kept frozen at −80 °C until assayed. Since NSE is also present in erythrocytes, hemolyzed samples were discarded. Serum levels of NSE were measured with commercially available quantitative enzyme-linked immunosorbent assay kits obtained from R&D Systems. Intra- and inter-assay coefficients of variation were <3% and <7%, respectively. And the minimum detection limits were 0.3 ng/mL for NSE. Determinations were performed in a laboratory blinded to clinical data.

2.3. Statistical analysis

The analysis was performed with SPSS 16.0 software (SPSS Inc). Continuous variables were described as mean ± SD or median and interquartile range, and compared with Student *t* test or Mann–Whitney *U* test, as appropriate. Number of patients and percentages for categorical variables were given, and compared using χ^2 or Fisher exact test as appropriate. A receiver-operating characteristic curve was applied to determine the cut-point of neuron specific enolase that distinguished between favorable and unfavorable outcome. The Spearman coefficient was applied to verify correlation between examined variables. The relative risks of each variable (with $p < 0.1$ in the univariate analysis) for favorable outcome were estimated as odds ratios (ORs) in a logistic regression analysis. A level of $p < 0.05$ was accepted as statistically significant.

3. Results

A total of 74 consecutive patients who fulfilled established criteria for intravenous rtPA treatment (0.9 mg/kg) were included in the study. Of these patients, seven were excluded; three patients due to follow-up loss at 90 days after stroke, three without neuron specific enolase examination due to hemolyzed samples, and one due to the lung cancer history. As a result, 67 patients (73.1% male; mean age, 63.6 ± 10.6 years) were enrolled into the present study. The median time from symptom onset to rtPA bolus was 195 min (30 patients ≤3 h, 37 patients between 3 and 4.5 h). Median NIHSS score before intravenous thrombolysis was 8 (range, 2 to 19), and median NIHSS score after thrombolysis 24 h was 4 (range, 0 to 29). The mean neuron specific enolase level of all patients was 15.60 ng/mL (range, 8.48 to 30.69). Serum concentrations of NSE for patients according to baseline characteristics are shown in Fig. 1. Serum concentrations of NSE were significantly higher in patients with AF than those without AF (18.37 ± 4.83 vs. 14.64 ± 4.14 ng/mL; $p = 0.003$), but no differences were observed with respect to sex, history of hypertension, diabetes mellitus.

At 90 days after stroke onset, 32 (47.8%) patients gained favorable outcome group with mRS 0–1 and 35 (52.2%) patients in unfavorable outcome group with mRS 2–6. Of the 12 intracranial hemorrhage (ICH) patients, 3 patient had symptomatic intracranial hemorrhage (sICH) and died within 7 days after thrombolysis, the other 9 patients with intracranial hemorrhage were asymptomatic. Among the 9 patients with death, 3 patient died of sICH and 2 patients died of malignant infarct associated complications in hospital, 1 due to fracture, and 3 due to other causes unrelated to stroke. Serum concentrations of NSE for patients according to different clinical outcomes subgroups are shown in Fig. 2. Compared to respective control group, patients tend to have higher NSE levels in those who had poor outcome (17.36 ± 4.16 vs. 14.66 ± 4.57 ng/mL; $p = 0.021$), and those who had ICH (18.37 ± 6.24 vs. 14.98 ± 3.96 ng/mL; $p = 0.019$). But there existed no difference between patients who died at 90 days and those not.

Included patients were divided into favorable outcome group and unfavorable outcome group according to mRS at 90 days. Baseline characteristics of the patients in the two groups are shown in Table 1. There were no significant difference between the two groups in terms of age, sex, history of hypertension and atrial fibrillation. In addition, with respect to various parameters of impaired glucose metabolism, including history of diabetes mellitus, baseline glucose, and HbA1C level, no differences were observed between the two groups. However, compared to favorable outcome group, unfavorable outcome patients were more likely to have higher NIHSS score both before (median 10 vs. 4.5; $p = 0.000$) and 24 h (median 9 vs. 2; $p = 0.000$) after rtPA. NSE levels were lower in favorable outcome group than in the unfavorable outcome group (14.00 ± 4.26 vs. 17.03 ± 4.45 ng/mL; $p = 0.006$).

The optimal cut-off value to distinguish favorable outcome from unfavorable outcome using a receiver operating characteristics (ROC) curve was 13.90 ng/mL, with sensitivity of 77.1% and specificity of 59.4%. To further estimate the clinical importance of the NSE level, the whole patients were divided into subgroups according to cut-off value of NSE: low NSE group when NSE levels <13.90 ng/mL, and high NSE group when NSE levels ≥13.90 ng/mL. Baseline Characteristics and