



Outcomes

Plasma gelsolin levels and 1-year mortality after first-ever ischemic stroke

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Abstract

Purpose: Plasma gelsolin depletion has been associated with poor outcome of critically ill patients. We sought to investigate change in plasma gelsolin level after ischemic stroke and to evaluate its relation with disease outcome.

Materials and Methods: Fifty healthy controls and 172 patients with first-ever ischemic stroke were included. Plasma samples were obtained within 24 hours from stroke onset. Its concentration was measured by enzyme-linked immunosorbent assay.

Results: Plasma gelsolin level in stroke patients was significantly decreased compared with healthy controls. A multivariate analysis showed that plasma gelsolin level was an independent predictor for 1-year mortality (odds ratio, 0.945; 95% confidence interval [CI], 0.918–0.974; $P = .0002$) and negatively associated with National Institutes of Health Stroke Scale (NIHSS) score ($t = -4.802$, $P < .001$) and plasma C-reactive protein level ($t = -4.197$, $P < .001$). A receiver operating characteristic curve identified that a baseline plasma gelsolin level less than 52.0 mg/L predicted 1-year mortality of patients with 73.0% sensitivity and 65.2% specificity (area under curve [AUC], 0.738; 95% CI, 0.666–0.802). The predictive value of the gelsolin concentration was similar to that of NIHSS score (AUC, 0.742; 95% CI, 0.670–0.806; $P = .940$). Gelsolin improved the AUC of NIHSS score to 0.814 (95% CI, 0.747–0.869; $P = .032$).

Conclusions: Plasma gelsolin level is a useful, complementary tool to predict mortality after ischemic stroke.

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1. Introduction

Plasma gelsolin is an actin-binding plasma protein that is part of an “actin-scavenging” system that buffers potentially harmful actin molecules released from injured tissues [1].

The consistent observation of lowered levels of plasma gelsolin in diverse states of acute injury and inflammation, such as hepatic failure, malaria, acute lung injury, myonecrosis, and cardiac injury [2–5], has led to a hypothesis that it participates in the clearance of actin from the circulation [1]. Further studies have revealed that critical extents of plasma gelsolin depletion in patients subjected to trauma, burns, major surgery, or hematopoietic stem cell transplantation are correlated with poor outcomes, including death [6–8]. In

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addition, the finding that plasma gelsolin binds inflammatory mediators such as platelet-activating factor and lysophosphatidic acid suggests that its physiological function may be to localize inflammation and blunt its systemic effects and that extensive plasma gelsolin depletion due to actin exposure after injury allows inflammatory mediators to cause widespread tissue damage [9].

It is evidenced that gelsolin knockout mice have largely increased cerebral lesion volumes after brain ischemia [10]. A recent study reported that plasma gelsolin is decreased and correlated with the rate of decline in Alzheimer disease [11]. However, there is a paucity of data available on circulating plasma gelsolin concentration in ischemic stroke. We therefore undertook a study to determine whether plasma gelsolin is decreased in the circulation of humans with ischemic stroke and if plasma gelsolin decrease is correlated with outcomes in these patients.

2. Materials and methods

2.1. Study population

All patients admitted between September 2007 and July 2009 with a presumable diagnosis of first-ever ischemic stroke were prospectively evaluated for inclusion in the study. Exclusion criteria from the study were concurrent renal or hepatic insufficiency, malignancy and recent infection, surgery, or major trauma. Renal insufficiency was defined as creatinine clearance less than 80 mL/min. Hepatic insufficiency was defined as Child-Pugh classification score higher than 5. Recent infection was defined as occurrence of infection within a year before the onset of stroke. Major trauma was defined as acute injury score higher than 3 in at least 1 of 3 body sites (head and neck, chest and abdomen and pelvis).

A control group consisted of 50 healthy age- and sex-matched subjects with normal results on brain magnetic resonance imaging and without vascular risk factors.

Informed consent was obtained from all subjects or their legal representatives, and the study protocol was approved by our institutional committee.

2.2. Clinical protocol

Cerebral infarction was defined as a focal neurologic deficit of sudden onset that persisted for more than 24 hours in surviving patients, documented by brain magnetic resonance imaging. Initial stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS). Participants were followed until death or completion of 1 year after stroke. Death included (1) sudden death; (2) death from myocardial infarction, congestive heart failure, new fatal stroke, systemic or pulmonary embolism, or peripheral arterial disease; and (3) death as consequence of the initial stroke in the absence of other intervening causes. For follow-

up, we used structured telephone interviews performed by 1 doctor, blinded to gelsolin levels.

2.3. Determination of gelsolin in plasma

The informed consents were obtained from all subjects or their legal representatives in all cases before the blood was collected. In the control group, venous blood was drawn at study entry. In the ischemic stroke patients, venous blood was drawn within 24 hours from stroke onset. The whole blood samples (3 mL) were collected into ethylenediamine-tetraacetic acid-containing tubes. After being centrifuged at 2500g for 5 minutes, plasma was harvested and frozen at -80°C until analysis. Plasma gelsolin levels were measured using an enzyme-linked immunosorbent assay, in accordance with the manufacturer's instructions (CoTimes, Beijing, China). Intra-assay and interassay coefficients of variation were 3.9% and 6.2%.

2.4. Statistical analysis

Statistical analysis was performed with SPSS 10.0 (SPSS Inc, Chicago, Ill) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The normality of data distribution was assessed by the Kolmogorov-Smirnov test or Shapiro-Wilk test. All values are expressed as median (lower quartile, upper quartile), mean $\pm$ SD, or counts (percentage), unless otherwise specified. Comparisons were made by using (1) χ^2 test or Fisher exact test for categorical data, (2) unpaired Student *t* test for continuous normally distributed variables, and (3) the Mann-Whitney *U* test for continuous nonnormally distributed variables. Correlations of gelsolin with other variables were assessed by Spearman correlation coefficient and multivariate linear regression. The relation of gelsolin to 1-year mortality was assessed in a logistic-regression model. For multivariate analysis, we included the significantly different outcome predictors as assessed in univariate analysis. A receiver operating characteristic curve was configured to establish the cutoff point of plasma gelsolin with the optimal sensitivity and specificity for predicting 1-year mortality. A *P* value of less than .05 was considered statistically significant.

3. Results

3.1. Patients characteristics

During the recruitment period, 219 patients were admitted, with an initial diagnosis of first-ever ischemic stroke, 181 (82.7%) patients fulfilled the inclusion criteria, and adequate data on admission and follow-up were available for 172 individuals (94 men and 78 women) (78.5%) who were finally included in the analysis. The median age was 70 years (range, 60-82 years). On admission, the median NIHSS score was 10 (range, 1-37). Table 1 summarized the other baseline

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