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Role of galectin-3 in plasma as a predictive biomarker of outcome after acute intracerebral hemorrhage

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ABSTRACT

Objective: Inflammation is involved in pathophysiological mechanisms underlying secondary brain injury after intracerebral hemorrhage. Enhanced circulating levels of galectin-3, a proinflammatory cytokine, have close relation to poor prognosis of some inflammatory illnesses. This study was designed to investigate whether plasma galectin-3 levels are related to the inflammation, severity and prognosis following intracerebral hemorrhage.
Methods: In this observational, prospective study, plasma galectin-3 levels of 110 patients and 110 controls were determined. We further assessed the association of galectin-3 levels with inflammation reflected by systemic C-reactive protein levels, severity indicated by hematoma volumes and National Institutes of Health Stroke Scale (NIHSS) scores, and endpoints including 1-week mortality, 6-month mortality, 6-month overall survival and 6-month unfavorable outcome (modified Rankin Scale score > 2).
Results: Plasma galectin-3 levels of patients were significantly higher than those of controls. Galectin-3 was identified as an independent prognostic predictor for 1-week mortality, 6-month mortality, 6-month overall survival and 6-month unfavorable outcome, as well as had strong relation to C-reactive protein levels, hematoma volumes and NIHSS scores. Compared with NIHSS scores and hematoma volumes, plasma galectin-3 levels had similar areas under receiver operating characteristic curve (AUC). Moreover, galectin-3 levels significantly improved AUCs of NIHSS scores or hematoma volumes alone for prediction of 6-month mortality and 6-month unfavorable outcome.
Conclusions: Elevated plasma galectin-3 levels are strongly associated with the inflammation, severity and poor prognosis after intracerebral hemorrhage, indicating galectin-3, involved in brain inflammation, might have the potential to be a prognostic biomarker for hemorrhagic stroke.

1. Introduction

Intracerebral hemorrhage (ICH) is a common subtype of stroke with high mortality and morbidity [1–3]. Inflammation is involved in pathophysiological mechanisms underlying secondary brain injury after ICH [4–9]. The β-galactoside-binding lectin, galectin-3, is characterized by a conserved sequence within the carbohydrate recognition domain and plays a key role in cell adhesion, activation, proliferation, apoptosis and cell migration [10–13]. It is also involved in inflammation as a pro-inflammatory mediator and has been extensively investigated in various inflammatory conditions, including heart diseases, cancers and systemic sclerosis [14–20]. Interestingly, galectin-3 can be expressed in activated glia; moreover, galectin-3 is required for resident microglia activation and proliferation in response to ischemic injury [21–24]. Furthermore, circulating galectin-3 levels are elevated in adults with mild traumatic brain injury and are highly associated with the occurrence of strokes following carotid endarterectomy [25,26]. Of note, plasma galectin-3 levels were recently found to have close relation to the severity and prognosis following severe traumatic brain injury [27], indicating galectin-3 might have the potential to be a prognostic biomarker for some neurological diseases. The present study was designed to investigate the change of plasma galectin-3 levels after ICH and further determine the relationships between galectin-3 levels and the severity and prognosis of ICH.

2. Materials and methods

2.1. Study population

This observational, prospective study at our hospital between September 2011 and September 2014 recruited those patients with acute spontaneous basal ganglia hemorrhage admitted within the first 24 h from onset of stroke. Exclusion criteria consisted of prior ischemic

Abbreviations: AUC, area under curve; CI, confidence interval; CT, computerized tomography; HR, hazard ratio; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; ROC, receiver operating characteristic.

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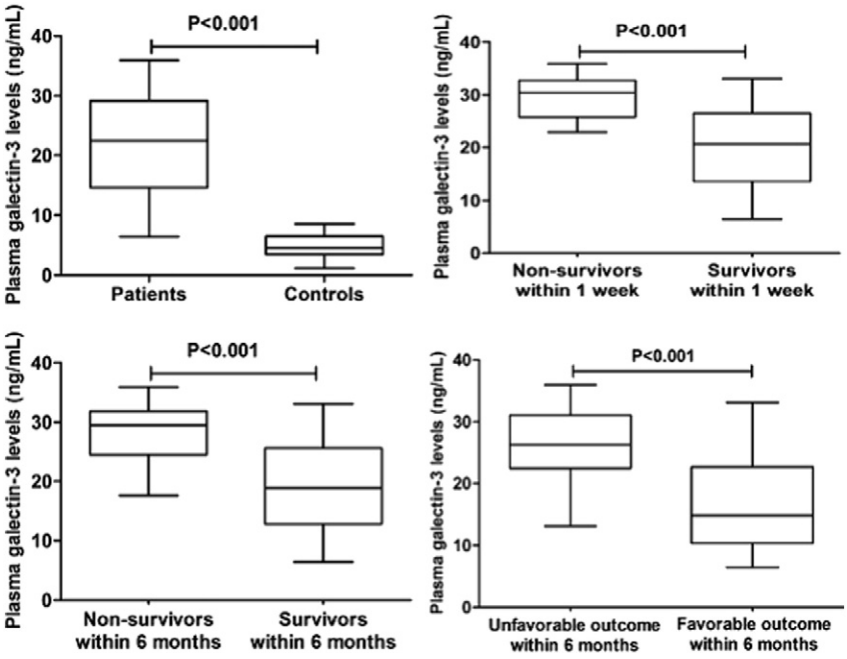

Fig. 1. Comparisons of plasma galectin-3 levels in controls and patients with intracerebral hemorrhage using *t*-test.

or hemorrhagic stroke, severe head trauma and use of antiplatelet or anticoagulant medication, presence of other systemic diseases including autoimmune diseases, uremia, liver cirrhosis, malignancy, and chronic heart or lung disease, recent infection (within a month), a surgical procedure and missing of follow-up. Control group was composed of healthy individuals who were matched in age and gender with the patients and attended our hospital for healthy examination between September 2013 and September 2014, subsequently being found free of any other medical illness and being demonstrated to have normal blood and biochemical laboratory tests. The protocol was approved by the ethics Committee at our hospital and conducted according to the Helsinki Declaration of 1971, as revised in 1983. Written informed consents were provided by the subjects or their legal guardians.

2.2. Assessment

At entry to emergency department, we recorded the following information: demographic data including sex and age, some vascular risk factors such as hypertension and diabetes mellitus, systolic blood pressure and diastolic blood pressure at presentation, as well as disease severity indicated by National Institutes of Health Stroke Scale (NIHSS) scores (assessed immediately after admission). Early neurological deterioration was defined as an increase of ≥4 points in the NIHSS score or death at 24 h from symptoms onset [28]. For each patient, at least 2 cranial computerized tomography (CT) scans, including an initial CT scan within 1 h of admission and follow-up CT scan at 24 h from symptoms onset, were performed. All CT scans were done in accordance with the neuroradiology department protocol, and were reviewed by investigators blinded to the clinical information. Hematoma volumes were measured according to the ABC/2 method [29]. Hematoma growth was defined as hematoma enlargement >33% at 24 h [30]. Follow-ups were carried out using structure telephone interviews by 1 doctor blinded to clinical information. Participants were followed up until death or completion of 6 months after stroke. An unfavorable outcome was defined as a modified Rankin Scale score > 2 at 6 months. The end points were death within 1 week and 6 months in addition to unfavorable outcome within 6 months after ICH.

2.3. Assay

We gathered blood samples from the patients at admission and from the healthy controls at study entry. Some common laboratory tests, for instance glycemia and C-reactive protein, were measured according to conventional methods. For the determination of galectin-3, plasma was aliquoted and frozen at −70 °C until assayed. In accordance with the manufacturer's instructions, plasma galectin-3 levels were in duplicate measured using a commercially available kit (BG Medicine, Inc., Waltham, MA, USA) by a same technician who was completely blinded to the clinical information.

2.4. Statistical analysis

Statistical analyses were done using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0 (MedCalc Software, Mariakerke, Belgium). Kolmogorov–Smirnov test was carried out to investigate data distribution. Categorical variables were reported as numbers and percentages.

Table 1
The factors correlated with plasma galectin-3 levels in patients with intracerebral hemorrhage.

Characteristics	*r* value	*P* value
Male	0.162	0.090
Age (y)	0.100	0.292
Hypertension	0.111	0.250
Diabetes mellitus	0.294	0.002
NIHSS score	0.603	<0.001
Hematoma volume (mL)	0.550	<0.001
Presence of intraventricular hemorrhage	0.254	0.008
Hemorrhage growth	0.225	0.018
Early neurological deterioration	0.235	0.014
Admission time (h)	0.068	0.481
Plasma-sampling time (h)	0.135	0.159
Systolic arterial pressure (mm Hg)	0.158	0.100
Diastolic arterial pressure (mm Hg)	0.165	0.085
Blood glucose level (mmol/L)	0.206	0.031
Plasma C-reactive protein level (mg/L)	0.378	<0.001

NIHSS indicates National Institutes of Health Stroke Scale.