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Clinical Study

Temporal profile of plasma adiponectin level and delayed cerebral ischemia in patients with subarachnoid hemorrhage

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ABSTRACT

Adiponectin affects nitric oxide production, and low plasma adiponectin levels are associated with impaired endothelium-dependent vasorelaxation. However, adiponectin pathophysiology in the acute phase after stroke, especially subarachnoid hemorrhage, is not well understood. The present study evaluated the changes in plasma adiponectin concentrations in patients with subarachnoid hemorrhage and investigated the relationship between plasma adiponectin and delayed cerebral ischemia. Serial plasma samples from 27 patients with subarachnoid hemorrhage were obtained on day 0 or 1 after hemorrhage, and days 3, 7, 10, 14, and 21. As a control, plasma samples were obtained from 26 healthy volunteers. Differences between patients with and without delayed cerebral ischemia were assessed to investigate the relationship between plasma adiponectin concentrations and the occurrence of delayed cerebral ischemia. There were no significant differences in the clinical characteristics of patients with and without delayed cerebral ischemia. The plasma adiponectin concentrations were significantly lower in patients on days 3 and 7 compared with controls. Plasma adiponectin concentrations in patients with delayed cerebral ischemia were significantly lower than in those without delayed cerebral ischemia on days 3, 7, 10, and 14. The present results indicate that low plasma adiponectin concentrations from day 3 to day 14 might be associated with the development of delayed cerebral ischemia.

1. Introduction

Cerebral vasospasm occurs most commonly between 4 and 14 days after subarachnoid hemorrhage (SAH) and may result in delayed cerebral ischemia (DCI), and so remains a major cause of death and morbidity [1]. Inflammation and leukocyte-endothelial cell interaction are important in the induction of cerebral vasospasm after SAH. Nitric oxide (NO) levels are known to decrease after SAH, so NO is considered to be a possible factor in the development of cerebral vasospasm [2].

Adiponectin is a hormone secreted exclusively by adipose tissue, and is important in the regulation of tissue inflammation and insulin sensitivity [3,4]. Due to these effects, adiponectin is described as an anti-diabetic and anti-atherogenic adipokine [5]. Low levels of plasma adiponectin are associated with increased risk of diabetes mellitus, hypertension, and coronary heart disease [6,7]. Adiponectin has been demonstrated to have a neuroprotective effect against cerebral ischemia in experimental studies [8–10]. Recently, decreased serum adiponectin concentrations have been reported in patients with acute illness, including sepsis, trauma, burns [11], acute ischemic stroke [12], and intracerebral hemorrhage [13]. Furthermore, adiponectin affects NO production [14], and low plasma adiponectin concentrations are associated with impaired endothelium-dependent vasorelaxation [15]. However, data on adiponectin pathophysiology in the acute phase after stroke, especially SAH, are limited [16,17].

The present study evaluated the changes in the plasma adiponectin concentrations in patients with SAH and investigated the relationship between plasma adiponectin and DCI.

2. Materials and methods

2.1. Patient population

This study was conducted with the approval of the ethics committee of the National Defense Medical College (# 855). Written informed consent was obtained from all patients. This study included 32 patients with SAH caused by ruptured aneurysms who were admitted to our hospital within 24 hours of onset between May 2011 and December 2012. Five patients who died within 2 weeks of onset were excluded. The medical records of the remaining 27 patients were reviewed, and age, sex, past history, World Federation of Neurosurgical Societies grade [18], Fisher group [19], aneurysm site, presence of DCI, laboratory data, and outcome were recorded.

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Table 1
Characteristics of subarachnoid hemorrhage patients

Age, years (mean ± SD)	64.1 ± 12.1
Sex	
Male	9 (33.3)
Female	18 (66.6)
Past history	
Hypertension	10 (37.0)
Diabetes mellitus	2 (7.4)
Current smoking	9 (33.3)
WFNS grade	
I	4 (14.8)
II	3 (11.1)
III	1 (3.7)
IV	10 (37.0)
V	9 (33.3)
Aneurysm site	
Internal carotid artery	8 (29.6)
Middle cerebral artery	10 (37.0)
Anterior cerebral artery	7 (25.9)
Posterior circulation	2 (7.4)
Central nervous system infection	3 (11.1)
Pneumonia and/or urinary tract infection	7 (25.9)
Sepsis	0 (0)
Deep vein thrombosis/pulmonary embolism	4 (14.8)
Delayed cerebral ischemia	7 (25.9)
Modified Rankin Scale score	
1	6 (22.2)
2	4 (14.8)
3	2 (7.4)
4	8 (29.6)
5	7 (25.9)

All data are presented as n (%) unless otherwise stated.
SD = standard deviation, WFNS = World Federation of Neurosurgical Societies.

DCI was defined as clinical deterioration attributable to vasospasm (clinical vasospasm) or a new infarct on brain CT scan related to vasospasm that was not visible on admission or immediate postoperative scan (new infarction attributable to vasospasm) or both [20]. All patients who experienced clinical deterioration underwent CT angiography to evaluate for vasospasm and to rule out other possible causes of deterioration (such as fever, hydrocephalus, rebleeding, cerebral edema). The outcome was assessed by the modified Rankin scale 3 months after onset [21]. As a control, plasma samples were obtained from 26 healthy volunteers (10 men, 16 women; age ranging from 23 to 55 years, mean of 34.6 years). We confirmed that none had a history of platelet defects and had not ingested any drugs for at least 15 days.

2.2. Biochemical measurements

Plasma samples were obtained on day 0 (day of hemorrhage) or 1, and days 3, 7, 10, 14, and 21, and stored at −80 °C for subsequent assay. Plasma adiponectin concentrations of all samples were quantitatively determined using a validated latex kit employing an adiponectin-specific antibody (Otsuka Pharmaceutical and Mitsubishi Kagaku Iatron, Tokyo, Japan). The limit of detection of this kit was 0.5 μg/ml.

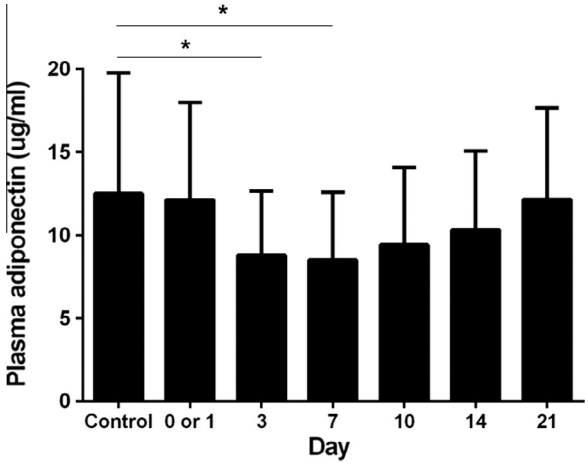

Fig. 1. Serial changes in plasma adiponectin concentrations of 27 patients with subarachnoid hemorrhage. Values are mean ± standard deviation. *$p < 0.05$.

2.3. Statistical analysis

Differences between continuous variables were analyzed using the *t*-test, and differences between categorical variables were analyzed using the Fisher' exact test. $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 11.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Clinical information of the patients is summarized in Table 1. All of the 27 patients underwent clipping. DCI occurred in seven of the 27 patients. CT angiography was performed in seven patients with DCI and in eight subjects without DCI. There were no significant differences in the characteristics between the patients with and without DCI (Table 2). The plasma adiponectin concentrations were significantly lower on days 3 and 7 compared to controls (both $p < 0.05$) (Fig. 1). The plasma adiponectin concentrations in patients with DCI were significantly lower than in those without DCI on days 3, 7, 10, and 14 (all $p < 0.05$) (Fig. 2). An illustrative patient with DCI associated with low plasma adiponectin concentration is presented in Fig. 3.

Table 2
Comparison between subarachnoid hemorrhage patients with and without delayed cerebral ischemia

	With DCI (n = 7)	Without DCI (n = 20)	*p* value
Age, years (mean ± SD)	58.4 ± 10.6	66.1 ± 12.2	0.153
Male sex	3 (42.9)	6 (30.0)	0.429
Past history			
Hypertension	3 (42.9)	7 (35.0)	0.525
Diabetes mellitus	1 (14.3)	1 (5.0)	0.459
Current smoking	2 (28.6)	7 (35.0)	0.571
WFNS grade IV or V	5 (71.4)	14 (70.0)	0.668
Central nervous system infection	2 (28.6)	1 (5.0)	0.156
Pneumonia and/or urinary tract infection	3 (42.9)	4 (20.0)	0.241
Deep vein thrombosis/pulmonary embolism	1 (14.3)	3 (15.0)	0.731
Modified Rankin Scale score 2–5	7 (100)	15 (75.0)	0.192

All data are presented as n (%) unless otherwise stated.
DCI = delayed cerebral ischemia, SD = standard deviation, WFNS = World Federation of Neurosurgical Societies.