European Review for Medical and Pharmacological Sciences 2014; 18: 3954-3958

Characteristic changes in estradiol and leptin levels in patients with subarachnoid hemorrhage induced cerebral-cardiac syndrome

W.-J. HUANG, W.-W. CHEN, X. ZHANG

Department of Neurology, Xuzhou Central Hospital, Xuzhou City, Jiangsu Province, China.

Abstract. – OBJECTIVE: To investigate the characteristic changes in serum estradiol and leptin levels in patients with cerebral-cardiac syndrome (CCS) induced by subarachnoid hemorrhage (SAH).

PATIENTS AND METHODS: Ninety-six female patients with early stage of SAH (within 48 h of onset), who were admitted in our department between February 2008 and February 2014, were included in this study. Clinical conditions of patients were rated using Hunt-Hess scale. Serum levels of estradiol, leptin and echocardiography were determined in patients with various neurological injuries as well as in post-SAH patients and patients with SAH-induced CCS.

RESULTS: No significant differences ($p > 0.05$) were observed in the levels of estradiol or leptin between patients with different Hunt-Hess grades. While serum levels of estradiol and leptin were significantly elevated in SAH and CCS patients compared to normal controls ($p < 0.05$) but the elevated levels were more profound in CCS patients. Meanwhile there were also variable extents of left ventricular expansion and decrease of ejection fraction in CCS patients, with the same trends of estradiol and leptin.

CONCLUSIONS: Thus the results show that a significant increase in estradiol and leptin levels occurred in post-SAH CCS patients.

Key words:
Subarachnoid hemorrhage, Cerebral-cardiac syndrome, Estradiol, Leptin

Introduction

Acute cerebrovascular disease and acute brain injury that cause increased intracranial pressure often induce secondary cardiac injury, and is clinically referred to as cerebral-cardiac syndrome (CCS). The prevalence of CCS in these patients can reach up to 61.2%. The main clinical features of CCS include myocardial damage, cardiac arrhythmia, and acute myocardial infarction also in some cases patients die of fatal cardiac arrhythmias and cardiac arrest (1). Higher prevalence of CCS after subarachnoid hemorrhage (SAH) was observed in our clinical practice and more commonly occurred in postmenopausal female patients. Estradiol and leptin were steroids and protein hormones, currently often used for acute ischemic cerebrovascular disease, and less research for subarachnoid hemorrhage. This study was designed to investigate the relationship between estradiol and leptin levels and post-SAH CCS patients.

Patients and methods

Patients

Inclusion criteria

Ninety-six female patients with average age of 56.4 years (age range 42-78 years) who were admitted to Neurological Department of our institution after being diagnosed as SAH according to the diagnostic criteria (established at the Fourth National Conference on Cerebrovascular Disease) between February 2008 and February 2014, were included in this study. All patients had first attack of SAH with no family history of SAH and were not taking any antiplatelet medications. In all patients SAH was confirmed by cranial CT examination within 48h of onset. Cardiac enzymes were evaluated and electrocardiography (ECG) examination was performed on the next day. Patients were divided into two groups: CCS group (n=51) in which patients exhibited cardiac arrhythmia, myocardial injury or myocardial ischemic changes and SAH group (n=45) in which no abnormalities were observed in patients. Forty healthy postmenopausal women of similar age, sex and educational level were randomly selected from health survey as controls. All patients enrolled voluntarily in the study.

Corresponding Author: Xia Zhang, MD; e-mail: baogaozx@163.com

Exclusion Criteria

Patients with the following conditions were excluded from the study: (1) SAH caused by trauma, intracranial hemorrhage, and arteriovenous malformations (2) with confirmed cardiac diseases before admission including coronary heart disease, valvular heart disease, and cardiac arrhythmias (3) undergoing treatment with anticoagulant drugs, birth control pills and estradiol replacement therapy (4) with diabetes, thyroid disease, pancreatic disease, autoimmune disease, primary infection, cancer, trauma, severe malnutrition, confusion and any other disease that might affect the result of the study. No significant difference existed in age, sex or body mass index (BMI) among various groups of patients.

Methods

Basic information of patients was recorded at the time of admission to the hospital. The conditions of individual SAH were graded using Hunt-Hess score. Patients were divided into groups according to the results of cardiac-specific markers and ECG. Blood samples (8 ml) were collected next morning of admission, and estradiol and leptin levels each were detected in 4 ml of blood. To analyze estradiol levels, blood samples (4 ml) were sent to the Isotope Laboratory of the hospital (Beckman Coulter, DXL800, Chemiluminescence, Fullerton, CA, USA). For leptin analysis, serum fraction was separated from blood (4 ml) by centrifugation, stored at –20°C and Human Leptin ELISA Kit (Sigma-Aldrich, St. Louis, MO, USA) was used. As for controls, fasting venous blood samples (8ml) were collected on any morning and serum levels of estradiol and leptin were evaluated using the same methods.

After admission, echocardiography examinations were performed within 48 hours. Variables to determine include left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular wall thickness (LVPWH), left ventricular ejection fraction (LVEF) and ventricular wall motion.

Statistical Analysis

All data are presented as mean ± SD. Data analysis was performed using statistical software SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Comparison of means between two groups was conducted using *t*-test and comparison of multivariate was performed using One-way ANOVA. A $p < 0.05$ was considered significant.

Results

Relationship between severity of CCS and serum levels of estradiol and leptin

CCS patients were grouped according to Hunt-Hess grade. Results showed no significant differences for leptin and estradiol levels among various groups ($p > 0.05$) (Table I).

Comparison of serum estradiol and leptin levels in patients of CCS and SAH groups and normal controls

Serum estradiol, leptin, TnI, CK and CRP levels in patients of SAH group were significantly elevated compared to normal controls ($p < 0.05$). Serum estradiol, leptin, TnI, and CK levels in CCS group were significantly higher than SAH group as well as normal controls ($p < 0.05$). Meanwhile, there was no significant differences for CRP levels among SAH ans CCS groups. (Table II).

Comparisons of cardiac ultrasound results among CCS and SAH groups and normal

All enrolled patients underwent cardiac ultrasound examinations. Normal findings of left ventricular function were observed in patients of the Normal Group and controls SAH group, without

Table I. Comparison of serum levels of estradiol and leptin of CCS patients with varied Hunt-Hess grades.± SD.

Groups	N	Estradiol (pg/ml)	Leptin (ng/ml)
Hunt-Hess grade I	10	66.28±11.37	14.61±5.89
Hunt-Hess grade II	13	71.39±23.48	16.97±6.97
Hunt-Hess grade III	16	72.27±19.69	13.87±6.51
Hunt-Hess grade IV/V	12	79.11±22.19	15.88±7.01
F		2.611	2.376
p		0.069	0.076

Table II. Serum estradiol and leptin levels in patients of CCS and SAH groups and normal controls.± SD.

Groups	N	Estradiol (pg/ml)	Leptin (ng/ml)	TnI ng/ml)	CK (U/L)	CRP (ng/ml)
Normal controls	40	52.32±24.11	8.97±3.64	0.19±0.12	28.43±12.34	6.87±4.13
SAH group	45	99.30±12.14	13.91±2.15*	3.15±0.91*	285.05±52.12*	12.93±2.18*
CCS group	51	112.64±27.21*#	18.72±3.06*#	4.63±1.02*#	396.51±68.67*#	13.34±1.87*

Note: *$p < 0.05$ vs. normal controls; #$p < 0.05$ vs. SAH group.

reporting inner diameter expansion of heart cavity and wall motion abnormalities. There were abnormalities of LVESD, LVEDD, LVPWH and LVEF to various extents in CCS group, and we found 11 cases of abnormal wall motion, respectively. See Table III for details.

Discussion

Cardiac injury after subarachnoid hemorrhage (SAH) is referred to as cerebral-cardiac syndrome (CCS). Its major clinical features include ischemic signs on ECG such as ST segment elevation or depression, flat or inverted T-wave and prolonged QT interval as well as premature ventricular contraction (PVC), sinus tachycardia, bradycardia or arrhythmia and atrioventricular block. These changes can last from several days to weeks and whether they are caused by functional or organic changes remains controversial[1,2]. In this study, postmenopausal women CCS patients with post SAH were enrolled to investigate the changes in serum leptin and estradiol levels in comparison to normal controls.

Estradiols are steroid hormones with a wide range of biological activities, originating primarily from theca cells and granulose cells of ovaries. Estradiol not only promotes and maintains gonadal organ development and secondary sexual characteristics but also have significant effect on endocrine system, metabolism, bone growth and maturation, skin and other organs[3]. In recent years, the study on estradiol has not been limited to the characteristics of sex hormones but has been more focused on its protective effect on the brain. The protective effect of estradiol on the brain includes: (1) increasing cerebral blood flow and decreasing ischemic brain injury; (2) preventing excitotoxic damage induced by increased glutamate concentration in synaptic cleft and over activation of N-methyl-aspartate receptors during cerebral ischemia; (3) inducing the release of endothelial cell-derived relaxing factors from endothelial cells; and (4) inhibiting ß-amyloidosis.

Protective effect of estradiol against acute ischemic stroke has recently been extensively studied. Several studies show that estradiol levels are significantly higher in both female and male ischemic stroke patients than those of normal controls, indicating the presence of estradiol imbalance at an acute stage of cerebral ischemia, which might be a result of a type of stress response and protective effect after brain injury[5]. However, only a few such studies have been conducted in hemorrhagic cerebrovascular disease. CCS often occurs after SAH insult. Thus, the present study is to investigate changes in estradiol levels in these subjects. There are three major forms of physiological estradiol in females: estrone, estradiol, and estriol. Estradiol is one of the major products of biosynthesis processes of ovaries. This study shows that there are no significant differences in estradiol levels between SAH patients with varying degree of severity. Compared with normal controls, estradiol levels in

Table III. Comparisons of cardiac ultrasound results among CCS and SAH groups and normal controls.± SD.

Group	N	LVESD (mm)	LVEDD (mm)	LVPWH (mm)	LVEF (%)	Abnormal wall motion (N)
Normal	40	32.26±2.35	41.19±3.31	7.99±0.92	55.18±1.34	0
Controls SAH	45	35.23±2.01	43.76±3.69	8.13±0.45	51.15±1.59	0
CCS group	51	41.18±1.97*#	52.23±2.82*#	10.48±0.73*#	42.17±2.48*	11

Note: *$p < 0.05$ vs. normal controls; #$p < 0.05$ vs. SAH group.

SAH patients are significantly elevated whereas in CCS patients the levels are elevated even further. Therefore, we consider the elevation of estradiol level in SAH and CCS patients has a protective effect on the brain.

Leptin is a protein hormone produced by adipose tissue. It is secreted in a circadian and/or a pulsatile pattern. Leptin was isolated in 1994 by Friedman's laboratory and influences hypothalamic mechanisms regulating appetite and energy balance. Further studies showed that leptin is involved in the regulation of many physiological and metabolic functions by binding to peripheral leptin receptors[6]. Recent studies suggested leptin is related to the pathogenesis of cerebrocardiac diseases[7-9], as shown by: (1) high levels of leptin can enhance platelet aggregation by increasing platelet reactivity to ADP; (2) leptin can induce oxidative stress, promote atherosclerosis; (3) leptin increases sympathetic nerve activity, causing increased secretion of catecholamines, resulting in the vasoconstriction in limbs, accelerated heart rate, increased cardiac workload and increased oxygen consumption, leading to myocardial ischemia and likely causing angina; (4) leptin regulates inflammatory reactions; (5) leptin promotes angiogenesis; (6) leptin induces the secretion of endothelin-1 in a time-dependent manner. Endothelin-1 is known to constrict blood vessels and promote proliferation of vascular smooth muscle cells and cell adhesion and (7) leptin induces proliferation and migration of vascular smooth muscle cells.

The studies on the role of leptin in cerebrovascular diseases have been limited mainly in ischemic stroke. In 1999, Soderberg et al[10] studied 94 cases of ischemic stroke and 19 cases of hemorrhagic stroke. Patients with hemorrhagic stroke had higher levels of BMI and systolic and diastolic blood pressure. Leptin levels were 72% and 59% higher in males and females respectively. Conditional logistic regression analysis showed that leptin is a risk marker independent of other risk markers for cardiovascular diseases. However, fewer studies have been focused on the changes of estradiol and leptin levels in patients with SAH induced CCS. Therefore the present study was designed to investigate the changes in leptin and estradiol levels in selected group of subjects. The results showed that no significant differences in leptin levels were observed between SAH patients with varying degree of severity. Leptin levels in CCS patients group were significantly higher than those of SAH group and normal controls. The changes in estradiol and leptin levels exhibited similar pattern.

Intra-cardiac structures, heart beat and blood flow could be dynamically demonstrated by echocardiography, which could be useful to detect changes of cardiac function of early stages and to formulate early interventions. As shown by echocardiography among CCS, SAH groups and normal controls, the variables of Normal Group and controls SAH group were essentially in the normal range, without the observation of regional wall motion abnormality, and left ventricular expansion to variable extents and decrease of ejection fraction were observed in CCS patients, with regional wall motion abnormalities reported in 11 cases. The changes in estradiol and leptin levels exhibited similar pattern, further confirmed that estradiol and leptin changes is related to cardiac dysfunction.

Conclusions

Hyperleptinemia and hyperestrogenemia in patients with SAH and more profound elevation in patients with SAH induced CCS led to leptin and estradiol resistance, manifested by insensitive or unresponsive to leptin and estradiol indicating an intricate relationship between leptin, estradiol and hemorrhagic stroke, which might be novel risk factors for predicting SAH especially for SAH induced CCS. Leptin secretion is related with many factors with estradiol being one of the important factors. Further research is warranted to study the underlying mechanisms by which leptin and estradiol are involved in the pathogenesis of SAH induced CCS, whether they directly affect the process or mediate it through blood pressure regulation and induction of insulin resistance. In addition, the interaction between leptin and estradiol during SAH insult will be studied further.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Claassen J, Perotte A, Albers D, Kleinberg S, Schmidt JM, Tu B, Badjatia N, Lantigua H, Hirsch LJ, Mayer SA, Connolly ES, Hripcsak G. Nonconvulsive seizures after subarachnoid hemorrhage: Multimodal detection and outcomes. Ann Neurol 2013; 74: 53-64.

2) Mertes PM, Bruder N, Audibert G. Cardiac complications of acute brain injury. Ann Fr Anesth Reanim 2012, 31: e91-96.
3) Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: from periphery to brain. Trends Mol Med 2013, 19: 197-209.
4) Kareva EN, Ole nikova OM, Panov VO, Shimanovski NL, Skvortsova VI. Estrogens and brain. Vestn Ross Akad Med Nauk 2012; 2: 48-59.
5) Guo J, Krause DN, Horne J, Weiss JH, Li X, Duckles SP. Estrogen-receptor-mediated protection of cerebral endothelial cell viability and mitochondrial function after ischemic insult in vitro. J Cereb Blood Flow Metab 2010; 30: 545-554.
6) Friedman J. Leading the charge in leptin research: an interview with Jeffrey Friedman. Dis Model Mech 2012; 5: 576-579.
7) Pan W, Hsuchou H, Tu H, Kastin AJ. Developmental changes of leptin receptors in cerebral microvessels: unexpected relation to leptintransport. Endocrinology 2008; 149: 877-885.
8) Lukasik M, Michalak S, Dworacki G, Siewiera K, Kaczmarek M, Watala C, Kozubski W. Reactive leptin resistance and the profile of platelet activation in acute ischaemic stroke patients. Thromb Haemost 2012; 108: 107-118.
9) Chao HH, Hong HJ, Liu JC, Lin JW, Chen YL, Chiu WT, Wu CH, Shyu KG, Cheng TH. Leptin stimulates endothelin-1 expression via extracellular signal-regulated kinase by epidermal growth factor receptor transactivation in rat aortic smooth muscle cells. Eur J Pharmacol 2007; 573: 49-54.
10) Soderbery S, Ahren B, Stegmayr B, Johnson O, Wiklund PG, Weinehall L, Hallmans G, Olsson T. Leptin is a risk marker for first-ever hemorrhagic stroke in a population-based cohort. Stroke 1999; 30: 328-337.