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Research Article

Comparison of Serum Soluble Corin Levels among Stroke Subtypes

Abstract

Background: Serum soluble corin was decreased not only in some cardiac diseases, but also in stroke. Cardiogenic sources play a critical role in ischemic stroke. Serum soluble corin level in stroke subtypes has not been studied. Here we aimed to study corin level in 4 stroke subtypes: hemorrhagic, thrombotic, embolic and lacunar stroke.

Methods: 116 hemorrhagic stroke, 320 thrombotic stroke patients, 48 embolic stroke patients and 102 lacunar stroke patients were studied. Serum soluble corin was measured and some conventional risk factors of stroke were collected. We compared corin level among different types of stroke in men and women respectively.

Results: Serum soluble corin level was significantly higher in ischemic stroke patients than hemorrhagic stroke patients in men (log-corin, mean±SD:7.53±0.34 *vs.* 7.42±0.28; *P* =0.013) and women (log-corin, mean±SD:7.22±0.27 *vs.* 7.12±0.31; *P* = 0.044). Then we studied serum soluble corin in subtypes of ischemic stroke. Unadjusted analysis failed to show a significant difference in log-transformed serum soluble corin among different ischemic stroke subtypes in both men and women. However, after adjustment for the covariables, the mean level of log-transformed serum soluble corin was significantly increased in embolic stroke patients compared with other subtypes in men (P <0.05). In women, embolic stroke patients also had the highest mean level of log-transformed serum soluble corin but with no significant difference. After excluding patients with a history of coronary heart disease, the mean level of serum soluble corin was still the highest in embolic stroke patients among men and women however with no significance.

Conclusions: Serum soluble corin was higher in ischemic stroke than hemorrhagic stroke and the highest in embolic stroke. Our findings indicated that corin may be a candidate biomarker used in the differentiate diagnosis of embolism from the heart.

Introduction

Stroke is a disease with heterogeneous pathogenesis. And it always presents protean clinical manifestation and sometimes confuses with stroke mimics [1]. These are likely to cause a difficulty in identifying the etiology of stroke accurately and rapidly, especially in the hyperacute stroke setting. As we know, appropriate and effective treatments of stroke are adopted according to its etiological subtypes, which will do much to its prognosis and outcome [2]. So accurate and rapid assays to identify different types of stoke is very important. Previous studies have evaluated brain imaging or some biomarkers to differentiate stroke and its subtypes. Nevertheless some of these methods for identifying different stroke subtypes have limitations. Specifically, they may be not valuable and sensitive in the early stages or in mild stroke or in patients with contraindication [3-5]. So it is of great significance to seek more sensitive, comprehensive and cost-effective methods for identifying stroke subtypes.

Corin, a type transmembrane serine protease that primarily expressed in cardiomyocytes, has been identified as physiological natriuretic peptides convertase [6,7]. To literature, corin levels were decreased in some cardiovascular diseases, e.g. heart failure, acute coronary syndrome [8,9]. We previously found that the level of serum soluble corin was also decreased in patients with stroke [10]. In ischemic stroke subtypes, cardiogenic sources account for about 10-26% among Chinese populations [11]. In other words, corin may be closely associated with embolic subtype of ischemic stroke. Consequently, we hypothesized that serum soluble corin level may be varied among stroke subtypes and perhaps used as a differentiator in stroke. However, serum soluble corin levels in stroke subtypes has not yet been studied in humans. Therefore, we studied serum soluble corin levels in 4 stroke subtypes: hemorrhagic, thrombotic, embolic and lacunar stroke.

Methods

Study population

The study was evaluated and approved by the Ethics Committee of Soochow University. And all subjects provided informed consent. This study consecutively recruited 597 patients with first-ever ischemic stroke (481) or hemorrhagic stroke (116) onset within 48 hours confirmed from 3 hospitals from January to May 2014. The inclusion criteria were as following: (1) Age ≥22 years; (2) Stroke onset within 48 hours confirmed by imaging; (3) Able and willing to sign informed consent by patients or their direct family members. Patients with one of the followings were excluded: (1) Recurrent stroke; (2) Current pregnant women; (3) Unable to participate in the follow-up examination. Stroke was diagnosed by an trained neurologist and confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI) scan.

Definition of subtypes of stroke

The patients were divided into hemorrhagic and ischemic stroke. And ischemic stroke was further divided into 4 subtypes —thrombotic, embolic, lacunar stroke and undetermined subtype according to the trial of ORG 10172 in acute stroke treatment criteria (TOAST) [12] and Cerebral Embolism Task Force for cerebral infarction subtypes [13].

Thrombotic stroke: Thrombotic stroke patients have clinical and imaging evidence of significant stenosis or occlusion (more than 50%) of a major brain artery or branch cortical artery. The clinical syndromes include brain stem or cerebellar dysfunction or cerebral cortical impairment, such as neglect, aphasia. Brain stem or subcortical hemispheric infarcts >1.5cm in diameter on CT/MRI are regarded as potential large-artery atherosclerotic origin. The supportive evidence include previous transient ischemic attack in the same vascular territory, a carotid bruit etc. Potential sources of cardiogenic embolism should be excluded.

Embolic stroke: Brain imaging and clinical syndromes are similar to thrombotic stroke. And patients should be identified with at least one sources of cardiogenic embolism. According to the report of the Cerebral Embolism Task Force [14], the patients with more than 2 primary clinical features or 1 primary clinical features and ≥2 secondary features can be diagnosed as this category. The primary features include abrupt onset of the maximal neurological deficit, presence of cardiogenic embolism and multiple brain infarcts. The secondary features involve hemorrhagic infarct, absence of atherosclerotic vascular disease, cardiac thrombi showed by echocardiography, CT or MRI etc., evidence of vanishing occlusions and embolism to other organs.

Lacunar stroke: Brain imaging shows a relevant brain stem or subcortical hemispheric lesion (<1.5 cm in greatest diameter) or a normal image. The patients have one of the traditional clinical lacunar syndromes (ataxic hemiparesis, pure sensory stroke, pure motor hemiparesis, etc.) without the evidence of cerebral cortical dysfunction.

The patients with two or more potential causes of stroke or the cause cannot be diagnosed should be classified as undetermined subtype. There were 11 (2.3%) ischemic stroke patients with undetermined etiology, therefore they were excluded.

Data collection

Data on clinical characteristics were recorded in accordance with previous published reports [10]. Blood samples were drawn immediately after hospitalization before receiving any drugs. And serum soluble corin measurements were blinded from the trained neurologist. To report, soluble corin was stable in blood samples frozen at -80°C after several cycles of freezing and thawing [15]. We used a quantikine human corin ELISA-based assays (R&D Systems, Inc., Minneapolis, USA. Catalog: DCRN00) to test soluble corin in serum. All the samples were processed in a duplicate assay. A standard curve was constructed and from which corin concentrations of unknown samples were determined. Intra- and inter-assay coefficients of variation were less than 2.7% and 6.3%, respectively.

Statistical analysis

Data were analyzed using SAS statistical software (version 9.1, Cary, North Carolina). Continuous data are presented as mean±SD (normally distributed data) or median (interquartile range, non-normally distributed data). Categorical data was presented as counts (%). Baseline characteristics between hemorrhagic stroke patients and ischemic stroke patients were analyzed by t-test for continuous variables with normal distribution, the Wilcoxon rank-sum test for continuous variables with skewed distribution, and the chi-square test for categorical variables. Log-transformed serum soluble corin in different stroke subtypes were analyzed in men and women, respectively. T-test and covariance analysis were used to compare log-transformed corin levels of thrombotic, embolic and lacunar stroke patients with hemorrhagic stroke patients, respectively. In ischemic stroke subtypes, one-Way ANOVA test and covariance analysis was used. The adjusted factors included age, body mass index, systolic blood pressure, triglycerides and fasting plasma glucose. All probabilities were two-tailed and P values0.05 was statistical significantly.

Results

Baseline characteristics

We studied 116 (19.8%) hemorrhagic stroke patients and 470 (80.2%) ischemic stroke patients. Baseline characteristics for these participants are listed in Table 1. There were no significant difference between the two groups in gender, cigarette smoking, hypertension, body mass index, waist circumference, total cholesterol and low density lipoprotein cholesterol. Systolic blood pressure, diastolic blood pressure, high density lipoprotein cholesterol, fasting plasma glucose, national institutes of health stroke scale score were all significantly higher while triglyceride was significantly lower in hemorrhagic stroke patients than ischemic stroke patients (all P <0.05). Patients with ischemic stroke were more likely to be older, have a history of coronary heart disease, family history of stroke and diabetes compared with hemorrhagic stroke patients (all P <0.05). Alcohol consumption was more often noted in hemorrhagic stroke patients (P <0.05).

Distribution of serum soluble corin by genders

Table 2 shows the serum soluble corin levels in ischemic and hemorrhagic stroke patients among men and women, respectively. Among men, the median level of serum soluble corin was significantly higher in ischemic stroke patients (1905.03 pg/mL) than hemorrhagic stroke patients (1739.19 pg/mL) (P <0.05). No significant difference in corin was found between ischemic and hemorrhagic stroke patients in women (1352.41 pg/mL *vs.* 1290.24 pg/mL). The mean level of log-transformed serum soluble corin was significantly higher in ischemic stroke patients than hemorrhagic stroke patients in both men and women (all P <0.05).

Serum soluble corin in stroke subtypes

As shown in Table 3, log-transformed serum soluble corin was compared among different stroke subtypes. Among men,

Table 1: characteristics of study patients.

Characteristic	HS (n=116)	IS (n=470)	P-value
Age, mean±SD	58.7±12.2	63.2±12.6	<0.001
Men, n(%)	76(65.5)	300(63.8)	0.734
Cigarette smoking,%	48(41.4)	193(41.1)	0.951
Alcohol consumption,%	41(35.3)	122(26.0)	0.043
FHS,%	34(29.3)	93(19.8)	0.026
History of CHD, n (%)	5(4.3)	52(11.1)	0.028
Hypertension, n (%)	76(65.5)	293(62.3)	0.526
Diabetes, n (%)	12(10.3)	112(23.8)	0.001
BMI, mean±SD	24.50±3.63	24.53±3.64	0.937
WC, mean±SD	83.64±9.91	84.56±11.11	0.567
SBP, mean±SD, mmHg	164.7±26.6	148.9±20.9	<0.001
DBP,mean±SD, mmHg	97.2±17.1	86.5±12.9	<0.001
TC, mmol/L	4.88(4.03-5.55)	4.91 (4.24-5.52)	0.623
TG, mmol/L	1.23(0.81-1.78)	1.42 (1.04-1.91)	0.031
LDL-C, mmol/L	2.89(2.29-3.57)	3.06 (2.59-3.62)	0.116
HDL-C, mmol/L	1.28(1.04-1.53)	1.09 (0.91-1.30)	<0.001
FPG, mmol/L	6.8(5.7-8.2)	6.0(5.3-7.4)	0.005
Nihss score,points	6(2-10)	4(2-7)	0.013

FHS: family history of stroke; CHD: coronary heart disease; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; FPG: fasting plasma glucose. Unless otherwise indicated, data are expressed with median (inter-quartile range) and n (%) for categorical data.

Table 2: level of serum soluble corin in ischemic and hemorrhagic stroke patients.

marker	Men(n=376)			Women(n=210)		
	IS(n=300)	HS(n=76)	P-value	IS(n=170)	HS(n=40)	P-value
Corin (median [interquartile range]),pg/ml	1905.03 (1557.72-2322.27)	1739.19 (1369.29-1967.30)	0.002	1352.41 (1150.61-1705.20)	1290.24 (1036.15-1548.52)	0.086
Log-corin, mean±SD	7.53±0.34	7.42±0.28	0.013	7.22±0.27	7.12±0.31	0.044

Table 3: Levels of log-corin in ischemic stroke subtypes compared with hemorrhagic stroke.

Log-corin	HS (n=116)	Thrombotic(n=320)			Embolic(n=48)			Lacunar(n=102)	
		Mean±SD	P-value		Mean±SD	P-value		Mean±SD	P-value
Unadjusted									
Men	7.42±0.28	7.51±0.34	0.037		7.63±0.35	0.002		7.52±0.32	0.055
Women	7.12±0.31	7.21±0.26	0.068		7.25±0.30	0.149		7.23±0.30	0.125
Adjusted									
Men	-	7.51±0.31	0.038		7.64±0.31	0.002		7.51±0.29	0.095
Women	-	7.21±0.27	0.117		7.25±0.31	0.131		7.25±0.32	0.038

Adjusted for age, body mass index, systolic blood pressure, triglycerides, fasting plasma glucose.

log-transformed serum soluble corin was significantly higher in thrombotic and embolic stroke patients than hemorrhagic stroke patients ($P < 0.05$), even after adjustment for age, body mass index, systolic blood pressure, triglyceride, and fasting plasma glucose. No significant difference in log-transformed serum soluble corin was observed between lacunar stroke patients and hemorrhagic stroke patients. Among women, we did not find a significantly increased level of log-transformed serum soluble corin in thrombotic or embolic stroke patients compared with hemorrhagic stroke patients. Instead, we found a significantly increased level of log-transformed serum soluble corin in lacunar stroke patients compared with hemorrhagic stroke patients ($P < 0.05$).

In addition, we further compared the levels of serum soluble corin among subtypes of ischemic stroke. As shown in Table 4, there were 320 (68.1%) thrombotic stroke patients, 48 (10.2%) embolic stroke patients and 102 (21.7%) lacunar stroke patients. Unadjusted analysis failed to show a significant difference in log-transformed serum soluble corin among different ischemic stroke subtypes in both men and women. However, after adjustment for the covariables, the

mean level of log-transformed serum soluble corin was significantly increased in embolic stroke patients compared with other subtypes in men (*P* <0.05). In women, embolic stroke patients also had the highest mean level of log-transformed serum soluble corin but with no significant difference.

Results of sensitivity analysis

After excluding the stroke patients with a history of coronary heart disease, the mean level of log-transformed serum soluble corin in embolic stroke patients was the highest and significantly higher than hemorrhagic stroke patients (Table 5). Nevertheless, we failed to observe a significant difference in log-transformed serum soluble corin among subtypes of ischemic stroke (Table 6).

Discussion

This study evaluated serum soluble corin levels in patients with

different types of stroke. We found that serum soluble corin levels were significantly higher in ischemic stroke patients than that in hemorrhagic stroke patients in both men and women. And it was also significantly higher in embolic stroke among ischemic stroke subtypes after adjusting for some confounding factors. The difference of ischemic stroke and hemorrhagic stroke is whether there is one or more infarctions [16]. So our results indicated that corin may play an important role in the formation of infarctions in ischemic stroke, especially in embolic stroke.

In our previous studies, serum soluble corin levels were higher in men than women regardless of ischemic or hemorrhagic stroke [10]. So we compared serum soluble corin levels among patients with different stroke types in men and women respectively. The results showed that corin levels were just higher in embolic stroke patients than that in other ischemic stroke subtypes in men but not in women.

Table 4: Levels of log-corin among subtypes of ischemic stroke.

Log-corin	Thrombotic (n=320)	Embolic (n=48)	Lacunar (n=102)	P-value
Unadjusted				
Men	7.51±0.34	7.63±0.35	7.52±0.32	0.200
Women	7.21±0.26	7.25±0.30	7.23±0.30	0.881
Adjusted				
Men	7.51±0.32	7.66±0.33a	7.52±0.33b	0.058
Women	7.21±0.28	7.25±0.28	7.23±0.28	0.831

Adjusted for age, body mass index, systolic blood pressure, triglycerides, fasting plasma glucose.
a compared with thrombotic stroke patients, P <0.05; b compared with embolic stroke patients, P <0.05.
All values are expressed with mean ± SD.

Table 5: Levels of log-corin in ischemic stroke subtypes compared with hemorrhagic stroke after excluding the stroke patients with a history of coronary heart disease.

Log-corin	HS (n=111)	Thrombotic(n=286)		Embolic(n=38)		Lacunar(n=94)	
		Mean±SD	P-value	Mean±SD	P-value	Mean±SD	P-value
Unadjusted							
Men	7.43±0.28	7.51±0.34	0.083	7.66±0.37	0.002	7.51±0.33	0.158
Women	7.11±0.31	7.20±0.25	0.085	7.27±0.29	0.086	7.22±0.31	0.123
Adjusted							
Men	-	7.43±0.31	0.094	7.63±0.31	0.016	7.51±0.29	0.085
Women	-	7.20±0.26	0.090	7.30±0.32	0.038	7.25±0.32	0.035

Adjusted for age, body mass index, systolic blood pressure, triglycerides, fasting plasma glucose.

Table 6: Levels of log-corin among subtypes of ischemic stroke after excluding the stroke patients with a history of coronary heart disease.

Log-corin	Thrombotic (n=286)	Embolic (n=38)	Lacunar (n=94)	P-value
Unadjusted				
Men	7.51±0.34	7.66±0.37	7.51±0.33	0.108
Women	7.20±0.25	7.27±0.29	7.22±0.31	0.628
Adjusted				
Men	7.50±0.32	7.64±0.33	7.53±0.33	0.159
Women	7.20±0.27	7.28±0.27	7.23±0.28	0.508

Adjusted for age, body mass index, systolic blood pressure, triglycerides, fasting plasma glucose.
All values are expressed with mean ± SD.

This may result from the few sample size of different stroke types in women. This is the first study to research the difference of serum soluble corin levels among stroke subtypes. It increased the possibility that corin may take part in the pathogenesis of stroke and provided a new idea for the research of stroke etiology. Furthermore, it provided a population-based evidence for clinical application of corin.

There have been reports that high B-type natriuretic peptide and midregional pro-atrial natriuretic peptide were significantly associated with a substantially increased risk of cadioembolic stroke, but the exact mechanisms were unknown [17,18]. And B-type natriuretic peptide had diagnostic value to identify cadioembolic subtype from other ischemic stroke subtypes [19,20]. As we know, corin can convert natriuretic peptides from inactive precursors to mature active forms [6,7]. In this study, we did not measure the serum level of B-type natriuretic peptide or A-type natriuretic peptide, so we did not know serum level of natriuretic peptides. In view of the relationship of corin and natriuretic peptides, it was unknown that corin directly affected stroke or indirectly affected stroke by the conversion of natriuretic peptide. Corin is a newly found protease and its biological functions are limitedly known. So the relationship between corin and cadioembolic stroke deserves further study.

We took a sensitivity analysis after excluding the patients with a previous coronary heart disease to examine the influence of coronary heart disease on corin level. Because some previous studies have proved that serum corin levels reduced in acute coronary syndrome [9]. We found that the differences of corin levels between patients of ischemic stroke subtypes and hemorrhagic stroke patients still existed while the differences among thrombolic, lacunar and embolic stroke patients did not exist. It suggested that the main source of infarction was cardiogenic because the phenomenon of elevated corin levels was disappeared after excluding the stroke patients with coronary heart disease. Soluble corin levels of embolic stroke patients were higher than patients with other ischemic stroke subtypes and were close to that in patients with coronary heart disease in previous study. We did not find a modifiable effect of coronary heart disease on the association of corin with stroke subtypes in our previous study. It indicated that corin was more closely associated with cardiovascular abnormalities than cerebral vascular abnormalities. And it can be used in the differential diagnosis of embolism from the heart.

To our knowledge, no previous study has examined the relationship between soluble corin and stroke subtypes. And our blood samples were drawn within 48 hours after the stroke onset, so we can exclude the influence of injuries resulting from cerebral ischemia or other outcomes associated with cerebral infarction, although the change of corin in different stages of ischemic stroke was unknown. Our study also has its limitations because of the small size of different types of stroke patients from a single ethnic. So the differences of corin levels among stroke subtypes need to be confirmed in other populations besides the Chinese nationality. The study was a case only study, which cannot infer a causal relationship between corin and embolic stroke. In addition, we only measured the serum corin levels, but not natriuretic peptides levels. So we did not infer that corin was directly or indirectly associated with the embolism from heart.

In conclusion, our study indicated that corin may be used in the differential diagnosis of embolism from the heart. Further study regarding to predictive and diagnostic value of corin is warranted.

Acknowledgements

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