Inflammatory Markers and Conventional Atherosclerotic Risk Factors in Acute Ischemic Stroke: Comparative Study between Vascular Disease Subtypes

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Background: *Large vessel atherosclerosis and small vessel disease are two major causes of ischemic stroke. In patients with large vessel disease, the lesions can be located in the extracranial carotid or intracranial arteries.*
Objective: *To search for the differences of risk factors and inflammatory markers among patients with each subtype of vascular disease.*
Material and Method: *Patients with acute ischemic stroke who had large vessel atherosclerosis or small vessel disease were studied. Patients with large vessel atherosclerosis were subdivided into extracranial carotid and intracranial stenosis groups. Blood samples were collected for c-reactive protein, erythrocyte sedimentation rate, hemoglobin A_{1C}, fibrinogen, fasting plasma glucose, cholesterol, triglyceride, and low-density and high-density lipoproteins. Risk factors and results of the blood tests between the groups of patients were compared.*
Results: *There were 116 patients in the study. Sixty-three patients had large vessel disease, whereas 53 patients had small vessel disease. More prevalence of diabetes and higher c-reactive protein were significantly found in patients with large vessel disease. c-reactive protein on admission was also higher in patients with extracranial carotid stenosis than those with intracranial stenosis. Serum cholesterol and low-density lipoprotein was significantly higher in patients with intracranial stenosis than those with small vessel extracranial disease.*
Conclusion: *Diabetes and higher c-reactive protein on admission were associated with large vessel disease. c-reactive protein was also higher in patients with extracranial carotid stenosis but their cholesterol and low-density lipoprotein were significantly lower than those with intracranial disease.*

Keywords: *Inflammatory markers, Risk factor, Ischemic stroke, Large vessel atherosclerosis, Small vessel disease, Intracranial stenosis, Extracranial carotid disease*

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Ischemic stroke is a major health problem worldwide. Understanding the pathophysiology of stroke is essential for its treatment and prevention. In general, there are three major causes of ischemic stroke, namely: large vessel atherosclerosis, cardiogenic embolism, and small vessel disease. Although, large vessel atherosclerosis and small vessel disease may share some common risk factors, such as old age, hypertension, and diabetes mellitus, special predilection of arterial involvement can be found in each patient. Among patients with large vessel atheroscleorosis, some had severe extracranial carotid stenosis without significant intracranial disease, whereas others may have intracranial stenosis without any evidence of extracranial carotid disease. One of the known factors that influence the site of vascular disease is race. For example, intracranial stenosis has been known to be more common among Asian populations[1,2]. Recently, many untraditional risk factors of the vascular disease

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have been established[3,4]. Among these, inflammatory markers and other atherosclerotic risk factors such as c-reactive protein, and fibrinogen have been shown to correlate with atherosclerotic vascular disease[5-8]. Here the authors studied the traditional and novel risk factors of vascular disease including inflammatory markers among patients with acute ischemic stroke between different subtypes of vascular disease in Asian populations.

Material and Method

Consecutive patients over 45 years old with acute ischemic stroke or transient ischemic attack (TIA) who were admitted to King Chulalongkorn Memorial Hospital from July to December 2004 were screened for eligibility. Patients were included if they presented with acute ischemic stroke or TIA by history and computerized tomography (CT) scan of the brain showed no evidence of intracerebral hemorrhage. Inform consent was required before their enrollment. Patients were excluded if they had clinical findings and underlying cause of cardiogenic embolism or any evidence of stroke etiology other than atherosclerosis and small vessel disease such as dissection, arteriovenous malformation, and hypercoagulable state. Patients with unknown cause of stroke were also excluded.

Baseline characteristics including the traditional stroke risk factors, body mass index (BMI), age, sex were recorded. To determine the risk factors for atherosclerosis, detailed medical history, physical examination and laboratory investigations were obtained. Hypertension was diagnosed when patients had a previous history of hypertension with records of blood pressure higher than 140/90 mmHg on two separate measurements or patients who were on antihypertensive agents. Likewise, diabetes mellitus was diagnosed in patients who had a previous history of fasting plasma glucose higher than 126 mg/dl, patients with random plasma glucose over 200mg/dl with clinical suggestion, or patients who were on hypoglycemic agents. Patients were diagnosed with dyslipidemia when their fasting cholesterol was higher than 200 mg/dl, fasting triglyceride higher than 150 mg/dl, high-density lipoprotein less than 40 mg/dl, low-density lipoprotein higher than 100 mg/dl, or when the patient was on a lipid-lowering agent. Smokers were defined as those who consumed over one cigarette per day, and patients who stopped smoking for less than five years before the presentation of ischemic stroke.

CT scan of the brain as well as carotid duplex ultrasound (CDUS) and transcranial Doppler ultrasound (TCD) were performed in all cases during admission within seven days after stroke. CDUS was done using Toshiba Corevision, Japan whereas TCD was performed by DWL Multiidopp T. Patients were classified as patients with large vessel atherosclerosis and patients with small vessel disease. The former group included those with extracranial carotid stenosis more than 50% by ultrasound criteria and those with evidence of intracranial large artery stenosis by TCD criteria. Patients with clinical findings of lacunar stroke whom CDUS and TCD did not demonstrate evidences of large vessel stenosis were classified as patients with small vessel disease.

For CDUS criteria, the authors used previously published velocity criteria for diagnosis of more than 50% carotid stenosis which included peak systolic velocity of the internal carotid artery more than 140 mm/sec and the internal carotid/common carotid ratio more than 2[9]. Diagnosis of intracranial stenosis was made by transcranial Doppler criteria for more than 50% stenosis. The criteria were peak systolic velocity more than 140 cm/sec for middle cerebral arteries, more than 120 cm/sec for anterior cerebral and distal internal carotid arteries, more than 100 cm/sec for posterior cerebral arteries, vertebral arteries and basilar artery[10].

On the day of admission or within the first morning after admission, fasting blood samples were collected for testing of total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, plasma glucose, c-reactive protein, erythrocyte sedimentation rate, hemoglobin A_{1C}, and fibrinogen. Another blood sample for c-reactive protein was collected on the day of their discharge. Patients with evidence of any infection, had a body temperature any time on the day of blood sampling more than 37.5°C, or patients who received HMG-coA reductase inhibitor before the presenting stroke were excluded from the analysis of c-reactive protein and erythrocyte sedimentation rate.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD and categorical variables were expressed as percentage. Logistic regression analysis was performed to get to patients' risk factor profiles. 95% confidence interval and laboratory results were then compared between those with large vessel atherosclerosis and the ones with small vessel disease by Mann Whitney U test, unpaired independent t-test for continuous variables and by Chi-square test for categorical variables. Subgroup analysis of patients with large vessel atherosclerosis (extracranial carotid artery stenosis

group and intracranial stenosis group) was also performed. Statistical analysis was done using SPSS computer program version 10.0. A two-tailed p-value of less than 0.05 was considered significant.

Results

There were 116 patients recruited into the present study. Their mean age was 62.7 years. Sixty-three patients were classified to have large vessel disease whereas 53 patients had small vessel disease. Among patients with large vessel disease, 11 had extracranial carotid stenosis and 52 were found to have intracranial stenosis without extracranial stenosis. There were 58.6% male patients. Their age ranged from 45 to 91 years with the mean age of 62.76 years. For the traditional stroke risk factors, hypertension was the most common (93.1%), followed by dyslipidemia (92.2%), diabetes (53.4%), and cigarette smoking (30.2). According to Oxfordshire Community Stroke Project's (OCSP) classification of stroke, patients with large vessel atherosclerosis had total anterior circulation infarction in 4.8%, partial anterior circulation in 46.8%, and posterior circulation infarction in 40.3% [11]. Conversely, all patients in the small vessel disease had lacunar infarction in which the diameter of infarction was less than 1.5 mm.

When patients with large vessel atherosclerosis and small vessel disease were compared, there were no significant differences of mean age, sex, body weight, height, body mass index, number of patients with hypertension, dyslipidemia, and patients who smoked cigarettes between the two groups. However, diabetes was significantly more common in patients with large vessel disease than those with small vessel disease. For the laboratory results, no significant differences between the lipid profiles, fasting plasma glucose, hemoglobin A_{1C}, erythrocyte sedimentation rate, and fibrinogen. Significant higher levels of c-reactive protein both on admission and on discharge in patients with large vessel atherosclerosis were observed. There was also a non-significant trend of higher level of erythrocyte sedimentation rate in patients with large vessel atherosclerosis. A comparison of risk factors and laboratory results in patients with large vessel atherosclerosis and small vessel disease is shown in Table 1.

Patients with large vessel atherosclerosis were classified into two groups: extracranial carotid

Table 1. Comparison of risk factors and laboratory results in patients with large vessel atherosclerosis and small vessel disease

Risk factors	Patients with large vessel disease	Patients with small vessel disease	p-value
Mean age (years)	62.7 ± 12.56	62.83 ± 11.17	0.953[a]
Male%	60.3	56.6	0.709[b]
Body weight (Kg)	60.5 ± 10.83	63.9 ± 12.61	0.194[a]
Height (Kg)	159.5 ± 7.90	158.4 ± 21.99	0.457[a]
Body mass index	23.78	24.48	0.467[a]
Diabetes%	55.5	35.8	0.041[b]
Hypertension%	93.7	92.5	1.000[b]
Dyslipidemia%	88.8	96.2	0.177[b]
Smoking%	31.7	28.3	0.839[b]
Cholesterol (mg/dl)	213.0 ± 51.7	205.1 ± 39.2	0.811[a]
Triglyceride (mg/dl)	134.6 ± 54.5	123.7 ± 53.5	0.273[a]
High density lipoprotein (mg/dl)	46.3 ± 12.1	48.6 ± 13.2	0.328[a]
Low density lipoprotein (mg/dl)	139.7 ± 41.9	131.3 ± 31.5	0.643[a]
Fasting plasma glucose (mg/dl)	123.9 ± 50.7	127.7 ± 31.5	0.592[a]
Hemoglobin A1C (%)	7.1 ± 2.0	7.4 ± 2.5	0.822[a]
ESR (mm/1st hour)	25.8 ± 18.6	25.3 ± 38.1	0.537[a]
Fibrinogen (g/l)	4.1 ± 1.6	4.1 ± 2.7	0.292[a]
c-reactive protein on admission (mg/l)	9.1 ± 13.4	5.3 ± 3.9	0.014[a]
c-reactive protein on discharge (mg/l)	13.1 ± 18.2	9.8 ± 20.1	0.001[a]

a = Mann-Whitney U test
b = Chi-square test

stenosis and intracranial stenosis. There was no difference in the subtypes of stroke detected in the two groups under OCSP criteria (p = 0.76). When the risk factors were compared, no significant differences between age, sex, body mass index, percentage of hypertension, dyslipidemia, diabetes mellitus, and cigarette smoking were found. Laboratory results showed a significantly higher level of c-reactive protein on admission in patients with extracranial carotid stenosis than those with intracranial disease. In contrast, serum cholesterol and low-density lipoprotein was higher in patients with intracranial stenosis. After performing logistic regression analysis, the authors found that c-reactive protein on admission was the only significant variable for predicting extracranial carotid disease (OR = 1.050, 95%CI 1.001-1.100, p = 0.045). A comparison of the risk factors and laboratory results in patients with extracranial carotid disease and intracranial stenosis is shown in Table 2.

Discussion

Strokes can be categorized according to their pathophysiology into three major subtypes, namely: large vessel atherosclerosis, small vessel disease, and cardiogenic embolism. The present study is aimed to search for the differences between patients with large vessel atherosclerosis and small vessel disease by comparing their risk factors and inflammatory markers. The authors also compared the factors in patients with extracranial carotid stenosis and intracranial disease.

Inflammatory process has recently been correlated with atherosclerosis of different vascular beds. Inflammatory markers especially high level of c-reactive protein has been found to be an independent risk factor of ischemic heart disease and stroke[6,12]. However, there has been no report of these markers in patients with different subtypes of ischemic stroke especially among patients with different sites of atherosclerosis. The present study demonstrated that c-reactive protein on admission was significantly higher in patients with large vessel atherosclerosis. Moreover, there was also a trend of higher ESR in this group. Both c-reactive protein and ESR are non-specific inflammatory markers that can be elevated in many conditions such as any infection or inflammation. The present study tried to eliminate the possibility of other non-stroke causes of high c-reactive protein and ESR by excluding patients with fever or evidence of infection. There-

Table 2. Comparison of risk factors and laboratory results in patients with extracranial carotid and intracranial atherosclerotic diseases

Risk factors	Patients with extracranial carotid stenosis	Patients with intracranial disease	p-value
Mean age (years)	60.8 ± 9.8	63.1 ± 13.1	0.589[a]
% Male	45.5	33.52	0.320[b]
Body weight (Kg)	58.5 ± 12.2	60.9 ± 10.6	0.814 [a]
Height (Kg)	157.0 ± 4.1	160.0 ± 8.4	0.122 [a]
Body mass index	23.8 ± 5.0	23.8 ± 3.7	0.964 [a]
% Diabetes	45.5	57.7	0.517 [b]
% Hypertension	81.8	96.2	0.137 [b]
% Dyslipidemia	81.8	90.4	0.595 [b]
% Smoking	36.4	30.8	0.732 [b]
Cholesterol (mg/dl)	185.0 ± 33.4	221.8 ± 53.2	0.018 [a]
Triglyceride (mg/dl)	114.7 ± 41.8	138.9 ± 56.3	0.170[a]
High density lipoprotein (mg/dl)	45.5 ± 11.9	46.4 ± 12.2	0.800[a]
Low density lipoprotein (mg/dl)	113.6 ± 24.1	145.4 ± 42.5	0.007 [a]
Fasting plasma glucose (mg/dl)	135.3 ± 56.7	121.7 ± 49.7	0.396 [a]
Hemoglobin A1C (%)	7.1 ± 1.8	7.1 ± 2.1	0.705[a]
ESR (mm/1st hour)	34.2 ± 28.2	24.0 ± 15.6	0.302 [a]
Fibrinogen (g/l)	4.0 ± 0.7	4.1 ± 1.7	0.550[a]
c-reactive protein on admission (mg/l)	18.1 ± 18.6	6.9 ± 11.5	0.033 [a]
c-reactive protein on discharge (mg/l)	13.4 ± 35.5	11.1 ± 11.9	0.270 [a]

a = Mann-Whitney U test
b = Chi-square test

fore, the high c-reactive protein in the present patients was likely to represent the etiology or the result of the presenting stroke. Previous studies compared the c-reactive protein on the first day of stroke, at one week and at 90 days after stroke and they showed that c-reactive protein at any time point correlated with long-term prognosis but not the severity of the acute stroke[13]. High c-reactive protein was also correlated with unstable carotid plaque[14]. Therefore, it is likely that the high level of c-reactive protein in patients with large vessel atherosclerosis in the present study is due to a more active inflammatory process in the large arteries. Another possibility, which is less likely to explain the high level of c-reactive protein, is the area of infarction. Since patients with large vessel atherosclerosis are more likely to have a larger area of infarction, whereas those with small vessel disease usually have little area of infarction in the deep structures; also, more inflammation of the brain parenchyma in patients with large vessel atherosclerosis can be expected. In one study, increased c-reactive protein was found to be significantly correlated with lesion volume and stroke severity[15]. In this study, increasing level of c-reactive protein on discharged when compared to c-reactive protein on admission was observed in most of the patients. This is compatible to previous study measuring serial c-reactive protein after acute stroke where elevation of c-reactive protein level was observed during the first few days[13].

Interestingly, when the subgroups of patients with large vessel atherosclerosis were studied, higher c-reactive protein was observed in patients with extracranial carotid stenosis. In patients with extracranial carotid disease, c-reactive protein level on admission was exceedingly high. This suggested more inflammation or more plaque instability in the larger arteries. Since the areas of infarction were not different in the two groups, the high level of c-reactive protein could not be explained by the infarct size. The authors are aware that the number of patients in the extracranial carotid stenosis group was quite small. This is due to the fact that in our population, like some other Asian countries, extracranial carotid stenosis is much less common than intracranial large vessel disease.

In the present study, serum cholesterol and low-density lipoprotein were significantly higher in patients with intracranial stenosis. In the Northern Manhattan Stroke Study, hypercholesterolemia was found to be associated with intracranial disease[16]. However, further investigation is needed to confirm the findings.

Conclusion

In patients with acute ischemic stroke, patients with large vessel atherosclerosis had a significantly higher level of c-reactive protein on admission than patients with small vessel disease. c-reactive protein was also higher in patients with extracranial carotid stenosis. However, cholesterol and low density lipoprotein was significantly lower in patients with intracranial disease.

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การศึกษาเปรียบเทียบตัวชี้วัดการอักเสบและปัจจัยเสี่ยงของการเกิดหลอดเลือดแข็งในผู้ป่วยที่มีภาวะสมองขาดเลือดที่เกิดจากสาเหตุต่าง ๆ กัน

นิจศรี ชาญณรงค์ สุวรรณเวลา, อรอุมา ชุติเนตร, กัมมันต์ พันธุมจินดา

ที่มา: *ภาวะหลอดเลือดแดงใหญ่แข็งและโรคของหลอดเลือดสมองขนาดเล็ก เป็นสาเหตุที่สำคัญของการเกิดสมองขาดเลือด ในผู้ป่วยที่มีภาวะหลอดเลือดแดงใหญ่แข็งอาจมีรอยโรคบริเวณหลอดเลือดคาโรติดบริเวณคอ หรือ หลอดเลือดใหญ่บริเวณฐานสมอง*

วัตถุประสงค์: *เพื่อเปรียบเทียบปัจจัยเสี่ยงและตัวชี้วัดทางด้านการอักเสบในผู้ป่วยที่มีสมองขาดเลือด ซึ่งเกิดจากรอยโรคของหลอดเลือดชนิดต่าง ๆ กัน*

วัสดุและวิธีการ: *ผู้ป่วยที่มีภาวะสมองขาดเลือดที่มีสาเหตุจากโรคของหลอดเลือดที่ไปเลี้ยงสมองที่มารับการรักษาที่โรงพยาบาลจุฬาลงกรณ์จะได้รับการเก็บข้อมูล และตรวจหลอดเลือดด้วยคลื่นเสียงความถี่สูงเพื่อใช้ในการแบ่งชนิดของโรคตามตำแหน่งของหลอดเลือดที่พบว่าผิดปกติ และมีการตรวจทางห้องปฏิบัติการเพื่อหาระดับของ c-reactive protein homocysteine erythrocyte sedimentation rate (ESR) แมกนิเซียม ไฟบริโนเจน ระดับน้ำตาลในเลือด ฮีโมโกลบิน A_{1C} และระดับไขมันต่าง ๆ ในเลือด จากนั้นจึงได้มีการวิเคราะห์ผลของการตรวจเลือด รวมทั้งปัจจัยเสี่ยงต่าง ๆ เปรียบเทียบกับชนิดหลอดเลือดที่เป็นสาเหตุ*

ผลการศึกษา: *มีผู้ป่วยจำนวน 116 ราย เข้าร่วมในการศึกษา ในจำนวนนี้ 63 ราย มีโรคของหลอดเลือดขนาดใหญ่และผู้ป่วย 53 ราย มีโรคของหลอดเลือดขนาดเล็ก ในจำนวนผู้ที่มีโรคของหลอดเลือดใหญ่ ผู้ป่วย 11 ราย มีการตีบของหลอดเลือดคาโรติดบริเวณคอ และอีก 52 รายมีโรคของหลอดเลือดใหญ่ในสมอง ในผู้ป่วยที่มีโรคของ หลอดเลือดใหญ่ พบว่ามีจำนวนผู้ที่เป็นเบาหวานมากกว่า และมีค่าเฉลี่ยของ c-reactive protein ขณะแรกรับไว้ในโรงพยาบาลสูงกว่ากลุ่มที่มีโรคหลอดเลือดขนาดเล็ก นอกจากนี้ยังพบว่าในผู้ป่วยที่มีการตีบของหลอดเลือดคาโรติดบริเวณคอมีค่าเฉลี่ยของ c-reactive protein สูงกว่า แต่มีระดับโคเลสเตอรอลและไขมันชนิดแอลดีแอลต่ำกว่าผู้ที่มีโรคของหลอดเลือดใหญ่ในสมอง*

สรุป: *การเป็นเบาหวานและการมีค่า c-reactive protein ในขณะแรกรับที่สูงมีความสัมพันธ์กับการมีภาวะหลอดเลือดแดงใหญ่แข็ง ค่า c-reactive protein ที่สูงนี้ยังพบในผู้ป่วยที่มีโรคของหลอดเลือดคาโรติดบริเวณคอมากกว่าผู้ที่มีโรคของหลอดเลือดใหญ่ในสมอง ในทางตรงกันข้ามระดับโคเลสเตอรอลและไขมันชนิดแอลดีแอลในผู้ที่มีโรคของหลอดเลือดคาโรติดที่คอน้อยกว่าผู้ที่มีโรคของหลอดเลือดใหญ่ในสมอง*