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ORIGINAL ARTICLES

Association Between Carotid atherosclerosis And High Factor VIII Activity In Ischemic stroke

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Abstract:

Background: *A sample of 60 subjects from population based study participated in a study on carotid color duplex ultrasonography that aimed to assess the relations of coagulation factors to stroke and carotid atherosclerosis. The association between severity of carotid atherosclerosis and high factor viii activity in ischemic stroke is still not clear.* ***Objective:*** *The present study was conducted to find out the association between carotid atherosclerosis and high factor viii activity in ischemic stroke.* ***Methodology:*** *This was a cross sectional analytical study carried out in the department of neurology,BSMMU during the period of july'2009 to june'2011.A total 60 subjects with ischemic stroke were included in this study and data were collected purposively. Chi square test was done and probability value <0.05 were considered as level of significance and 95% confidence limit were taken.* ***Result:*** *In patients with e"50% carotid stenosis, 7(23.33%) had high factor VIII activity and 23(76.67%) had normal factor VIII activity. In patients with <50% carotid stenosis, 2(6.67%) had high factor VIII activity and 28(93.33%) had normal factor VIII activity. No significant difference (P>0.05%) was found between the high factor VIII activity and normal factor VIII activity related to severity of carotid stenosis.* ***Conclusion:*** *The roles of hypertension, hypercholesterolemia, and hypertriglyceridemia have been implicated in the pathogenesis of the carotid atherosclerosis but in the present study did not find any association between the severity of the carotid atherosclerosis with high factor viii activity in ischemic stroke.*

Key words: *Factor viii activity, Carotid atherosclerosis , Ischemic stroke.*

Introduction:

Stroke is a clinical syndrome characterized by rapid onset of focal or global neurological signs or disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin, non-epileptic and non-traumatic in nature[1]. This definition includes stroke from both infarction and hemorrhage. Transient ischemic attack (TIA) is identical to that of stroke, except that the symptoms last less than 24 hours. About 85% of stroke is caused by primary cerebral ischemia resulting in infarction (ischemic stroke) and 15% are caused by cerebral hemorrhage (hemorrhagic stroke)[2,3].

Stroke is a major global health problem. It is a major cause of mortality, morbidity and disability in developed countries and increasingly in less developed countries. Worldwide, it is the leading cause of healthy years lost in late adulthood, and evidence indicates that the burden of stroke, particularly in terms of morbidity and disability, will almost certainly increase in the foreseeable future[4].

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Stroke is the third most common cause of death in the developed world and is the most common cause of adult physical disability[5]. It is a common medical emergency with an annual incidence of approximately 160 per 100,000 population per year[6]. The incidence rises steeply with age; the incidence is rising in many developing countries due to adoption of less healthy lifestyle.

There are several risk factors associated with stroke. Some of which are non modifiable and some are modifiable. Non-modifiable factors are age, gender, race, heredity, previous vascular events (MI, stroke), high fibrinogen. Modifiable factors are high blood pressure, ischemic heart disease, diabetes mellitus, hyperlipidemia, smoking, excess alcohol consumption, polycythemia, elevated homocystiene, elevated anticardiolipin antibodies, obesity and oral contraceptives[7] .For ischemic stroke there are some potential new risk factors, which include some genotypes, inflammatory markers, infectious agents, biomarkers hemostasis, high factor VIII activity , Von-Willbrand factor and platelet related factors[8] .

The prevalence rate of stroke of India is 250-350/ 100,000 in last decade. Incidence of stroke in Bangladesh is 2.55/1000 population/year in both sexes (Bangladesh bureau of statistics, 2009). About 40-50% of beds are occupied by stroke patients in neurology ward which is reported in a developing country like ours[9].

It is interesting to note that coronary artery disease mortality was reduced in haemophilic patients with very low level of factor VIII observed both the 5-years and 16.1 years studies of the Northwick Park Heart Study. They also found modest association between high factor VIII activity and coronary artery disease[10]. These findings encourage the previous researchers to elucidate the association between carotid atherosclerosis and high factor VIII activity in ischemic stroke patients.

Factor VIII, an essential blood coagulation factor, is a large glycoprotein having a molecular weight of approximately 360,000 [11]. Factor III is a cofactor involved in activation of factor X by activated factor IX in the presence of membrane surfaces and calcium. Normal levels of factor VIII do not saturate this enzymatic reaction. When factor VIII level increase above the normal level, a given quantity of factor IX can generate larger quantities of activated factor X, which in turn generate large quantities of thrombin and thus fibrin[12]. Factor VIII and Von Willebrand factor as potential markers of endothelial cell injury[13]. Plasma factor VIII might interact with platelet glycoprotein-I, endothelium and subendothelium thus deposition of platelet on damage endothelium.

Deposited platelets may release growth promoting peptides which stimulate proliferation of intima and smooth muscle of blood vessels leading to atherosclerosis[14].This biochemical observation and previous reports of thromboembolic disease in patients with high factor VIII elevation, a causal relationship between high factor VIII and thromboembolic stroke appears likely.

Arteriography has been long regarded as the gold standard diagnostic tool for carotid stenosis. It is a costly and invasive technique with potentially serious complications. The results of arteriography have not been standardized which makes comparison of results from different laboratories difficult. Duplex ultrasound is a non-invasive, inexpensive and can provide functional and anatomical information about vessel stenosis and plaque morphology. Color duplex flow ultrasonography has thus became a routine noninvasive method of assessing extracranial cerebrovascular occlusive disease because it avoids the expense and risk of arteriography. The sensitivity and specificity of carotid duplex ultrasound range from 90% to 95% for measurement of carotid diameter reduction, and duplex ultrasound may be more sensitive for detection of minimum atherosclerotic plaque. The goals of carotid imaging can be described as early detection, clinical staging, surgical road mapping and postoperative therapeutic surveillance[15].

The purpose of the study was to evaluate the association between carotid atherosclerosis and factor VIII activity in ischemic stroke.

Subjects and Methods:

Study population:

It was a cross sectional analytical study done in the department of neurology ,Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2009 to

June 2011.A total of 60 patients with ischemic stroke were included in this study. In this study normal range of plasma factor viii activity was defined by 50-150% and elevated range by >150%.The severity of carotid stenosis was defined by mild as <50%,moderate as 50-69% and severe as >70%.

acute thrombotic event Study population was WHO defined stroke patients, ischemic in type, confirmed by CT scan of head/MRI of brain, presented after 7 days after the event. The sampling technique was purposive and included both sexes. Patients were excluded from the study who refuse to participate, with cardioembolic conditions on clinical and electrocardiographic grounds, like atrial fibrillation, aortic or mitral valve disease, recent myocardial infarction (<6 weeks), prosthetic cardiac valve, heart failure, patients with, acute inflammatory conditions, malignancy, liver & renal disease, pregnancy, history of recent surgery.

Statistical analysis:

All data were recorded systematically in preformed data collection form and data were expressed as mean and standard deviation and qualitative data as frequency distribution and percentage. Risk factors were analyzed by Chi square test. Statistical analysis was performed by using SPSS for windows version 16.0. 95% confidence limit was taken. Probability value <0.05 was considered as level of significance.

Observations and Results:

This cross sectional study was conducted in the Department of Neurology, BSMMU, Dhaka from July'2009 to June' 2011 for duration of two years. Total 60 ischemic stroke patients were enrolled in this study. The findings of the study are presented here.

Table-I

Age distribution of the study population (n=60)

Age	Number of Patients	Percentage
£40	4	6.7
41 – 50	12	20.0
51 – 60	19	31.7
61 – 70	17	28.3
71 – 80	7	11.7
>80	1	1.7
Mean ±SD	58.0±10.7	
Range	35-85	
Total	60	100

The study included 60 patients and the mean age was 58.0±10.7 years with range from 35 to 85 years. Nearly one third 19(31.7%) of the patients was found in the age group of 51-60 years. The results are shown in the table I.

Table-II

Sex distribution of the study population(n=60)

Sex	Number of Patients	Percentage
Male	37	61.7
Female	23	38.3
Total	60	100

Table II shows the sex distribution of the patients and it was found that 37(61.7%) male and 23(38.3%) female. Male female ratio was almost 1.6:1 in this study patient.

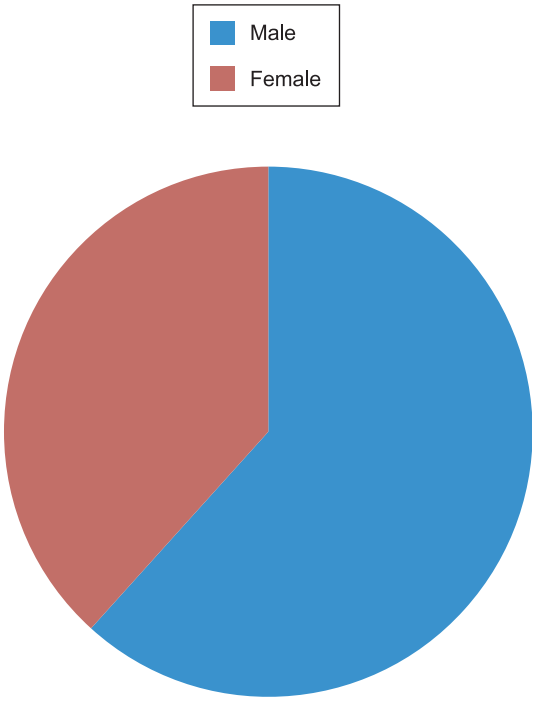

Fig.-1: *Pie chart shows sex distribution*

Table-III

Distribution of 60 study population according to socioeconomic condition

Characteristics	Carotid stenosis >50% (n=30)		Carotid stenosis <50% (n=30)		P Value
Income (TK.)	N	%	n	%	
<10.000	8	26.67	13	43.33	0.175^{ns}
>10.000	22	73.33	17	56.67	
Total	30	100	30	100	

NS=Not significant
P value reached from chi square test.

In patient with >50% carotid stenosis, 8(26.67%) had monthly family income of d" 10,000 taka and 22(73.33%) had monthly family income of > 10,000 taka. In patient with <50% carotid stenosis, 13(43.33%) had monthly family income of <10,000 taka and 17(56.67%) had monthly family income of > 10,000 taka. No Significant (P>0.05) difference regarding socioeconomic status was found between < 50% and >50% Carotid Stenosis. The results are shown in the table III.

Table-IV

The distribution and Status of Carotid Stenosis (n=60)

Carotid Stenosis	Number of patients	Percentage
Mild	30	50.0
Moderale	16	26.7
Severe	14	23.3
Total	60	100

Among the 60 patients of the study showed mild Carotid Stenosis in 30 patients (50%), moderate carotid stenosis in 16 patients (26.7%) and severe carotid stenosis in 14 patients (23.3%) The results were shown in table IV.

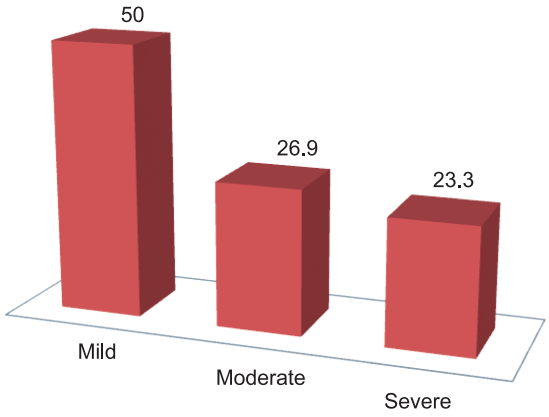

Fig.-2: *Bar diagram shows status of carotid stenosis*

Table-V

Distribution of the study of subjects whose age was a risk factor for carotid stenosis (n=60)

Age group	Carotid stenosis >50% (n=30)		Carotid stenosis <50%(n=30)		OR	(95%CI)	P Value
	n	%	N	%			
>50 years	28	93.33	12	40	21.33	3.71-85.7	0.001^{s}
<50 years	2	6.67	18	60			
Total	30	100	30	100			

S=Significant
P value reached from chi square test.

In patient with >50% carotid stenosis, 28(93.33%) had age >50 years and 2(6.67%) had age d"50years. In patient with <50% carotid stenosis, 12(40%) had age>50 years and 18(60%) had age d"50years. Significant difference (p<0.05) was found regarding severity of carotid stenosis in age group betweend"50 years and >50 years. The results were shown in table V.

Table-VI

Distribution of sex as a risk factor for carotid stenosis (n=60)

Sex	Carotid stenosis >50% (n=30)		Carotid stenosis <50%(n=30)		OR	(95%CI)	P Value
	n	%	N	%			
Male	17	56.67	20	66.64	0.65	0.20-2.11	0.425^{ns}
Female	13	43.33	10	33.36			
Total	30	100	30	100			

NS=Not significant

P value reached from chi square test.

Table-VII

Distribution of smoking as a risk factor for carotid stenosis (n=60)

Smoking	Carotid stenosis >50% (n=30)		Carotid stenosis <50%(n=30)		OR	(95%CI)	P Value
	n	%	N	%			
Yes	22	73.33	21	70	1.18	0.33-4.19	0.774^{ns}
No	8	26.67	9	30			
Total	30	100	30	100			

NS=Not significant

P value reached from chi square test.

Table-VIII

Distribution of hypertension as a risk factor for Carotid Stenosis (n=60)

Hypertension	Carotid stenosis >50% (n=30)		Carotid stenosis <50%(n=30)		OR	(95%CI)	P Value
	n	%	N	%			
Yes	26	86.67	15	50	6.50	1.59-28.69	0.002^{s}
No	4	13.33	15	50			
Total	30	100	30	100			

S= Significant

P value reached from chi square test.

Table-IX

Distribution of diabetes mellitus as a risk factor for carotid stenosis (n=60).

Diabetes	Carotid stenosis >50% (n=30)		Carotid stenosis <50%(n=30)		OR	(95%CI)	P Value
	n	%	N	%			
Yes	16	53.33	7	23.33	3.76	1.09-13.34	0.016[s]
No	14	46.67	23	76.67			
Total 30		100	30	100			

S= Significant

P value reached from chi square test.

Table-X

Distribution of dyslipidaemia as a risk factor for carotid stenosis (n=60)

Dyslipidaemia	Carotid stenosis >50% (n=30)		Carotid stenosis <50%(n=30)		OR	(95%CI)	P Value
	n	%	N	%			
Yes	17	56.67	20	66.67	0.65	0.20-2.11	0.425[ns]
No	13	43.33	10	33.33			
Total	30	100	30	100			

NS=Not significant

P value reached from chi square test.

Table-XI

Distribution of study of Factor VIII as a risk factor for carotid stenosis (n=60)

Factor activity	Carotid stenosis >50% (n=30)		Carotid stenosis <50%(n=30)		OR	(95%CI)	P Value
	n	%	N	%			
High	7	23.33	2	6.67	4.26	0.70-33.16	0.072[ns]
Normal	23	76.67	28	93.33			
Total	30	100	30	100			

NS=Not significant

Among the patient with e”50% carotid stenosis, 17(56.67%) had male gender and 13(43.33%) had female gender. In patient with <50% carotid stenosis, 20(66.67%) had male gender and 10(33.33%) had female gender. Severity of carotid stenosis was not significant (p>0.05) among male and female gender. The results were shown in table VI.

In patient with e”50% carotid stenosis, 22(73.33%) were smoker and 8(26.67%) were non smoker. In patient with <50% carotid stenosis, 21(70%) were smoker and 9(30%) were non smoker. No significant difference (p>0.05) was found between smokers and non-smokers group related to severity of carotid stenosis. The results were shown in table VII.

In patient with e”50% carotid stenosis, 26(86.67%) were hypertensive and 4(13.33%) were normotensive. In patient with <50% carotid stenosis, 15(50%) were hypertensive and 15(50%) were normotensive. Severity of carotid stenosis among hypertensive and normotensive group was statistically significant (p<0.05).The results were shown in table VIII.

In patient with e”50% carotid stenosis, 16(53.33%) diabetic and 14(46.67%) were non diabetic. In patient with <50% carotid stenosis, 7(23.33%) diabetic and 23(76.67%) were non diabetic. Significant difference (p<0.05) was found between diabetic and non-diabetic group related to severity of carotid stenosis. The results were shown in table IX.

In patient with e”50% carotid stenosis, 17(56.67%) were dyslipidaemic and 13(43.33%) were normal lipid profile. In patient with <50% carotid stenosis, 20(66.67%) had dyslipidaemic and 10(33.33%) had normal lipid profile . Severity of carotid stenosis was not significant (p>0.05) between dyslipidaemic and non-dyslipidaemic group. The results were shown in table X.

In patient with e”50% carotid stenosis, 7(23.33%) had high factor VIII activity and 23(76.67%) had normal factor VIII activity. In patient with <50% carotid stenosis, 2(6.67%) had high factor VIII activity and 28(93.33%) had normal factor VIII activity. No significant difference (P>0.05%)between high factor VIII activity and normal factor VIII activity related to severity of carotid stenosis. The result are shown in table XI.

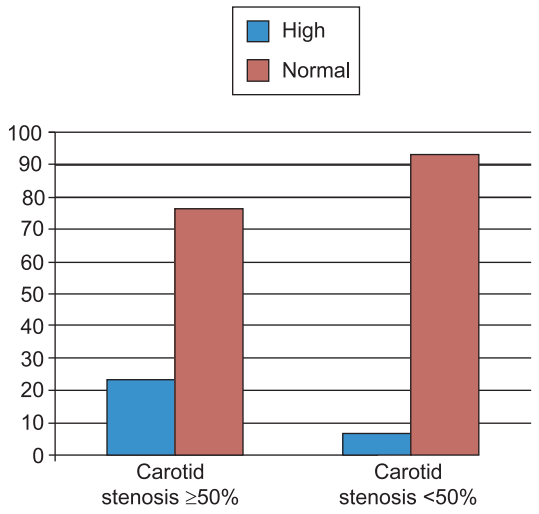

Fig.-3: *Bar diagram shows relation between severity of carotid stenosis and factor VIII activity*

Discussion:

This cross sectional study was carried out with an aim to explore the association between carotid atherosclerosis and high factor VIII activity in patients with ischemic stroke. For this purpose, a total 67 patients of ischemic stroke age ranging from 35 to 85 years were purposively selected who attended in the Department of Neurology of Bangabandhu Sheikh Mujib Medical University, Dhaka during July, 2009 to June, 2011. Among them, seven patients were excluded from the study because of four had chronic kidney disease, two had valvular heart disease and one had chronic liver disease. Finally 60 patients were enrolled in this study .

Previous population based study done by Beamer et al[16] shown the mean age of the patients having ischemic stroke was 66±8 years, whereas the mean age of patients in our study was 58.0±10.7 years.

In this study it was observed that 61.7% were male and rest 38.3% were female patients and male female ratio was 1.6:1 In a similar study done previously by Khan[17] the ratio was found 2.75:1. Another study found M:F 2.53:1 in stroke patients irrespective of types[18] . The present hospital based study may not reflect the actual ratio in the community because in our society female stroke patients usually do not get admitted to hospital because of religious ground and lack of attention by their family.

Regarding monthly family income, no significant (P>0.05) difference was found between <50% and >50% carotid stenosis in this study.

In the present cross sectional study of 60 ischemic stroke patients we found mild carotid stenosis in 30 patients (50%), moderate stenosis in 16 patients (26.7%) and severe stenosis in 14 patients (23.3%).This observation is supported by Hadi et al[19] and Razzaq et al[20].

Change et al [21] in their cross sectional study found the strongest correlation of age with >50% carotid stenosis. They had also explored, after age 20, every 10 year increase in age would double the risk of having <50% carotid stenosis to becoming >50% carotid stenosis. The present study also showed that age more than 50 year is a significant predictor of >50% carotid stenosis (OR: 21.33, 95%. CI: 3.71-

85.7, P=0.001). Similar observations were obtained from different investigators[22,23]. Our study did not find any association between gender and carotid stenosis (OR: 0.65, 95% CI: 0.20-2.11, P=0.425). Similar result was obtained in an other study(OR:0.055,95%CI:0.30-0.99,P value0.06)[23].However O'Leary et al[24] and Caplan et al[25] observed male sex was a significant predictor of moderate to severe carotid stenosis than female.

SU et al[26] in their community based observational study with 3602 ischemic stroke patients in Taiwan shows smoking is a significant predictor of >50% carotid stenosis (OR: 1.52, 95% CI: 1.30-1.89, P value <0.05) where as our study failed to display any association between smoking and carotid stenosis(OR:1.18,95%CI:0.33-4.19,P value=0.774). The difference is probably due to difference in selection criteria and small sample size in this study. Further large population based longitudinal studies are needed to identify the relation between smoking and severity of carotid stenosis.

The present study shows that hypertension is significant predictor of >50% carotid stenosis (OR: 6.50, 95% CI: 1.59-28.69, P=0.002).Similar observations were found by SU et al. [26] and Fisher et al.[27].

The present study reveals significant association between diabetes and severity of carotid stenosis (OR: 3.76, 95% CI: 1.09-13.34, P=0.016). Hillen et al [30] in their observational cross sectional study found a significant correlation between carotid stenosis and diabetes (OR: 2.92, 95% CI: 0.98-11.23, P<0.05).Several studies have shown diabetes is an independent risk factor of carotid atherosclerosis and atherothrombotic cerebral infarction[28,29],whereas Change et al. failed to confirm the result (OR: 1.28, 95% CI: 0.77-2.11, P= 0.34)[21].

Our study did not found any association between dyslipidaemia and severity of carotid stenosis (OR: 0.65, 95% CI: 0.20-2.11, P value 0.425).Several hospital based case control studies have suggested an association between high cholesterol and extracranial carotid stenosis[31,32] whereas other population based study showed a conflicting result both for high cholesterol and triglyceride in the prediction of carotid intima-media thickness[33].

The potential source of bias may be related to the study design since lipid lowering therapy were not taken into account. Further, multiple measurement and time integrated effect of longitudinal study are needed to identify the relation between dyslipidaemia and the severity of carotid stenosis.

In this study, patient with e"50% carotid stenosis, 7(23.33%) had high factor VIII activity and 23(76.67%) had normal factor VIII activity. In patient with <50% carotid stenosis, 2(6.67%) had high factor VIII activity and 28(93.33%) had normal factor VIII activity. No significant difference was found (P>0.05%) between high factor VIII activity and normal factor VIII activity related to severity of carotid stenosis. Our present study did not found any association between high factor VIII activity and severity of carotid carotid stenosis(OR:4.26,95% CI:0.70-33.16,P=0.072). Pan et al[34] in their case control study found high factor VIII activity was associated with moderate and severe carotid stenosis (OR: 3.35, 95% CI: 0.55-3.33, P value <0.05). Our study is not consistent with this study. The difference of result probably due to a potential source of bias, demographic variations between Chinese and Bangladeshi population and difference of study design. On the other hand as Von Willebrand antigen is the carrier protein for factor VIII, both factor VIII and Von Willebrand antigen should be measured to access the association between high factor VIII activity and carotid atherosclerosis.

The application of multiple measurements and time integrated effect of longitudinal study may further evaluate the association between degree of carotid stenosis and high factor VIII activity.

In regard to the relation between carotid stenosis and risk factors, evidence from the various literatures are quite discordant. Of all the risk factors investigated age, hypertension and diabetes has independent association with severity of carotid stenosis. Although sex, smoking, dyslipidaemia and high factor VIII activity were considered important risk factors for atherosclerosis, the present study did not find any association.

Conclusion:

The aim of the study was to explore the association between carotid atherosclerosis and high factor VIII activity in ischemic stroke. The present study did not find any association between severity of carotid atherosclerosis and high factor VIII activity in ischemic stroke.

Limitation of the study

This is a study based on data collected from Neurology department of BSSMU, Dhaka. The patients with ischemic stroke, who do not attend this department, were not included in this study population. Therefore, the sample lacks representation of the population. Furthermore, many confounding variables like age, sex, smoking, hypertension, diabetes, dislipidaemia & dietary habit may influence the result of the study. On the other hand, as Von Willebrand factor is the carrier protein for factor VIII further studies are needed to elucidate the role of both protein in relation to carotid atherosclerosis.

In order to include all of the patients suffering from ischemic stroke it will require such a study that would be conducted over a large population of vast area. But such an extensive study was not feasible for several constraints like time, resources and financial etc.

Recommendations

Besides traditional risk factors such as hypertension, diabetes and dyslipidaemia additional treatable risk factors that can be easily measured and highly prevalent in the general population. Although this study did not find any association between carotid atherosclerosis and high factor VIII activity, further application of multiple measurements and time-integrated effect of longitudinal study may evaluate the association between severity of carotid atherosclerosis and high factor VIII activity in ischemic stroke.

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