Computed Tomography Evaluation of Intracranial Vascular Calcification in Major Ischemic Stroke Patients (Vascular Territory) - Its Distribution and Association with Vascular Risk Factors: A Retrospective Trial

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Objective: *Our objective was to determine the distribution of intracranial atherosclerotic calcification, its association with risk factors, and cerebrovascular events in patients with major ischemic stroke.*
Material and Method: *In this retrospective study, 327 patients who underwent CT scan of brain were included and the clinical parameters were recorded. Two neuroradiologists evaluated the non-contrast axial CT images for any of intracranial arteries, based on a standard CT scoring system for extent (0-4) and thickness (0-4). The composite CT score for extent and thickness of these vascular segments or vessels were recorded on all patients.*
Results: *Based on of MDCT features, 155 major ischemic stroke and 172 non-ischemic stroke were enrolled. The highest prevalence of calcification was seen in intracranial internal carotid artery (IICA) (73%), and less commonly in the vertebral artery (8%). There were higher prevalence of intracranial artery calcification in ischemic stroke patients than non-ischemic stroke patients (82% vs. 52%, p<0.0001). Hypertension (OR = 1.903, 95% CI: 1.019-3.552, p<0.05), intracranialartery calcification (OR = 2.147, 95% CI: 1.143-4.033, p<0.05), moderate degree of calcification (OR = 2.631, 95% CI: 1.299-5.260, p<0.05), and severe degree of calcification (OR = 3.479, 95% CI: 1.500-8.068, p<0.05) were found to be independently associated with ischemic stroke.*
Conclusion: *Significant intracranial atherosclerosis as determined by severe CT calcification had higher incidence in ischemic stroke patients. Intracranial artery calcification with moderate and severe degree of calcification and hypertension were independently significant associated with ischemic stroke. CT calcification score might serve as an indicator of intracranial atherosclerotic disease and might be useful in predicting ischemic stroke.*

Keywords: *Computed tomography, Intracranial arterial calcification, CT score, Stroke, Risk factors*

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Stroke is the third most common cause of death[1]. Leading cause of long-term neurological impairment of the stroke survivors approximately 30% are permanently disabled[2]. Annually, almost 500,000 new cases of stroke occur in USA[1]. About 150,000 new cases of stroke occur in Thailand[1]. The vascular risk factors are hypertension, diabetes, hyperlipidemia, cigarette smoking, alcohol consumption, obesity, and metabolic syndrome[3].

Of all strokes, approximate 70% are first-time events, thus primary-care physicians have a great opportunity to identify patients who may benefit from risk factor modification[4]. Initiation of primary prevention strategies may have the greatest impact on the disease and its enormous toll on the healthcare system[4].

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Intracranial artery calcification is frequently observed in computed tomography (CT) brain, which is a process of atherosclerosis[5]. The previous study reported the intracranial artery calcification in consecutive patients referred for CT brain scanning at Siriraj Hospital[6]. There is an association between intracranial artery calcification in posterior circulation and ischemic stroke of posterior fossa[6].

In this retrospective study, we sought to determine the distribution of intracranial atherosclerotic calcification, its association with risk factors, and cerebrovascular events in patients with major ischemic stroke at Siriraj Hospital.

Material and Method

Patient cohort

Our report included all the patients referred to the Siriraj Hospital for brain CT imaging between October 1, and November 30, 2010. CT scan of brain was performed in each patient at least once during

this period. Exclusion criteria were patients who had previous history of brain surgery, intracranial hemorrhage or previous history of intracranial hemorrhage, age less than 35 years and transient ischemic attack (TIA) patients.

Their medical histories related to atherosclerosis, including history of hypertension, diabetes, and hyperlipidemia was determined by medical record at Siriraj Hospital. All patients' subjects were defined as hypertension if their systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or if they were receiving blood pressure-lowering medication[7]. Patients were considered diabetes if fasting plasma glucose ≥7 mmol/L (126 mg/dL) or if when a history of treatment for diabetes[8]. Hyperlipidemia was diagnosed when serum showed total cholesterol >220 mg/dl, triglyceride level >150 mg/dl, high-density lipoprotein (HDL) cholesterol <40 mg/dl or when a history of treatment for hyperlipidemia[8].

MDCT protocol

All CT examinations were done with a 64-slice multidetector-row computed tomography (MDCT) (Siemens and General Electric medical systems). Following parameters: 120 KVp, field of view: head, 300 mA, detector combination 64x1.25 mm and 64x1.5 mm, axial mode, the whole brain was covered from the skull base to the vertex.

Image analysis

The results were evaluated by two experienced neuroradiologists blinded to all the clinical data of the study population. Area of calcification was evaluated by using wide bone window (window width/level = 2,000/400). Then area of infarction was evaluated by brain window (window width/level = 80/30). The area of infarction was defined as hypodensity area.

Foci of calcification were defined as hyperdense foci with attenuation number more than 90 HU[9] (Fig. 1). Severity of calcification was further classified as extent (Fig. 2-5) and thickness (Fig. 6) according to Grading scales for CT scoring from Mak et al[10]. A composite CT score of 0 to 2, 3 to 5, and 6 to 8 were classified as mild, moderate, and severe degree of intracranial atherosclerosis, respectively (Table 1). A consensus reading was obtained if there was any discrepancy between the two radiologists.

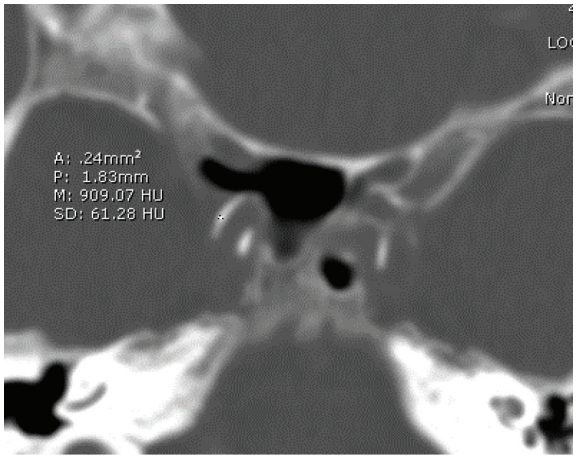

Fig. 1 Examples of intracranial artery calcification. CT images of intracranial internal carotid artery calcification showed hyperdense foci with attenuation number more than 90 HU.

Statistical analysis

The Chi-square test was used to compare the proportions of prevalence of intracranial artery calcification and vascular risk factors between ischemic stroke patients and non-ischemic stroke patients. Stepwise multiple logistic regression analysis was used to identify variables (age, gender, history of hypertension, diabetes and hyperlipidemia and intracranial artery calcification) that contributed significantly to the occurrence of ischemic stroke. Statistical analysis was performed with a statistical software package (SPSS, version 18). The *p*-value

Table 1. Grading scales for CT scoring

Grade	Extent of calcification of intracranial artery
0	No calcification
1	Dot of calcification
2	Crescentic area of calcification <90° of carotid wall circumference
3	Calcification 90-270° circumference
4	Calcification 270-360° around carotid circumference
Grade	Thickness of calcification of intracranial artery
0	No calcification
1	Calcification 1 mm thick
2	Calcification 2 mm thick
3	Calcification 3 mm thick
4	Calcification >3 mm thick

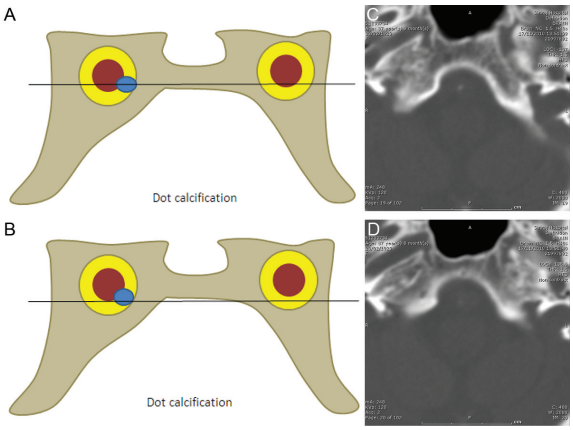

Fig. 2 Examples of extent of calcification grade 1 (Dot calcification). (A, B) Schematic measurement the extent of ICA calcification on coronal view. (C, D) Axial CT scan correlated to the A and B, respectively.

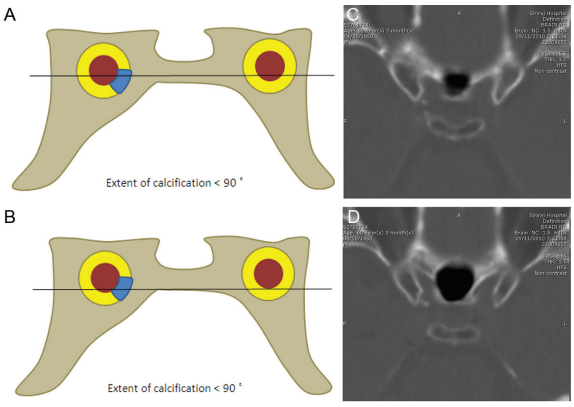

Fig. 3 Examples of extent of calcification grade 2 (Crescentic area of calcification <90° of carotid wall circumference). (A, B) Schematic measurement the extent of ICA calcification on coronal view. (C, D) Axial CT scan correlated to the A and B, respectively.

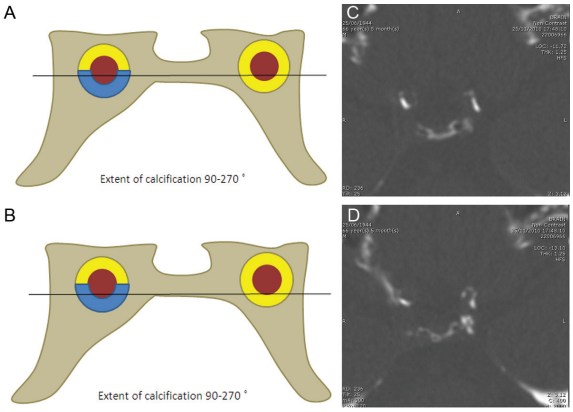

Fig. 4 Examples of extent of calcification grade 3 (Calcification 90-270° circumference). (A, B) Schematic measurement the extent of ICA calcification on coronal view. (C, D) Axial CT scan correlated to the A and B, respectively.

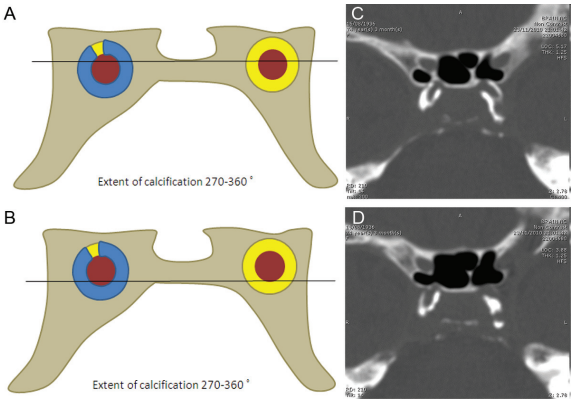

Fig. 5 Examples of extent of calcification grade 4 (Calcification 270-360° around carotid circumference). (A, B) Schematic measurement the extent of ICA calcification on coronal view. (C, D) Axial CT scan correlated to the A and B, respectively.

<0.05 was taken as statistically significant was taken as statistically significant.

Results

Three hundred twenty seven patients that included 155 (47%) ischemic stroke patients and 172 (53%) non-ischemic stroke patients were included in this study. There was a higher prevalence of intracranial artery calcification in ischemic stroke patients than non-ischemic stroke patients (82% vs. 52%, $p<0.0001$) (Table 2).

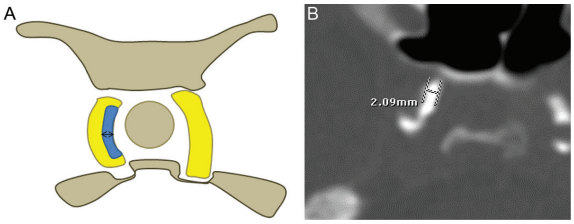

Fig. 6 Examples measurement of thickness of calcification. (A) Schematic measurement the extent of ICA calcification on axial view. (B) Axial CT scan correlated to A.

Two hundred sixteen patients (66%) had intracranial artery calcification. The prevalence of intracranial artery calcification in ischemic stroke patients was highest in intracranial internal carotid artery (IICA) (73%) and less common in vertebrobasilar system (8%).

Moreover, the prevalence of intracranial artery calcification was calculated by age group. In 327 patients, patients with intracranial artery calcification had higher prevalence than patients with no intracranial artery calcification in age group 61 to 80 years and older than 80 years than those with no intracranial artery calcification (58% vs. 13% in age group 61 to 80 years and 13% vs. 1% in age older than 80 years, $p<0.0001$) (Table 2). Gender was not different as compared between intracranial artery calcification patients and no intracranial artery calcification patients.

Stepwise multiple logistic regression analysis (Table 3) was performed to find the independent factors associated with intracranial artery calcification. The variables entered in the logistic regression model included age group, hypertension, diabetes, and hyperlipidemia. The result found that age group 41 to 60 years (OR = 4.104, 95% CI: 1.500-11.223, $p = 0.006$), age group 61 to 80 years (OR = 35.000, 95% CI: 11.691-104.779, $p<0.0001$), age group >80 years (OR = 99.644, 95% CI: 10.791-920.074, $p<0.0001$), and diabetes (OR = 8.711, 95% CI: 2.530-29.997, $p = 0.001$) were independently associated with intracranial artery calcification.

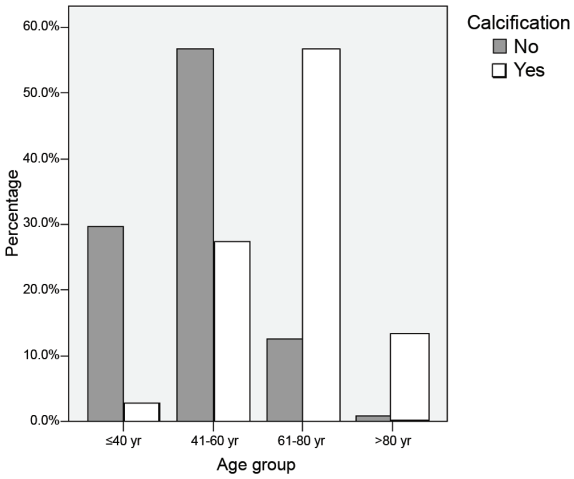

Fig. 7 Relationship between intracranial artery calcification and age group.

Among the 155 ischemic stroke patients, there was 7% mild calcification, 40% moderate calcification, and 35% severe calcification according to composite CT scoring. The ischemic stroke patients had higher prevalence of moderate and severe calcification than

Table 2. Univariate comparison between patients with and without intracranial artery calcification

Variable	Intracranial artery calcification (n = 216)	No intracranial artery calcification (n = 111)	*p*-value
Age group			<0.0001
≤40 years	3%	29%	
41-60 years	27%	57%	
61-80 years	57%	13%	
>80 years	13%	1%	
Gender			0.23
Male	45%	52%	
Female	55%	48%	
Hypertension	56%	17%	<0.0001
Diabetes	38%	4%	<0.0001
Hyperlipidemia	34%	11%	<0.0001

Table 3. Multivariate analysis to identify correlates of intracranial artery calcification

	p-value	Odds ratio	95% CI	
			Lower	Upper
Age group 41-60 years	0.006	4.104	1.500	11.223
Age group 61-80 years	<0.0001	35.000	11.691	104.779
Age group >80 years	<0.0001	99.664	10.791	920.074
Diabetes	0.001	8.711	2.530	29.997

non-ischemic stroke patients (40% vs. 25% in moderate calcification and 36% vs. 14% in severe calcification, $p<0.0001$) (Table 4).

The ischemic stroke patients had higher prevalence of vascular risk factor than non-ischemic stroke patients, hypertension (57% vs. 30%, $p<0.0001$), diabetes (37% vs. 16%, $p<0.0001$), or hyperlipidemia (33% vs. 20%, $p = 0.007$) (Table 4). The ischemic stroke patients had higher prevalence of age group 61 to 80 years and older than 80 years than non-ischemic stroke patients (53% vs. 31% in age group 61 to 80 years and 14% vs. 5% in age older than 80 years, $p<0.0001$) (Table 4). Gender was not difference as compared between ischemic stroke and non-ischemic stroke patients.

Stepwise multiple logistic regression analysis (Table 5) was performed to find the independent factors associated with ischemic stroke. The variables entered in the logistic regression model included age group, hypertension, diabetes, hyperlipidemia, intracranial artery calcification, and classification of intracranial artery calcification. The result found that hypertension (OR = 1.903, 95% CI: 1.019-3.552, $p = 0.043$), intracranial artery calcification (OR = 2.147, 95% CI: 1.143-4.033, $p = 0.018$), moderate degree of calcification (OR = 2.631, 95% CI: 1.299-5.260, $p = 0.007$) and severe degree of calcification (OR = 3.479, 95% CI: 1.500-8.068, $p = 0.004$) were independently associated with ischemic stroke.

Discussion

In this retrospective study, ischemic stroke patients were used to evaluate the clinical significance of intracranial artery calcification. About 82% of our ischemic stroke patients in the present study showed intracranial artery calcification. Intracranial artery calcification, moderate and severe degree of calcification, and hypertension were independently associated with ischemic stroke. Similar study performed in Hong Kong reported by Chen et al[9] that higher prevalence of intracranial artery calcification in ischemic stroke patients than controls (92.6% vs.

Table 4. Univariate comparison between patients with and without ischemic stroke

Variable	Ischemic stroke (n = 155)	Non-ischemic stroke (n = 172)	*p*-value
Age (year) (mean)	66	56	
Age group			<0.0001
≤40 years	7%	17%	
41-60 years	27%	46%	
61-80 years	53%	31%	
>80 years	13%	5%	
Gender			0.27
Male	45%	50%	
Female	55%	50%	
Hypertension	57%	30%	<0.0001
Diabetes	37%	16%	<0.0001
Hyperlipidemia	33%	20%	0.007
Intracranial artery calcification	82%	52%	<0.0001
Classified of calcification			<0.0001
Mild	7%	13%	
Moderate	40%	25%	
Severe	36%	14%	

Table 5. Multivariate analysis to identify correlates of ischemic stroke

	p-value	Odds ratio	95% CI	
			Lower	Upper
Hypertension	0.043	1.903	1.019	3.552
Intracranial artery calcification	0.018	2.147	1.143	4.033
Moderate degree of calcification	0.007	2.613	1.299	5.260
Severe degree of calcification	0.004	3.479	1.500	8.068

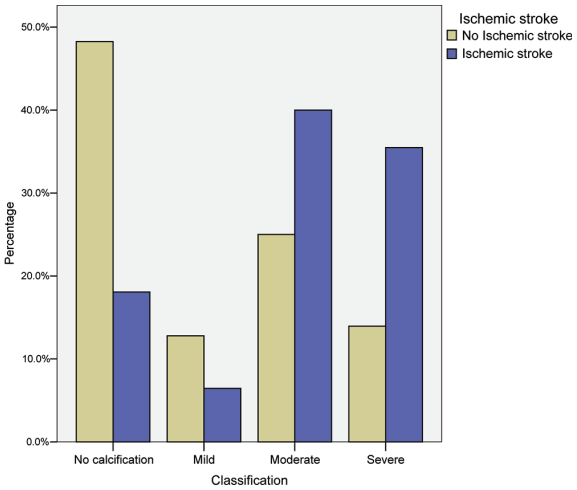

Fig. 8 Relationship between ischemic stroke and classification of intracranial calcification.

76.4%, $p<0.001$). Intracranial artery calcification, hypertension, smoking, hyperlipidemia, and atrial fibrillation were found to be independently associated with ischemic stroke. Similarly, Bugnicourt et al demonstrated that the IAC score was a strong and independent predictor of all-cause mortality and ischemic vascular events after hospital discharge, even after adjustment for other possible predictors[11]. Chung et al also found that cerebral artery calcification was common in patients with ischemic stroke and calcification was associated with white matter hyperintensities[12]. Erbay et al found that acute small vessel ischemia, chronic small vessel ischemia, and acute large vessel ischemia were associated with a high ICAC grade[13]. The results presented in the article by Bos et al, arterial calcification in major vessel beds is associated with vascular brain disease on magnetic resonance imaging[14].

Chen et al[9] also found in their CT screening study for intracranial artery calcification that clinical variables such as age, history of ischemic stroke and white cell count were independently associated with intracranial artery calcification. Similar to our study, they found that clinical variables such as age more than 40 years and diabetes were independently associated with intracranial artery calcification. Study by Erbay et al demonstrates high intracranial atherosclerosis cavernous carotid artery calcification (ICAC) patients were older and had more commonly history of stroke and diabetes mellitus, which similar to our study. Therefore, hypertension, CAD, and atrial fibrillation were common association. However, the difference between high and low ICAC for sex and cholesterol was not statistically significant[15].

Our result showed 7% of the patients had mild calcification, 40% moderate calcification and 35% severe calcification. Our grading of intracranial artery calcification was based on the modification by Babiarz et al[16] of method originally described by Woodcock et al[17]. Babiarz et al enabled the assessment of both CCAs for absent calcification (grade 0), dots (grade 1), arcs (grade 2), incomplete (grade 3), and complete (grade 4) circumferential calcification of the carotid artery. In addition, the thickness of the calcification was estimated by using the centimeter scale. They used CT scores and CT thicknesses separately and together to maximize ability to grade the atherosclerosis. However, they found that circumferential degree or thickness of cavernous artery calcification was not correlated with middle cerebral artery (MCA) or non-MCA infarctions. In addition, CCA calcification scores did not differ between patients with stroke and those without stroke[16]. Woodcock et al, calcification was characterized as absent, mild (thin, discontinuous), moderate (thin, continuous or thick, discontinuous), or severe (thick, continuous). In addition, they found correlation between severe calcification and greater than 50% stenosis of carotid siphon as determined angiographically[17]. Sohn et al also indicated the underlying etiology of either large artery atherosclerosis or lacunar stroke that cerebral arterial calcification[5]. Taoka et al found positive correlation between calcium scores on CT and angiographic findings there were statistically significant differences between the "smooth" and "irregular", "irregular" and "stenosis" and the "smooth" and "stenosis". However, no significant differences in calcium scores were observed between patients groups who did or did not experience a cerebral stroke[18]. Nandalur et al found that calcium scores in the cervical carotid arteries might represent an independent marker for luminal stenosis and ischemic symptoms[19].

Our study used attenuation number more than 90 HU to determine the calcification. While, de Weert et al found that MDCT was able to quantify total plaque area, calcifications, and fibrous tissue in atherosclerotic carotid plaques. The measured Hounsfield values were 657±416 HU and 88±18 HU for calcifications and fibrous tissue, respectively[20].

As for the distribution of different intracranial artery calcification in our study population, the highest prevalence of calcification was seen in IICA, at about

73% and less common in vertebrobasilar system at about 8%. The distribution pattern of calcification was similar to Hong Kong study reported by Chen et al[9] that highest prevalence of calcification in IICA at about 80.4% and less common in vertebral artery at about 35.6%. Mak et al[10] also found a high prevalence of intracranial calcification of IICA at about 94%. Similarly, Chung et al found that I-ICA was the most frequently and most severely affected cerebral artery[12].

Our study found that vascular risk factors, such as hypertension, intracranial artery calcification, moderate and severe degree of calcification might be independently predictor of ischemic stroke. However, the association between vascular calcification and ischemic vascular disease is still controversial[2]. Some investigator reported that vascular calcification was a marker of atherosclerosis as well as a major cause of poor arterial compliance.

Conclusion

Intracranial artery calcification was most common in IICA. Age older than 40 years and diabetes were independently associated with intracranial artery calcification. Whereas, intracranial artery calcification, moderate and severe degree of calcification and hypertension were independently associated with ischemic stroke. Hence, this CT calcification score might serve as an indicator of intracranial atherosclerotic disease and might be useful in predicting chance of ischemic stroke.

What is already known on this topic?

Ischemic stroke patients were used to evaluate the clinical significance of intracranial artery calcification. Intracranial artery calcification is common in patients with ischemic stroke and calcification is associated with white matter hyperintensities. The previous study reported the intracranial artery calcification in consecutive patients referred for CT brain scanning at Siriraj Hospital[6]. There is an association between intracranial artery calcification in posterior circulation and ischemic stroke of posterior fossa.

What this study adds?

Significant intracranial atherosclerosis as determined by severe CT calcification was higher incidence in ischemic stroke patients. Intracranial artery calcification, moderate and severe degree of calcification and hypertension were independent significant associated with ischemic stroke. CT calcification score might serve as an indicator of intracranial atherosclerotic disease and be useful in predicting chance of ischemic stroke.

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เอกซเรย์คอมพิวเตอร์ในการประเมินภาวะแคลเซียมเกาะที่หลอดเลือดสมองในผู้ป่วยที่มีภาวะสมองขาดเลือดไปเลี้ยงเป็นบริเวณกว้างและปัจจัยเสี่ยงที่สัมพันธ์กัน

พิพัฒน์ เชี่ยววิทย์, สิริอร ตริตระการ, เต็มพร เครือมาก

วัตถุประสงค์: *เพื่อที่จะประเมินรูปแบบการเกาะของหินปูนที่ผนังหลอดเลือดในสมองและปัจจัยเสี่ยงที่สัมพันธ์กับภาวะนี้ ในผู้ป่วยที่สมองขาดเลือดที่มีบริเวณกว้าง*

วัสดุและวิธีการ: *การศึกษาย้อนหลังผู้ป่วย จำนวนทั้งสิ้น 327 ราย ที่ได้รับการตรวจ CT สมอง และมีการบันทึกข้อมูล ปัจจัยเสี่ยง โดยมีการแปลผลการตรวจ CT สมองที่ไม่ฉีดสารทึบรังสี โดยรังสีแพทย์ทางระบบประสาท 2 คน โดยมีการแบ่งคะแนนการสะสมแคลเซียมตามมาตรฐานดังนี้ ขอบเขต (0-4) ความหนา (0-4) และมีการบันทึกตัวแปรทางคลินิก และคะแนนที่ได้*

ผลการศึกษา: *การตรวจด้วยเอกซเรย์คอมพิวเตอร์ของผู้ป่วยจำนวนทั้งสิ้น 327 ราย วินิจฉัยว่าเป็นผู้ป่วยที่สมองขาดเลือดที่มีบริเวณกว้างจำนวน 155 ราย และผู้ที่ไม่พบสมองขาดเลือดในผู้ป่วยจำนวน 172 ราย การศึกษาพบอุบัติการณ์การสะสมแคลเซียมสูงในหลอดเลือดแดงสมองของ internal carotid (IICA) ร้อยละ 73 และพบอุบัติการณ์การสะสมแคลเซียมน้อยในหลอดเลือดแดงสมองของหลอดเลือด vertebrobasilar ร้อยละ 8 มีอุบัติการณ์สูงของการพบว่ามีการสะสมแคลเซียมในหลอดเลือดแดงในผู้ป่วยสมองขาดเลือดมากกว่าผู้ป่วยสมองไม่ขาดเลือด (82% vs. 51%, p<0.0001) และไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างความดันโลหิตสูง ระดับการสะสมแคลเซียมในหลอดเลือดแดง ทั้งผู้ที่มีการสะสมแคลเซียมในหลอดเลือดแดงน้อย (OR = 2.147, 95% CI: 1.143-4.033 p<0.05) ผู้ที่มีการสะสมแคลเซียมในหลอดเลือดแดงปานกลาง (OR = 2.631, 95% CI: 1.299-5.260, p<0.05) และผู้ที่มีการสะสมแคลเซียมในหลอดเลือดแดงจำนวนมาก (OR = 3.479, 95% CI: 1.500-8.068 p<0.05) กับการเกิดภาวะสมองขาดเลือด*

สรุป: *การตรวจด้วยเอกซเรย์คอมพิวเตอร์มาใช้ในการบอกระดับการสะสมแคลเซียมในหลอดเลือดแดงมีประโยชน์ในการประเมินโอกาสการเกิดสมองขาดเลือด โดยพบอุบัติการณ์สมองขาดเลือดสูงในผู้ป่วยที่การตรวจ CT สมองมีการสะสมแคลเซียมในหลอดเลือดแดงมาก และพบมีความสัมพันธ์อย่างไม่เกี่ยวข้องกันระหว่างอุบัติการณ์สมองขาดเลือดกับระดับการสะสมแคลเซียมในหลอดเลือดแดงสมองขนาดปานกลาง ขนาดมาก และภาวะความดันโลหิตสูง*