

Intracranial Internal Carotid Artery Calcification: a Predictor of Stroke in the Next Five Years

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ABSTRACT

Objective: The fact that calcification in the coronary artery is associated with ischaemic heart disease is well-known. Calcification is also very common in the transcranial and intracranial segments of internal carotid arteries. Previous studies on the association of calcification in the intracranial segment of the internal carotid arteries with stroke have yielded controversial conclusions. In this study we aimed to investigate the relationship between calcification of the transcranial and intracranial internal carotid arteries and the five-year stroke risk.

Methods: This was used as a case-control retrospective cohort study designed to avoid recall bias and allow more aggressive risk factor evaluation. Consecutive patients aged 50 to 80 years referred for computed tomography of the brain over a five-week period in 2005 were studied. The computed tomography images were reviewed by two radiologists blinded to clinical outcomes to assess the presence and degree of calcification in the transcranial and intracranial segments of both internal carotid arteries semi-quantitatively. Each artery was given a calcium score to reflect the calcium burden (none = 0, dot calcification = 1, thin or thick calcification affecting one side of the wall / thin calcification affecting both sides of the wall = 2, thick calcification affecting both sides of the wall = 3). The scores of both arteries were summed and thus patients with no internal carotid artery calcification had 0 scores and those with the highest calcium load scored 6. Each patient was categorised into two groups reflecting the calcium burden in these arteries, namely low calcium score (0-2) and high calcium score (3-6). Clinical records were reviewed over the subsequent five-year period to identify the development of a clinical acute stroke. The age, gender, history of smoking, diabetes mellitus, hypertension, hyperlipidaemia, and previous stroke were documented. Patients with the presence of an intracranial mass, extra-axial haemorrhages, or previous intracranial radiotherapy were excluded. Multiple logistic regression was applied to determine the association between incident acute stroke in the study period and internal carotid artery calcium scores and other stroke risk factors. The odds ratios for stroke and internal carotid artery calcium score and other risk factors were calculated and statistical significance was set at 5%. Possible multicollinearity among the factors was checked by the correlation matrix method and examination of tolerance.

Results: A total of 678 patients underwent computed tomography of the head over a five-week period between July and August 2005, and 461 (aged 50 to 80 years; 240 males, 221 females) were included in our study. In all, 271 (58.8%) patients were designated a low calcium score and 190 (41.2%) a high calcium score. Fifty-four patients developed a new onset of clinical stroke in the subsequent five-year period, resulting in a five-year stroke incidence of 11.7%. Binary logistic regression analysis revealed that those with high calcium score had a statistically significant higher incidence of stroke over that period compared to those with a low calcium score (adjusted odds ratio = 2.70; $p < 0.05$). This was independent of age, gender, smoking history, diabetes, hypertension, hyperlipidaemia, and previous stroke.

Conclusions: The presence of high rather than low calcium burden in the transcranial and intracranial segments of internal carotid arteries is an independent predictor of a higher clinical stroke risk in the ensuing five-year period. The odds (risk) ratio of five-year incident stroke in patients with a high score was 2.7-fold that of those with low scores.

Key Words: Carotid artery, internal; Cohort studies; Risk factors; Stroke; Vascular, calcification

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中文摘要

顱內頸動脈鈣化：五年內中風的預測因子

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目的：眾所週知，冠狀動脈的鈣化與缺血性心臟病有關。而經顱及顱內的頸內動脈出現鈣化很常見。過往有關顱內頸動脈鈣化與中風關係的研究結果有爭議。本文探討經顱及顱內頸內動脈鈣化情況與患者五年內中風的風險是否相關。

方法：為避免病人偏差以及積極地評估風險因素，本研究採取病例對照的回顧性研究。研究對象為2005年的連續五個星期內被轉介作腦CT的所有50至80歲的病人。兩名不知道病患預後的放射科醫生回顧CT影像，並為病人經顱及顱內的內頸動脈是否出現鈣化以及鈣化程度來作半定量分析。他們為每根動脈評價其鈣化積分來反映血管的鈣化程度：0=無鈣化、1=點狀鈣化、2=厚或薄鈣化並影響一邊血管壁，或薄鈣化影響兩邊血管壁、3=厚鈣化現象影響兩邊血管壁。然後把兩根血管的鈣化積分加起來。因此未有發現頸內動脈鈣化的病人的鈣化積分會是0，而鈣化積分為6的病人的血管鈣化負荷為最高。再按每位病人血管的鈣化負荷分為兩組：低鈣化積分（即0至2分）及高鈣化積分（即3至6分）。從2005年開始檢閱病人五年間的病曆紀錄找出他們是否有急性中風的情況。臨床紀錄記載了病人年齡、性別、吸煙紀錄、糖尿病、高血壓、高血脂和中風紀錄。而有顱內腫瘤、神經軸外出血、及曾接受顱內放射治療的病人則不被列入研究範圍內。利用多重邏輯回歸分析決定研究期間急性中風的發生與內頸動脈鈣化積分以及其他中風危險因素的關係，並計算其比數比，5%為達至統計顯著性。再用相關係數矩陣及檢測限差的方法找出多項因素的多元共線性。

結果：2005年7月至8月的五個星期內共678名病人接受腦CT檢測，其中461人被納入研究範圍（年齡介乎50至80歲的240男性及221女性）。271人（58.8%）屬低鈣化積分，另190人（41.2%）屬高鈣化積分。54人在其後的五年內出現首發中風，即五年中風率為11.7%。二元變數邏輯回歸分析顯示鈣化積分高的病人比鈣化積分低的病人的中風率明顯高（調整後比數比=2.70； $p < 0.05$ ）。這點獨立於病人年齡、性別、吸煙紀錄、糖尿病、高血壓、高血脂和中風病史。

結論：經顱及顱內的內頸動脈有高度鈣化的情況是患者五年內中風風險的一項獨立預測因子。鈣化積分高的病人五年內中風的風險是鈣化積分低的病人的2.7倍。

INTRODUCTION

Stroke is the second commonest cause of death and major disability worldwide.¹ A decreasing trend in stroke incidence in high-income countries but an increasing trend in mid- to low-income countries has been demonstrated over the past four decades.² This can be attributed to westernisation of lifestyle of mid-low income countries but more importantly in the high-income countries, implementation of reduction in risk factors for cardiovascular diseases, which have been proven effective at reducing stroke incidence significantly.^{3,4}

Arterial calcifications are very likely an indicator of atherosclerotic disease.⁵ The fact that calcification in

the coronary artery is associated with ischaemic heart disease is well-known.^{6,7} Calcification in the cervical carotid arteries is also related to the degree of luminal stenosis and ischaemic symptoms.⁸ Calcification is very common in the transcranial and intracranial segments of internal carotid arteries (ICAs). However, studies targeting these segments of the ICA are very limited, and conclusion from them about the association between calcification in the transcranial and intracranial segments of the ICAs and cerebral ischaemia have resulted in controversy.⁹⁻¹⁶ In this study, we aimed to identify the relationship between calcification of the transcranial / intracranial of ICA and the five-year stroke risk.

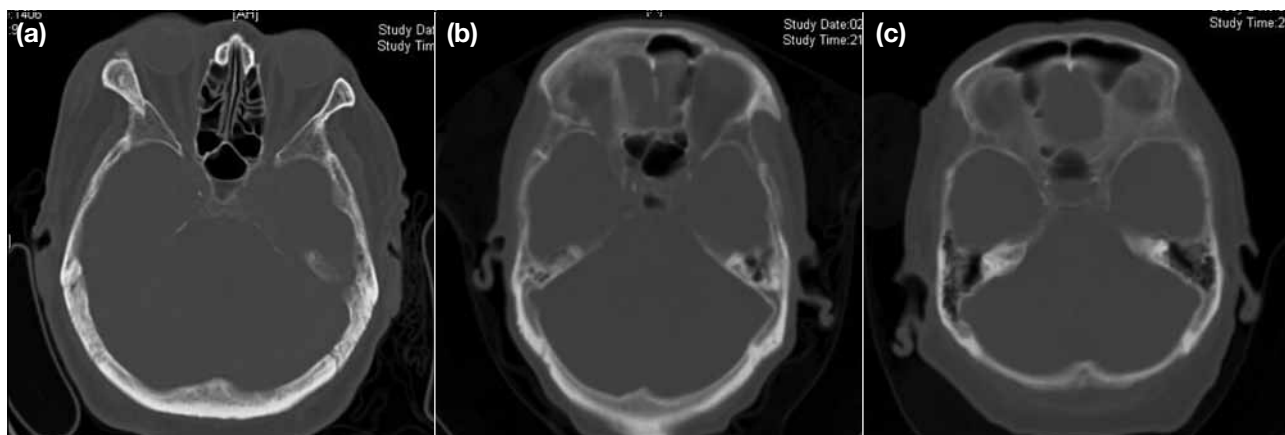


Figure. Examples of calcification scores given to the internal carotid artery using a bone window. (a) The score on the left is 0 and on the right is 1, (b) scores on both the left and right are 2, and (c) scores on both the left and right are 3.

METHODS

We undertook a retrospective case-control study to investigate the relationship between calcification of the transcranial / intracranial ICAs and the five-year stroke risk, while avoiding the bias of recall and aggressively assessing other risk factors. Consecutive patients aged 50 to 80 years referred for computed tomography (CT) of the brain over a five-week period between July and August 2005 were studied. Multidetector computed tomography (MDCT) with non-contrast scans of the brain were performed with 16-slice Philips Brilliance CT (Philips, The Netherlands). Scan parameters were as follows: 120 kV; 200 mA, thickness / increment – 3 mm / 3 mm. The CT images were reviewed on a Picture Archiving and Communication System station (AGFA IMPAX, Mortsel, Belgium) with the images processed to 6 mm of thickness. The images were reviewed by two radiologists blinded to the clinical outcomes, in order to assess the presence and degree of calcification in the transcranial and intracranial segments of both ICAs, including the petrous, cavernous, lacerum, clinoid, ophthalmic and communicating segments evident in the CT head examination. The presence of calcification in each artery was assessed using an image window of 300 Hounsfield Units (HU) and level of 100 HU. The degree of calcification in each artery was then assessed semi-quantitatively by first selecting the axial slice with most calcification and using an image window of 1800 HU and a level of 450 HU (bone window). A calcium score was given to reflect the calcium burden as follows (none = 0, dot calcification = 1, thick or thin calcification on one side of the wall / thin calcification on both sides of the wall = 2, thick calcification on both sides of the wall = 3). Sample images with different

scores are illustrated in the Figure. The scores of both ICAs were summed and thus a patient with no ICA calcification would have 0 score, and those with the highest calcium load would be scored 6. Each patient was then categorised into two groups reflecting the calcium burden in these arteries, namely low calcium score (0-2) and high calcium score (3-6). Clinical records were reviewed over the subsequent five-year period to identify the development of a clinically acute stroke. Patient age, gender, history of smoking, diabetes mellitus, hypertension, hyperlipidaemia, and previous stroke were documented. Patients having an intracranial mass, extra-axial haemorrhages, or previous intracranial radiotherapy were excluded. Binary logistic regression was performed to determine the association between incident acute stroke in the five-year period and the ICA calcium score together with other stroke risk factors. The odds ratios (OR) for ICA calcium scores and other risk factors were calculated and statistical significance was set at 5%. Possible multicollinearity among the factors was checked by the correlation matrix method and examination of tolerance. Interobserver reliability analysis using the Kappa statistic was performed. All analyses were performed with the Statistical Package for the Social Sciences (Windows version 16.0; SPSS Inc, Chicago [IL], US).

RESULTS

A total of 678 patients underwent CT of the head over a five-week study period in July and August 2005, of which 461 (age, 50-80 years; 240 males, 221 females) were included in our study. All the patients were of Chinese ethnicity. ICA calcification was found in 77% of our patients, which was comparable to most other

studies.^{12,13,15} In these patients, 271 (58.8%) had a low calcium score and 190 (41.2%) had a high score. The clinical characteristics of the two patient groups are shown in Table 1. In all, 54 patients developed new onset of clinical strokes in the ensuing five-year period, resulting in a five-year stroke incidence of 11.7%. Table 2 shows that in the subsequent five years, 17 and 37 patients developed strokes in the low calcium score and high calcium score groups, respectively. Binary logistic regression analysis revealed that those with high calcium scores had a statistically significant higher incidence of stroke in the ensuing five-year period than those with low calcium scores (adjusted OR = 2.687; 95% confidence interval [CI], 1.342-5.378) [Table 3]. Patients with a prior or presenting history of stroke also had a statistically significant higher incidence of stroke in the next five years (adjusted OR = 2.833; 95% CI, 1.392-5.769). The interobserver reliability was found to have a Kappa of 0.75 (p < 0.001).

DISCUSSION

Identification and correction of risk factors for stroke is without doubt effective in reducing the incidence of stroke which is a major cause of morbidity worldwide.

Table 1. Characteristics of the low- and high-calcium score groups.

Characteristics	No. (%) of patients*	
	Low calcium score	High calcium score
Mean age (years)	63.7	71.7
Gender		
Male	139 (30.2)	101 (21.9)
Female	132 (28.6)	89 (19.3)
Smoking history		
Non-smoker	137 (29.7)	83 (18.0)
Ex/current smoker	94 (20.4)	73 (15.8)
Unknown smoking history	40 (8.7)	34 (7.4)
Diabetes mellitus (type 2)	54 (11.7)	89 (19.3)
Hypertension	140 (30.4)	128 (27.8)
Hyperlipidaemia	49 (10.6)	42 (9.1)
Previous / present with stroke	110 (23.9)	121 (26.2)

* Unless otherwise stated.

Table 2. Occurrence of stroke over five years in the low- and high-calcium score groups.

	No. of patients	
	No new occurrence of stroke	New occurrence of stroke
Low calcium score	254	17
High calcium score	153	37
Total	407	54

Table 3. Results of logistic regression with stroke incidence in five years as dependent variable correlated with calcium score and other possible stroke risk factors.

	Odds ratio	95% Confidence interval	p Value
Age	1.005	0.966-1.047	0.791
Gender			
Female	1		
Male	1.041	0.537-2.019	0.906
Smoking history			
Non-smoker	1		
Smoker	0.611	0.291-1.286	0.195
Unknown smoking history	1.108	0.493-2.490	0.805
Diabetes mellitus (type 2)	1.175	0.616-2.243	0.625
Hypertension	1.098	0.551-2.187	0.791
Hyperlipidaemia	1.183	0.591-2.371	0.635
Previous / present with stroke	2.833	1.392-5.769	0.004
Calcium score			
Low calcium score	1		
High calcium score	2.687	1.342-5.378	0.005

Calcium burden in the coronary arteries and cervical carotid arteries has been associated with ischaemic heart disease and cerebrovascular accidents. Therefore it was logical to investigate whether calcification of the transcranial and intracranial segments of the ICA (readily assessable on routine brain CT) might be associated with stroke.

Limited numbers of studies have been undertaken to examine such a relationship, and the results have been controversial. Severe calcification at the carotid siphon was shown to correlate with more than 50% stenosis on angiography.^{9,10} However, Sohn et al¹¹ failed to demonstrate any association between calcification with haemodynamically significant stenosis of the involved arteries. Nevertheless, they only identified calcification in 40% of their patients which was far below the proportion detected in subsequent studies. Chen et al¹² in 2006 found calcification in nearly 70% of their patients and found an association between age, ischaemic stroke, and calcification. By means of a case-control study, they further demonstrated that calcification was an independent risk factor for stroke.¹³ However, in their study they only classified the patients as having the mere presence or absence of calcification and did not take the degree of calcification into consideration. The association between calcification and acute small vessel infarcts, i.e. lacunar infarcts has been documented.¹⁴ Calcification was also shown to be associated with white matter hyperintensities on magnetic resonance imaging and lacunar infarcts in stroke patients.¹⁵ On

the other hand, another study showed that there was no correlation between calcification and infarcts in middle cerebral artery (MCA) or non-MCA territories.¹⁶ A drawback of most of these studies was that people with no history of stroke were not investigated.

To date, no study using a retrospective cohort design to evaluate the relationship between transcranial and intracranial calcification and clinical stroke risk had been performed. Our study design also allowed more aggressive investigation of other putative risk factors. By using a longitudinal study design, we also obtained results relating to stroke incidence in contrast to stroke prevalence (demonstrated in prior studies). Our study also applied to calcification in patients with no history of stroke. We used clinical stroke as our focus, which was also different from previous studies.

Patients with an intracranial mass or extra-axial haemorrhage were excluded, since they could have had neurological deficits unrelated to stroke, rendering subsequent diagnosis of incident stroke unreliable. Previous intracranial radiotherapy treatment was also considered an exclusion criterion as it may cause non-atherosclerotic stenosis of arteries.

Unlike calcium score assessment of the coronary arteries, there is no standardised method to assess the ICAs, particularly the transcranial and intracranial segment. Therefore a semi-quantitative method to assess the calcium burden in arteries was utilised. A specified image window was used to assess the degree of calcification so as to enable the results to be more reproducible. A bone window reduces the blooming artefact caused by the calcification and allows for its assessment only when it attains a given degree of density. We identified calcification in 77% of our patients, which was comparable to most other studies.

Using logistic regression of potential risk factors for stroke, compared to patients with a low calcium score, those with a high score turned out to have a statistically significant risk of developing a new clinical stroke over a five-year period. The adjusted OR of which was just slightly lower than that for patients with a previous or presenting stroke (the strongest risk factors in our study). A positive correlation (though not statistically significant) was evident with other risk factors including age, diabetes, hypertension, and hyperlipidaemia. The OR for a smoking history was paradoxically less than 1.0, though not statistically significant. A major reason

for this phenomenon could be that many smokers had died of other causes (e.g. carcinoma) and thus did not survive long enough to develop stroke. Other contributing factors include missing data on smoking status as well as lack of a detailed smoking history, as it is known that being an ex-smoker versus active smoker and the period of abstinence all have effects on stroke risk.

Sampling bias was one of the limitations of our study, although we reviewed all consecutive patients referred for CT of the head. This is because many of these patients presented with some sort of neurological deficit and thus were clinically labelled as stroke, irrespective of the underlying pathology, and might explain why our stroke incidence was higher than expected. Another limitation was that our study only illustrated the effects of calcification in an older population, whereas the association between ICA calcification and stroke in younger age-groups remains undetermined. Thus, the generalisability of our study may be limited. Furthermore, although the assessors were blinded to the patient's history of stroke, they were not totally blinded to radiological evidence of previous cerebral infarction during their evaluation of both the ICAs. This might lead to over-estimation of calcium score in patients with CT evidence of infarction.

Our study showed that calcification of the transcranial and intracranial segments of the ICAs is associated with clinical stroke incidence. This is in line with previous studies that demonstrated the relationship with various radiological features of cerebral ischaemia. Our results imply that the relationship may even be stronger than for known traditional risk factors of stroke. Whether or not anti-platelet therapy could reduce stroke incidence in asymptomatic patients with intracranial ICA calcification is another important clinical issue to resolve. Thus, our study serves as an important guide to the design of future clinical trials on this issue.

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