PREVALENCE AND ITS ASSOCIATED FACTORS OF EXTRACRANIAL CAROTID STENOSIS IN PATIENTS WITH TRANSIENT ISCHEMIC OR ISCHEMIC STROKE IN BACH MAI HOSPITAL

Bui Nguyen Tung[1, 2, ✉], Mai Duy Ton[1], Pham Manh Hung[1,2]

[1]Bach Mai Hospital
[2]Hanoi Medical University

Incidence of transient ischemic attack (TIA) or ischemic stroke has increased in recent years in Viet Nam due to lifestyle changes. Carotid stenosis is a common cause of TIA/ischemic stroke. The purpose of this study was to estimate current prevalence and identify risk factors of ipsilateral internal carotid artery (ICA) stenosis in patients with TIA/ischemic stroke. We recruited patients hospitalized to Bach Mai hospital in the first half of 2021 who suffered from TIA/ischemic stroke. The primary outcome is the presence of significant carotid stenosis, defined as atherosclerotic narrowing of 50 percent or greater, and confirmed by multidisciplinary team (MDT) discussion. In total, 328 consecutive patients with TIA/ischemic stroke were included in this study. Of these, 29 (8.84%, 95% confidence interval (CI): 6.0 -12.45) have 50-99% ipsilateral ICA stenosis. Patients with considerable ICA stenosis are more likely to have type 2 diabetes, ischemic heart disease (IHD) and higher creatinine serum level. On multivariate logistic regression, type 2 diabetes (OR 2.61; CI 95%: 1.14 -5.97, p = 0,034), IHD (OR 5.27; CI 95%: 1.68 - 16.56, p < 0.001), creatinine level (OR 1.15/10 mmol/l ; CI 95%: 1.01 -1.3, p = 0.031) are statistically significant risk factors for 50-99% ICA stenosis. The prevalence of extracranial ICA stenosis in TIA/ischemic stroke patient in Viet Nam is lower than Western countries but quite similar to Asia regions. Diabetes mellitus, IHD and high creatinine level are important risk factors for symptomatic ICA stenosis.

Keywords: Carotid stenosis, prevalence, ischemic stroke, transient ischemic attack, diabetes, ischemic heart disease, creatinine.

I. INTRODUCTION

Large artery atherosclerotic disease is a crucial cause of TIA/ischemic stroke according to TOAST classification.[1] Extracranial internal carotid artery stenosis (ICA) is the most important cause of large artery stroke and when comparing to the different etiological sub-types of ischemic stroke, the highest risk for early recurrent stroke was found in these patients.[2]

Studies in Western countries on ICA stenosis in patients with TIA/ischemic stroke reported a prevalence ranging from 12% to 25%.[2,3] Meanwhile, studies in Asia recorded this rate to a lower extent from about 3.5 to 8%.[4,5] Therefore, screening for carotid stenosis plays an important role in the treatment and prevention. To improve the effectiveness of secondary prevention, it is important to identify the risk factors associated with carotid stenosis. In 2019, a study performed at a stroke center in London, UK found that hypertension, dyslipidemia, diabetes and coronary artery disease were risk factors for carotid stenosis.[6] Similarly, a study conducted by Den Brok et

Corresponding author: Bui Nguyen Tung
Bach Mai Hospital
Email: Nguyentung1238@gmail.com
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al. 2020 in the Netherlands found correlation between older age, male sex, and smoking with carotid stenosis.[7]

In VietNam, the rate of stroke in general and TIA/ischemic stroke in particular is increasing due to economic development and lifestyle changes.[8] A study conducted in 2016 by Yamanashi showed that the crude annual incidence rate of total first-ever stroke in central VietNam was 90.2 per 100,000 population (95% CI 81.1–100.2).[8] Latest stroke management guidelines recommended referring all patients with TIA/ischemic stroke for screening of carotid stenosis to plan a suitable treatment included carotid revascularization as necessary. In addition, to improve prevention strategies, it is important to identify risk factors for ICA stenosis.[9] However, there is currently no study in VietNam to evaluate the prevalence of carotid stenosis and associated risk factors in TIA/ischemic stroke patients.

We aim to assess contemporary prevalence and identify risk factors of ipsilateral internal carotid artery (ICA) stenosis in patients with TIA/ischemic stroke in Bach Mai hospital, a biggest tertiary center in the North of VietNam.

II. METHODS

We prospectively studied consecutive TIA/ischemic stroke patients admitted to the Stroke center (SC) and Viet Nam Heart Institute (VNHI), Bach Mai Hospital from 2021 January to 2021 June. Inclusion criteria were:

(1) TIA/ischemic stroke were diagnosed according to AHA/ASA 2013

(2) within 14 days from first event.[10]

Exclusion criteria were:

(1) previous carotid endarterectomy or stenting

(2) Discharged or death before screening carotid artery condition

(3) unable to provide consent or refused to participate in the study. Written informed consent was obtained from all participants.

Baseline patient characteristics were collected and included age, sex, history of atrial fibrillation, diabetes mellitus, hypertension, symptomatic peripheral vascular disease, hyperlipidemia, IHD, renal failure. Fundamental laboratory findings included creatinine, glucose, total cholesterol, LDL- C, HDL-C, triglyceride, HbA1c, electrocardiogram (ECG), echocardiography. Data were collected from medical records and patient measurement. Information from medical records were extracted using a predefined data collection form.

Carotid stenosis, identified by DUS, CTA or MRA, was defined by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria as: mild (less than 50 per cent stenosis), moderate (50-70 per cent), severe (over 70 per cent), or occlusion.[11]

With DUS, the degree of ICA stenosis was based on a combination of the presence of plaque and the flow rate defined as peak systolic velocity (PSV). A PSV of < 125 cm/s was diagnosed as stenosis of < 50%, a PSV of 125-230 cm/s as stenosis of 50 - 69% and a PSV above 230 cm/s as stenosis of 70 - 99%. Near-occlusion was defined as a considerably narrowed lumen with either a high, low or undetectable PSV. When near-occlusion was suspected on DUS, a CTA was performed to confirm this diagnosis. Complete occlusion of ICA was diagnosed when no patent lumen and no detectable flow was visible on DUS. When CTA and MRA were employed, the degree of ICA stenosis percentages were calculated following NASCET criteria, using the narrowest part of the ICA stenosis and a normal vessel distal to the stenosis.

Statistical analysis

Analysis of the data was performed using STATA for Windows V.16.0 (Statacorp. Texas, US). Continuous variables are presented as mean (± SD), and categorical variables as frequency and percentage. Comparisons were assessed using X^2 tests for categorical variables and Student's t-tests for continuous variables. Two- tailed p values <0.05 were considered statistically significant.

Multivariate logistic regression was applied to identify relating factors for prevalence of ICA stenosis. Univariate logistic regression was performed on sociodemographic factors (age, sex) and other potential factors that contribute to ICA stenosis such as medical history, creatinine. Only variables that had a p value < 0.10 on univariate analysis were selected for multivariate analysis.

Ethics approval

The study was approved by the Ethics Committee of the Hanoi Medical university, Vietnam, (Reference Number: IRB-VN01.001/IRB00003121/FWA 00004148).

III. RESULT

We included 328 participants with TIA/ischemic stroke in the first half of 2021. There were 208 (63.41%) males, with a mean age of 64.5 ± 12.9 years. All have had at least 1 vascular imaging modality to assess carotid artery. Hypertension was the most common comorbidity in 225 patients (68.2%). While the least reported comorbidity was peripheral vascular disease (3.35%). Atrial fibrillation accounted for 14.33% of the study population. Baseline characteristics and vascular risk factors of the study population are shown in **table 1.**

Table 1. Baseline characteristics of included patients, stratified by degree of stenosis in patients with acute TIA/ischemic stroke

	Total (n = 328)	Symptomatic ICA stenosis		P
		< 50% or no stenosis (n = 274)	50 - 100% stenosis (n = 54)	
Age, $\bar{x}$ ± SD	64,5 ± 12,9	64,1 ± 13,2	66,6± 11,2	0.18
Male gender, n (%)	208 (63.41%)	167 (60.95%)	41 (75.93%)	0.04
Hypertension, n (%)	225 (68.60%)	186 (67.88%)	39 (72.22%)	0.53
Hyperlipidemia, n (%)	89 (27.13%)	74 (27.01%)	15 (27.78%)	0.91
Diabetes mellitus, n (%)	60 (18.29%)	46 (16.79%)	14 (25.93%)	0.11
IHD, n (%)	21 (6.40%)	12 (4.38%)	9 (16.67%)	0.001
PVD, n (%)	11 (3.35%)	6 (2.19%)	5 (9.26%)	0.008
Renal failure, n (%)	25 (7.62%)	19 (6.93%)	6 (11.11%)	0.29
Previous stroke, n (%)	54 (16.46%)	45 (16.42%)	9 (16.67%)	0.97
Atrial fibrillation, n (%)	47 (14.33%)	40 (14.60%)	7 (12.96%)	0.75

IHD: ischemic heart disease; PVD: peripheral vascular disease

Prevalence of ICA stenosis

Overall, 29 patients (8.84%; 95% CI: 6.0-12.45) had an ICA stenosis of 50-99% with subgroup of moderate stenosis (50-69%) and severe stenosis (70 – 99%) comprised of 9 patients (2.74%; 95% CI: 1.26-5.14) and 20 patients (6.1%; 95% CI: 3.76-9.26), respectively (**table 2**). Total occlusion was reported in 25 patients (7.62%; 95% CI: 4.99-11.04).

Table 2. Absolute numbers and percentages of internal carotid artery (ICA) stenosis in the total cohort and subgroups

Degree of stenosis	Total (n = 328)	Male (n = 208)	Female (n = 120)
50 - 69%, n (%; 95% CI)	9 (2.74; 1.26-5.14)	7 (3.37; 1.36-6.81)	2 (1.67; 2.02-5.89)
50 - 99%, n (%; 95% CI)	29 (8.84; 6.0-12.45)	21 (10.1; 6.36-15.02)	8 (6.67; 2.92-12.71)
70 - 99%, n (%; 95% CI)	20 (6.1; 3.76-9.26)	14 (6.73; 3.73-11.04)	6 (5.0; 1.86-10.57)
100%, n (%; 95% CI)	25 (7.62; 4.99-11.04)	20 (9.62; 5.97-14.46)	5 (4.17; 1.37-9.46)

Risk factors for ICA stenosis

Univariate logistic regression of potential risk factors for significant ICA stenosis is presented in **table 3.**

In multivariate logistic regression, diabetes mellitus (adjusted OR 2.59, 95% CI 1.07 to 6.24), ischemic heart disease (adjusted OR 6.7, 95% CI 2.4-18.68), higher creatinine serum level (adjusted OR 1.15, 95% CI 1.01-1.3) were statistically associated with ICA stenosis. Finally, a non-significant association was found for ICA stenosis and age with cut – off 65 years (2.36; 95% CI: 0.97-5.76) **(table 3).**

Table 3. Univariable and multivariable analyses: unadjusted and adjusted associations between variables and internal carotid artery (ICA) stenosis of 50-99%

	Univariate OR			**Multivariate OR**		
	OR	**CI 95%**	**p**	**OR**	**OR 95%**	**p**
Age, cutoff 65	**2.82**	**1.21 - 6.59**	**0.016***	**2.36**	**0.97 - 5.76**	**0.06**
Male gender	1.68	0.72 - 3.93	0.230	-	-	-
Atrial fibrillation	0.43	0.10 - 1.89	0.266	-	-	-
Diabetes mellitus	**2.61**	**1.14 - 5.97**	**0.023***	**2.59**	**1.07 - 6.24**	**0.034**
Hyperlipidemia	1.65	0.75 - 3.66	0.217	-	-	-
Hypertension	2.27	0.84 - 6.15	0.107	-	-	-
PVD	1.60	0.19 - 13.73	0.671	-	-	-
IHD	**8.32**	**3.06 - 22.59**	**< 0,001***	**6.7**	**2.4 - 18.68**	**<0.001**
Creatinine (per 10 mmol/L)	**1.16**	**1.03 - 1.31**	**0.015***	**1.15**	**1.01 - 1.3**	**0.031**

*: p < 0.10 and included in multivariable analysis.

IV. DISCUSSION

To our knowledge, this is the first study describing the prevalence and risk associations of ICA stenosis among Viet Nam stroke patients. Our study indicate that the frequency of 50-99% ICA stenosis was 8.84% of included patients. This finding is lower than result reported on studies in Europe countries as UK or Netherlands.[3,7] The observational study performed by Netherlands authors in 2020 with more 800 patients TIA/ ischemic stroke had contemporary prevalence of ICA stenosis at 12.5%.[7] A possible explanation might be that the investigators only selected cases with TIA/ischemic stroke in one of the ICA territories and excluded vertebrobasilar ischemic stroke patients. A cohort study, the Oxford Vascular Study (OXVASC) also reported a high prevalence of patients with ICA stenosis (50–99% stenosis: 15.8%), which could be due to the exclusion of patients with a disabling event (defined as a modified Rankin scale score higher than 2).[3]

However, our findings were in line with previous studies in Asia, which showed that less than 10% of TIA/ischemic stroke patients have significant ICA stenosis. In a study in Taiwan, the prevalence of 50- 99% ICA stenosis in patient with hemisphere stroke was 8%, another study in Thailand also reported comparable result of 9.2%.[5,12] This finding could be explained by the similarity of ethnic and current pattern of diseases in Asian area. The ethnic differences even contribute to explain the discrepancy on the prevalence of ICA stenosis between Western and Eastern.

Our study demonstrated that essential risk factors for ICA stenosis in patients with TIA/ischemic stroke were diabetes mellitus, ischemic heart disease and high creatinine serum level. Diabetes mellitus is one of the most common cause negatively effect on cardiovascular. Thus, carotid artery is a popular site could be injured in diabetes patient. A study was completed by S.F.Cheng et al in 1252 TIA/ischemic stroke patients had proven the association of diabetes mellitus with carotid artery lesion.[6] Besides, ischemic heart disease is strictly related with ICA stenosis according to result of this study. One study aimed to assess the prevalence in patients with coronary artery disease in Japanese population found that this rate was 25.4%.[13] It is obvious that atherosclerosis condition could spread out on the whole vascular system. Higher age with a cutoff at 65 years old also is a significant cardiovascular risk factor related to ICA stenosis based univariate analysis (but not in multivariate audit). To sum it up, we suggest that an medical treatment such as aspirin, statins with LDL-C target of less than 70 mg/dl, glycemic control with HbA1C goal of less than 7% could diminish the risk of recurrence of TIA/ischemic stroke.[9,14]

Interestingly, in our study, elevated creatinine serum level was associated with increased risk of ICA stenosis. There has been no data of previous publications in the relation of renal failure and significant ICA stenosis in patient with TIA/ischemic stroke. However, a study was conducted by Japanese authors to find out if chronic kidney disease (CKD) could be associated with atherosclerosis carotid and symptomatic ischemic stroke. The finding showed that the mean carotid intima–media thickness (IMT) in patients with CKD was significantly higher than in patients without CKD ($p < 0,001$).[15] Therefore , our result suggests that further research on this problem should be conducted to clarify the role of renal function in carotid stenosis.

The strengths of our study include the large number of consecutive patients with ischemic

stroke studied in a tertiary hospital, screening of carotid artery lesion with DUS, CTA or MRA scanning in all patients, and prospective data collection minimizing recall bias and selection bias. Since stroke care is organized accordingly in other parts of Viet Nam, we hope this cohort can be apply for the general stroke population. However, this study has some limitations. First, due to burden of patient volume, some cases were rapidly discharged or exchanged to other hospital without carotid artery assessment. Second, participants were recruited on a short period (6 months). Therefore, we need to extend time to engage more patients on research.

V. CONCLUSION

The prevalence of extracranial ICA stenosis in TIA/ischemic stroke patients in Viet Nam is lower than Western countries but quite similar to Asia regions. Diabetes mellitus, IHD and elevated creatinine level are important risk factors for symptomatic ICA stenosis.

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BNT, MDT, PMH conceived the study, participated in its design and implementation and wrote the manuscript. BNT analyzed the data. All the authors read and approved the final manuscript.

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