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Original Research Article

Characteristics of intracranial atherosclerosis disease in stroke cases in Indonesia utilizing cerebral digital subtraction angiography

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ABSTRACT

Background: Intracranial atherosclerosis disease is a cause of ischemic stroke. Risk factors of ICAD included age, gender, race/ethnicity, hypertension, diabetes mellitus, and dyslipidaemia. This study aimed to describe the profile of ICAD in first-ever stroke and its association of recurrent stroke.
Methods: The was a prospective cohort study conducted at a private hospital in Indonesia between January 2021 and June 2022. Inclusion criteria included patients with first-ever stroke and intracranial stenosis confirmed through digital subtraction angiography. The incidence of recurrent stroke was observed at six-month follow-up.
Results: Of 40 subjects, 25 (62.5%) were females and most ages ranged from 20 to 40 years old. The prevalent site of intracranial stenosis were internal carotid artery in 19 (23.2%) and anterior cerebral artery in 19 (23.2%) subjects. Following six-month follow-up, there was only a patient with recurrent stroke.
Conclusions: In first-ever stroke in Indonesia, ICAD was predominantly described in younger men within 41-60 years old. Stroke recurrence was observed in a patient who was old and had multiple comorbid. Further studies using a larger area and longer duration of follow-up may be considered to provide a more generalized description of ICAD in Indonesia.

Keywords: Cerebral digital subtraction angiography, Intracranial atherosclerotic disease, Stroke recurrence

INTRODUCTION

Atherosclerosis, a lifelong and systemic disease, is a significant contributor to stroke, myocardial infarction, ischemic gangrene, and mortaloty. Despite efforts to control associated risk factors, the progression of atherosclerosis remains gradual.[1,2] Cerebral atherosclerotic disease is generally classified as extracranial and intracranial artery disease (ICAD). The extracranial arteries included cervical to clinoid segment of internal carotid artery (ICA) and V1-V3 segment of vertebral artery (VA). Conversely, ICAD occurred due to uncontrolled atherosclerosis of intracranial arteries including the V4 segment of VA, basilar artery (BA) and its branches, ICA from the upper segment of clinoid, anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA). Intracranial artery disease (ICAD) is a major contributor of ischemic stroke worldwide by producing intracranial artery stenosis, which leads to transient or permanent cerebral ischemic events.[1,2] Some recognized risk factors for ICAD included age, gender, race/ethnicity, hypertension, diabetes mellitus, and dyslipidaemia.

The prevalence of ICAD has been reported higher in females older than 63 years old compared with males

within the same age group. Several studies suggest that race/ethnicity is a predisposing factor, especially in combination with acquired risk factors such as lifestyle. Individuals of Hispanic, African-American, and Asian (Chinese, Japanese, and Korean descent) ethnic backgrounds have a significantly higher incidence and prevalence of ICAD compared to non-Hispanic whites. The difference in the incidence of ICAD among different ethnicities could be caused by differences in certain genetic predispositions or morphological characteristics of the cerebral arteries. Dyslipidaemia, a risk factor that is linked to coronary atherosclerosis and myocardial infarction, is also associated with ICAD.[3] Intracranial stenosis accounts for nearly 10% of ischemic strokes in the United States and up to 50% in Asia. It is more prevalent in African Americans, Hispanics, and Asians as compared with whites. The race-ethnic variations in the prevalence of ICAD are probably influenced by variations in risk factor profiles, lifestyle behaviour, and genetic predispositions. The higher prevalence of ICAD in African American patients may be associated with a larger burden of hypertension, diabetes mellitus, and hyperlipidaemia. On the other hand, genetic and environmental factors play a role in the pathogenesis of ICAD in Asians.[4]

Studies of ICAD in Indonesia are currently limited. A previous study in Bethesda hospital Yogyakarta Indonesia involving 234 ischemic stroke patients revealed that 37% subjects had intracranial stenosis confirmed using Trans-cranial doppler (TCD).[5] Studies of ICAD in Indonesia using the gold standard of digital subtraction angiography (DSA) are also limited.[6] Intracranial atherosclerotic disease is a cause of ischemic stroke and a risk factor for future ischemic stroke. It resulted in territorial pattern of infarcts either through direct thrombo-occlusion of the stenotic artery or via artery-to-artery emboli due to the occlusion of more distal arterial branches by a ruptured plaque of the proximal ICAD. It may also manifest as watershed borderzone territorial pattern of infarcts attributed to hypoperfusion distal to the stenotic artery. High-grade stenosis of ICAD may produce mixed borderzone and embolic pattern of infarcts. In autopsy studies, ICAD accounted for 10% of strokes, and in a pooled analysis of 2,593 patients, its presence ranged from 3.5% to 13% of the population, which varies based on age and ethnicity.[7]

Aim and objectives

This study aimed to describe the incidence of stroke recurrence within 6 months after first-ever ischemic stroke who had intracranial artery stenosis.

METHODS

This was a prospective cohort study conducted at a private hospital, Jakarta, Indonesia, from January 2021 to June 2022. The eligibility criteria were patients with ischemic stroke based on medical record and intracranial artery stenosis confirmed by DSA. The data retrospectively collected from medical record included age, gender, ethnicity, and comorbids of hypertension, hypertensive heart disease, diabetes, dyslipidaemia, coronary artery disease, acute kidney injury, etc. The location of intracranial stenosis and the number of stenosis was recorded from the expertise of DSA.

Stroke recurrence was documented as positive if the subject reported at least one symptom including sudden weakness of one side of the body, sudden paraesthesia/numbness of one side of the body, sudden visual disturbance, sudden dysarthria/slurred speech, or sudden dizziness or vertigo. It was documented at six-month follow-up following stroke. Patients who were uncontactable or refused to be enrolled in this study were excluded. Using the population-based prevalence of intracranial-extracranial stenosis in Asia of 4.7%, type I error of 95%, and absolute precision of 5.5%, the sample size was estimated to be 30 subjects. However, we conducted total sampling within the study duration and enrolled 40 subjects. Results were presented in percentage for categorical data and median with range for abnormally distributed numerical data.

RESULTS

Of 925 ischemic stroke patients who had DSA performed within the study period, there were 40 (4.3%) subjects who had ICAD and fulfilled the eligibility criteria. The majority of these subjects were male (62.5%), with the mean age of 55.8 years (Table 1).

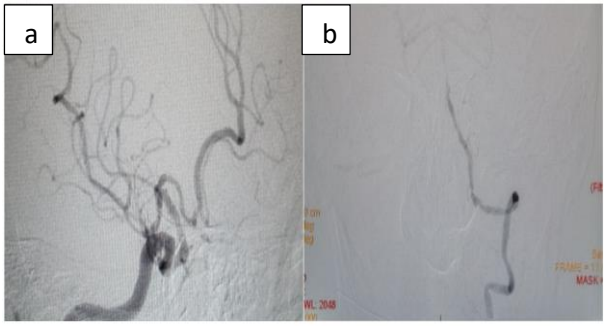

Figure 1: Cerebral DSA examination of a patient; a) Multiple stenosis on ICA, b) Stenosis on Ver and Bas.

By ethnicity, the subjects were predominantly Betawi (35.0%) and Java (30.0%). Most subjects had only one comorbid disease, with hypertensive heart disease being the most prevalent (63.5%). Intracranial atherosclerosis was more frequently found in multiple sites (57.5%), predominantly at two to three locations (Table 2, Figure 1). The stenosis was mostly documented at segment C6-C7 of ICA (23.2%) and ACA (23.2%).

Within six months of follow-up, there was only a subject with recurrent stroke (Table 3). He was a 72-year-old male with multiple risk factors including acute kidney

injury (AKI), diabetes mellitus (DM), and hypertensive heart disease (HHD). He also had multiple intracranial stenosis at ICA, VA, and BA. During the follow up, patient experienced the severe body weakness on one side body with loss of consciousness.

Table 1: Characteristics of subjects (n=40).

Parameters	N	%
Gender		
Male	25	62.5
Female	15	37.5
Age (mean±SD) (years)	56 (22-90)	
Ethnicity		
Arab	1	2.5
Betawi	14	35
Sunda	7	17.5
Java	12	30
Bima	1	2.5
Tionghoa	4	10
Manado	1	2.5
Comorbid		
Hypertensive heart disease	33	63.5
Diabetes	14	26.9
Acute kidney injury	2	3.8
Hypertension	1	1.9
Dyslipidaemia	1	1.9
Coronary artery disease	1	1.9

Table 2: Intracranial atherosclerotic disease findings on digital subtraction angiography.

Parameters	N	%
Number of stenosis		
1 Location	17	42.5
2 Locations	9	22.5
3 Locations	10	25.0
4 Locations	3	7.5
5 Locations	1	2.5
Stenosis locations		
ICA	19	23.2
MCA	11	13.4
ACA	19	23.2
VA	10	12.2
BA	17	20.7
PCA	6	7.3

Table 3: Prevalence of stroke recurrence in the study.

Stroke recurrence	N	%
Yes	1	2.5
No	39	97.5

DISCUSSION

This study reported that the prevalence of ICAD in ischemic stroke was 4.3%. Intracranial artery stenosis was more common in male than females. This result is contradictive with the previous studies, which was possibly due to the differences ages of the samples. The subjects in this study were predominantly males between 41-60 years old whereas the previous study demographics were mostly women older than 63 years old.3 Another contributing factors to the observed difference was the race/ethnic and culture differences on the study. A parallel study in Indonesia also noted a dominance of younger subjects in the prevalence of ICAD, with 65% of cases aged ≤60 years and 35% aged ≥60 years, with a higher prevalence in men than women.[5] It is important to note that the previous ICAD research in Indonesia utilized Transcranial Doppler (TCD) sonography, while our current study employed cerebral Digital Subtraction Angiography (DSA), considered the current gold standard for ICAD diagnosis. This methodological advancement provides a notable advantage in drawing more conclusive results. Therefore, it can be inferred that ICAD in Indonesia is primarily observed in younger men, specifically within the age range of 41-60 years.

Regarding the ethnic/race distribution, the subjects in this study were predominantly from the Jawa and Betawi ethnic group. This data aligned with a previous study by Ramadhani et al which reported that 84.8% of stroke patients were from Jawa ethnic group.[8] However, there is currently no existing literature explaining the association between ethnic/race and ICAD in Indonesia. It is important to note that the dominance of these ethnic groups in this study may be influenced by the fact that the study was conducted in a private hospital located in Jakarta, where Jawa and Betawi are two of the most prominent ethnic/racial groups. Further studies with diverse regions, multicentre participation, and heterogenous ethnic groups are necessary to obtain a more comprehensive understanding of the relationship between ethnic/race and the prevalence of ICAD in different regions and among various ethnic groups in Indonesia. This study identified hypertensive heart disease (HHD) as the most prevalent comorbid disease in individuals with ICAD. Individuals with ICAD who had hypertension without associated heart disturbances comprised a small percentage (1.9%). Hypertensive heart disease encompasses a range of alterations in the left ventricle, left atrium, and coronary arteries resulting from sustained elevation of blood pressure. This chronic pressure elevation imposes increased workload on the heart, inducing structural and functional changes. Notably, these changes involve left ventricular hypertrophy, which can progress to heart failure.[9] A study in China revealed an association between systolic blood pressure (SBP) and ICAD, particularly with multivessel stenosis, among the general middle-aged and elderly population. This relationship was particularly notable in the SBP ≥160 mmHg group.[10] Our findings corroborate and extend this earlier research, given that HHD is a consequence of chronic blood pressure elevation. Similarly, those with dyslipidaemia and coronary artery disease (CAD) in isolation from heart disturbances were also limited to 1.9%. This data suggests that patients with

ICAD typically present with long-standing risk factors with complications of the heart such as HHD.

The study of ICAD in Indonesia is still limited. From previous study in Indonesia, ICAD was more commonly observed in ischemic stroke patients (41%) than the combination of ICAD and extracranial artery disease (ECAD) (34%) as well as ECAD alone (26%).[11] Therefore, we are interested to study regarding the incidence stroke recurrence in patients with ICAD over 6-month follow up period. In this research, there were a very low incidence of stroke re-attacks in patients with ICAD, with only one recorded case. This low incidence could be attributed to the fact that most patients received anticoagulant or antiplatelet therapy during the follow-up period, mitigating the risk factors for stroke recurrence. Another contributing factor might be the relatively short duration of follow-up, as dictated by the limitations of our study. It is noteworthy that the single patient who experienced a stroke recurrence ultimately succumbed during the follow-up period. Cerebral examination using DSA identified stenosis in three locations: ICA, VA, and BA. Although the number of stenoses was not the highest compared with the other subjects, this particular patient presented with the most comorbid diseases (AKI, HHD, and diabetes mellitus). A stroke recurrence in many comorbid was thought to result in a more progressive and deteriorating condition. Notably, there was also a patient with three comorbid diseases in this study who survived and did not experience stroke recurrence. This subject was younger than the those with stroke recurrence (55 vs. 72 years old, respectively). This assumption aligns with previous studies indicating that the incidence of stroke increases with age, doubling every 10 years after the age of 55.12 Consequently, older patients had 2-4 times higher risk of experiencing stroke recurrence compared with their younger counterparts. Stroke recurrence, especially in conjunction with multiple comorbid diseases, tends to lead patients to a worsened condition and, in some cases, may result in mortality.

Limitations

This study had limitations due to the restriction in the location and duration of the follow-up period. The location limitation restricted a comprehensive description of subject characteristics, particularly concerning the heterogenous ethnic/race groups presented in Indonesia. Furthermore, the relatively short follow-up duration of six months may explain the lower incidence of recurrent stroke following ICAD in this study. However, the strength of this study was the description of intracranial artery stenosis using the gold standard of DSA. To address these limitations and enhance the understanding of the contribution of ICAD to first-ever and recurrent stroke, we recommend future studies with larger sample size and recruiting participants from various locations to provide a more comprehensive insight into the characteristics of ICAD, especially within the diverse population of Indonesia. Extending the follow-up duration may allow for a better examination of the association between ICAD and stroke recurrence.

CONCLUSION

In Indonesia, ICAD in first-ever stroke is primarily observed in younger men, specifically within the age range of 41-60 years. Most stenosis occurred at ICA and ACA and HHD was reported as the most common comorbid. The incidence of stroke recurrence in first-ever stroke with ICAD was also low, particularly associated with older subjects with multiple comorbid. Further studies involving wider geographical scope and longer duration of follow-up is needed to provide a more generalized description of ICAD in Indonesia.

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