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Original Research Article

Characteristics of brain MRI abnormalities associated with symptomatic internal carotid artery stenosis: a retrospective single-center study

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ABSTRACT

Background: Carotid artery stenosis (CAS) may manifest with stroke, transient ischemic attack (TIA), or more covert non-hemispheric symptoms. While symptoms can be subtle, brain MRI abnormalities may already reflect substantial changes. This study aimed to determine the association between brain MRI abnormalities and symptomatic CAS.
Methods: A retrospective cross-sectional study was conducted to subjects with symptomatic ICA stenosis admitted to a private secondary hospital in Jakarta, Indonesia, from January to December 2022. Symptoms were categorized to stroke/TIA and non-hemispheric symptoms (vertigo, headache, presyncope, etc.). Properties of CAS were recorded using digital subtraction angiography report. Brain abnormalities were recorded using MRI report.
Results: Brain MRI abnormalities were detected in 96.2% CAS cases and similar between stroke (96.2%) and non-hemispheric symptoms (96.0%). The abnormalities tended to be in bilateral hemisphere (61.0%), predominantly periventricle (41.9%), basal ganglia (26.1%), and internal capsule for mild CAS (16.8%). Ipsilateral brain lesions were significantly associated with severe CAS (20.9% versus 10.8% for non-ipsilateral brain lesion, p=0.042) and stroke (45.9% versus 24.0% in non-hemispheric symptoms, p=0.035). Non-ipsilateral brain lesions were significantly associated with mild CAS (49.6% versus 40.7% for ipsilateral brain lesion, p=0.042) and non-hemispheric symptoms (72.0% versus 50.3% in stroke, p=0.035).
Conclusions: Brain MRI abnormalities were very prevalent in CAS. There were no specific markers of brain MRI abnormalities associated with CAS. Brain abnormalities had been found since mild CAS, which presented in bilateral hemisphere as non-hemispheric symptoms. This study underlines the importance for the assessment of CAS in subjects since non-hemispheric symptoms with brain ischemic-related pathologies.

Keywords: Brain MRI abnormalities, Internal carotid artery stenosis, Ischemic stroke, Non-hemispheric symptoms, Symptomatic carotid artery stenosis

INTRODUCTION

Carotid artery atherosclerosis (CAA) is a subgroup of carotid artery disease and has been recognized as an important risk factor for ischemic stroke.[1] It is due to atherosclerosis in the internal carotid artery (ICA) or vertebral artery (VA), especially at the bifurcation area, with pathological findings of decreased vessel diameter ranging from increased intima-media thickness to carotid artery stenosis (CAS).[2] Internal carotid artery stenosis contributes to one-fifth of ischemic stroke prevalence and the highest risk factor for early stroke recurrence compared with cardioembolism and small vessel disease.[3] Acute ischemic stroke due to ICA stenosis of ≥50% was reported to be 15-20% across studies in 2000 and remained at 18.7% in 2021 as reported by von Velzen et al on 1480 subjects in the Netherlands.[4,5] The prevalence of symptomatic CAS was also reported in China to be

59.4% and at a single hospital-based study of 185 subjects in Egypt (2021), to be 64.3%, of which 37.0% had stenosis of ≥70%. The prevalence of asymptomatic CAS was even higher, reaching 70% in 1189 subjects of Framingham study aged 66-93 years.[6]

Carotid artery atherosclerosis may be asymptomatic or symptomatic.[1] Advanced management including carotid endarterectomy and carotid artery stenting for symptomatic moderate-to-severe CAS, as well as improvements in medical treatment for asymptomatic CAA, has led to decreased current yearly stroke rate to less than 1%.

Regardless of the advancement in diagnosis and management of CAA, there were issues arising from the heterogeneous definition of symptomatic CAA as well as its impact on brain ischemia. Current guidelines defined symptomatic CAA as ischemic stroke, amaurosis fugax, or transient ischemic attack (TIA).[7-9] However, the definition does not include non-hemispheric symptoms of vertigo, presyncope, or migraine (especially with aura), which may be associated with CAA-related hypoperfusion.[10-14] There is no recommendation regarding screening and management of CAA for those population until the subject presents with overt stroke. Moreover, American Stroke Association and United States Preventive Services Task Force and European Stroke Organization recommend against screening for asymptomatic CAS in general adult population.[12,15] Delay in recognizing symptomatic CAA may delay the initiation of recommended treatment and results in increasing risk of not only stroke or TIA, but also downstream effects due to cerebral hypoperfusion.[2] The risk of recurrent ipsilateral stroke in symptomatic CAA were 2.7% within the first day to 18.8% within 90 days of onset.[8]

Large stroke, lacunar infarct, or cerebral hypoperfusion had been reported on brain neuroimaging, including routine brain CT scan, brain MRI, or advanced imaging technique (perfusion test, nuclear medicine test), since asymptomatic CAA.[2] Up to recent studies, there were only few studies investigating the association between CAA and brain imaging abnormalities.

This study aimed to describe the relationship between brain MRI abnormalities and symptomatic CAS, including not only stroke and TIA but also non-hemispheric symptoms. It was based on the report that even in asymptomatic CAS of <60% stenosis, ipsilateral silent infarction was one of the features associated with increased risk of cerebrovascular accident.[16] This study would provide results regarding the necessities for further assessing CAS in subjects with brain MRI abnormalities.

METHODS

A retrospective cross-sectional single-center study was conducted on subjects with symptomatic CAA in a private secondary hospital in Jakarta, in January to December 2022. Adults (≥18 years) with symptomatic CAA who underwent both digital subtraction angiography (DSA) and brain MRI were included in the study. Subjects with spinal stroke or other structural etiology of brain (brain tumor, on-therapy brain infection, acute traumatic brain injury), history of carotid endarterectomy or carotid artery stenosis, as well as those without data regarding DSA or MRI, were excluded. 210 enrolled subjects were studied.

The data recorded were (1) demographics including age, sex, and body mass index (BMI); (2) comorbidities including history of stroke, hypertension, diabetes, and heart disease; (3) final diagnosis as stated in the medical record; (4) properties of CAS based on DSA expertise report, including degree of stenosis, stenosis location, and unilateral or bilateral involvement; (5) brain MRI lesion in the expertise report, including lesion characteristics, unilateral or bilateral involvement, ipsilateral or non-ipsilateral impact, and its distribution.

The final diagnosis of symptomatic CAA was defined as stroke, TIA, vertigo, presyncope or syncope, migraine, and other symptoms plausibly explained with hypoperfusion in CAA. This was further categorized to stroke/TIA and non-hemispheric syndrome.[14] Stroke was defined as clinical syndrome of acute sudden global or focal neurological deficits involving brain parenchyma or retina that persisted >24 hours whereas TIA was diagnosed when the neurological deficit was completely resolved within 24 hours and no symptomatic lesion on brain imaging.[17] Non-hemispheric symptoms were applied to other "global" symptoms of symptomatic CAA besides stroke/TIA, in accordance to the European Society for Vascular Surgery (ESVS) clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease in 2023.[14]

Demographic data of age was recorded numerically whereas BMI was recorded numerically and categorically using the Asia category to underweight (<18.5 kg/m^2), normoweight (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2), obese type 1 (25-29.9 kg/m^2), and obese type 2 (≥30 kg/m^2). Comorbidities were recorded dichotomously.

Data regarding CAS and brain MRI were recorded in accordance with the expertise result stated in the medical record. Carotid artery stenosis was classified based on (1) degree of severity by North American Symptomatic Carotid Endarterectomy Trial (NASCET) ratio into mild (<50%), moderate (50-69%), and severe (≥70%) stenosis; (2) location into intracranial, postbifurcation extracranial, bifurcation extracranial, and multiple stenosis; (3) extent of involvement into unilateral or bilateral CAS.[9,18] Carotid artery stenosis was determined using the gold standard (DSA) to increase the value of detection.[1,19]

Lesion in brain MRI was classified based on (1) morphology into infarct, white matter hyperintensities (WMH), microhemorrhage, and brain atrophy; (2) extent of involvement, which was categorized into ipsilateral or non-ipsilateral involvement.[2] Ipsilateral brain lesions were determined when (1) there was unilateral lesion associated with the same unilateral CAS side; (2) there was unilateral lesion associated with the same side of worse vessel of bilateral CAS; (3) there were bilateral lesions predominantly involving the same hemisphere as the location of CAS. Non-ipsilateral brain lesion was determined when (1) there was unilateral lesion associated with contralateral unilateral CAS; (2) there was unilateral lesion associated with contralateral side of the worse vessel of bilateral CAS; (3) there were bilateral lesions predominantly involving the different hemisphere from the location of CAS; (4) the brain lesion was not lateralized.

The association between CAS and brain MRI abnormalities were bivariately compared with respect to demographics, comorbidities, and properties of CAS. Analysis was conducted using chi square or Fisher as indicated. The association was then adjusted multivariately using logistic regression. Statistics were performed using SPSS version 20.0 with statistical significance of $p<0.05$.

RESULTS

Demographics, brain MRI abnormalities, and carotid artery stenosis among all subjects

Of 210 enrolled subjects, subjects were predominantly male (63.8%), 58 (20-85) years old, with comorbidities of overweight to obese type I (BMI 24.9±3.9 kg/m^2), hypertension (75.7%) and prior history of stroke (57.6%, Table 1).

Brain MRI abnormalities were found in 202 (96.2%) cases of CAS. The brain abnormalities observed were cerebral small vessel disease (71.4%) and infarct (79.5%) and were mostly located on bilateral hemisphere (61.0%), periventricle (41.9%) and basal ganglia (26.1%). The characteristics of CAS in this study were predominantly mild (45.2%) to moderate (39.1%), unilateral (84.8%) CAS, which was located on extracranial segment, especially on bifurcation (49.3%, Table 2).

Demographics, brain MRI abnormalities, and carotid artery stenosis among stroke versus non-hemispheric symptoms

There were 185 (88.1%) stroke and 25 (11.9%) non-hemispheric cases in this study. The non-hemispheric cases included headaches (10/25, 40.0%), vertigo (6/25, 24.0%), general paresthesia (3/25, 12.0%), vertebrobasilar insufficiency (2/25, 8.0%), neck pain (1/25, 4.0%), cognitive impairment (1/25, 4.0%), and others (2/25, 8.0%). There were similar age, sex, and BMI on both groups. Significant difference was found on cardiac disease (15.2% versus 0.0% in stroke versus non-hemispheric, p=0.037) and history of stroke (65.4% versus 0.0%, in stroke versus non-hemispheric, p<0.001, Table 1). These differences were insignificant when adjusted multivariately to the other variables.

Brain MRI abnormalities were equally found on stroke and non-hemispheric subjects (96.2% versus 96.0% in stroke versus non-hemispheric, p=1.00). Infarct was the only significant abnormalities found in stroke (83.2% versus 52.0% in stroke versus non-hemispheric, p<0.001) whereas all other pathologies were equally found between those two groups. While bilateral lesion involvement was more common in both groups, unilateral brain lesion was more commonly found in stroke (37.8% vs 16.0%, p=0.031). Albeit insignificant, brain lesions in stroke and CAS tended to be at lateral peri ventricle, basal ganglia, temporal, and pons (Table 2).

Table 1: Subject characteristics.

Demographics	Total (n=210)	Stroke (n=184)	Non-stroke (n=26)	P value
Sex (male)	134 (63.8%)	121 (65.4%)	13 (52.0%)	0.19
Age (years)	58 (20-85)	57 (26-85)	58.5 (20-76)	0.49
BMI (kg/m^2)	24.9±3.9	24.9±15.3	25.2±4.2	0.31
Underweight	9 (4.3%)	7 (3.8%)	2 (8.0%)	
Normoweight	55 (26.2%)	50 (27.0%)	5 (20.0%)	
Overweight	52 (24.8%)	49 (26.5%)	3 (12.0%)	
Obese type I	72 (34.3%)	60 (32.4%)	12 (48.0%)	
Obese type II	22 (10.5%)	19 (10.3%)	3 (12.0%)	
Comorbidities				
Stroke	121 (57.6%)	121 (65.4%)	0 (0.0%)	<0.001*
Hypertension	159 (75.7%)	143 (77.3%)	16 (64.0%)	0.15
Diabetes	40 (19.0%)	35 (19.0%)	5 (19.2%)	1.00
Cardiac disease	28 (13.3%)	28 (15.2%)	0 (0.0%)	0.037*

Table 2: Carotid artery stenosis and brain MRI abnormalities parameter in this study.

Parameter	Total (n=210)	Stroke (n=184)	Nonstroke (n=26)	P value
DSA findings				
Stenosis grade (%)	50 (10-100)	50 (10-100)	40 (20-70)	0.14
Mild	95 (45.2%)	80 (43.2%)	15 (60.0%)	Ref
Moderate	82 (39.1%)	73 (39.5%)	9 (36.0%)	0.35
Severe	33 (15.7%)	32 (17.3%)	1 (4.0%)	0.07
Stenosis location				
Intracranial	19 (9.0%)	17 (9.2%)	2 (8.0%)	Ref
Post bifurcation extracranial	70 (33.3%)	65 (35.1%)	5 (20.0%)	0.64
Pre bifurcation extracranial	103 (49.3%)	88 (47.6%)	15 (60.0%)	1.00
Multiple	18 (8.6%)	15 (8.1%)	3 (12.0%)	0.66
Stenosis involvement				
Unilateral ICA	178 (84.8%)	154 (83.2%)	24 (96.0%)	0.14
Bilateral ICA	32 (15.2%)	31 (16.8%)	1 (4.0%)	
Brain MRI abnormalities	202 (96.2%)	178 (96.2%)	24 (96.0%)	1.00
Lesion characteristics				
Small vessel disease	150 (71.4%)	130 (70.3%)	20 (80.0%)	0.31
Infarct	167 (79.5%)	154 (83.2%)	13 (52.0%)	<0.001*
White matter hyperintensities	81 (38.6%)	69 (37.3%)	12 (48.0%)	0.30
Atrophy	59 (28.1%)	50 (27.0%)	9 (36.0%)	0.35
Microbleed	7 (3.3%)	7 (3.8%)	0 (0.0%)	1.00
Lesion involvement				0.10
Unilateral	74 (35.2%)	70 (37.8%)	4 (16.0%)	0.41
Bilateral	128 (61.0%)	108 (58.4%)	20 (80.0%)	1.00
Unilateral versus bilateral				0.031*
Lesion distribution				
Lateral peri ventricle	88 (41.9%)	79 (42.7%)	9 (36.0%)	0.52
Frontal	36 (17.1%)	33 (17.8%)	3 (12.0%)	0.47
Temporal	25 (11.9%)	25 (13.5%)	0 (0.0%)	0.050
Parietal	54 (25.7%)	50 (27.0%)	4 (16.0%)	0.24
Occipital	14 (6.7%)	13 (7.0%)	1 (4.0%)	1.00
Basal ganglia	55 (26.1%)	50 (27.0%)	5 (20.0%)	0.45
Putamen	14 (6.7%)	13 (7.0%)	1 (4.0%)	1.00
Caudate nucleus	5 (2.4%)	5 (2.7%)	0 (0.0%)	1.00
Centrum semiovale	17 (8.1%)	15 (8.1%)	2 (8.0%)	1.00
External capsule	25 (11.9%)	22 (11.9%)	3 (12.0%)	1.00
Internal capsule	25 (11.9%)	24 (13.0%)	1 (4.0%)	0.32
Corona radiata	30 (14.3%)	29 (15.7%)	1 (4.0%)	0.22
Thalamus	33 (15.7%)	30 (16.2%)	3 (12.0%)	0.78
Cerebellum	11 (5.2%)	11 (5.9%)	0 (0.0%)	0.37
Mesencephalon	6 (2.9%)	6 (3.2%)	0 (0.0%)	1.00
Pons	26 (12.4%)	26 (14.1%)	0 (0.0%)	0.050

DSA: digital subtraction angiography; ICA: internal carotid artery; MRI: magnetic resonance imaging

Association between brain MRI abnormalities and carotid artery stenosis

There were 8 (3.8%) subjects with normal MRI, 91 (43.3%) subjects with lesions predominant in ipsilateral CAS, and 111 (52.9%) subjects with lesions predominant in non-ipsilateral CAS (Table 4). There were no single parameter of brain lesion characteristics and distribution that was significantly associated with the degree or the location of CAS. Lesion at internal capsule was the only significantly location found in mild compared with severe CAS (16.8% versus 7.8%, p=0.045, Table 3).

Compared to those with normal MRI findings (3.8%), subjects with CAS and abnormal MRI group were significantly older (57.4±10.0 versus 49.4±15.2 years in abnormal versus normal MRI, p=0.031) and tended to have higher BMI (24.9±4.0 versus 23.8±2.1 kg/m^2 in abnormal versus normal MRI, p=0.44) and proportion of

hypertension (76.7% versus 50.0% in abnormal versus normal MRI, p=0.10, Table 4). No statistical significance was found between abnormal MRI and properties of CAS (Table 5). Adjusting with demographics, comorbidities, and properties of CAS, increasing age was the sole factor associated with brain MRI abnormalities (B=1.067, 95% CI 1.005-1.133, p=0.035, OR 1.067 (1.005-1.133), R^2 7.1%).

Table 3: Association between brain MRI abnormalities and degree of carotid artery stenosis.

Brain MRI abnormalities	Degree of stenosis		P value
	<50%	≥50%	
Lesion characteristics			
Small vessel disease	69 (72.6%)	81 (70.4%)	0.73
Infarct	74 (77.9%)	93 (80.9%)	0.6
White matter hyperintensities	35 (36.8%)	46 (40.0%)	0.64
Atrophy	25 (26.3%)	34 (29.6%)	0.6
Microbleed	5 (5.3%)	2 (1.7%)	0.25
Lesion distribution			
Lateral peri ventricle	43 (45.3%)	45 (39.1%)	0.37
Frontal	12 (12.6%)	24 (20.9%)	0.12
Temporal	13 (13.7%)	12 (10.4%)	0.47
Parietal	21 (22.1%)	33 (28.7%)	0.28
Occipital	8 (8.4%)	6 (5.2%)	0.35
Basal ganglia	20 (21.1%)	35 (30.4%)	0.12
Putamen	9 (9.5%)	5 (4.3%)	0.14
Caudate nucleus	2 (2.1%)	3 (2.6%)	1
Centrum semiovale	4 (4.2%)	13 (11.3%)	0.06
External capsule	11 (11.6%)	14 (12.2%)	0.9
Internal capsule	16 (16.8%)	9 (7.8%)	0.045
Corona radiata	13 (13.7%)	17 (14.8%)	0.82
Thalamus	15 (15.8%)	18 (15.7%)	0.98
Cerebellum	6 (6.3%)	5 (4.3%)	0.55
Mesencephalon	3 (3.2%)	3 (2.9%)	1
Pons	10 (10.5%)	16 (13.9%)	0.46

Table 4: Subject characteristics based on ipsilateral or non-ipsilateral brain MRI abnormalities of carotid artery stenosis (CAS).

Stenosis	MRI findings							
	Normal (n=8)	Abnormal (n=202)	P value	Abnormal				
				Non-ipsilatera CAS (n=111)	P (versus normal)	Ipsilateral CAS (n=91)	P (versus normal)	P (non versus ipsilateral CAS)
Demographics								
Sex (male)	4 (50.0%)	72 (64.4%)	0.46	69 (62.2%)	0.71	61 (67.0%)	0.44	0.47
Age (years)	49.4±15.2	57.4±10.0	0.031*	58.8±9.3	0.035*	55.7±10.6	0.28	0.09
BMI (kg/m^2)	23.8±2.1	24.9±4.0	0.44	25.0±4.1	1.00	24.9±3.9	1.00	1.00
Underweight	0 (0.0%)	9 (4.5%)		5 (4.5%)		4 (4.4%)		
Normoweight	2 (25.0%)	53 (26.2%)		29 (26.1%)		24 (26.4%)		
Overweight	4 (50.0%)	48 (23.8%)		28 (25.2%)		20 (22.0%)		
Obese type I	2 (25.0%)	70 (34.7%)		35 (31.5%)		35 (38.5%)		
Obese type II	0 (0.0%)	22 (10.9%)		14 (12.6%)		8 (8.8%)		
Comorbidities								
Stroke	6 (75.0%)	115 (56.9%)	0.31	56 (50.5%)	0.28	59 (64.8%)	0.71	0.040*
Hypertension	4 (50.0%)	155 (76.7%)	0.10	88 (79.3%)	0.08	67 (73.6%)	0.22	0.34
Diabetes	2 (25.0%)	38 (18.8%)	0.65	24 (21.6%)	1.00	14 (15.4%)	0.61	0.26
Cardiac disease	2 (25.0%)	26 (12.9%)	0.29	13 (11.7%)	0.27	13 (14.3%)	0.35	0.59
Diagnosis								
Stroke	7 (3.8%)	178 (96.2%)	1.00	93 (50.3%)	1.00	85 (45.9%)	0.46	0.035*
Nonstroke	1 (4.0%)	24 (96.0%)		18 (72.0%)	Ref	6 (24.0%)	Ref	Ref

Table 5: Association between properties of carotid artery stenosis and ipsilateral or non-ipsilateral brain MRI abnormalities.

Stenosis	MRI findings							
				Abnormal				
	Normal (n=8)	Abnormal (p=202)	P value	Non-ipsilateral CAS (n=111)	P (versus normal)	Ipsilateral CAS (n=91)	P (versus normal)	P (non versus ipsilateral CAS)
Degree of stenosis	50 (20-95)	50 (10-100)	0.50	50 (10-100)	0.48	50 (10-100	1.00	0.09
Mild	3 (37.5%)	92 (45.5%)	Ref	55 (49.6%)	Ref	37 (40.7%)	Ref	Ref
Moderate	3 (37.5%)	79 (39.1%)	1.00	44 (39.6%)	1.00	35 (38.4%)	1.00	0.59
Severe	2 (25.0%)	31 (15.3%)	0.60	12 (10.8%)	0.25	19 (20.9%)	1.00	0.042*
Location								
Intracranial	0 (0.0%)	19 (9.4%)	Ref	10 (9.0%)	Ref	9 (9.8%)	Ref	Ref
Post bifurcation	3 (37.5%)	67 (33.2%)	1.00	37 (33.3%)	1.00	30 (33.0%)	1.00	0.84
Pre bifurcation	3 (37.5%)	100 (49.5%)	1.00	58 (52.3%)	1.00	42 (46.2%)	1.00	0.67
Multiple	2 (25.0%)	16 (7.9%)	0.23	6 (5.4%)	0.18	10 (11.0%)	0.49	0.37
Involvement								
Unilateral	6 (75.0%)	172 (85.1%)	Ref	96 (86.5%)	Ref	76 (83.5%)	Ref	Ref
Bilateral	2 (25.0%)	30 (14.9%)	0.351	15 (13.5%)	0.32	15 (16.5%)	0.62	0.56

There were significant association between brain MRI lesions and predominant ipsilateral or non-ipsilateral CAS (Table 4). Predominant ipsilateral-CAS brain lesions were more significantly found in stroke (45.9% versus 24.0% in stroke versus non-hemispheric, p=0.035), history of stroke (65.8% versus 50.5% for yes versus no, p=0.04), and severe CAS (20.9% versus 10.8% in ipsilateral versus non-ipsilateral CAS, p=0.042).

On the other hand, predominant non-ipsilateral-CAS brain lesions were more significantly found in non-hemispheric symptoms (72.0% versus 24.0% in non-hemispheric versus stroke, p=0.035) and mild CAS (49.6% versus 40.7% in non-ipsilateral versus ipsilateral CAS, p=0.042). In addition, multiple stenosis tended to be associated with ipsilateral brain MRI lesion albeit insignificant (11.0% versus 5.4% in ipsilateral versus non-ipsilateral brain lesion, respectively, p=0.37, Table 4 and 5).

Multivariate adjustment was also conducted among demographics, various brain MRI abnormalities, and properties of CAS. Ipsilateral brain MRI abnormalities were significantly associated with increasing age in years [p=0.019, OR 0.965 (95% CI 0.937-0.994)] and the interaction between increasing percentage of CAS and the clinical diagnosis of stroke [p=0.001 OR 1.020 (95%CI 1.008-1.032)] with R^2 score of 10.0%. On the other hand, non-ipsilateral brain MRI abnormalities were significantly associated with age [p=0.024, OR 1.035 (95% CI 1.005-1.067)], increasing percentage of CAS [p=0.027, OR 0.984 (95% CI 0.970-0.998)], and its interaction with non-hemispheric symptoms [p=0.024, OR 1.028 (95% CI 1.004-1.053)] with R^2 score of 10.5%.

DISCUSSION

Demographics, brain MRI abnormalities, and carotid artery stenosis among all subjects

This was one of few reports regarding symptomatic CAS and its association with brain abnormalities in Indonesia using the gold standard of DSA and MRI. This study had provided the following findings: (1) the number of brain abnormalities in CAS was high (96.2%); (2) brain MRI abnormalities occurred equally in CAS with either non-hemispheric symptoms or stroke; (3) no specific brain MRI abnormalities parameter was associated with the degree of CAS, thus brain MRI abnormalities may occur in CAS regardless of the degree of stenosis; (4) increasing age was the sole factor for brain MRI abnormalities in CAS; (5) brain MRI abnormalities in stroke was associated with ipsilateral CAS, especially in severe degree of CAS, but global brain MRI abnormalities had already occurred since mild degree of CAS.[11] This effect was maintained after being adjusted with all variables. Therefore, this study provided report to support performing MRI and further evaluation of CAS if abnormalities were detected in subjects with cardiovascular disease (CVD) risk factors and symptoms suggesting either focal or global neurological deficits.

Despite the advancement of CVD risk factors, the prevalence of CAS remains high. This may be due to the substantial decades and risk factors needed to develop CAS, which resulted in the longer duration needed to lower the prevalence.[5] Poor control of CVD risk factors including hypertension, smoking, dyslipidemia, diabetes, unhealthy diet, obesity, and sedentary lifestyle may cause stroke directly, or indirectly by causing CAS.[5,6,8] In

addition, low socio-economic status was associated with most CVD risk factors and increased the burden of stroke in developing countries including Indonesia. Carotid artery stenosis also contributed worse functional outcome after stroke (modified Rankin scale ≥2), with an adjusted OR of 1.66 (95%CI 1.3-2.1).[5]

This study analyzed 210 subjects with symptomatic CAS, most of which were male (63.8%) aged 58 (20-85) years, overweight (BMI 24.9±3.9 kg/m^2), had hypertension (75.7%), and had history of stroke (57.6%). Hypertension was also the most common risk factors in most studies whereas the number of diabetes in this study was lower those reported in other studies.[5,6] However, this study had similar characteristics with a study in Netherlands that analyzed symptomatic CAS. It was reported that increasing age (OR 1.4 per 10 years, 95% CI 1.16-1.63), male (OR 2.8, 95%CI 1.83-4.19), retinal ischemia (OR 2.5, 95%CI 1.32-4.76), and current smoking (OR 1.8, 95%CI 1.09-2.79) were significantly associated with symptomatic CAS of 50-99% stenosis.[20] Smoking was not assessed in this study whereas higher age, percentage of male, and the insignificance of diabetes in this study was similar to those in Netherlands to contribute to symptomatic CAS.

In this study, there were 96.2% brain MRI abnormalities, most of which were small vessel disease (CSVD, 74.1%) and infarct (79.5%), which was followed by WMH (38.6%) and brain atrophy (28.1%). Carotid artery stenosis had been recognized to be associated with higher prevalence of ischemic brain lesion and CSVD, including lacunar infarct, WMH, cerebral microbleed, and brain atrophy,which resulted in cognitive impairment.[21,22] A meta-analysis had reported that CAS was associated with significant change of MRI perfusion parameter and white matter microstructural damage including CSVD and WMH.[2,21,23] White matter hyperintensities was also associated with definite alterations in cerebral small vessels, blood brain abnormalities, and local inflammation.[24] Another study has reported the number of lacunar infarcts in CAS with >30% stenosis to be 40.4%. In addition, that study also reported an additional brain MRI pathology, named cortical microinfarct, which was found to be 29% of 89 subjects with CAS of >30% stenosis and significantly associated with lacunar infarct (RR 1.54, 95%CI 1.00-2.44).[21] While this study had limitation in assessing details including cortical microinfarct, this study supported the report of brain MRI abnormalities in CAS from other studies. More infarcts than WMD in this study may be due to more subjects with symptomatic stroke that were recruited.

In addition, CAS may be a biomarker for poor control of CVD risk factors and potentiated brain tissue loss overtime.[3] This was reflected in this study by 28.1% cases of brain atrophy, regardless of the clinical symptoms (27.0% in stroke vs 36.0% in non-hemispheric symptoms, p=0.35) and the degree (26.3% in <50% stenosis vs 29.6% in ≥50% stenosis, p=0.60) and location of stenosis (31.6% intracranial versus 30.0% extracranial post-bifurcation versus 24.3% extracranial bifurcation versus 38.9% multiple sites, p=0.57). Ghaznawi et al in 2022 studied 654 subjects with CAS, aged 57±9 years, and described that stenosis of ≥50% was an independent risk factor for ipsilateral brain volume loss. However, we considered that it may not reach clinical significance (B=-0.72% intracranial volume, 95% CI -1.09 to -0.35, compared to mild-moderate CAS).[3] Therefore, while brain MRI abnormalities were well-known to be associated with CAS, there were no specific types of brain MRI abnormalities may be associated with CAS.

In the aspect of the location of brain MRI lesions, there were also no specific lesion location associated with CAS. However, this study found lesion predominance on bilateral hemisphere (61,0%), periventricle (41.9%), basal ganglia (26.1%), and more significantly on internal capsule in mild CAS. A study regarding brain perfusion and brain MRI abnormalities on 50 subjects with symptomatic CAS of ≥50% also reported decreased percentage of cerebral blood flow and mean transit time in gangliocapsular and deep white matter region of 12.5% and 26.5%, respectively, in asymmetrical compared to symmetrical CSVD, with 100% sensitivity and specificity.[25] Another study focusing on WMH observed that periventricular WMH was associated with cognitive dysfunction, higher mean arterial pressure, and age whereas deep WMH was associated with higher body mass index.[26] The association between WMH and detailed clinical profile was beyond the scope of this study.

Evaluating from the aspect of CAS, brain abnormalities may occur equally on either mild or moderate-severe CAS (p=0.73 for CSVD and 0.60 for infarct) and on either intracranial or extracranial location of CAS (p=0.24 for CSVD and 0.32 for infarct). Theoretically, bifurcation area from common carotid artery to ICA and external carotid artery (ECA) was reported to be an important area of CAS due to the change in blood flow.[27] However, we did not find the association between the degree of CAS and brain MRI abnormalities. Therefore, symptomatic CAS was associated brain abnormalities regardless of the degree or location of stenosis.

Due to the large prevalence of brain MRI abnormalities in CAS, but no specific brain structural abnormalities and properties of CAS were found, CAS should be considered in all subjects with CVD risk factors and brain MRI-related ischemia.

Demographics, brain MRI abnormalities, and carotid artery stenosis among stroke versus non-hemispheric symptoms

Many studies regarding symptomatic CAS only included stroke or TIA. However, the European Society for Vascular Surgery (ESVS) Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral

Artery Disease, 2023, also took non-hemispheric symptoms into account for the symptoms of symptomatic CAS.[14] This study found that there were similar large prevalence of brain MRI abnormalities among those two populations (96.2% versus 96.0%, p=1.00). This was in conjunction with a cross-sectional diagnostic study by Dorobisz et al with 61 subjects of severe CAS and 32 controls, which reported that equilibrium disturbance was significantly found in those with severe CAS.[28] Due to the recommendation of not screening asymptomatic CAS in several guidelines, clinicians should aware that non-hemispheric symptoms may present as symptoms of brain hypoperfusion in subjects with CVD risk factors and CAS.[12,15]

There were still few studies that specifically addressed non-hemispheric symptoms in symptomatic CAS. This study found that non-hemispheric symptoms may produce bilateral brain lesion from the mild CAS. On the other hand, stroke was more associated with unilateral brain involvement.

Association between brain MRI abnormalities and carotid artery stenosis

Carotid artery stenosis is a marker of large artery atherosclerosis (LAA) and further increases the risk of stroke or TIA through progressive stenosis or arterio-arterial embolization.[2,5,6,29] This statement was also supported by this study, which reported significantly increased proportion of ipsilateral CAS-related brain MRI abnormalities (20.9% versus 10.8% in ipsilateral versus non-ipsilateral lesion, p=0.042 with reference to mild CAS) and was especially found in stroke (45.9% in stroke versus 24.0% in non-stroke, respectively, p=0.035). Severe CAS had already been a well-recognized risk factor for stroke and this study also supported that finding.[2]

Despite the aid from primary collaterals from the circle of Willis and secondary collaterals from leptomeningeal and pial arteries, CAS may produce ipsilateral brain abnormalities and symptoms if (1) the degree of stenosis was severe enough to cause cerebrovascular reserve decompensation distal to the stenosis site, or if (2) arterio-arterial emboli was formed, clogged the distal circulation after the primary collateral, and cannot be compensated by the pial collaterals.[25] These pathogenesis contributed to acute sudden symptoms of stroke with larger size of cerebral infarction due to LAA, or acute sudden emboli that was quickly resolved before producing brain abnormalities in TIA. For the latter, a milder CAS with unstable plaque composition may be resposible.[29] A study reported that the presence of intraplaque hemorrhage, lipid-rich necrotic core, and thinning or rupture of fibrous cap on MRI of carotid plaque in CAS were associated with increased risk of stroke in the future.[30] Plaque pathologies were beyond the scope of this study.

Carotid artery stenosis may also be symptomatic by disturbing cerebral hemodynamics secondary to stenosis.[2,25] In this study, brain abnormalities had occurred since mild CAS (49.6% versus 40.7% in non-ipsilateral versus ipsilateral CAS, p=0.042 with reference to severe CAS) and especially in the group with non-hemispheric symptoms (72.0% versus 50.3% in stroke, p=0.035 with reference to ipsilateral CAS). The occurrence of non-ipsilateral brain abnormalities in CAS supported that CAS may impact not only ipsilateral cerebral hemodynamics, i.e. in stroke, but also global cerebral hemodynamics, which was represented by non-hemispheric symptoms.

The impact of CAS on global cerebral hemodynamics depended on the ability of the collaterals to sustain cerebral perfusion, which may vary widely across individuals.[25] Some CAS may not be significant enough to produce clinical ipsilateral symptoms as stated above, but it may reduce the global cerebrovascular reserve and increase the susceptibility for symptomatic manifestation, especially in patients with less anatomical collaterals and less healthy collaterals. The failure to sustain global cerebral perfusion may be symptomatically presented as non-hemispheric symptoms and radiologically presented as CSVD, including lacunar infarcts and WMD.[25] Another study regarding collateral flow in symptomatic CAS showed that there was increased contralateral carotid flow to compensate the decreased flow in ipsilateral CAS.[31] In addition, another study has reported that in low-grade CAS of 20-40%, plaque characteristics including large plaque may increase the risk of ischemic stroke.[32] The study of flow and plaque characteristics was also beyond the scope of this study.

Brain MRI abnormalities of 96.2% in this study represented high burden of brain abnormalities in CAS. Therefore, CAS should be considered even in non-hemispheric symptomatic patients with brain ischemic-related MRI abnormalities.

There were several limitations due to the retrospective design, including; (1) limited data of risk factors including dyslipidemia, types of cardiac abnormalities, autoimmune, antiplatelet or anticoagulant use, risk factor control compliance, etc.; (2) inadequate data to classify the ethology of ischemic stroke; (3) insufficient data to further describe stenotic lesion using DSA, including flow assessment, collaterals, and plaque characteristics; (4) inability to perform MRI protocol with similar power (tesla); (5) unavailability of brain MRI re-expertise by specialised neuroradiologists.[4,8,28-30,32] In addition, the cross-sectional study design may not explain the cause-and-effect relationship between symptomatic CAS and brain MRI abnormalities. This study also did not analyze the involvement of VA stenosis.

However, this is one of few studies in Indonesia reporting the association between brain MRI abnormalities and CAS using the recommended gold standard of DSA with

hundreds of subjects. Retrospective studies blinded the findings from DSA and brain MRI, thus preventing observer bias. The inclusion criteria which included non-hemispheric symptoms may underline the 'covert' clinical manifestation of CAS. Further studies regarding the non-hemispheric symptoms of CAS, detailed properties of CAS including plaque characteristics, blood vessel collaterals, and blood vessel flow characteristics were needed, especially prospectively, to further describe the complex relationship between vessel anatomy, flow, physiology alteration of CAS, and clinico-radiological manifestation of CAS. Studies regarding the effect of best medical treatment to changes in the degree of CAS were also needed to re-evaluate the application of guideline recommendation in the Asian population, especially in Indonesia.

CONCLUSION

Brain MRI abnormalities were very prevalent in symptomatic CAS, including stroke and non-hemispheric symptoms. Bilateral hemispheric lesion, CSVD, infarct, and lesion location on periventricular, basal ganglia, and internal capsule tended to be found on symptomatic CAS, albeit insignificant. While ipsilateral CAS-related brain lesions were associated to stroke, brain MRI abnormalities had also been detected on mild CAS. Therefore, awareness should be heightened in patients with symptomatic CAS, from non-hemispheric symptoms to stroke, with multiple CVD risk factors to be assessed regarding the possibility of brain ischemic lesions using MRI. Any positive brain ischemia findings were suggested to be further assessed for the possibility of CAS. Early detection of CAS may lead to early best medical therapy administration, which may result in reduced morbidity rate due to brain ischemia.

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REFERENCES

1. Mintz BL, Hobson RW. Diagnosis and treatment of carotid artery stenosis. J Am Osteopath Assoc. 2000;100(11 Suppl):1-6.
2. Baradaran H, Gupta A. Brain imaging biomarkers of carotid artery disease. Ann Transl Med. 2020;8(19):1277-7.
3. Ghaznawi R, Rissanen I, De Bresser J, Kuijf HJ, Zuithoff NPA, Hendrikse J, et al. Carotid artery stenosis and progression of hemispheric brain atrophy: the SMART-MR study. Cerebrovasc Dis. 2022;52(2):226-33.
4. Kerwin WS. Carotid artery disease and stroke: assessing risk with vessel wall MRI. ISRN Cardiol. 2012;2012:1-13.
5. van Velzen TJ, Kuhrij LS, Westendorp WF, van de Beek D, Nederkoorn PJ. Prevalence, predictors and outcome of carotid stenosis: a sub study in the Preventive Antibiotics in Stroke Study (PASS). BMC Neurol. 2021;21(1):1-6.
6. Khedr E, Tony AA, Habeel M, Nasreldein A. Frequency and risk factors of carotid artery disease among ischemic stroke patients in the south Egypt: hospital-based study. Egypt J Neurol Psychiatr Neurosurg. 2021;57(1).
7. Wabnitz AM, Turan TN. Symptomatic carotid artery stenosis: surgery, stenting, or medical therapy? Curr Treat Options Cardiovasc Med. 2017;19(8).
8. Zhu Z, Yu W. Update in the treatment of extracranial atherosclerotic disease for stroke prevention. Stroke Vasc Neurol. 2020;5(1):65-70.
9. Abbott AL, Paraskevas KI, Kakkos SK, Golledge J, Eckstein HH, Diaz-Sandoval LJ, et al. Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis. Stroke. 2015;46(11):3288-301.
10. Dorobisz K, Dorobisz T, Zatoński T. The assessment of the balance system in cranial artery stenosis. Brain Behav. 2020;10(9):1-10.
11. Boggs R, Ross M, Tall M. Diagnosis of internal carotid artery stenosis in a patient referred to a physiotherapist for dizziness. J Prim Health Care. 2019;11(4):373-9.
12. Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, et al. Screening for asymptomatic carotid artery stenosis: US Preventive Services Task Force Recommendation Statement. J Am Med Assoc. 2021;325(5):476-81.
13. Magalhães JE, Barros IML de, Pedrosa RP, Sampaio Rocha-Filho PA. Migraine and markers of carotid atherosclerosis in middle-aged women: a cross-sectional study. Headache. 2019;59(1):77-85.
14. Naylor R, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A, et al. Editor's Choice-European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur J Vasc Endovasc Surg. 2023;65(1):7-111.
15. Bonati LH, Kakkos S, Berkefeld J, de Borst GJ, Bulbulia R, Halliday A, et al. European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. Eur Stroke J. 2021;6: I-XLVII.
16. Messas E, Goudot G, Halliday A, Sitruk J, Mirault T, Khider L, et al. Management of carotid stenosis for primary and secondary prevention of stroke: state-of-the-art 2020: a critical review. Eur Heart J. 2020;22:M35-42B.
17. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition

of stroke for the 21st century: a statement for healthcare professionals from the American heart association/American stroke association. Stroke. 2013;44(7):2064-89.
18. Chinda B, Tran KH, Doesburg S, Siu W, Medvedev G, Liang SS, et al. Functional MRI evaluation of cognitive effects of carotid stenosis revascularization. Brain Behav. 2022;12(4):1-14.
19. Del Brutto VJ, Gornik HL, Rundek T. Why are we still debating criteria for carotid artery stenosis? Ann Transl Med. 2020;8(19):1270.
20. den Brok MGHE, Kuhrij LS, Roozenbeek B, van der Lugt A, Hilkens PHE, Dippel DWJ, et al. Prevalence and risk factors of symptomatic carotid stenosis in patients with recent transient ischaemic attack or ischaemic stroke in the Netherlands. Eur Stroke J. 2020;5(3):271-7.
21. Takasugi J, Miwa K, Watanabe Y, Okazaki S, Todo K, Sasaki T, et al. Cortical cerebral microinfarcts on 3t magnetic resonance imaging in patients with carotid artery stenosis. Stroke. 2019;50(3):639-44.
22. Guan S, Kong X, Duan S, Ren Q, Huang Z, Li Y, et al. Neuroimaging anomalies in community-dwelling asymptomatic adults with very early-stage white matter hyperintensity. Front Aging Neurosci. 2021;13(August):1-9.
23. Baradaran H, Mtui EE, Richardson JE, Delgado D, Dunning A, Marshall RS, et al. White matter diffusion abnormalities in carotid artery disease: a systematic review and meta-analysis. J Neuroimag. 2016;26(5):481-8.
24. Moroni F, Ammirati E, Hainsworth AH, Camici PG. Association of white matter hyperintensities and cardiovascular disease: the importance of microcirculatory disease. Circ Cardiovasc Imag. 2020;13(8):E010460.
25. Mohimen A, Gupta A, Gill S, Sahu S, Anadure R. Correlation of CT perfusion with MRI brain in symptomatic carotid artery stenosis. Med J Armed Forces India. 2022;(June).
26. Griffanti L, Jenkinson M, Suri S, Zsoldos E, Mahmood A, Filippini N, et al. Classification and characterization of periventricular and deep white matter hyperintensities on MRI: a study in older adults. Neuroimage. 2018;170(March 2017):174-81.
27. Bouteloup H, Marinho JG de O, Chatpun S, Espino DM. Computational analysis to predict the effect of pre-bifurcation stenosis on the hemodynamics of the internal and external carotid arteries. J Mech Eng Sci. 2020;14(3):7029-39.
28. Sudheer P, Vibha D, Misra S. Asymptomatic carotid stenosis: Several guidelines with unclear answers. Ann Indian Acad Neurol. 2022;25(2):171-6.
29. Elhfnawy AM, Heuschmann PU, Pham M, Volkmann J, Fluri F. Stenosis length and degree interact with the risk of cerebrovascular events related to internal carotid artery stenosis. Front Neurol. 2019;10(APR):1-8.
30. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: A systematic review and meta-analysis. Stroke. 2013;44(11):3077.
31. Fang H, Song B, Cheng B, Wong KS, Xu YM, Ho SSY, et al. Compensatory patterns of collateral flow in stroke patients with unilateral and bilateral carotid stenosis. BMC Neurol. 2016;16(1):4-9.
32. Elhfnawy AM, Volkmann J, Schliesser M, Fluri F. Symptomatic versus asymptomatic 20-40% internal carotid artery stenosis: does the plaque size matter? Front Neurol. 2019;10(October):1-7.

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