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## Distribution, Severity and Radiologic Features of Intracranial Stenosis in Asymptomatic Pakistanis

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### Abstract

**Background**—Intracranial atherosclerotic disease (ICAD) is the most common ischemic stroke subtype globally. It accounts for 30–50% of all ischemic strokes in Asians.

**Aims**—The aim of the study is to report the frequency of asymptomatic ICAD and its associated Magnetic Resonance Imaging (MRI) findings.

**Methods**—200 adult participants were recruited from the Radiology Departments of two major diagnostic centers in Karachi. Eligible participants were confirmed for the absence of stroke symptoms via the Questionnaire for Verifying Stroke Free Status (QVSFS). QVSFS negative subjects underwent MRI on a 1.5 Tesla scanner. Images were centrally reviewed on Di com Viewer 3.0 with electronic calipers to calculate the degree of ICAD.

**Results**—Mean age of subjects was 37.1 years (S.D 15.1) with 50.5% men (n=101) and 49.5% women (n=99). Asymptomatic ICAD was found in 34.5% (n=69) subjects. Of the 3800 intracranial arteries studied, 2.2% (n=88) had biological disease. 20.5% (n=18) of these vessels had atherosclerotic irregularities, 43.2% (n=38) had mild stenosis, 11.4% (n=10) had moderate stenosis, 5.7% (n=5) had severe stenosis while 19.3% (n=17) were completely occluded. The posterior cerebral artery (42% of stenosed arteries, n=37) was most affected. 23.5% (n=47) of subjects had peri-ventricular lucencies, 10.5% (n=21) had brain atrophy while 3.5% (n=7) had silent brain infarcts. There was a significant association between asymptomatic ICAD and peri-ventricular lucencies (PR 1.59; 95% CI 1.35–1.99).

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**Conclusion**—Asymptomatic ICAD is common in young Pakistanis, with no gender predilection; it preferentially affects the posterior circulation. Silent infarcts are rare compared to periventricular lucencies and atrophy.

### Keywords

Stroke; Intracranial Stenosis; Developing Countries; Asymptomatic; Radiology; Prevention; Epidemiology

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### Background

Two-thirds of stroke-related mortality worldwide is attributable to stroke in low and middle income countries [1]. Pakistan, currently the world's sixth most populous nation [2,3], reports a 1 in 4 lifetime prevalence of stroke symptoms over the age of 35 years [4]. Intracranial atherosclerotic disease (ICAD) is a major subtype of ischemic stroke [5] with an estimated prevalence of 20–54% amongst South Asians [6]. In fact, about 30–50% of all ischemic strokes in Asians occur due to ICAD [7].

The Karachi Intracranial Stenosis Study (KISS) [8], that looked at symptomatic ICAD stroke in hospitalized patients reported that 80% patients had significant concomitant asymptomatic stenosis (> 70% stenosis).

### Aims

There is a relative paucity of data on asymptomatic ICAD especially from regions where it is most prevalent and wherein the window for intervention for primary prevention lies. The aim of the asymptomatic ICAD study is to determine the frequency of ICAD in those without clinically evident stroke and its associated Magnetic Resonance Angiography (MRA) findings. Findings from this study will help us determine the magnitude of asymptomatic ICAD in the Pakistani population and with it identifies the need to act early and focus on primary prevention.

### Methods

We have summarized this study in this paper and provided relevant details. The entire study protocol is accessible at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) at Study ID: NCT0207287.

### Study Design and Setting

A prospective cross-sectional study was carried out from March to June 2013 at the Radiology Departments of Aga Khan University [9] and Dow University of Health Sciences (DUHS) in Karachi.

### Participating centers

Aga Khan University is a private not for profit academic center with a fee for service system. The Dow University Radiology Center is public sector, government funded and subsidized entity. Radiology departments in both centers are equipped with 1.5 Tesla MRI scanners.

### City/Country setting

These centers are located in Karachi, Pakistan's largest city with inhabitants of all ethnicities; Karachi has a population of 13 million inhabitants [10] and these centers cover the bulk of MRI scanning for the city and the country with combined volumes of greater than 2000 scans per month. These are general volumes of patient turnover.

### Study population

We recruited adult Pakistani patients >18 years who presented to the participating centers for MRI Brain for indications other than transient ischemic attack (TIA) or stroke (headache, epilepsy, rhino sinusitis etc.). Subjects were required to have no clinical history of stroke or TIA, confirmed by a negative result on the Questionnaire to Verify Stroke-free Status (QVSFS).

### Data collection procedures/ study flow

Non-probability purposive sampling was used to recruit consecutive patients prospectively from the two study sites. All eligible participants were screened for presence of stroke symptoms via QVSFS by trained data collectors after which an informed consent was taken for enrollment into the study. A previously tested Urdu version of QVSFS was used [4,11,12]. QVSFS consists of eight questions, six of which are related to stroke symptoms namely hemiplegia, hemi-anesthesia, hemianopia, loss of vision in one eye, inability to speak and inability to understand [13]. Those who consented to the study and were QVSFS negative were subject to detailed interview and an additional 5 minute Time of flight MRA without contrast was performed. Images were then collected on Compact Disks (CD) for centralized image viewing and quantification. The reviewers were experienced investigators who had previously systematically reviewed vasculature and were unaware of the medical history of the participant.

### Data collection tools/variables

A standardized Data collection form (DCF) was used to collect baseline demographic information.

A magnetic resonance imaging (MRI) reading form adapted from the work of Ward law [14,15] was used to review imaging findings. Modifications made to the form included using angiographic data to record information on cerebral vasculature. In each subject, 19 arteries (bilateral anterior cerebral arteries (A1&A2), bilateral middle cerebral arteries (M1&M2), bilateral posterior cerebral arteries, bilateral vertebral arteries, bilateral internal carotid artery-petrous bilateral internal carotid artery-cavernous, bilateral internal carotid artery-supraclinoid and basilar artery) were examined for the number, degree, and distribution of stenosis. Biologically relevant disease ranging from atherosclerotic irregularity to measurable stenosis was noted and measured. The following radiologic variables were noted : stroke [16], acute stroke lesions [17], silent brain infarcts [18], cortical infarcts [19], lacunar infarcts [19], atrophy [20], leukoaraiosis [21], arterial review [22,23]. All radiologic data were directly archived into a centralized computer using Dicom 3.0 software. The method used to calculate stenosis was adapted from the one used in the Warfarin versus Aspirin in Symptomatic Intracranial Disease [24] study which is as follows:

$$\text{Percentage stenosis} = [1 - (D_{\text{stenosis}}/D_{\text{normal}})] * 100 [14, 25]$$

Where  $D_{\text{stenosis}}$  is the diameter of the artery at the site of the most severe stenosis, and  $D_{\text{normal}}$  is the diameter of the proximal normal artery.

The software allowed zooming, panning, measurements, annotations and segmentation of the images. It has the ability to rotate (90, 180 degrees) and flip (horizontal, vertical) images. It also provides angle values which helps in measuring stenosis around corners. Intracranial occlusive lesions were rated by giving them 1 of 5 grades depending on the narrowness of the arteries as follows: <25% as atherosclerotic disease, 25% to 49% reduction as mild stenosis, 50% to 74% reduction as moderate stenosis, 75% to 99% reduction as severe stenosis, and no opening graded as complete occlusion [17]. Any vessel that was congenitally absent or atretic was not counted as stenosed.

Peri ventricular lucency was classified according to the 3 point system proposed by van Swieten et al. [21].

Silent brain infarcts were defined as vascular disease manifesting as infarcts as detected on MRI in the absence of transient ischemic attack or stroke [18].

### Ethical approval and human subjects' protections

All participants provided written informed consent. This was taken after explaining the risks and benefits associated with taking part in the study. Ethical approval was taken from AKU Ethical Review Committee and the Institutional review board of DUHS. (ERC number 2327 CHS ERC 12 and IRB 360/DUHS 2012). All scans were reviewed within 24 hours by the radiology faculty and there was provision in the study to report any critical incidental findings like aneurysms first to the referring physician and in his absence or inability to contact, the report was communicated to the patient with an urgent specialist referral. All gathered data was numerically coded so as not to reveal the identity of the participants. All electronic transfer within centers was done through decoded CDs that were centralized to a single password protected workstation for analysis.

### Sample size estimation

A minimum sample size of 200 participants was required in order to achieve 80 % power for detecting a minimum difference of 20% in the prevalence of radiological findings between asymptomatic ICAD positive and ICAD negative persons assuming a 1:3 ratio in patients with ICAD versus no ICAD and at a level of significance of 5%.

### Statistical analysis

For categorical variables (brain atrophy, silent brain infarcts and peri-ventricular lucencies proportions were calculated. The independent contribution of any ICAD-associated finding was examined in the Univariate Cox proportional hazards model, which was used to calculate prevalence ratios. In order to compute the statistically adjusted Prevalence Ratios (PR), multivariable Cox regression analysis was done. The level of significance of 0.05 was set for the analysis. Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS); Version 19.

## Results

Mean age of the participants was 37.1 years (S.D 15.1 years) with nearly 62% (n=124) of the participants being younger than 40 years. There was a roughly equal proportion of males (50.5%, n=101) and females (49.5%, n=99) in the study (Table I – Demographic Data).

### MRI-MRA Findings

A total of 3800 intracranial arteries in 200 patients were studied. ICAD was found in 34.5% (n=69) of the subjects.

A total of 88 vessels were found to have any degree of stenosis. Of these, majority of the vessels were either mildly stenosed (43.2%, n=38) or had atherosclerotic irregularities (20.5%, n=18). The commonest artery affected was the posterior cerebral artery (PCA) (42% of stenosed arteries, n=37) followed by vertebral artery (34% of stenosed arteries, n=30). Detailed findings are presented in Table 2 (Figure 1).

A mean of 1.3 vessels were diseased per patient (88 vessels in 69 subjects) among those who had ICAD with the highest number of affected vessels in a single patient being 3.3.5% (n=7) of all subjects had silent brain infarcts (Figure 2), 23.5% (n=47) subjects had peri-ventricular lucencies (Figure 3) while 10.5% (n=21) showed cortical brain atrophy (Figure 4). Peri-ventricular lucencies were found to be statistically associated with asymptomatic ICAD (PR 1.59; 95% CI 1.35–1.99) when Cox Regression analysis was applied. Asymptomatic ICAD was not significantly associated with brain atrophy or silent brain infarcts.

## Discussion

This study shows us that asymptomatic ICAD is present in approximately one third (34.5%, n=69) of Pakistani South Asians presenting for MRI without a history or symptoms of prior stroke. The most commonly affected arteries were the Posterior Cerebral arteries followed by Vertebral and Middle Cerebral arteries. Of all affected arteries, about 20% (n=17) showed complete occlusion in clinically silent areas.

Our reported prevalence (34%) is relatively higher than previously reported figures of 4–29% in international data. This is particularly concerning since prior studies have targeted higher risk populations [26–28] as compared to the general population that was selected for our study. Regionally comparable data is sparse; however another study from Karachi on hospitalized stroke patients reported the prevalence of stenosis to be 80% on the asymptomatic side [29]. Other prevalence studies [28,30–37] in asymptomatic patients have mostly used transcranial Doppler ultrasound (TCD) for detecting ICAD which is less sensitive than an MRA for detecting stenosis and is limited to fewer and larger arteries (usually MCA) (Table 3).

The majority of our subjects were patients younger than 50 years. This finding is very much in line with the findings of another burden study from Karachi where the average age for stroke was 50 years [4]. Hence, our results reiterate the exceptionally high burden of atherosclerotic diseases at a relatively younger age in Pakistan.

Associated MRI findings showed that only 3.5% (n=7) of study subjects had silent cortical brain infarcts while 23.5% (n=47) had peri ventricular lucencies. Per ventricular lucencies are usually found as lacunars infarctions caused by occlusion of small penetrating cerebral arteries resulting from arteriosclerotic changes of parent cerebral arteries [38]. They are considered an important risk factor for clinical cerebrovascular disease in the general population and are strongly associated with small-vessel vasculopathy. We theorize that the small sub cortical strokes found in this population may be due to undetected hypertension causing direct small vessel disease and asymptomatic ICAD causing penetrator artery disease resulting in small sub cortical disease more frequently than silent cortical brain infarcts.

Atherosclerosis of the intracranial arteries has also been found to be associated with cerebral atrophy leading to cognitive impairment and dementia [35]. Whereas the majority of studies evaluating the relation of ICAD and brain volume reduction have been performed in symptomatic patients with severe stenosis, recent population based studies [33,37] have also suggested that asymptomatic intracranial atherosclerosis is also related to poorer neuropsychological [39] performance, even with mild degrees of stenosis.

We think that our observed higher proportion of ICAD is because we used a sensitive modality like MRI for detecting intracranial stenosis; our methods were standardized with the help of special software designed for measuring stenosis. International studies have mostly used Transcranial Doppler ultrasound for detecting ICAD which is less sensitive than an MRA for detecting stenosis; they have different cutoffs and also restrict their observations to single arteries compared to our observation of disease on the entire circle of Willis. We performed our literature search on PubMed using keywords asymptomatic ICAD, Intracranial Stenosis and limited our search to English articles only. We also searched accompanying references.

This study also has diagnostic limitations since we have not used a 4 vessel angiogram for diagnosing ICAD. This is because 4 Vessel angiography is an invasive procedure and it would be dangerous and unethical if used on otherwise healthy stroke free patients since it increases the risk of disabling stroke by 1.5 to 3 % [40], which is unacceptable ethically and doesn't justify the risk of investigation. However we have used an excellent noninvasive tool with the same technical capacity at both centers. Thus the diagnostic limitations are homogenous in our study population. This study is also limited in that it is a study based on convenience sampling of participants presenting for MRI at diagnostic centers, thus it isn't exactly a community based observation which would be a better representation of ICAD prevalence.

Our study has several strengths. We did not bias participation to those who were medically high risk (known HTN, DM, and PAD etc). We verified asymptomatic status using a validated questionnaire (QVSFS) and validated regionally applicable tools for risk assessment. We used the same diagnostic at both the centers and evaluated them with a centralized offline assessment performed by experienced investigators using a standardized definition and approach. We also had several limitations. We did not use a gold standard e.g. angiography, however a procedure with an inherent risk of stroke would not be ethically



justified in stroke free participants. A 3.0 Tesla study with plaque characterization would have yielded more insight into pre stroke mechanisms. Although we were able to study a wide range of younger participants with no stroke risk factors, we were unable to randomly draw subjects from a community-based population due to resource limitations and logistics. Our study has applicability to mostly urban transitional Pakistan, as we do not have significant rural representation.

In conclusion, our observation of prevalent asymptomatic atherosclerosis in young participants supports the need for future global studies focused on community-based longitudinal imaging with increased precision to further define natural history and perhaps consider early prevention from strokes from symptomatic ICAD.

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## Disclosures

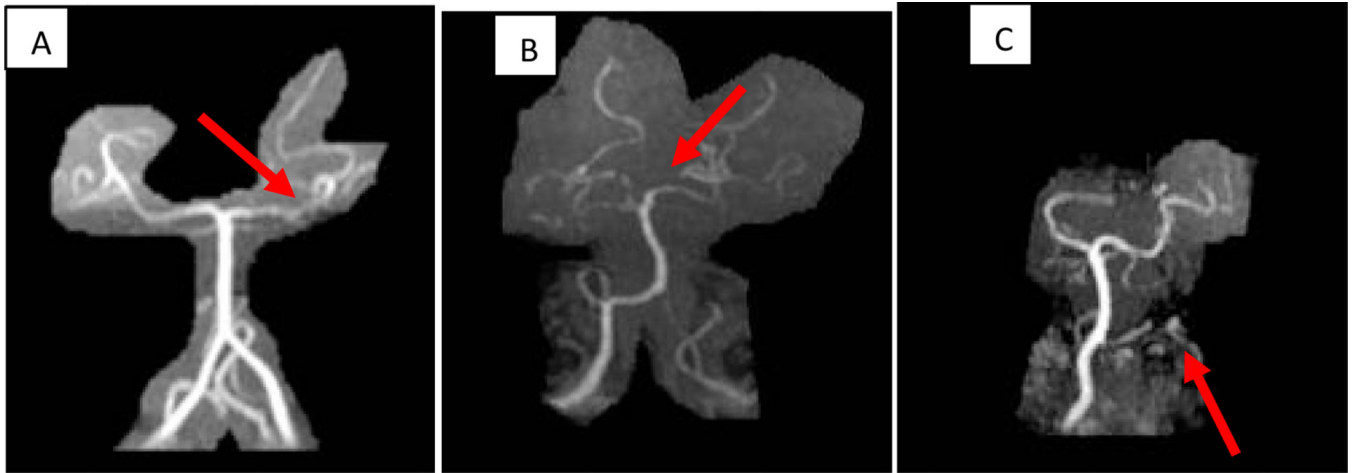
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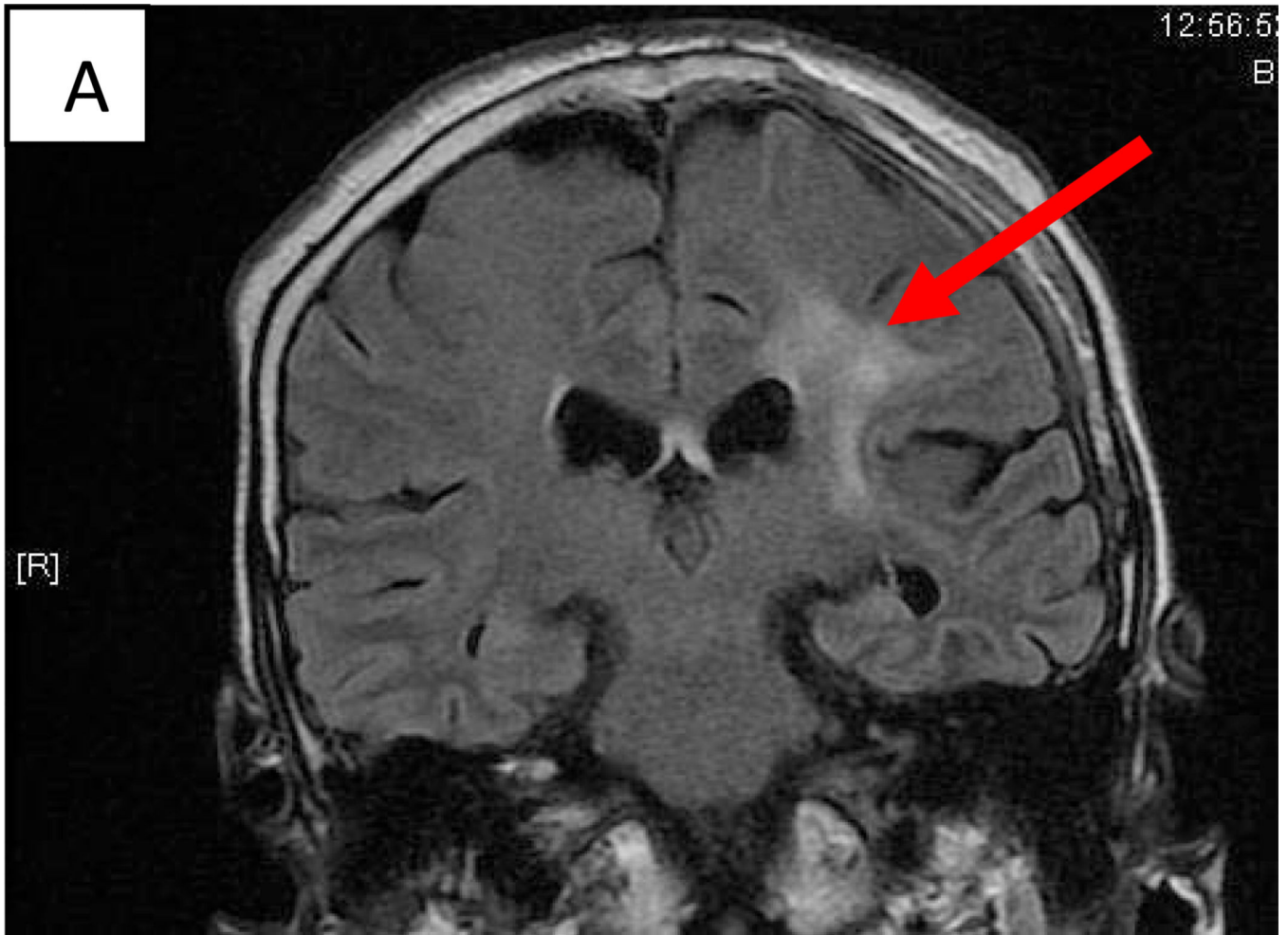
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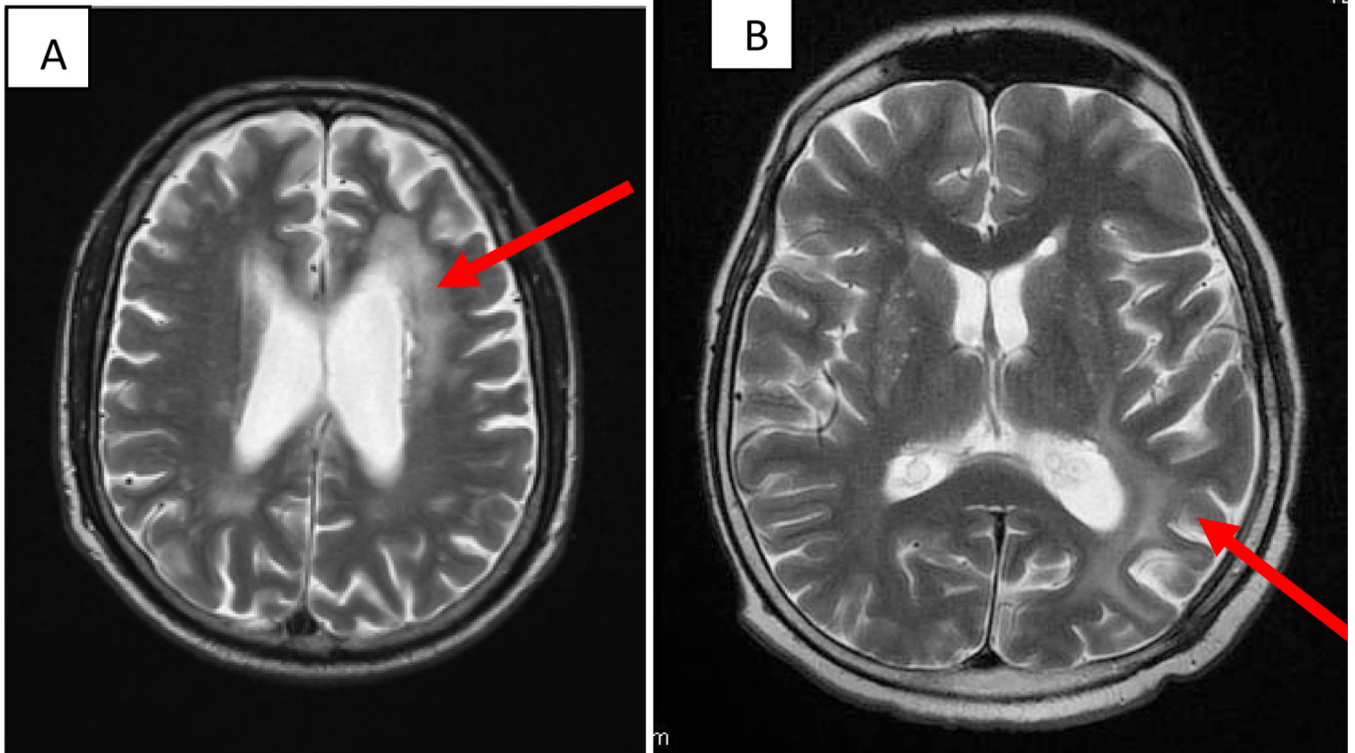
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**Figure 1. MRI images showing Asymptomatic ICAD in the posterior circulation**  
The arrows point at the point of stenosis in each vessel (A) Left Posterior Cerebral Artery  
(B) Right Posterior Communicating Artery (C) Left Vertebral Artery.

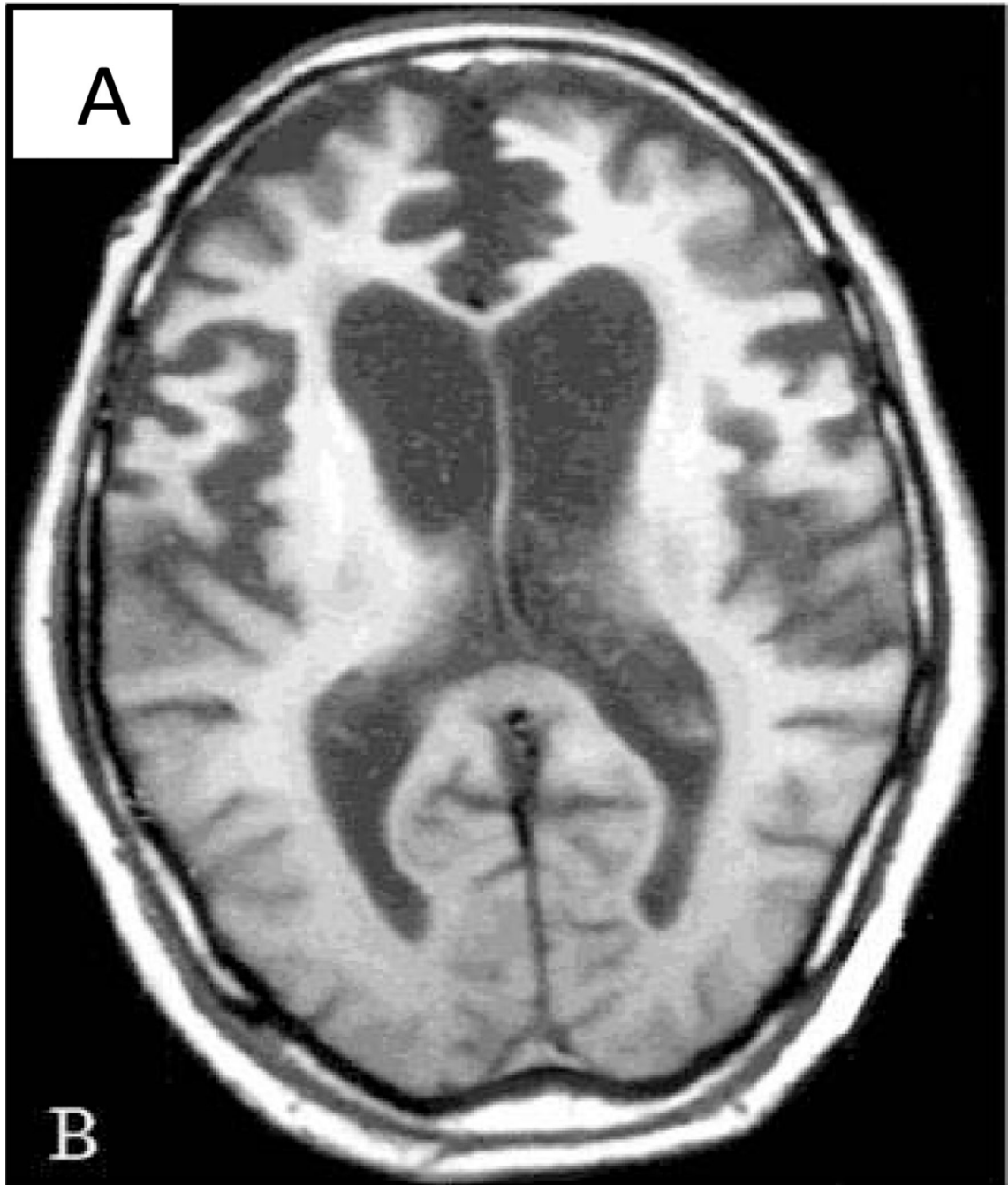


**Figure 2. Silent brain infarct**  
The Arrow points at the region of infarction.



**Figure 3. Periventricular Hyperintensities**

Increased signals as pointed by the arrows is evident on T2 images in the periventricular areas.



**Figure 4. Brain volume reduction**

Diffuse reduction in brain volume is evident by the narrowing of gyri and widening of sulci.

**Table 1**

Baseline Demographics of Participants.

	<b>Frequency in patients with ICAD 69 (34.5%) n (%)</b>	<b>Frequency in patients with no ICAD 131 (65.5%) n (%)</b>
Age (Years)		
Mean (SD)	38.6 (15.1)	36.31 (15)
Gender		
Males	36(52.2%)	65(49.6%)
Females	33 (47.8%)	66 (50.4%)
Clinical Risk factors		
Diabetes	4 (5.8%)	14 (10.7%)
Hypertension	17 (24.6%)	36 (27.5%)
Dyslipidemia	7 (10.3%)	3 (2.2%)
CVD	2 (2.9%)	1 (.8%)
A.Fib	1 (1.4%)	2 (1.5%)



**Table 2**

Stenosed Vessels by degree of stenosis and vessel type.

Vessel	<25%	25–49%	50–74%	75–99%	Complete occlusion	Total
MCA	5 (5.7%)	10 (11.4%)	5 (5.7%)	-	-	20 (22.7%)
ACA	-	1 (1.1%)	-	-	-	1 (1.1%)
Vertebral	3 (3.4%)	14 (16%)	1 (1.14%)	2 (2.27%)	10 (11.4%)	30 (34.1%)
PCA	10 (11.4%)	13 (14.7%)	4 (4.5%)	3 (3.4%)	7 (8%)	37 (42.0%)
Total	18 (20.5%)	38 (43.2%)	10 (11.4%)	5 (5.7%)	17 (19.7%)	88

**Keywords:** MCA: Middle Cerebral artery; ACA: Anterior cerebral Artery; PCA: Posterior cerebral artery.

**Table 3**

Prevalence Estimates of Asymptomatic Intracranial Stenosis in Asia.

Study	Population	Prevalence	Comments
Uehara et al (2005) [40]	425 Japanese asymptomatic patients requesting evaluation for cerebrovascular disease via MRA (mean age 64 ± 20 years; 57% men)	3.5% for ≥50%, 9.6% for ≥ 25%	Patients requesting cerebrovascular evaluation likely to have higher prevalence of risk factors and intracranial disease.
Huang et al (2007) [35]	1,068 subjects aged 50 years from random population-based sample with no previous history of stroke or TIA, and adequate acoustic windows evaluated by TCD	5.9% (MCA stenosis)	Only MCA studied
Wong et al (2007)[33]	590 (92%) of geographically defined Chinese population aged 40 years. Accessed using Transcranial Doppler (TCD)	6.9%	Unclear if 52 of total 642 contacted are missing due to technically inadequate study or subject accessibility issues; 19 with previous history of stroke.
Tang et al (2007) [37]	3057 Chinese patients aged > 50 yrs. with at least one vascular risk factor (hypertension, diabetes, and hyperlipidemia) and no prior stroke or TIA were accessed using TCD	12.6% (MCA stenosis)	The prevalence escalated quadratically with increasing number of associated factors: from 7.2% for one, to 29.6% for four associated factors.
Uehara et al (2000) [27]	156 Japanese subjects with no evidence of stroke who presented at a neurologic clinic with concerns about a possible stroke (mean age 63 years) underwent MRA	14.7%	11.5% extra-cranial carotid stenosis. Age and hypertension are significant predictors for intracranial artery stenosis. MRA is sufficiently efficient in patients in whom cerebral artery occlusive lesions is suspected.
Uehara&Tabuchi et al (2001) [36]	151 Japanese asymptomatic patients scheduled to undergo CABG evaluated via MRA	21% with > 50% intracranial stenosis	16.6% subjects had extra cranial stenosis.
Park et al (2006) [28]	835 asymptomatic Korean adults who voluntarily underwent a health screening examination and MRA. The subjects had no history of stroke or cardiovascular disease.	3%	ICAS was distributed as follows: ACA 16%, MCA 52%, PCA 26%, and distal internal carotid arteries 6.5%. The ratio of ICAS to extra cranial atherosclerosis was 6:1.
Elmore et al (2003) [34]	510 asymptomatic persons referred for carotid Doppler ultrasound (mean age 71 ± 11 years, 50% men)	12.9%	Laboratory accuracy 93%, extra cranial carotid stenosis in 39.2%.
Thomas et al (2004) [26]	2165 Chinese type II diabetic patients with no prior history of stroke (mean age 54± 11 yrs.) evaluated using TCD.	29.6% (MCA stenosis)	Age, hypertension and dyslipidemia were independent predictors of MCA stenosis.