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Subtypes of Ischemic Stroke and their Risk Factors in Western Rajasthan: A Cross Sectional Study at Tertiary Centre

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Abstract

Background: The aim of the study was to characterize stroke subtypes based on clinical and magnetic resonance angiogram (MRA) imaging findings and to correlate each subtype with conventional risk factors and prognosis.

Material and Methods: This observational study was conducted in a tertiary care teaching hospital of Dr S N Medical College Jodhpur from Jan 2015 to Mar 2016. A total of 100 admitted patients during this time period with acute ischemic stroke were clinically evaluated for conventional risk factors along with relevant blood investigations. Magnetic resonance imaging (MRI) brain along with MRA of neck and brain vessels were performed and results were categorized into extra-cranial (EC), intracranial (IC) or both. Patients enrolled were categorized as per TOAST classification.

Results: Mean age was 60.84 yrs (15 - 98) with male preponderance (79%). Most common subtype was large artery atherosclerosis (44%) followed by small vessel disease (39%), cardio-embolic (10%), other determined etiologies (4%) and undetermined etiologies (3%). There was predominance of intra cranial (81%) than extra cranial (45%) atherosclerosis which is the most notable difference from western studies. Small vessel disease was more commonly associated with risk factors like hypertension (76%), diabetes (56%) and dyslipidemia (53%) with a significant p value of < 0.05. Recurrent CVA, TIA, higher mean NIHSS score and mortality was more commonly associated with large vessel disease.

Conclusion: Ischemic stroke is a disease with multiple etiologic factors with marked difference among subtypes regarding risk factors and outcome. Large artery atherosclerosis was predominant type and intracranial MCA involvement was most common MRA finding.

Keywords: *Magnetic Resonance Angiography; Extra-Cranial; Intracranial; Cerebro-Vascular Disorders*

Introduction

Stroke is classically characterized as a neurological deficit attributed to an acute focal injury to the central nervous system by a vascular cause including cerebral infarction, intra-cerebral hemorrhage and subarachnoid hemorrhage. It is a major cause of disability and death worldwide [1]. In India, the age adjusted prevalence rate for stroke ranges between 84 - 262/100000 in rural and 334-424/100000 in urban areas. Annual incidence rate of first ever stroke is 119 - 145/100000, based on recent population based studies [2]. India has a high stroke burden and is likely to face stroke epidemic, unless preventive measures are taken out rightly.

Stroke registries have attempted to study its subtypes and have recorded a higher frequency of ischemic stroke (83.6%) in comparison to hemorrhagic stroke (11.6%) [3]. TOAST (Trial of Org 10172 in Acute Stoke Treatment) classification have been used to further characterize ischemic stroke based on underlying mechanism. This denotes five subtypes of ischemic stroke; large artery atherosclerosis, small vessel occlusion, cardio embolism, stroke of other determined etiology and stroke of undetermined etiology [4]. Each subtype of stroke is characterized by different age group, risk factors, co-morbidities, treatment strategy and prognosis. Large hemispheric infarcts usually occur due to occlusion of internal carotid or proximal middle cerebral artery and they respond better to endovascular treatment than intravenous thrombolysis [5]. Carotid end-arterectomy is of proven value in preventing recurrent stroke in cases of large artery stenosis while anti-platelets are more of value in small vessel occlusive diseases [6,7].

There are few Indian studies on subtypes of ischemic stroke from different regions. Intracranial atherosclerosis was predominant in these studies with differences in involvement of vessels, hence the study was planned to observe the pattern of atherosclerosis in patients of western Rajasthan. Our primary aim was to characterize Ischemic stroke (IS) subtypes based on clinical and MRA (Magnetic Resonance Angiography) findings. We also correlated each subtype with conventional risk factors and prognosis.

Material and Methods

It was an observational study carried out in Department of Neurology, Dr. S N Medical College Jodhpur from January 2015 to March 2016. All the patients admitted during this period with ischemic stroke were included. They were evaluated for conventional risk factors along with relevant blood investigations and imaging. The study was approved by institutional ethical committee. Informed written consent was obtained from all patients or close relatives for the necessary investigations, data collection, analysis and publication of data and images.

The risk factors evaluated includes hypertension (BP > 140/90 mmHg, history of hypertension or on antihypertensive drugs), diabetes (fasting blood sugar > 126 mg%, two hour postprandial > 200 mg%, glycosylated hemoglobin > 6.5% or on antidiabetic drugs) and dyslipidemia (abnormal lipid profile that required dietary or pharmacological intervention [8].

Patients were considered smokers if they were smoking at the time of presentation or had been smoking for 5 years previously. History of alcohol consumption and stroke in first degree relatives were noted. Apart from routine blood investigations, special investigations like antinuclear antibodies(ANA), cANCA, pANCA, homocysteine, lactic acid, anti-phospholipid antibody syndrome(APLA) and thrombocheck profile were carried out in selected patients. All patients were subjected to electrocardiogram (ECG), transthoracic ECHO and Holter monitoring while only few patients underwent trans-esophageal ECHO. We excluded patients with liver failure, kidney failure and venous sinus thrombosis.

MRI along with MRA were carried out in all patients using 1.5 T MR Scanner with a quadrature head coil for intracranial MRA and neurovascular array or spinal array coil for the extra-cranial MRA in the region of neck. The sequences used were multislab three dimensional spoiled gradient based on time of flight principle. Narrowing in vessel diameter of 50% or more was regarded as significant stenosis on both extracranial (EC) and intracranial(IC) vessels and patients enrolled were categorized as per TOAST classification which is as follows:

- **Macroangiopathy (Large-Artery Atherosclerosis):** Macroangiopathy is defined as the presence of an occlusion or a stenosis with > 50% diameter reduction of a major brain-supplying artery due to atherosclerosis.
- **Cardioembolism:** Cardioembolism is defined as the presence of a high- or medium-risk source of cardiac embolism.
- **Microangiopathy (Small-Vessel Disease):** Microangiopathy is defined as the presence of lacunar syndromes, infarction(s) < 1.5 cm of diameter or normal CT/MRI examination. Evaluation of the large extracranial arteries should not demonstrate a stenosis of >50% in an ipsilateral artery.
- **Other Determined Etiologies:** Spontaneous dissection, traumatic dissection, vasculitis, hematologic disorders, coagulopathies.
- **Undetermined Etiology:** This category included patients in whom a likely etiology could not be determined despite an extensive evaluation [9].

Basic demographic data and data regarding clinical, laboratory and radiological profile were collected in a predesigned proforma. Qualitative data were presented as proportion and were analyzed using chi square test. Quantitative data were presented as mean ± SD and to find out the difference between two groups student's t-test was applied. For statistical purposes both sided p value less than 0.05 was considered significant. SPSS version 20 was used for statistical analysis.

Results

During study period, consecutive 100 patients qualified to be included in the study. Mean age of the cohort was 60.84 years (range 15 - 98 yrs) with male preponderance (79%). Most common subtype was large artery atherosclerosis (44%) followed by small vessel disease (39%), cardio-embolic (10%), other determined etiologies like hyper-homocysteinemia, Anti-phospholipid antibody syndrome and vasculitis (4%) and undetermined etiologies (3%) (Figure 1). Large and small vessel disease was common in elderly (mean age-64.75 yrs) while remaining subtypes were more common in younger age group (mean age-37.81 yrs). There was predominance of intracranial (81%) than extra-cranial (45%) atherosclerosis. Proximal MCA was the most commonly involved (41.6%) followed by intracranial ICA (22%). Basilar artery involvement was found in 5.5%, while vertebral, anterior cerebral and posterior cerebral artery was involved in 2.7% each. There were multiple sites of involvement in anterior circulation in 11.1% and 2.7% in posterior circulation. Both anterior and posterior circulation were involved in 8.3% (Table 1).

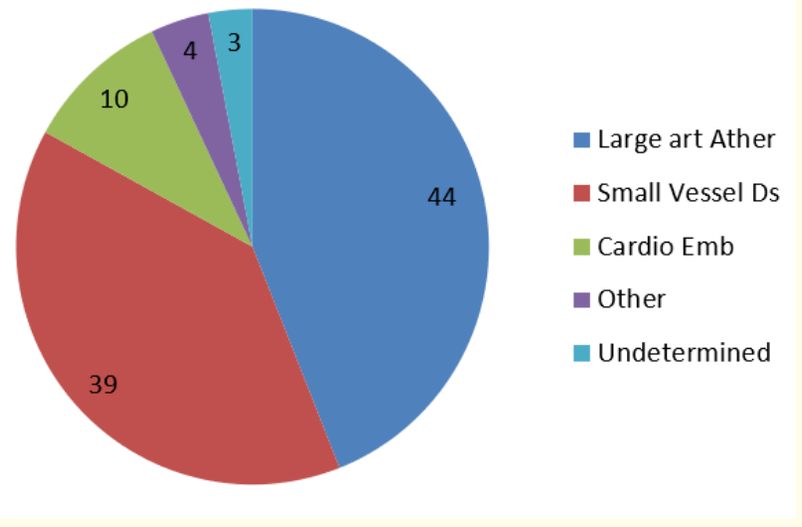

Figure 1: *Subtypes of Ischemic Stroke (%).*

Extra Cranial Involvement (N = 20)		Intra Cranial Involvement (N = 36)		Both (N = 9)	
Artery	**Patients (%)**	**Artery**	**Patients (%)**	**Artery**	**Patients (%)**
CCA	2 (10)	ICA	8 (22)	ICA+ICA	3 (33.3)
ICA	8 (40)	MCA	15 (41.6)	ICA+MCA	5 (55.6)
VA	4 (20)	VA, PCA, ACA	1 (2.7)	VA+VA	1 (11.1)
CCA+ICA	3 (15)	BA	2 (5.5)		
ICA+VA	3 (15)	Multiple site in AC	4 (11.1)		
		Multiple site in PC	1 (2.7)		
		Both AC and PC	3 (8.3)		

Table 1: *MRA findings in patients of Ischemic Stroke and their subtypes.*

Note: CCA: Common Carotid Artery; ICA: Internal Carotid Artery; VA: Vertebral Artery; MCA: Middle Cerebral Artery; BA: Basilar Artery; PCA: Posterior Cerebral Artery.

MR angiography of neck vessels showed most common involvement of cervical ICA (Figure 2) in 40% cases followed by vertebral artery in 20%. Combined CCA and ICA were involved in 15% while isolated atherosclerosis of carotid siphon was found in 10%. In 15%, there was involvement of both internal carotid artery and vertebral artery; of these, total occlusion was found in 5 patients (ICA -4 and VA-1). Small vessel disease was more commonly associated with risk factors like hypertension (76%), diabetes (56%) and dyslipidemia (53%) with p value of < 0.05. Recurrent CVA, TIA, higher mean NIHSS (National Institute of Health Stroke Scale) score and mortality was more in large vessel disease (Table 2).

Figure 2: *Photograph of MRA showing Occlusion at various levels.*

	Large (44)	Small (39)	Cardio Emb (10)	Others (4)	Undetermined (3)
Male	35	31	9	1	3
Female	9	8	1	3	0
Mean Age (yrs)	61.5	68.05	50.1	32.0	31.33
Hypertension	23	30	4	1	0
Diabetes	15	22	1	0	0
TIA	8	4	0	0	0
Dyslipidemia	7	21	1	1	0
Obesity	9	6	2	0	0
Smoking	20	20	2	0	0
Alcohol	16	13	2	0	0
Mean NIHS	10.23	6.79	7.0	8.5	5.3
Mortality	5	1	0	0	0

Table 2: *Risk factors of ischemic stroke and their correlations.*

Discussion

The present study covered 100 cases of ischemic stroke from Western Rajasthan and test battery for diagnosis was individualized on case by case basis depending upon possible risk factors. All patients were subjected to MRA imaging and thus were categorized as per TOAST classification [4]. Overall mean age was 60.84 yrs (15 - 98) with male preponderance (79%). Similar sex difference was found in other studies from India and abroad, suggesting some protective mechanism in women [10,11]. Family history of stroke was found in 18%, both paternal and maternal history of stroke was associated with increased stroke risk [12]. This may be due to familial occurrence of risk factors, genetic susceptibility and common environmental and life style factors. Cardio-embolic stroke was common in younger age group as majority of the patients had rheumatic heart disease. This is in contrast to study by Grau., *et al.* where it was common in older age group, this is most likely caused by increase in atrial fibrillation parallel to aging [9]. Among the atypical causes, hyper-homocystinemia (2%), antiphospholipid antibody syndrome (1%) and vasculitis (1%) were found in younger age group as it was found in a study of stroke in young from northern India [13].

Most common subtype found in all studies was large artery atherosclerosis (LAA) followed by small vessel disease (SVD) as observed in our study also [9,11,14]. Small vessel disease (SVD) was most commonly associated with hypertension, diabetes and dyslipidemia while recurrent CVA, TIA, higher mean NIHSS score and mortality were common in LAA which was similar to a German study correlating risk factors and outcome with various subtypes of ischemic stroke [9]. These results confirm the hypothesis that hypertension, diabetes were more common in microangiopathic stroke than other subtypes. In the NINCDS (National Institute of Neurological and Communicative disorders and Stroke) data bank, hypertension and diabetes were more common in lacunar stroke than in cardioembolic [15]. In the Rochester study, the prevalence of hypertension was not different and diabetes was less common in LAA than in lacunar stroke [16].

Most common MRA finding in our study was preponderance of intracranial (IC) atherosclerosis compared to extracranial (EC) atherosclerosis and so is the internal carotid large artery disease, the most common stroke subtype worldwide [17]. Intracranial atherosclerosis appears to be much more common in the Asian as compared to the Western population which has been attributed to differences in vascular risk factors in different races [18,19]. Blacks have a different lipid profile than do Whites and the presence of carotid artery disease correlates with different apolipoprotein polymorphisms in blacks than in whites. Lipoprotein (a) is a lipid component influenced by genetic factors and is found by various studies to be higher in blacks than in whites. This difference in atherosclerosis pattern however has not been noted in IHD or PVD [20].

Among IC vessels, proximal MCA was most commonly involved followed by ICA while among EC vessels, ICA occlusion was followed by CCA occlusion. In a study by Kim, MCA stenosis was most common type of atherosclerotic lesion in one third of patients with stroke [21]. Asymptomatic patients with vascular risk factors also frequently have significant degrees of IC stenosis, Wong found 12.6% of at risk individuals had significant MCA stenosis [22].

MCA disease may precede EC atherosclerosis, this sequence is suggested by the lack of substantial carotid stenosis in a group of patients with IC atherosclerosis, while nearly all those with EC atherosclerosis also had concomitant IC lesions. Therefore detecting IC atherosclerosis may enable clinicians to intervene early [23]. In a similar study from north India, EC MRA was abnormal in 56.3% and IC MRA in 63.3%. Among IC MRA, abnormalities were found in 15.6% in ICA, 15.6% in MCA and 1% in vertebral and basilar artery each [24]. One year data from hospital based stroke registry done by Kaul., *et al.* have also found predominance of IC rather than EC location of atherosclerosis [11]. Some studies have found increased vertebral artery (14%) and posterior cerebral artery involvement 13% as compared to our study [25]. This difference in our study may be due to 1.5T scanner which has lower sensitivity and specificity in detecting IC small vessel abnormality compared with DSA. The gold standard DSA (Digital Subtraction Angiography) is too invasive to screen for stenosis following ischemic events despite its greater level of spatial resolution. MRA offers good equivalency with DSA for detection of >50% stenosis with reported sensitivity, specificity, and accuracy of 92%, 91%, and 91%, respectively but falls short of the 100% and 99% sensitivity and specificity of CTA (CT Angiography) [26].

Limitations of Our Study

Of course CTA is better as compared with MRA for the purpose of determining degree of stenosis as it is not subject to the flow void artifacts and overestimation that is frequently encountered in MRA studies. But on the other hand, CTA also carries the burden of radiation exposure, use of iodinated contrast, post processing steps, and technical limitations related to calcification of the arterial wall [26,27]. Another limitation of MRA is that regions of extremely narrowed lumen can appear completely occluded due to de-phasing of blood concomitant to the increased velocity of spins through the vessel due to narrowing [28]. This flow void phenomenon, nevertheless, indicates a region of extremely narrowed lumen and may not affect clinical practice [29]. In addition, review of source images rather than maximum intensity projection images alone aids in reducing this source of artifacts [30].

We also suggest that for better defining the results the results of our study there is need of further verification in larger studies, preferably by DSA.

Conclusion

Ischemic stroke is a disease with multiple etiologic factors with marked difference among subtypes regarding risk factors, treatment and outcome. Large artery atherosclerosis is predominant type and intracranial involvement is more common.

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