

## ORIGINAL ARTICLE

# Etiology of Ischemic Stroke and Correlation with Common Risk Factors in a Tertiary Care Centre

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## ABSTRACT

**Introduction:** Stroke is the third leading cause of mortality worldwide and a matter of grave public importance in India. Ischemic stroke accounts for 80% of all cases. This study aims at classifying patients of ischemic stroke according to TOAST system.

**Aims and objectives:** The specific objectives of the study are to document various etiology of ischemic stroke and correlate clinical presentations and risk factors with the different subtypes.

**Methodology:** An observational study was carried out among 100 ischemic stroke patients using both prospective and retrospective data. History, clinical examination and different laboratory and radiological investigations were carried out. Etiology was classified by Trial of Org 10172 in Acute Stroke Treatment criteria and clinical presentations grouped by NIHSS score. Comparisons were done between groups stratified by stroke subtype.

**Results:** Among the 100 patients 25 had cardioembolic, 13 large artery atherosclerosis, 21 small vessel stroke, 33 undetermined and 8 others type of stroke. Among the risk factors there was significant preponderance of hypertension, diabetes, ischemic heart disease, dyslipidemia, ECG, Echocardiographic abnormality, propensity for basal ganglia and paraventricular involvement among certain subtypes. There was no substantial relation between the subtypes and addictions, past history of stroke, and other territorial involvement.

**Conclusion:** The etiological diagnosis of stroke in young adults has changed over time as a result of improvements in diagnostic workup. A notable portion of these patients remains without an evident stroke mechanism according to TOAST criteria.

**Keywords:** ischemic stroke, TOAST classification, cardioembolic, NIHSS score

## INTRODUCTION

A stroke (previously known as a cerebrovascular accident) is rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid haemorrhage) loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin (Hatano 1976)-WHO. Its importance as a public health matter can be envisioned from the fact that worldwide after coronary heart disease (CHD) and cancer of all types combined strokes are the third leading cause of death. And among Asians the prevalence of stroke is more than that of CHD. In the early 1980s the prevalence rates of stroke were around 500-700 per 100,000 in the western countries<sup>1</sup> and 900 per 100,000 in Asia.<sup>2</sup> Stroke can be broadly classified into ischemic and haemorrhagic type and among them 85% are of ischemic etiology. Accurate definition of the mechanism of stroke is

crucial as this will guide the most effective care and therapy. Ischemic stroke can be classified based on etiology according to various classification systems. A good stroke classification system is the key to select patients for genetic phenotyping, conduct epidemiological studies, and make treatment decisions and prognostic predictions. One of the most popular classification systems is the TOAST classification which was originally formulated for the purpose of investigating any potential efficacy of the anticoagulant danaparoid for treatment of various types of ischemic strokes but has been used extensively for other purposes, such as identifying new genetic markers and risk factors.<sup>3</sup> So we studied 100 patients of ischemic stroke and classified them according to TOAST classification based on etiology and studied the correlation of the important risk factors with the individual subtypes.

## METHODOLOGY

This observational study was carried out at Medical College Kolkata in the period from January 2014 to 2015. Approval for this study was granted by Institutional Ethics Committee for human research. 100 patients of ischemic stroke who were admitted in the wards or had attended outpatient department were chosen initially based on clinical features and in cases where the diagnosis was confirmed based on CT scan they were included in the study as per the inclusion criteria. Patients with other causes of stroke like intracerebral haemorrhage, subarachnoid haemorrhage, and transient ischemic attack were excluded. The selected patients were informed about the research protocol and written informed consent was taken from 85 patients. In the remaining 15 patients with moderate to very severe stroke who had altered consciousness written consent was taken from next of kin.

**Procedure:** On admission or during first visit the clinical features of the patient was noted and assigned a value according to National Institute of Health Stroke Scale (NIHSS). Detailed history was taken from the patient or relatives particularly history of diabetes, hypertension, atherosclerotic risk factors, prior history of stroke or Transient Ischemic Attack, addictions like smoking, alcohol intake. The patients were then subjected to different laboratory investigations namely complete haemogram, platelet count, serum urea, Creatinine, fasting blood sugar, lipid profile, coagulation profile (in some cases). They also underwent radiological investigations namely ECG, Echocardiography, bilateral carotid artery Doppler, MRI of brain and Magnetic Resonance Imaging in few selected cases. Based on the results of these clinical and laboratory parameters the patients were categorised into one of 5 etiological subtypes of ischemic stroke based on TOAST classification. After classifying these patients according to etiology correlation analysis was carried out as per their NIHSS score.

**Statistical Analysis:** - Categorical variables were expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes. Continuous variables were expressed as Mean  $\pm$  Standard Deviation and compared across the groups using one way ANOVA Test. The statistical software SPSS version 20 was used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it was considered as significant.

## RESULTS

100 patients of ischemic stroke who fulfilled the inclusion criteria were included in the study. Among them 66 were male and 34 were female patients. As

for other basic demographic data 63 patients were from rural areas and 37 from urban areas. Occupation wise non manual skilled workers were highest 21%, followed by 19% elderly, 16% unemployed, semiskilled workers 14%, manual workers 13%, unskilled 12%, and 5% were semi-professionals. From the history, clinical examination findings, laboratory and radiological reports the patients were divided into one of the 5 categories of TOAST Classification. Among 100 patients, 25 had cardioembolic variety, 13 had large artery atherosclerosis, 21 had small vessel stroke, causes of 33 was undetermined and 8 patients had other etiology of stroke.

Next statistical significance was determined between each subtype of stroke and different risk factors of cerebrovascular accident. The mean age was 45.76 among patients of cardioembolic variety, 59.92 among large artery atherosclerosis, 64.10 among patients with small vessel stroke, 36.38 among stroke due to other causes and 62 among patients whose cause could not be determined. So it was found that stroke due to other causes tends to occur in younger population whereas small vessel stroke occurred in the older age group. There were 63 patients with hypertension and 37 were non-hypertensive. There was significant relationship between hypertension and incidence among different subtypes of stroke. Patients with stroke due to large artery atherosclerosis were more likely to be hypertensive with a P Value of 0.020. Conversely patients with stroke due to other causes were less likely to be hypertensive only 3.17%. There were 50 patients who were diabetic and 50 who were nondiabetic. It was found that there was significant difference between diabetes and incidence among subtypes of stroke. Small vessel stroke patients were more likely to be diabetic 85.7% with a P Value  $<0.001$ . Patients with cardioembolic variety were more likely to be non diabetic 20%. There were 16 patients with ischemic heart disease and 84 patients who had not. Among 33 patients with stroke due to undetermined cause only 1 had ischemic heart disease (IHD) and among stroke due to other causes none had IHD. Among the various subtypes small vessel stroke had maximum incidence about 38% and 50% of all cases of IHD. 18 patients had past history of stroke while 82 had not. However there was no significant probability of having past history of stroke among the different subtypes. Among the 100 patients there were 55 people who were smokers and 45 had not. There was no significant relationship between smoking and incidence of a specific subtype of stroke among the 55 patients who smoked. There were 16 alcoholic patients and 84 who didn't drink. The incidence was maximum among cardioembolic variety, 31% whereas there was 18% with large artery atherosclerosis, 25% with small vessel stroke, 12.5% in patients with other causes and 12% in patients with stroke due to unde-

terminated cause. But there was no significant statistical relation between alcohol intake and propensity to have a specific subtype of stroke. There was significant relation between deranged lipid profile values and specific subtype of stroke. As evident from Table 1 high cholesterol was associated with large artery atherosclerosis and small vessel variety while other causes of stroke had the least values. An increased

level of triglyceride also was found among large artery atherosclerosis and small vessel subtype and least among others variety. Low density lipoprotein was associated with small vessel stroke having a much higher value 121+/-41 than other subtypes. But there was no significant association of the mean levels of Very low density lipoprotein with the different subtypes of ischemic stroke.

**Table 1: Relation of different subtypes of stroke with lipid profile (Mean ± SD)**

Variables	TOAST					p Value
	Cardioembolic	Large Artery Atherosclerosis	Small Vessel	Others	Undetermined	
Cholesterol	140.56 ± 23.56	195.08 ± 39.47	192.24 ± 45.58	137.63 ± 25.29	143.91 ± 27.11	<0.001
Triglyceride	126.28 ± 29	174.77 ± 38.2	155.29 ± 35.57	108.5 ± 20.66	123.76 ± 27.54	<0.001
LDL	79.84 ± 20.69	115.46 ± 35.09	121.62 ± 41.64	82.88 ± 18.11	79.82 ± 17.7	<0.001
HDL	44 ± 6.71	32.62 ± 10.5	42.67 ± 5.84	43.25 ± 5.44	43.91 ± 4.99	<0.001
VLDL	33.16 ± 13.79	38 ± 21	32.24 ± 9.73	31.25 ± 11.21	34.7 ± 13.54	0.757

**Table 2: Distribution of subtypes of stroke according to NIHSS subgroup**

TOAST	NIHSS				Total	p Value
	Minor Stroke	Moderate	Moderate to Severe	Very Severe		
Cardioembolic	0(0)	22(27.85)	3(21.43)	0(0)	25(25)	0.066
Large Artery Atherosclerosis	2(33.33)	9(11.39)	2(14.29)	0(0)	13(13)	
Small Vessel	0(0)	15(18.99)	6(42.86)	0(0)	21(21)	
Others	2(33.33)	4(5.06)	2(14.29)	0(0)	8(8)	
Undetermined	2(33.33)	29(36.71)	1(7.14)	1(100)	33(33)	
Total	6(100)	79(100)	14(100)	1(100)	100(100)	

The relationship between the subtypes of stroke and various laboratory parameters were also carried out. Among 100 patients 57 had normal ECG findings. 13 patients had atrial fibrillation, 12 had ischemic changes, 10 had chamber enlargement or hypertrophy, 7 had different types of block and 1 patient had ventricular aneurysm. There was significant relation between any particular ECG abnormality and occurrence of a particular type of stroke. All patients with atrial fibrillation had cardioembolic type of stroke. There was similar incidence of ischemic changes (41%) among cardioembolic variety and small vessel stroke. There was also similar incidence of chamber enlargement (20%) among cardioembolic and stroke due to undetermined causes. In the patients with stroke due to other causes only one patient had an abnormality and rest 7 had normal ECG findings. Among 100 patients 42 had normal ECHO findings, 13 had valvular heart diseases, 9 had cardiomyopathy, 32 had chamber enlargement or hypertrophy and 4 had other abnormalities. There was significant relation between cardiac abnormality on ECHO and occurrence of a particular subtype of stroke. All 13 patients with rheumatic valvular abnormality had cardioembolic stroke. 55% of patients with cardiomyopathy had cardioembolic variety and 46% of patients having some chamber enlargement had stroke

due to undetermined cause. Significantly none of the patients with stroke due to other causes had any ECHO abnormality. Then the association of different types of stroke with site of involvement based on MRI findings was determined. It was seen among 100 patients 34 patients had some affliction of the basal ganglia while 66 had no such. There was significant relation between basal ganglia involvement and possibility of occurrence of a particular subtype of ischemic stroke. Cardioembolic variety had the maximum occurrence about 44% among the subtypes, while undetermined variety had least about 8% as evident by only 3 out of 33 patients had basal ganglia involvement. Among 100 patients 47 patients had Paraventricular infarct while 53 had no such. It occurred maximally about 49% in undetermined causes and there was no patient with other causes who had Paraventricular infarcts. Also it was found that cardioembolic variety had very less occurrence of such stroke, only 2 out of 25. Conversely in undetermined causes 23 out of 33 patients had Paraventricular infarct about 69.6%. Arterial territory wise also there was significant association between Middle cerebral artery infarcts and particular stroke subtype. Among 100 patients 50 had middle cerebral artery (MCA) involved and the rest had not. In the cardioembolic variety 19 among 25 patients (76%) had MCA stroke,

conversely only 10 patients out of 33 in the undetermined variety had MCA stroke.

After admission the NIHSS score was calculated for each patient and plotted in tabular form. Out of 100 patients 6 had minor stroke, 79 had moderate symptoms, 14 had moderate to severe symptoms and 1 had very severe stroke. By statistical analysis there was no specific relation between any types of stroke having a specific NIHSS symptom of severity. All subtypes had equal propensity of majority presenting with moderate symptoms.

## DISCUSSION

This study was an observational study with a modest sample size of 100 patients utilising both prospective and retrospective data. There were 66 male patients and 34 female. Among the males 15(22%) had cardioembolic, 10(15%) had large artery atherosclerosis, 16(24%) had small vessel stroke, 6(9%) had other causes, and cause was undetermined in 19 (28%) cases. Among the females 10(29%) had cardioembolic, 3(8%) had large artery atherosclerosis, 5(14%) had small vessel stroke, 2(5%) had other causes and 14(41%) had stroke due to undetermined cause. We observed no gender difference in those with cardioembolism or other determined etiology as was suggested by some studies<sup>4,5</sup>. Similarly there was no predilection for a particular type of stroke based on occupation, religion, housing.

In our study we looked into prevalence of some common modifiable risk factors in our subjects and searched for any association with etiology. For this purpose we first segregated them into 5 subgroups according to TOAST system of classification. 25 had cardioembolic type, 13 had large artery atherosclerosis, 21 had small vessel stroke, 8 had other types (among which 1 had Moyamoya disease, 1 had Takayasu's Arteritis, 3 had SLE, 2 had dissection of cervical artery, and 1 had Cerebral sinus venous thrombosis) and cause was undetermined despite extensive evaluation in 33 patients. Then association with certain risk factors were tested separately with these subgroups by Pearson's Chi Square Test and we found the following results.

In our study 63 patients were hypertensive. Among the various subtypes it occurred in the highest frequency in large artery atherosclerosis patients and those with small vessel stroke which was similar to other studies<sup>6</sup>. Incidence tends to increase with age and was commoner among males.

As for association with ischemic heart disease 16 patients had evidence of such clinically or during investigations and majority of them had lacunar infarcts or small vessel stroke. A strong negative association was also found that none of the patients with stroke due

to other causes had ischemic heart diseases. This also correlated with the younger age trends in this type of ischemic stroke<sup>7</sup>. Trials like SAHLIS have shown past episode of stroke predispose to same events and it was highest among large artery atherosclerosis variety<sup>8</sup>. The same analogy could not be drawn from our study because of the small sample size and accurate records of past ischemic events could not be found out due to non maintenance of prescriptions. There were 50 diabetics and the most predominant stroke type among them was small vessel stroke. This is in accordance with the results of other large scale studies<sup>9</sup>. Smoking has been accepted as a traditional risk factor for ischemic stroke<sup>10</sup>. This was also shown in our study as the majority of patients 55 out of 100 were smokers. But there was no predilection for a particular stroke subtype among them. This may be due to the fact among the subjects very few women smoked and almost similar sex ratio between the subgroups led to these results. Similar scenario was seen in cases of alcohol intake and other drug addictions.

Dyslipidemia was consistently associated with ischemic cerebrovascular accident by traditional studies<sup>11</sup>. Higher levels of cholesterol, triglyceride, Low density lipoprotein and low levels of High density lipoprotein were seen in small vessel disease and large artery atherosclerosis. The reverse situation was found in cardioembolic and others variety. This situation tallied with traditional studies as regarding other subgroup. As for anomaly in cardioembolic variety this was because in our study most of the cases were of rheumatic heart disease not of cardiomyopathy. Furthermore it tallied with the results in the Iranian study which also had a higher proportion of rheumatic heart disease patients<sup>12</sup>. As regarding non modifiable risk factors the mean age of the patients belonging to cardioembolic group was 45.76. This was due to the fact high prevalence of rheumatic heart disease as a cause of embolus which occurred in younger age group. The mean age of large artery disease is 59.92, small vessel stroke is 64.10, undetermined cause is 62 and other cause is 36.38. In accordance with other studies small vessel and large artery disease occurred in older patients while other causes occurred in younger age group<sup>13</sup>.

In our study the highest number was that of undetermined causes 33 out of 100, followed by cardioembolism 25, small vessel stroke 21, large artery atherosclerosis 13 and lastly 8 cases of stroke due to other causes. Now the proportion differed considerably in various studies worldwide. In a large scale European study Stroke etiology was reported in detail for 3331 patients aged 15-49 years with first-ever IS according to Trial of Org in Acute Stroke Treatment (TOAST) criteria: large-artery atherosclerosis (LAA), cardioembolism (CE), small-vessel occlusion (SVO), other determined etiology, or undetermined

etiology. CE was categorized into low- and high-risk sources. Other determined group was divided into dissection and other non-dissection causes. Comparisons were done using logistic regression, adjusting for age, gender, and centre heterogeneity. The results were etiology remained undetermined in 39.6%. Other determined etiology was found in 21.6%, CE in 17.3%, SVO in 12.2%, and LAA in 9.3%<sup>3</sup>. In a similar Indian study at Sri Chitra Tirunal Institute of Medical Sciences and Technology (SCIMST), Trivandrum, patients of ischemic stroke were classified based on Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria; 25.2% patients had cardioembolic stroke, 12.6% had large artery atherosclerosis and 7.5% had lacunar infarcts. Strokes due to other determined etiology were 11.2% (7.0% arterial dissection, and one patient each with lupus erythematosus, primary antiphospholipid antibody syndrome and protein S deficiency). Four patients had stroke due to other causes (one case each of Moyamoya disease, Takayasu's arteritis, fibro muscular dysplasia and nephritic syndrome)<sup>14</sup>. Our study had undetermined category as maximum. Because treatment options are influenced by a presumed cause, an evaluation on a case-by-case basis is warranted. If strict diagnostic criteria are used, the diagnosis of stroke of undetermined etiology considerably increases. While such strict criteria are important in clinical trials that test new interventions, the value of the application of such methodologies to stroke in adults, needs clarification. In particular, the usefulness of categorizing a stroke as undetermined when two or more possible causes are identified needs to be explored.

In our study left hemisphere strokes were more frequent compared with right hemisphere strokes. This observation is in accordance with the observations from the large German Stroke registry<sup>15</sup>. The side preference reflects the poor recognition of right hemisphere stroke as aphasia is generally absent.

Most of the infarcts affected anterior circulation (80), whereas a minority 13 had posterior circulation or infarcts in both territories (7). Nearly a one-fourth of our patients had multiple visualized infarcts in MRI including both silent and current lesions. In our patients 46 out of 100 of them had evidence of leukoriosis. They were quite prevalent in small vessel and undetermined variety. These patients with small vessel stroke also had higher prevalence of hypertension and diabetes so a positive correlation with leukoriosis was found. As the availability and quality of imaging techniques improve, doctors are identifying more patients with no history of transient ischemic attack or stroke in whom imaging shows brain infarcts. Until recently, little was known about the relevance of these lesions. In a systematic review, Vermeer S et al gave an overview of the frequency, causes, and consequences of MRI-defined silent brain

infarcts, which are detected in 20% of healthy elderly people and up to 50% of patients in selected series. Most infarcts are lacunes, of which hypertensive small-vessel disease is thought to be the main cause. Although silent infarcts, by definition, lack clinically overt stroke-like symptoms, they are associated with subtle deficits in physical and cognitive function that commonly go unnoticed<sup>16</sup>.

## CONCLUSION

In our study consisting of 100 patients according to TOAST system of classification the etiology of stroke was determined and the highest prevalence was seen in undetermined causes followed by cardioembolic, small vessel, large artery atherosclerosis and other causes. Correlating these subtypes with the traditional risk factors hypertension was significantly associated with undetermined causes and large artery atherosclerosis. Diabetes and Ischemic heart disease was seen more often in small vessel stroke. Dyslipidemia was seen more often in large artery atherosclerosis and small vessel stroke. But there was no predilection for a specific subtype of ischemic stroke with respect to past history of cerebrovascular accident, smoking or alcohol addiction. There was a preponderance of left hemisphere stroke (57%) and anterior circulation affection (80%). On neuroimaging infarcts involving basal ganglia and ischemic leukoriosis were common which was seen maximally in cardioembolic and undetermined variety respectively. Larger population based studies should be carried out to determine the etiology of stroke because if we can address this issue in the primary preventive stage it will be rewarding for an important public health problem like ischemic stroke. Also utmost efforts should be carried out to minimise the proportion of undetermined variety by astute clinical and laboratory investigations and reassessment of diagnostic protocols.

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