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Stroke Progression

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Abstract Early neurological deterioration following stroke is quiet common and is associated with significant morbidity. Etiology for stroke is very well understood, whereas etiology behind neurological worsening is not clear and is different. In our study we found posterior circulation infarct, left hemisphere & bihemispheric infarct are associated with significant neurological worsening. Our study also demonstrated that large artery disease and cardioembolic mechanisms are associated with neurological worsening in the acute phase of stroke.

Keywords Stroke Progression, Neurological Worsening of Stroke, Early Deterioration of Ischemic Stroke. Early Neurological Deterioration, Mechanism of Stroke Progression

1. Introduction

It is estimated that annually 15 million people worldwide suffer a stroke, of which 5 million death occurs and another 5 million are left permanently disabled. The estimated projected burden of stroke is 61 million DALY (Disability adjusted light year) by 2020 [1]. Stroke can be either ischemic or hemorrhagic. Ischemic stroke accounts for about 80% of all strokes[6]. Various studies has shown that early neurological worsening in acute stroke is common ranging from 20 – 40%.[2,3,4,5,]

Various risk factors for stroke has been well established like High blood pressure, disorders of heart rhythm, smoking, high blood cholesterol & other lipids, physical inactivity, diabetes mellitus, end stage renal disease & chronic kidney disease [6][7] .

Early neurological deterioration following stroke is quiet common and is associated with significant morbidity .Etiology for stroke is very well understood, whereas etiology behind neurological worsening is not clear and is different. There are only a few studies on early neurological deterioration following acute stroke in Asian context. Since the etiology behind neurological worsening is different and not fully understood, we would like to evaluate various risk factors and mechanism behind the worsening in Indian population.

2. Materials and Methods

2.1. Study Design

A prospective study was done on 75 patients, to identify factors affecting neurological worsening of acute ischemic stroke in patients presenting to Emergency Room of Amrita Institute of Medical Science, Kochi during the period of November, 2012 to December 2013.

2.2. Inclusion & Exclusion criteria

- Those patients presenting within 7 days of onset of stroke and age >18 years were included.
- Those patients with intracranial hemorrhages were excluded.

2.3. Methodology

Patients included in the study where evaluated and initial NIHSS Score was noted. All patients were subjected to CT/MRI to diagnose acute ischemic stroke. MRA/CTA was done to look for any large vessel disease. Patients were subjected to Electrocardiogram, Echocardiography, holter monitoring for evaluation of any potential cardioembolic source for stroke. Blood investigations like HbA1C, Lipid profile was sent.

Patients where reassessed for neurological worsening after 48 hrs and end of 5th day. Neurological worsening was defined as an increase in NIHSS score by 2 points from the baseline[3,4,12]. Patients where then divided into two groups

1) Neurological worsening group or Progressive group
2) Stable group.

All patients were also classified according to TOAST classification system at the end. Statistical analysis where then done between the progressive and stable group.

NIHSS Scoring was used in the study for neurological

evaluation and assessing neurological worsening as it has good reliability[10,11]. Neurological worsening was defined as increases in NIHSS Score ≥2 as defined widely in various studies[3,4,8].TOAST classification of subtype of acute ischemic stroke was chosen as it is simple, straight forward, etiology based classification[9] & moreover it has high degree of interrater agreement in stroke subtype[9].

2.4. Statistical Analysis

Percentage of stroke cases with neurological worsening was computed. All continuous variables data were presented as mean ±SD and categorical variables were presented as percentage. To compare the averages of continuous variables between two groups the data of which are not following normal distribution, Mann Whiteny U test was performed. To compare two categorical variables Chi square test was applied, if any expected cell has <5 Fisher's Exact Test was applied. The p-Value <0.05 was considered as statistically significant. Statistical analysis was done using IBM SPSS Statistics 20

3. Results

The total study population was 75, composed of 58 males (77.3%) and 17 females (22.7%). Mean age of the study population was 61.8 ± SD 10.966. Neurological worsening was seen in 18(24%) patients.

3.1. Age and Gender

The total number of males in the study was 58 and females where 17 of which 13 males (22.4%) and 5 females (29.4%) had neurological worsening(Table 2), but there was no statistically significant difference in the progression rates between the two groups with regards to gender (p = 0.536)

The mean age among the progressive group was 65.06 ± 10.423 while among stable group was 60.77 ± 11.019 (Table 2). There was no statistically significant difference between both groups with regard to age (p =0.170).

3.2. Co- Morbidities

At, the time of admission 38 patients had a past history of diabetes mellitus of which only 6 (33.3%) patients developed neurological worsening, whereas out of 37 patients without diabetes 12(66.7%) patients developed neurological worsening (Table 1) . There was no statistically significant difference between the two groups (p = 0.157).

At, the time of admission 47 patients had past history of hypertension of which 8 (44.4%) patients developed neurological worsening, whereas out of 28 patients without hypertension 10(55.6%) patients developed neurological worsening(Table 1). There was no statistically significant difference between the two groups (p = 0.120) .

At, the time of admission 15 patients had past history of coronary artery disease of 5 (20%) patients developed neurological worsening, whereas out of 60 patients without past history of coronary artery disease 13 (72.2%) patients developed neurological worsening (Table 1). There was no statistically significant difference between the two groups (p = 0.335).

3.3. Blood Investigations

Mean total cholesterol and LDL level among the progressive group was 194.28 ± 48.392 & 131.22 ± 40.78 respectively, while among stable group was 182.15± 51.116 & 123.10 ± 41.96 respectively. There was no statistically significant difference in the average between both groups (Table 2).

Mean HbA1C among the progressive group was 7.011 ± 1.954, while among stable group was 7.581 ± 2.1410. There was no statistically significant difference in the average between both groups (Table 2)

Mean INR among the progressive group was 1.0156 ± 0.1700, while among stable group was 1.0112 ± 0.129. There was no statistically significant difference in the average between both groups(Table 2).

Table 1. Gender, Co- Morbidities, cardioembolic source & its assosciation with stroke progression.

Variable		Total No.	Progressive Group	p-Value
Gender	Male Female	58 17	13 (22.4%) 5 (29.4%)	0.536
Co -Morbidities				
Diabetes Mellitus	Present Absent	38 37	6 (33.3%) 12(66.7%)	0.157
Hypertension	Present Absent	47 28	8 (44.4%) 10 (55.6%)	0.120
Coronary Artery Disease	Present Absent	15 60	5 (20.0 %) 13 (72.2%)	0.335
Cardioembolic Source				
Atrial Fibrillation	Present Absent	7 68	4(57.1%) 14 (20.6%)	.053
HOCM	Present Absent	2 73	1(50%) 17(23.3%)	0.425
Severe LV Dysfunction	Present Absent	4 71	1(25.0%) 17(23.9%)	1.00
LV Thrombus	Present Absent	3 72	2(66.7%) 16(22.2%)	0.141

Table 2. Age & Blood Investigations

Variable	Progressive Group (n= 18) (Mean ± SD)	Stable Group (n = 57) (Mean ± SD)	p-Value
Age	65.06 ± 10.423	60.77 ± 11.019	0.170
T. Cholesterol	194.28 ± 48.392	182.15 ± 51.116	0.251
LDL	131.22 ± 40.780	123.10 ± 41.961	0.388
HbA1C	7.011 ± 1.954	7.581 ± 2.1410	0.309
INR	1.0156 ± 0.1700	1.0112 ± 0.129	0.367

3.4. Cardioembolic Source

A total of 7 patients were found to have AF of which 4(57.1%) patients developed neurological worsening, whereas out of 68 patients without AF 14(20.6%) developed neurological worsening. The p- value was found to be 0.053. There was no statistically significant difference between these two groups.

2 patients were found to have hypertrophic cardiomyopathy as a source of cardioembolism of which only 1(50%) patient had worsened, whereas out of 73 patients without HOCM 17(23.3%). The p- value was 0.425 which is not statistically significant (Table 1).

Another 4 patients had severe left ventricular dysfunction of which only 1(25%) patient progressed, whereas out of 71 patients without severe LV dysfunction 17 (23.9%) developed neurological worsening. The p value was calculated as 1.00 which is not statistically significant.

3 patients had LV thrombus of which 2 patients (66.7%) developed neurological worsening whereas out of 72 patients without LV thrombus 16(22.2%) patients developed neurological worsening. The p value was 0.141 which was not statistically significant (Table 1).

3.5. CT/MRI Findings

Out of the 75 patients studied, 32 patient developed infarct on the right side of which 4(12.5%) developed neurological worsening. 35 patients had infarct on the left side of which 10(28.5%) developed neurological worsening. 8cases developed bilateral infarcts of which 4 (50%) patients developed neurological worsening (Table 3). The p value was .058.

Table 3. Imaging Findings

Variable		Total Number	Progressive group (n = 18)	P-Value
Side	Right Left Bilateral	32 35 8	4 (12.5%) 10 (28.5%) 4 (50%)	.058
Infarct Territory	ACA Territory MCA Territory PCA Territory Combined	3 48 19 5	2 (66.7%) 7 (14.6%) 7 (36.8%) 2 (40.0%)	.052
Region	Cortical & Subcortical Deep Nuclei Brain stem &Cerebellum Combined	43 11 15 6	9 (20.9%) 1 (9.1%) 6(40 %) 2(33%)	.266
High thrombus load	ICA with MCA occlusion MCA occlusion	17 3	5(29.4%) 2 (40%)	.531
	VA//BA occlusion	10	4 (40.0%)	.240

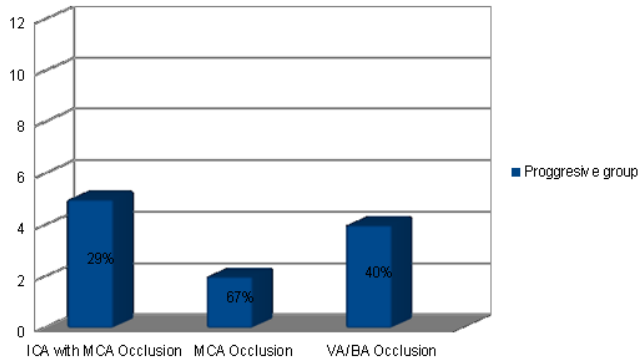

Figure 1. Thrombus Load

Out of the 75 patients studied, 48 patients had infarct of MCA territory of which 7(14.6%) developed neurological worsening. 19 patients had infarct over PCA territory of which 7 (36.8%) patients developed neurological worsening. 3 patient developed infarct over ACA territory of which 2(66.7%) patients developed neurological worsening & 5 patients had involvement of multiple territories of which 2(40%) patients developed neurological worsening (Table 3). The p value was .052

Out of the 75 patients studied, 43 patient had infarcts over cortical and subcortical region of which 9 patients (20.9%) developed neurological worsening. 15 patients had infarcts over the brain stem and cerebellum of which 6 (40%) patients developed neurological worsening. 6 patients had infarct over different territories of which 2(33%) patients developed neurological worsening, whereas 11 patients had infarcts over the deep nuceli of which only 1 (9.1%) developed neurological worsening. The p value was 0.266 which is not statistically significant.

3.6. CTA/MRA Findings

A total of 66 patients out of 75 underwent either CT or MR angiogram. 17 patients had ICA with MCA occlusion of which 5(29.4%) patients developed neurological worsening. Another 3 patients had MCA occlusion of which 2(40%) patients had developed neurological worsening (Table 3, Figure 1). The p value is 0.531. A total of 10 patients had either VA/BA occlusion of which 4(40%) patients developed neurological worsening (Table 3, Figure 1). The p value was 0.24.

3.7. TOAST Classification

At, the end of the study the patients were classified based on TOAST subtype classification of stroke. Out of 75 patients, 9 patients were excluded from TOAST classification as angiogram was not done on these patients.

A total of 22 patients were found to have large vessel disease of which 8 (36.3%) patients developed neurological worsening. 11 patients were found to have cardioembolic source of which 5(45.4%) patients developed neurological worsening. 9 patients had small vessel disease of which

only 2 (22.2%) patients had neurological worsening, whereas 24 patients where included in unknown etiology of which only 1(4.1%) patient deteriorated (Table 4). The p value was 0.021 which is statistically significant.

Table 4. TOAST Classification

TOAST Classification	Total Number	Progressive Group	P - value
Large Vessel Disease	22	8(36.3%)	.021
Cardioembolic	11	5(45.4%)	
Small vessel disease	9	2(22.5%)	
Unknown etiology	24	1(4.1%)	

4. Discussion

In our prospective study, neurological deterioration was seen in 24% of total patients which is comparable to other studies[2,3,4,5].

Our study did not find any significant association between neurological deterioration and patient's age. This is in contrast to study done by Yousry[2] & Macciochi et al [12] which found that older patients were significantly more likely to develop neurological deterioration. Our study also demonstrated that there is no significant association between gender and neurological deterioration.

Our study did not find any significant association between neurological deterioration and past history of hypertension, diabetes mellitus, coronary artery disease. Similar findings where seen in studies done by De Gabra et al[13], Cheng- Ter Ong[4], Maccicocchi, [12]. These findings are encouraging and suggest that patients with co morbidities still can have a good functional recovery. But other studies have demonstrated that history of diabetes, hypertension and high glucose levels are associated with early neurological worsening[9,14,15,16]. Since the findings are controversial further studies are warranted.

We also tried to find any association between blood cholesterol levels, long term control of diabetes and neurological worsening, our results demonstrates that there is no significant association between them.

Even though our study did not demonstrate a significant association between various cardiac source and neurological worsening, it was observed in our study that 4 out of 7 (57.1 %) patients with atrial fibrillation without thrombus was associated with neurological worsening (P value = 0.05), demonstrating the association of atrial fibrillation and risk of neurological deterioration. De Gabra et al & Mostafa Awadh et al demonstrated significant association between neurological worsening and atrial fibrillation [13,26].

Our study has demonstrated that infarcts on the bilateral side & dominant hemisphere have more chance of developing neurological worsening. In our study about 50% of bilateral and 24% of infarcts on the dominant hemispheres was associated with neurological worsening. Our study has demonstrated that infarct located on brain stem and cerebellum has higher chance of worsening. Our study also demonstrated that patients with lacunar infarcts have better neurological outcome. Our findings where similar to the study done by De Gabra[13].

Our study also demonstrated that posterior circulation infarcts (36.8%) where associated with higher chance of neurological deterioration which was expected. Our results were similar to other studies done by Jones [18] et al & Harauko et al [17].

We also studied the association of large vessel disease and neurological worsening. We found that 40 % of patients with vertebral artery or basilar artery occlusion, 40% of patients with MCA occlusion and 29% of ICA with MCA occlusion had neurological worsening. Even though our study population is small, the findings suggest the strong association of large vessel disease and neurological worsening. Our findings are similar to other studies by Heinsius et al [19]. Hence we emphasize the need for early neurovascular imaging and therapeutic intervention for a better outcome.

Finally we classified the patients based on TOAST classification of subtype of acute ischemic stroke. . 36 % of patients with large vessel disease and 45% of patients with cardioembolic source had neurological worsening. The P value was 0.021 which is statistically significant. Thus we demonstrate that patients with cardioembolic source and large vessel disease have higher chance of neurological worsening.

4.1. Mechanism of Worsening

We also studied the post neurological worsening images to find out possible causes for neurological worsening. Infarct progression was seen in 55% of patients with neurological worsening. New infarcts where seen in 16% of patients. These findings supports the findings in other studies[16,20,21].

Hemorrhagic transformation was seen in 22% of the cases with neurological worsening. Studies have also shown that hemorrhagic transformation is one of the common mechanisms for neurological worsening [22,23,24].

Cerebral edema and herniation was associated with neurological worsening in 11% of the patients. These findings were also similar to other studies [16,25].

5. Conclusions

Early neurological deterioration following stroke is quiet common and is associated with significant morbidity. Major predictors of neurological worsening are location of the infarct and the mechanism of stroke. In our study posterior circulation infarct, left hemisphere & bihemispheric infarct are associated with significant neurological worsening. Even though our study population is small, we could demonstrate a statistically significant relationship between large artery diseases, cardioembolic mechanisms with neurological worsening in the acute phase of stroke. Hence we emphasize the need for early neurovascular & cardiac evaluation from emergency room itself.

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