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Neurology

A Prospective Study of Deteriorating Acute Ischemic Stroke in Non-Thrombolysed Patients

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Abstract		Original Research Article

Context: Progression of stroke is likely multifactorial; however, risk of deterioration in acute ischemic stroke can be predicted in great majority of cases at admission by careful close observation. ***Aims:*** To study the causes of neurological deterioration of non-thrombolysed stroke patients. ***Settings and Design:*** This was a prospective observational study of non-thrombolysed stroke patients admitted at the Stroke ICU of a teaching hospital in Kerala, India for a period of one year from between January 2017 to January 2018. ***Methods and Material:*** All stroke patients with first episode of acute ischemic stroke were admitted and evaluated forneurologic deterioration (defined as an increase in National Institute of Health Stroke Scale Score (NIHSS score) by 2 or more points, after admission during the first week). ***Results:*** 80 out of 320 patients with acute stroke patients developed neurological deterioration and were analyzed for clinical, biochemical and radiological features associated with deterioration. ***Clinical features -*** Stroke severity (high NIHSS Score), altered consciousness at admission, persistent gaze deviation, bulbar dysfunction, atrial fibrillation, recent myocardial infarction, systemic diseases (hypertension, hepatic and renal dysfunction) and deep vein thrombosis were associated with deterioration. ***Biochemical features -*** Uncontrolled blood sugar and hyponatremia were associated with deterioration. ***Imaging features -*** ASPECT score less than 7, large infarct at admission, dense MCA sign, hemorrhagic transformation, proximal large vessel occlusion and lack of correlation between clinical deficits with initial CT picture were associated with higher risk of deterioration. ***Conclusion:*** Each stroke case needs prompt individualized evaluation and management. Interventions based on pathophysiology identified by imaging features and patient's clinical condition and management of systemic diseases and complications will improve the outcome.
Keywords: Stroke, deterioration, clinical, imaging features, predictors.

INTRODUCTION

Stroke incidence and mortality are higher in Asian countries than in western countries [1]. Based on few epidemiological studies in India, the crude prevalence rate of stroke was reported between 44 and 842 strokes per 100,000 persons, and annual incidence rate is between 13 and 124 strokes per 100,000 persons [2]. Trivandrum stroke registry, which is based on a community study in our district, in south India, recorded an adjusted annual incidence rate of 135 per 100 000 (95% confidence interval between 123 and 146) [3]. About one third of ischemic stroke patients deteriorate after admission to a hospital. It is associated with serious consequences on the short term (morbidity and death) and long term disability [4, 5]. Different studies have pointed out different markers to predict the deterioration and outcome in acute ischemic stroke. They include stroke severity on admission [6-8], the presence of large vessel occlusion [4, 9-11], history of coronary artery disease or myocardial infarction [12, 13], presence of Atrial Fibrillation [4], diabetes mellitus [4, 12-15], acute or chronic hyperglycemia [12, 13, 15, 17, 18], elevated blood pressure [19, 20], early recurrent ischemic stroke [21] and symptomatic hemorrhagic transformation [16, 22]. Advances in brain and vascular imaging have provided insight into the underlying causes of deterioration, enabling clinicians to use preventive and therapeutic interventions, specifically targeted at them like endovascular early revascularization (intra-arterial thrombolysis,

angioplasty, mechanical thrombectomy and extended window mechanical thrombectomy), endarterectomy and early de-compressive craniectomy [4]. The present study was conducted to study the causes of neurological deterioration of non-thrombolysed stroke patients at the Stroke Intensive Care Unit (ICU) of a teaching hospital in Kerala, India.

MATERIALS AND METHODS
This was a prospective observational study of non-thrombolysed stroke patients admitted at the Stroke ICU of a teaching hospital in Kerala, India for a period of one year from between January 2017 to January 2018 with the approval of the college Ethics Committee. All patients admitted with first episode of acute ischemic stroke were admitted and treated as per American Stroke Association (ASA) protocol. Neurologic deterioration was defined as an increase in National Institute of Health Stroke Scale Score (NIHSS score) by 2 or more points, after admission during the first week (5). They were included in the study. Informed consent was obtained in all cases.

INCLUSION CRITERIA
- Patients admitted with a diagnosis of first episode of acute ischemic stroke were included.
- A deterioration in National Institute of Health Stroke scale score (NIHSS) equal to or more than two points after admission during the first week of admission were included in the study.

EXCLUSION CRITERIA
- Thrombolysed patients were excluded. Thrombolysis was not done for these patients because of medical or personal reasons (financial, unwillingness)
- Hemorrhagic stroke and stroke mimics.
- Strokes secondary to systemic illness/infections.
- Cases of hypotension leading to global ischemia.
- Recurrent stroke
- Severe stroke at admission (NIHSS > 20) because they carry high risk for further deterioration.

The baseline characteristics of these patients were noted at the time of admission - vascular risk factors, clinical features (vitals, level of consciousness, NIHSS score) and radiological features. Alberta Stroke Program Early Computed Tomogram Score (ASPECTS) scoring was done in all cases. Biochemical parameters (blood sugar, urea, serum creatinine, electrolytes, serum lipid profile, platelet count, prothrombin time, activated partial thromboplastin time (APTT), liver function test) and blood counts were done in all cases. HBA1C level was assessed in all diabetic patients.

These patients were monitored carefully for any evidence of deterioration. Blood pressure, oxygen saturation, and electrocardiogram (ECG) were monitored continuously. Neck vessel Doppler scan was done for all patients. Cardiac evaluation, X-ray chest and echo cardiogram were done within 24 hours for all. Computed Tomogram Angiogram (CTA) of brain and neck vessels were done when Doppler of neck vessels showed stenosis or occlusion to assess site of occlusion and collateral flow.

Swallowing function was evaluated in all patients and nasogastric tube was inserted in cases with swallowing difficulty. Endotracheal intubation was resorted to, as and when required. Prevention of bedsore was done by using air bed, frequent change of posture, passive physiotherapy. Foleys catheter was put for all patients who had altered sensorium or unable to pass urine. Spouse and family members were interviewed to get the relevant clinical details - the onset time and symptoms, past illnesses and drug history. A standard 5-point questionnaire with one point for each question was presented to patient or to spouse/caregiver when patient was aphasic or unable to cooperate (What is stroke / Risk factors of stroke / Symptoms of stroke / How long to continue drugs /Stroke helpline number). This questionnaire was used to identify their awareness regarding stroke, risk factors of stroke, the frequency of checking and degree of control of risk factors, life style, and stroke prevention. They were taught stroke prevention measures, patient care and community rehabilitation.

Any deterioration in sensorium (quantified by Glasgow Coma Scale (GCS) score) or worsening of deficit (NIHSS Score increase by 2 points or more) was considered as deteriorating stroke. These patients were further evaluated clinically and investigated as follows – repeat imaging [CT brain with CT Angiogram or Magnetic Resonance Imaging (MRI) brain with Magnetic Resonance Angiogram(MRA)], biochemical parameters (blood sugar, electrolytes, renal function, hepatic function, coagulation parameters, C-reactive protein) and cultures were sent to rule out infections and further managed based on etiology. Patients with large Middle cerebral artery (MCA) infarcts were closely monitored for deterioration and neurosurgery team was alerted for possible early craniectomy. Antiepileptic drugs were started in case of seizures or electroencephalogram (EEG) showing any evidence of Non Convulsive Status epilepticus. Disability was assessed using Modified Rankin Scale (MRS) at the time of discharge and at three month follow up. The data was recorded systematically and analyzed.

RESULTS
Age and gender
Out of 320 patients admitted to stroke ICU with first acute ischemic stroke, 80 patients (25%) who deteriorated satisfied the inclusion criteria. The mean age of the deteriorated stroke patients was 61.5 ± 24.5 years with a range of 36 to 91 years. The age

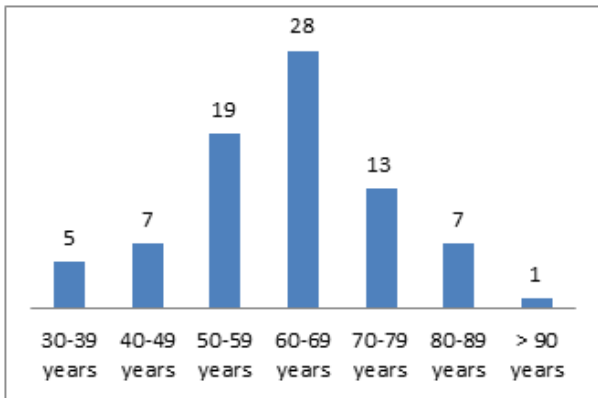distribution of patients is shown in Figure 1. There were 54 (67.5%) males and 26 (32.5%) females.

Fig-1: Age distribution of deteriorated patients

Economic status

45 (56.3%) patients belonged to middle income group, 34 (42.5%) in low income and 1 (1.2%) in high income group according to the modified Kuppuswami scale) [51].

Education

56 (70%) patients had less than primary education, 19 (23.75%) had secondary education and 5 (6.25%) were graduates.

Stroke awareness questionnaire

All performed very poorly. (Score < 1 in 68 patients, 1 in 12 patients).

Time to door

Time to door was calculated as the time from last seen normally /symptom onset to hospital door in hours.

Only 3 (3.75 %) reached hospital within 3 hours, only 18 (22.5%) reached hospital before 4.5 hours of the onset of symptoms. The time to door details is shown in table 1.

Table-1: Time to door details of deteriorated patients

Time to door (hours)	Frequency (n=80)	Percent
Less than 3 hours	3	3.3
3 to 4.5 hours	15	18.7
4.5 to 6 hours	40	50
6hours to 24 hours	22	28

Risk factors

Hypertension – 68 (85%) patients were known hypertensives. Regular monitoring and treatment was observed only in 12 patients (15%). Only 10% had awareness regarding hypertension and complications.

Diabetes Mellitus – 34 patients (42.5%) were diabetic, only one patient (2.9%) had diabetic

awareness regarding control of blood sugar, importance of regular monitoring and complications of diabetes.

Dyslipidemia – 50 patients (62.5%) had dyslipidemia (high LDL cholesterol, low HDL cholesterol). Of this, 36 also had hypertriglyceridemia.

Tobacco smoking – 33 (41.3%) were smokers. Out of them, 25 (75%) were current and 8 (25%) were former smokers who stopped within the last 5 years. None of the female patients were smokers.

Alcohol use – 4 patients (5%) were heavy alcoholics, 34 (30%) were social drinkers and 52 (65%) were non alcoholics, which included all the 26 females.

Cardiac illness – 25 patients (31.25%) had already diagnosed coronary artery disease. 7 patients (8.8%) had rheumatic heart disease (RHD). 45 patients (56.3%) had no diagnosed cardiac illness at admission. The details of cardiac co-morbidities are shown in table 2.

Atrial fibrillation (AF) – 8 patients (10%) had atrial fibrillation (3 with rheumatic heart disease, 2 had coronary artery disease (CAD), lone AF in 3 patients, of which one had Chronic obstructive pulmonary disease (COPD). AF was transient in 2 patients and continuous ECG monitoring helped in identification. None were on anti-coagulation.

Table-2: Cardiac co-morbidities

Cardiac Risk Factors	Frequency (n=80)	Percent
Lone AF	3	3.8
CAD	23	28.8
CAD + AF	2	2.5
RHD	4	5.0
RHD + AF	3	3.8
No known cardiac illness	45	56.3
Total	**80**	**100.0**

Transient Ischemic Attacks (TIA) – 14 patients (17.5%) had TIA within one week prior to admission.

Peripheral vascular disease ((PVD) – PVD was detected in 2 patients (2.5%).

COPD – 4 (5%) deteriorated patients had COPD.

Drug default - 77% patients were not regular in monitoring their vascular risk factors (hypertension, diabetes mellitus and dyslipidemia) and had defaulted their medications.

Family history of vascular disease 49 (61.3%) patients. had first degree relatives with stroke or CAD

Stroke symptoms

11 Patients (13.8%) had wake up stroke, 42 (52.5%) had onset of symptoms in morning hours (before 12 noon); and 27 (33.8%) had onset in the afternoon hours (after 12 noon).

Vascular Territory affected

76 patients (95%) had anterior circulation stroke. 34 patients (42.5%) had right MCA territory stroke (left hemiplegia) and 42 patients (52.5%) had left MCA territory stroke (right hemiplegia +/- aphasia), and 4 patients (5%) had posterior circulation stroke (Table 3).

Table-3: Vascular Territory affected

Territory	Frequency (n=80)	Percent
Right MCA (Left hemiplegia)	34	42.5
Left MCA(Right hemiplegia)	42	52.5
Posterior circulation	4	5

Level of consciousness at admission

28 patients (35%) were drowsy at admission. 52 patients (65%) were fully conscious at presentation, but sensorium worsened with worsening of deficit in 48 patients.

Persistent gaze deviation to one side

7 out of the 76 MCA territory stroke patients had persistent gaze deviation towards the lesion side at admission along with altered consciousness, and they all had large infarcts (ASPECT score less than 7) and all deteriorated. In NIHSS it is one component, but it was strikingly associated with large infarcts and deterioration.

Blood pressure at admission.

Joint National Committee (JNC – 8) classification of hypertension is as follows: <120/80 = normal; 120-139/80-89 – Pre hypertension; 140-159/90-99- Stage 1 hypertension; >160/>100 – Stage 2 hypertension.Among the 80 patients deteriorated, 14 had pre-hypertension, 7 had stage 1 hypertension and 59 had stage 2 hypertension.

NIHSS score at admission

NIHSS score at admission is shown in table 4

Table-4: Admission NIHSS score

Admission NIHSS score		Frequency (n=80)	Percent
0-4 (minor)		0	0
5-15 (moderate)	5-9	27	33.7
	10-15	51	63.8
16-20 (moderate to severe)		2	2.5
> 20 (severe)		Excluded in study	Excluded

Blood sugar and HbA1C at admission

36 (45%) patients were diabetic. Very high blood sugar values (>400 mg%) was present in 6 deteriorated diabetic patients. 20 had blood sugar values between 200% and 399 mg% at admission

Neurologic Deterioration

Nature of deterioration

Nature of deterioration was assessed as either deterioration in deficit or as deterioration of both consciousness and deficit. Deterioration in both consciousness and deficit was detected in 76 (95%) patients and deterioration in deficit only in 4 (5%).

Timing of deterioration

78 (97.5%) patients had deteriorated within 72 hours of admission (END - Early neurological deterioration). 35 patients (43.8%) had neurological deterioration within 24 hours, 38 (47.5%) deteriorated on second day and 5 patients (6.3%) showed deterioration on 3rd day. One patient each deteriorated on 5th and 6th day (1.3% each).

Causes of deterioration

Multiple factors contributed to neurologic deterioration (Table 5).

Table-5: Causes of neurologic deterioration

Causes of deterioration	Frequency	Percent
Cerebral Causes		
Brain edema	72	90
Extension of infarct	70	87.5
Haemorrhagic transformation	17	21.25
Seizure	9	11.25
Aspiration pneumonia	50	62.5
Metabolic factors	32	40
Cardiac illness (CAD,RHD,AF)	9	11.25
Deep vein thrombosis	4	5
Pulmonary Embolism	2	2.5
Infections (Urinary tract infection, sepsis)	1	1.25

Cerebral causes – brain edema, extension of infarct and hemorrhagic transformation – contributed to deterioration, along with seizures in 9 cases. There was one case of non-convulsive status epilepticus detected by EEG monitoring.

Initial Imaging findings in deteriorated patients (at admission)

In our study, ASPECT score at admission CT, was less than or equal to 7 in 60 (75%) patients and ASPECT score was > 7 in 20 (25%) deteriorated patients (Table 6). Internal carotid artery (ICA) occlusion or near total occlusion was identified in 4 patients, and M1 or M2 segment of MCA occlusion confirmed on CT or MR angiogram in 38 patients with deterioration.

Table-6: Non-contrast CTImaging and admission

Initial imaging findings	No. of patients
Large infarct - ASPECT Score 7 or less than 7. (hypo density in 3 or more parts, of 10 parts of MCA territory)	60
Dense MCA sign/MCA dot sign.	3
Hypo attenuation involving cortex and sub cortical areas (superficial MCA and deep perforator territories of MCA)	6
Extensive bilateral small vessel ischemic changes	5
Multiple infarcts involving watershed zones.	3
ICA occlusion on CT angiogram/ carotid Doppler	4

Hemorrhagic transformation

17 cases (15 anterior circulations and 2 posterior circulations) suffered hemorrhagic transformation of infarct (Table 7). Smokers more frequently developed hemorrhagic transformation.

Table-7: Etiologic causes of hemorrhagic transformation

Etiological factors identified	Frequency (n=17)
Large infarct – ASPECTS (equal to or less than 7)	12
Current heavy smokers	6
Uncontrolled blood pressure	5
Uncontrolled blood sugars	4
CAD, Acute MI	4
Atrial fibrillation	3
Uraemia	2
Dual Antiplatelets (Aspirin + Clopidogrel)	2
Post circulation stroke - Top of basilar syndrome	2
Dense MCA sign	1
Hepatic failure	1

Seizures

Following features were identified in 9 patients who developed seizures (Table 8).

Table-8: Etiology of seizures

Etiological factors	Frequency (n=9)
Large infarcts (cortical /extension to cortex)	9
Atrial fibrillation with embolic CVA	5
Very low serum sodium < 120meq/L	4
Uncontrolled diabetes (very high blood sugar)	2
CAD, recent myocardial infarction, cardiac failure	2
Haemorrhagic transformation of infarct	1
ICA occlusion –with deterioration of stroke	1
Status epilepticus	1
Heavy smoker	1

Metabolic Causes

Metabolic causes contributed for deterioration in 32 patients. The metabolic abnormalities are shown in table 9

Table-9: Metabolic abnormalities in deteriorated patients

Metabolic abnormalities	Frequency (n=32)	Percent
Hyponatremia	27	84.3
Uncontrolled blood sugar	5	15.6
Renal dysfunction	5	15.6
Hepatic dysfunction	1	3.13

Hyponatremia

27 patients had hyponatremia during hospital stay. It was found in patients with large infarcts, between 2nd and 14th day in majority and correlated with the size of infarct. Large infarcts were associated with hyponatremia, and all had altered sensorium and 4 patients with very low sodium of less than 120 millieq/L developed seizures. Hyponatremia was reversible by early identification and appropriate management. Of the 9 patients who died during hospital stay, 6 had hyponatremia.

Outcome

There was significant disability in great majority at discharge, though notable improvement occurred on follow up. The Modified Rankin Scale (MRS) Score at discharge and at 3 months follow up is shown in Table 10. 9 patients died during hospital stay, and one patient died during the three month follow-up. The person who died during follow-up had MRS of 5 at discharge, and had CAD and old myocardial infarction. Majority showed improvement in their disability score at 3 months.

Table-10: MRS score at discharge and at 3 months follow up

MRS	At Discharge		At 3 Months	
	No. of patients	Percentage	No. of patients	Percentage
2 or <2	2	2.5%	12	15%
3	7	8.75%	30	37.5%
4	37	46.25%	24	30%
5	25	31.25%	4	5%
6 (DEATH)	9	11.25%	10	12.5%

(MRS Score: 1.No disability despite symptoms; 2. Slight disability, able to carry out all ADL;3.Moderate disability, require some help, walk independently; 4. Moderate to severe disability, unable to walk; 5.severe disability, bedridden, need constant nursing care; 6.Death).

Mortality

A total of 9 patients died. (8 patients died during the initial admission and 1 patient died after discharge). All patients who died had large infarcts with mass effect and deteriorated early. Multiple factors contributed to their deterioration and death (Table 11). The one patient who died after discharge had CAD, DM, HT, Old myocardial infarction (MI) and experienced sudden death, due to MI / arrhythmia.

Table-11: Factors that contributed to deterioration and death in 9 patients

	ASPECT score	Mass effect	Hemorrhagic transform-ation	Seizure	Aspiration pneumonia	Hyponatremia	High blood pressure	Uncon trolled DM	Smoker	DVT, Pul. embolism	CAD, MI	ICA occlusion
1	7	+			+	+	+		+		+	
2	6	+				+	+	+		+		
3	8	+	+			+	+	+		+		
4	7	+			+		+	+	+			
5	6	+									+	+
6	5	+	+		+	+				+		
7	6	+	+	+	+	+	+	+				
8	9	+			+						+	+
9	6	+				+		+		+		

DISCUSSION

In this prospective observational study, 80 cases (25%) of 320 total cases of first ischemic stroke of moderate and moderately severe degree, deteriorated after admission in the first week. Severe strokes with NIHSS score > 20 were excluded as severe stroke carry high risk of progressive deterioration and bad outcome. Awareness regarding stroke, and vascular risk factors were very poor irrespective of formal education or economic strata in the group deteriorated.

Kerala state has a higher prevalence of vascular risk factors, compared to national average [24, 25, 26, 27, 28, 29]. Among our deteriorated stroke patients, 85% were hypertensives, 42.5% were diabetics, 62.5% had dyslipidemia and 41.3% were smokers. Only 18 patients (22.5%) arrived at the hospital before 4.5 hours. Lack of awareness regarding early symptoms, importance of transient symptoms as harbingers of a major stroke, early treatment options, limited access to newer imaging techniques, unaffordable cost, lack of universal insurance coverage, influence of alternative systems of medicine contributed to delayed arrival to a stroke care center. There is lack of well-equipped acute stroke care units and rehabilitation centers at rural areas. Newer treatment options are available only in urban centers, where infrastructure is very limited.

Neurologic deterioration & Outcome

In this prospective observational study, neurologic deterioration was seen in 25% of first acute ischemic stroke cases (80 out of 320 patients). In the previous studies, the prevalence varied between 13% and 38% [30]. In European progressing stroke studies, early neurologic deterioration was seen in 26% of patients in first 3 days after acute ischemic stroke and any neurologic worsening (transient or persistent for at least three days) occurred in 33% [31]. In a recent Chinese study, 32% of first ever stroke showed early neurologic deterioration [5]. Early neurological deterioration (END) was defined as an increment in motor power of at least one point or total NIHSS score deterioration of >/=2 points within the first week after admission. During acute phase, deterioration was a strong predictor of short term and long term unfavorable outcome (functional disability and mortality) in patients with first ever ischemic stroke [5].

In the current study, of the 320 first ever acute ischemic stroke cases, 80 patients (25%) deteriorated. 9 of them (11.3%) died (MRS 6) during hospital stay, and one more died at three months follow up. 77.6% (MRS - 4 and 5) were left with severe disability, with inability to walk at discharge. At 3 months, of the 70 patients who survived, 28 were unable to walk independently, 30 required some help for activities of daily living (MRS - 3), again proving that deterioration after the admission is associated with early worsening and long term disability in survivors.

Factors at admission predictive of deterioration

They were grouped as clinical, radiologic and biochemical features.

Clinical features at admission predictive of deterioration

a. **NIHSS Score at admission** – Higher the NIHSS score at admission, more severe is the stroke and higher is the chance of deterioration. In one study, patients with an initial NIHSS score less than or equal to 7 experienced lower frequency of worsening (14.8%) than those with a score > 7 (65.9%), with a dichotomy in early outcome surrounding an initial NIHSS score of 7 [32]. Siegler [33], reported that a worsening of NIHSS Score >/= 2 points after admission is a sensitive indicator of poor outcome. In our study also, deteriorated stroke had moderate and moderate to severe stroke at admission (NIHSS score of 5 to 20) - NIHSS score of 5 to 9 in 27 patients, 10 to 15 in 51 patients, and 16 to 20 in 2 patients. Severe stroke with NIHSS score > 20 were excluded in our study.

b. **Altered sensorium (drowsiness) at admission** – Altered sensorium suggests large area affection, brain edema and mass effect or hemorrhagic transformation and was predictive of deterioration. Altered sensorium due to post ictal stage, non-convulsive status epilepticus, and metabolic encephalopathy need exclusion. In our study, 28 patients (35%) were drowsy at admission

c. **Persistent gaze deviation, towards the lesion** suggestive of gaze pathway affection in cortex or sub cortical regions (suggestive of large infarct) was associated with deterioration. In present study, 28 patients (35%) had altered sensorium (drowsiness) at admission

d. **Proximal large vessel occlusion** - High NIHSS score cannot predict proximal large vessel occlusion with certainty. Patients with low NIHSS score at admission also can have proximal large vessel stenosis or occlusion. Hence acute stroke imaging algorithm should include head and neck CT angiogram, along with non-contrast CT [38]. CT angiogram has better resolution than MR angiogram. Doppler study of neck vessels, CT or MR Angiogram, ultrasound or MR plaque imaging to identify vulnerable plaques are all important in acute stroke evaluation.

e. **Atrial fibrillation** was associated with neurologic deterioration in 8 patients. They carry high risk of recurrent embolism and hemorrhagic transformation. Three out of 8 patients with atrial fibrillation had hemorrhagic transformation. They also can develop recurrent embolism or hypotension which can lead to deterioration. Atrial

fibrillation was transient in 2 patients and continuous ECG monitoring helped in their identification.

f. **Myocardial Infarction** – Evidence of recent myocardial infarction was there in 6 patients (2 patients also had atrial fibrillation), and both myocardial infarction and atrial fibrillation in 2 patients who deteriorated. They carried high risk of embolic stroke, hemorrhagic transformation and deterioration. One previous study found that coronary artery disease was associated with poor long term outcome [37]. Such patients require cardiac evaluation to assess the embolic risk early. They need repeat imaging of brain, in case of any neurologic deterioration. One of our patients with CAD recovered from acute stroke with severe disability, succumbed to CAD and sudden death one month after discharge.

g. **Dual antiplatelets, anticoagulants and fibrinolytics** used were associated with high risk of hemorrhagic transformation, especially in large infarcts. 2 patients with CAD on dual antiplatelet therapy with aspirin and clopidogrel developed hemorrhagic transformation. 1 patient with hepatic dysfunction and 2 patients with renal dysfunction also deteriorated with hemorrhagic transformation of infarct. They carry increased risk of hemorrhagic transformation due to their effect on coagulation system.

h. **Seizures** – Seizures were present in 9 patients (11.23%) and it contributed to deterioration. One patient with altered sensorium and hyponatremia (< 120meq/L) had non convulsive status epilepticus, and was detected by bed side EEG monitoring. Embolic stroke, involvement of cortex and hemorrhagic transformation carried increased risk of seizures. Severe hyperglycemia and hyponatremia were the metabolic causes identified in our patients with seizures. Seizures are common in large cortical infarcts and they account for early neurologic deterioration in about 5% of ischemic stroke patients [48].

i. **Persistently elevated BP** was associated with risk of worsening brain edema, hemorrhagic transformation and deterioration in deficit and sensorium. This occurred in 2 of our patients with renal dysfunction.

j. **Bulbar dysfunction and Aspiration pneumonia** – Evidence of tracheal aspiration and pneumonia was present in 50 (62.5%) patients. Dense hemiplegia with bulbar dysfunction and altered sensorium increase the risk of aspiration pneumonia. Protection of airway is very important in them. Presence of bilateral infarcts, and extensive bilateral small vessel ischemic changes in imaging increased the risk of prolonged bulbar dysfunction (pseudo bulbar) and associated complications. Swallowing function needs to be assessed daily, as per American Academy of Neurology guidelines, before starting oral feeds. Asymptomatic aspiration was also common.

k. **Older age and high BMI** were independent predictors in long term outcome in some studies [5]. Wang *et al.* reported old age as an independent predictor of disability and death [39]. As age advances, reduced cerebro-vascular reserve and multiple co-morbidities increase the risk. But we could not find such an association. 49 (61%) patients were above 69 years of age

l. **Tobacco smoking** was detected in 41.3% of patients who deteriorated after admission. Tobacco smoke induces inflammation, endothelial dysfunction, vasoconstriction and increased thrombotic tendency. It also increases the risk of subarachnoid hemorrhage. Two fifths of all stroke deaths under the age of 65 years are linked to smoking [40].

m. **DVT and pulmonary embolism** – Prevention of DVT and pulmonary embolism is an important priority and must be started early with physiotherapy, pneumatic compression devices and prophylactic heparin. Of our patients deteriorated, 4 had evidence of DVT and 2 developed pulmonary embolism. Daily monitoring for calf pain, asymmetric edema, tenderness and local rise of temperature of calf are helpful signs. Doppler ultrasound study of leg veins upto IVC can detect DVT in majority of cases.

n. **Malignant MCA infarct**–Large MCA infarct with early evidence of brain edema and mass effect need early neurosurgery consultation and decompressivecraniectomy to save life in selected patients. We had 3 cases that underwent hemicraniectomy, two improved to MRS score 3 at 3 months follow up, and the other was left with severe disability (MRS 5). Hemicraniectomy performed early, within 48 hours significantly reduces mortality, and improves functional outcome in selected patients [41].

Biochemical parameters at admission predictive of deterioration

a. **Blood sugar and HbA1C at admission** – Very high blood sugar (> 400mg%, with elevated HbA1C > 9%) values were present in 6 of 36 (16.6%) deteriorated diabetic patients. 20 had blood sugar values between 200 and 399 mg% at admission. Diabetes is reported as independent predictor of deterioration in many studies [12, 42, 43]. Diabetic microangiopathy and chronic

hypertension impair micro vascular function, reducing the potential for collateral development. This leads to reduced oxygen delivery and regional metabolic disturbances, which may aggravate cellular damage by enhancing brain edema and free radical injury [46, 47].

b. **Hyponatremia –** Hyponatremia was seen in 27 patients with deterioration, was more with large infarcts and occurred from 3rd to 14th day of infarct; it was associated with altered sensorium. There were seizures in four patients with serum sodium value < 120meq/L. Prompt identification of cause and management is critical. SIADH was more common than cerebral salt wasting, which was seen in only one patient. Volume status (degree of hydration) is the clue.

Radiological features at admission predictive of deterioration

a. **Initial CT brain - ASPECTS score -** ASPECTS is a 10 point quantitative score used to assess early ischemic changes on non-contrast CT head [23]. In our study, ASPECT score at admission CT was less than or equal to 7 in 60 deteriorated patients (75%), and ASPECT score was more than 7 in 20 (25%) deteriorated patients. Many studies showed a linear inverse relationship between ASPECT score and risk of deterioration [44, 45]. Two of our patients who arrived early in less than 2 hours of onset of symptoms had ASPECTS score of 10. There was no evidence of even early changes of infarct; however they developed full blown MCA infarct within 24 hours. MRI Diffusion Weighted imaging could be beneficial in such patients as MRI can pick up acute infarcts as early as 30 minutes.

b. **Proximal large artery stenosis or occlusion**
Patchy hypo densities involving cortical, sub cortical and deep perforator regions, in MCA territory, or dense MCA sign/MCA dot sign, superficial and deep watershed area infarcts suggest possible proximal ICA or stem occlusion of MCA with some collateral flow. (Figure 2-4). Large vessel occlusion and failure of collaterals is the most common mechanism of neurologic deterioration (END) (4). Angiogram and penumbra imaging (MRI perfusion diffusion mismatch) are the guides for intervention. Percentage stenosis of ICA also can be calculated with ultrasound study. CT Angiogram or DSA is confirmatory.
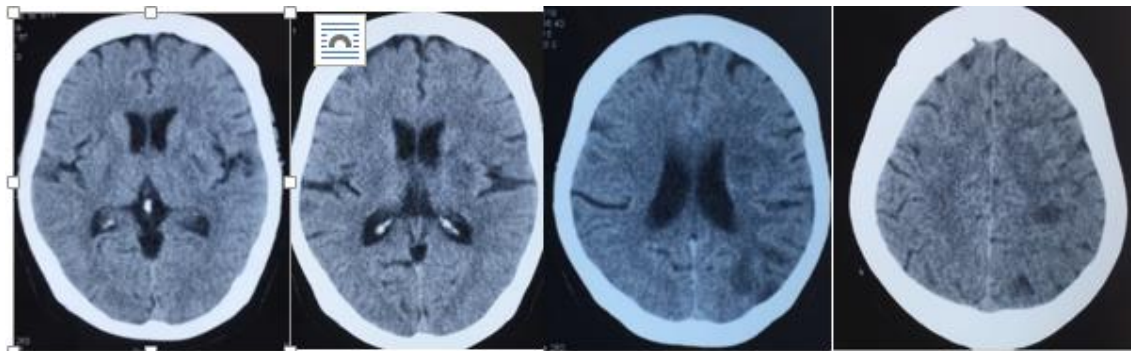
Fig-2: Evolution of MCA infarct over 48 hours.58 year old lady acute onset aphasia, right hemiplegia, UL>LL, drowsy at admission, second day, sensorium worsening with bilateral ptosis, bilateral extensor plantar response- evolution over 48 hours
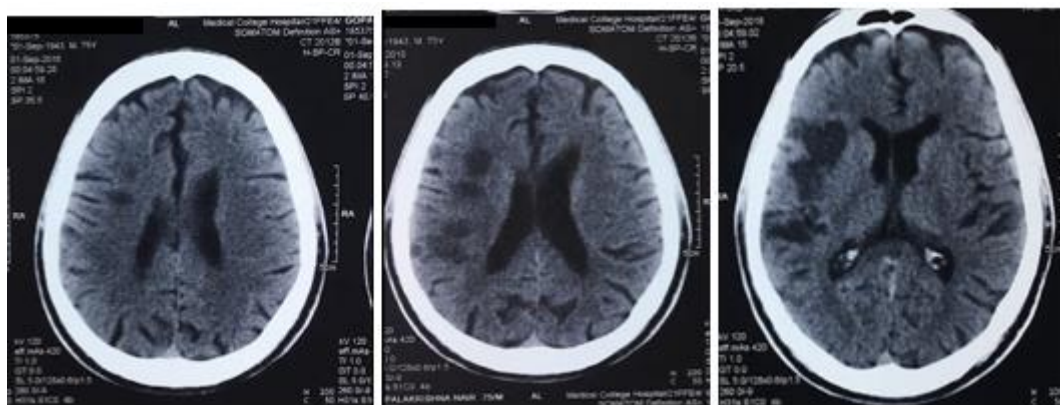
Fig-3: Collateral failure and progression of distal M1 occlusion: multiple patchy watershed infarcts with deterioration over 48 hours
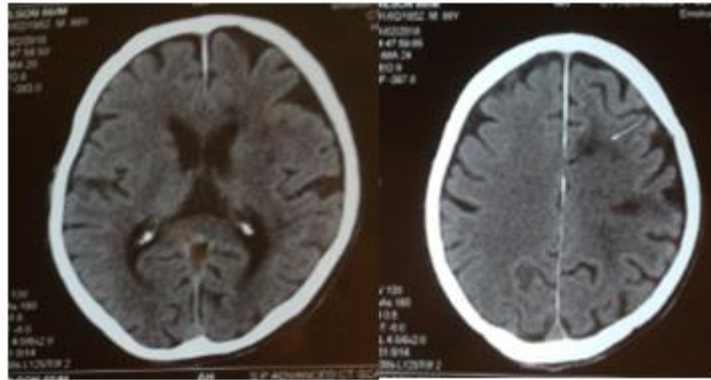
Fig-4: Multiple patchy hypodensities in left MCA territory

c. **Hemorrhagic transformation of infarcts** this is more common with large infarcts, embolic strokes and patients following thrombolysis or coagulopathy. In the present study, there were 17 cases with hemorrhagic transformation. (Figure 5,6) Other causes of hemorrhagic transformation include embolic stroke, on dual antiplatelets, renal dysfunction, hepatic dysfunction and patients with uncontrolled hypertension. Hemorrhagic transformation range from small asymptomatic petechiae, to large hematoma with mass effect.
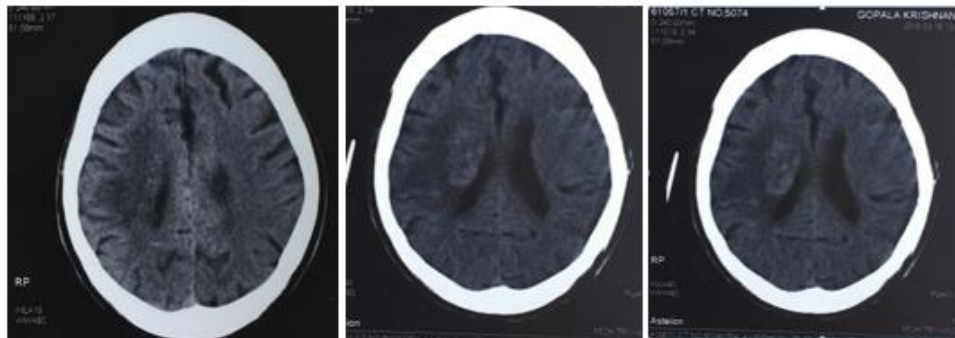

Fig-5: Hemorrhagic transformation of right MCA infarct
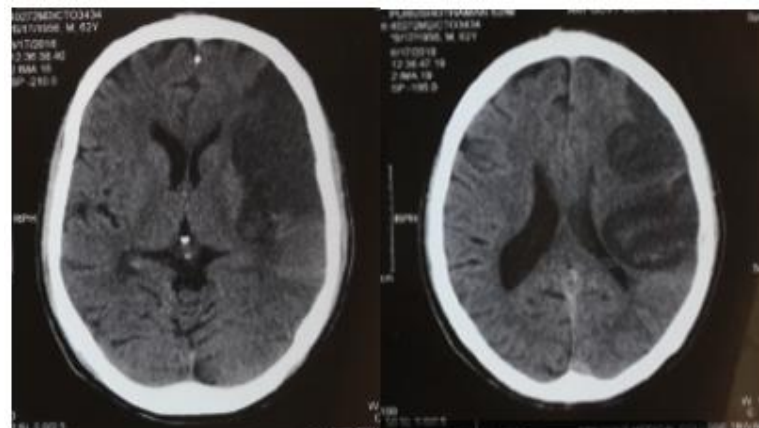

Fig-6: Left MCA occlusion with hemorrhagic transformation, RHD AF embolic stroke

d. **Diffuse bilateral subcortical and periventricular hypo densities** suggesting diffuse small vessel disease, also carried higher risk of deterioration because of bilateral disease, poor reserve, and high risk for pseudo bulbar dysfunction, tracheal aspiration and pneumonia. MRI can show micro hemorrhages also.

e. **Multiple infarcts** in different vascular territories, bilateral infarcts, and wedge shaped infarct, hemorrhagic transformation – all suggest possible embolic etiology.

f. **Clinico-radiologic dissociation**
Lack of correlation between clinical deficit with initial CT picture, deficit with lack of imaging correlate initially (early CT), deficit with small

infarct or multiple watershed infarcts or small infarct with altered sensorium (seizures and metabolic causes ruled out) often suggest proximal large vessel occlusion and higher risk of deterioration. Such patients need further imaging-Doppler, MRI (DWI, FLAIR, MR/ CT perfusion, MR Angiogram or CT Angiogram).

LIMITATIONS OF THE STUDY

Small sample size is the major limitation in our study. A larger sample size comparing deteriorated to non-deteriorated patients shall provide more information regarding the causes of deterioration.

CONCLUSIONS

Progression of stroke is likely multifactorial; however, risk of deterioration in acute ischemic stroke can be predicted in great majority of cases at admission by careful close observation of clinical, biochemical and imaging characteristics, and by performing necessary investigations early. High NIHSS score, alteration in sensorium at arrival, persistent gaze deviation, and early features of raised intracranial pressure were predictive of deterioration in our study. Clinico-radiologic dissociation features at admission like focal deficit with normal early CT, or deficit/altered sensorium with only minor imaging finding in initial CT brain scan, which cannot be explained by a small infarct were associated with high risk of deterioration. In such scenarios MRI Angiogram or CT angiogram may be more beneficial. High blood sugars and hyponatremia were the metabolic factors associated with deterioration. Imaging features like large infarct with early edema and mass effect features of proximal large artery stenosis and bilateral extensive small vessel ischemic changes were associated with deterioration. In conclusion, each stroke case needs prompt individualized evaluation and management. Interventions based on pathophysiology identified by imaging features and patient's clinical condition and management of systemic diseases and complications will improve the outcome.

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