Predictors of Early Progression in Ischemic Stroke

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ABSTRACT

Background: Some patients with ischemic stroke have progression of their neurological deficits even after starting medical treatment, but it is not known which patients will progress or why they progress. Objectives: To study the relative importance of different factors that may affect the progression of ischemic stroke within the early period after stroke onset and how neurologists can prevent or minimize this progression as early as possible. Patients and Methods: The study evaluated 62 patients (32 men, 30 women; age, 58.5±8.2 years) with first-ever acute ischemic stroke in the MCA territory with onset less than 24 hours on presentation. The patients was classified into two groups, group with progressive acute MCA territory ischemic stroke (21 patients) and another group with stable (or improving) acute MCA territory infarction (41 patients). All patients were subjected to full history and daily neurological examination. The stroke severity was assessed on presentation and on daily basis using National Institutes of Health Stroke Scale (NIHSS). The study compared the progressive acute MCA territory infarction with stable (or improving) acute MCA territory infarction. Results: Of 62 patients, 21 patients (33.9%) had progressive ischemic stroke. Severity of stroke on admission was related to stroke progression as Patients with base line NIHSS score ≥ 15 were more liable to developed early stroke progression however more than 75% of patients with base line NIHSS score ≤ 7 did not develop any progression. Also the other factors that significantly associated with progression of acute MCA territory infarction were age at onset ≥ 60 years old, past history of hypertension and diabetes mellitus (DM), significant reduction of systolic blood pressure (SBP) a day after admission, significant higher blood sugar level on admission, elevated temperature after admission, presence of MCA sign on computerized topography of the brain (CT brain) on admission, large size of infarction and presence of co-existing silent ischemic lesions on magnetic resonant image of the brain (MRI brain), presence of low void sign or occluded MCA in brain magnetic resonant angiography (MRA brain) and presence of MCA occlusion or MCA flow asymmetry in transcranial Doppler (TCD). Conclusion: It seems that various factors combine to cause early progression of neurological deficits of ischemic stroke. Understanding of these various factors that affect progression at the earliest stages of stroke will greatly assist the clinicians in understanding ischemic stroke and ultimately in better treating this disease. (Egypt J. Neurol. Psychiat. Neurosurg., 2007, 44(1): 207-223).

INTRODUCTION

With the advent of promising therapies for acute ischemic stroke comes a higher expectation for rapid recovery and good outcome. Despite these new therapies, poor outcome may still occur because ischemic stroke is a heterogeneous disease in which outcome is influenced by many factors.

Some patients with ischemic stroke have progression of their neurological deficits, but it is not known which patients will progress or why they progress.

Recent literature has identified many of the important factors helpful in predicting outcome even within the early period after stroke onset. Demographic variables, risk factors, clinical examination finding, laboratory test result, and imaging studies all provide important insight regarding outcome.

Understanding the different factors that may affect the progression of ischemic stroke & their relative importance will help the clinician in making more accurate evaluation methods to predict which patients will progress & how they can prevent or minimize this progression as early as possible.
A stroke in evolution or stroke in progression is one in which focal neurological deficits worsen over the course of minutes or hours [1]. Approximately 20% of the anterior circulation strokes show evidence of progression. Anterior circulation strokes may progress within the first 24 hours, whereas posterior circulation strokes may progressive for up to 3 days [1][2]. Kang et al. [3] defined stroke in evolution as increasing neurological deficits hours or days after the initial abnormality of the stroke become stable.

Kothari and Barsan [4] and Zivin [5] defined stroke in evolution as increasing or deterioration of neurological deficit or appearance of new stroke symptoms (or signs) after admission, meaning that there was worsening of their clinical findings even after medical care began [6].

Exclusion criteria were; (1) patients with any cerebral hemorrhage on presentation, (2) patients presented 24 hours or more after becoming aware by their stroke symptoms, (3) patients presented with complete ischemic stroke, (4) presence of pre-existing significant non-ischemic stroke neurological deficit (including dementia or extrapyramidal diseases), (5) patients with past history of previous ischemic stroke, and (6) patients deteriorated due to systemic causes, rather than vascular causes (like, hypoxia, hyperglycemic coma, infection, renal or liver impairments). All of these patients were excluded to avoid any hamper interpretation of clinical and radiological data.

Ischemic cerebral stroke was defined as a clinical signs of focal disturbances of cerebral function lasting > 24 hours with no other cause than vascular, after exclusion of primary intracranial hemorrhage on CT or MRI brain scan [7][8].

The stroke onset was defined as the time the patient was last known to be without neurological deficit [9]. We also identified patients with complete stroke as patients with all of the manifestations of one common stroke syndromes [10]. Accordingly distinction between a complete and an incomplete stroke, as a practical matter, was based on whether a patient had all the manifestations of one of the common stroke syndromes or just some of them.

**PATIENTS AND METHODS**

**Patients**

This study included 62 patients with acute MCA territory cerebral stroke. They selected from patients admitted to stroke Unite of Aim Shams Specialized hospital from start of January 2003 to end of June 2003. We studied MCA territory stroke because the MCA is the vessel most frequently involved in stroke syndromes and is readily visualized on MRA [11][12].

Patients were eligible for this study if they met the following criteria: (1) final diagnosis of acute MCA territory cerebral ischemic stroke, (2) the onset of stroke was less than 24 hours on admission and accordingly patients with transient ischemic attack due to MCA territory ischemia included in this study (3) both sex and any age were included.

The patient classified into two groups: those with stroke in-evolution or progressive stroke and those with stable (or even improving) stroke based on the assessment of neurological impairment using National Institute Health Stroke Scale (NIHSS) on admission and after 24 hours.

The term stroke - in - evolution or progressive strokes has various definitions. In current study we defined progressive stroke (a strokes in evolution) as increasing or deterioration of neurological deficit or appearance of new stroke symptoms (or signs) after admission.
Methods

All patients were subjected to full neurological history and examination on admission and on daily basis. The stroke severity was assessed on presentation and on daily basis using NIHSS and clinical deterioration findings. The NIHSS is a 42-point clinical examination scale (NIHSS 0 = Normal examination, NIHSS 1-7= mild neurological deficits, NIHSS 8-14= moderate deficits and NIHSS >15= severe deficits) that has become the standard clinical severity scale in most clinical trials 13,14.

We classified our patients into two groups. First Group (group of patients with progressive MCA territory cerebral ischemic stroke) consisted of 21 patients with clinical deterioration and increasing NIHSS score in comparison to the score on presentation. Second Group (group of patients with stable or even improving acute MCA territory cerebral ischemic stroke) were 41 patients with stable or even improving NIHSS score and clinical findings.

The following factors were considered on assessment of clinical profile of each patient: Time of arrival at hospital after awareness of stroke symptoms, age, gender, history of hypertension (defined as past use of anti-hypertensive agent, a blood pressure recording before stroke onset with systolic blood pressure ≥ 160 mmHg or diastolic Blood pressure ≥ 95 mmHg 15), history of diabetes mellitus (use of insulin or oral hypoglycemic agents, fasting blood glucose 140 mg/dl or random blood glucose ≥ 200 mg/dl 15), history of hypercholesterolaemia (use of antilipotropic agents, or total cholesterol ≥ 220mg/dl [15]) and past history of Atrial fibrillation, ischemic heart disease or any other cardiac events.

On admission we assessed systolic and diastolic blood pressure, body temperature, and peripheral pulsations and fasting blood sugar. Then they reassessed again 24 and 48 hours after admission. Blood pressure was measure by mercury sphygmomanometer with the patient supine. Three consecutive measurements with an interval of 15 minutes were used to calculate the blood pressure on admission as well as on 24 and 48 hours of admission. The reduction in blood pressure was calculated between the following time points (1) on admission to 24 hours after admission (2) 24 hours to 48 hours after admission, according to the formula [(follow up BP)-baseline B.P]/ baseline B.P X 100.

Antihypertensive treatment was given according to the protocol of stroke unite of Aim Shams Specialized hospital with understanding of post stroke hypertension.

Also some lab investigations were done to all patients on the first day of admission including ESR, Hematocrite %, Lipid profile (particularly total cholesterol level & LDL) & serum uric acid.

The hematocrite percentage was done also 24 and 48 hours after admission. The change of it was calculated by same way like B.P.

C.T brain was done for all patients on admission to (1) exclude any hemorrhagic events (2) detect the early signs of ischemic stroke (3) detect the site and size of the infarction. CT brain was done also after neurological deterioration for progressive stroke patients to document that the neurological deterioration was due to new cerebral ischemic changes or progression of the presenting ischemic insult and not due to secondary cerebral hemorrhage. CT brain was performed using a General Electric CT scanner 9800, with 512 × 512 matrix and 2- or 3-second scan time. The section thickness was 3 mm with 5-mm increments from the foramen magnum to the suprasellar region and 10-mm contiguous slices above.

MRI brain with axial, coronal and sagittal T1 and T2 cuts in addition to FLAIR (FLuid-Alternated-Invasive Recovery) and diffusion imaging were done for all patients on admission using 1.5 tesla–general electric machines with slice thickness of 5mm to detect the coexisting silent ischemic lesions, site and size of ischemic lesion. These MRI studies were done also after neurological deterioration (detected clinically & by NIHSS) for progressive stroke patients to
document that the neurological deterioration was
due to new cerebral ischemic changes or
progression of the presenting ischemic insult.

The condition of MCA trunk was also
evaluated using Magnetic Resonance
Angiography (MRA) performed at the same
time as MRI brain. Patients were analyzed based on
presence or absence of MCA flow.

Transcranial Doppler (TCD) measurement
was done for all patients on admission and a day
after admission using MDX TCD-7 (Version 7.3,
DWL, Germany) apparatus (a multi-channel
Doppler combined with very powerful computer
hardware) operating at 2 MHz. The study
included insonation of MCA bilaterally. The
trans temporal window was used to insonate the
MCA bilaterally. Identification of MCA was
dependent on the angle, depth of the ultrasound
beam and the direction of blood flow within the
insonated vessel. The mean flow velocity (MFV)
of MCA was measured in centimeters per second.
The diagnosis of abnormal main flow velocity
(MFV) of MCA was made considering
abnormality as one standard deviation ± mean
values of MFV of MCA of normal Egyptians
which was done in our laboratory using the same
apparatus in the different decades by Fahmy16
(Table 1). A side-to-side difference greater than
30% was also considered abnormal.

*Table 1. MFV of MCA in different decades in normal Egyptians.

<table>
<thead>
<tr>
<th>MFV of MCA (mean±SD)</th>
<th>10-20 years</th>
<th>20-30 years</th>
<th>30-40 years</th>
<th>&gt; 40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72.5± 9.9</td>
<td>66.7± 13.3</td>
<td>70.8± 10.2</td>
<td>60.6± 8.7</td>
</tr>
</tbody>
</table>


In addition to the previous work up, patients
also underwent duplex examination of the
extracranial circulation (common, external, and
internal carotid arteries) and complete
Echocardiographic study. In carotid duplex
presence or absence of moderate to severe
ipsilateral or contralateral carotid arteries stenosis
and/or presence of soft plaque in one of carotid
arteries particularly internal carotid artery (ICA)
or common carotid artery (CCA)] were reported.
In this study 50% -69% luminal reduction
considered as moderate stenosis while ≥ 70%
luminal reduction considered as severe
stenosis17,18.

The cardiac abnormalities including atrial
fibrillation (AF), prosthetic valve disease,
rheumatic heart disease, bacterial endocarditis,
atrial myxoma, myocardial infarction, left
ventricular thrombus, dilated cardiomyopathy,
aortic arch atheroma, atrial septal aneurysms,
mitrval valve prolapse, mitral annular calcification
and valvular strands (primarily of fibrinous
deposits on valve leaflets)19,20 were reported.
Patients in each group of this study were classified
as patients with AF on admission (confirmed by
examining ECG recordings), patients with one or
more of the other cardiac events mentioned before
and patients without any cardiac events.

Statistics

Statistical analysis was performed using
program Statistical Package for Social Sciences
(SPSS) version 10.0 for windows. Data are
presented as mean±SD. Proportions between
progressive and stable infarctions were compared
by chi-square test. Student's t-test, as appropriate,
was used to compare continuous variables.
Table 2. Summary of the results.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Progressive Group</th>
<th>Stable Group</th>
<th>P-Valve</th>
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<tbody>
<tr>
<td></td>
<td>No. Of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 (33.9%)</td>
<td>41 (66.1%)</td>
<td></td>
</tr>
<tr>
<td>Age in year ± SD</td>
<td>61 ± 5</td>
<td>56 ± 6.4</td>
<td>0.61</td>
</tr>
<tr>
<td>≥ 60 Years old, No (%)</td>
<td>14 (66.7%)</td>
<td>17 (41.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Men/Women</td>
<td>15/6 (71.4% / 28.6%)</td>
<td>27/14 (65.9% / 34.1%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Time to presentation (Mean hours ± SD)</td>
<td>9.4 ± 6.1</td>
<td>10.9 ± 7.7</td>
<td>0.39</td>
</tr>
</tbody>
</table>

**NIHSS Score**

| On admission (Mean ± SD)                     | 11.8 ± 3.2        | 7.4 ± 2.4    | 0.02    |
| Patients with NIHSS score ≥ 15 (16 = 25.8%)   | 12 (57.2%)        | 4 (9.8%)     | <0.001  |
| Patients with NIHSS score 7 to < 15 (14 patients = 22.6%) | 5 (23.8%) | 9 (22 %) | 0.34    |
| Patients with NIHSS score ≤ 7 (32 patients = 51.6%) | 4 (19%) | 28 (68.2%) | <0.001  |

**Risk factors No (%)**

| Past history of hypertension on admission   | 15 (71.4%)        | 19 (46.3%)   | 0.03    |
| Past history of Diabetes Mellitus          | 11 (52.4%)        | 9 (22%)      | 0.01    |
| Past history of dyslipidemia               | 5 (23.8%)         | 11 (26.8%)   | 0.73    |
| Past history of Atrial Fibrillation (AF), ischemic heart disease and/ or any cardiac risk factors | 6 (28.6%) | 14 (34.1%) | 0.67    |

**Systolic blood pressure mmHg ± SD**

| On admission                                | 170 ± 22.1        | 160.6 ± 18.3 | 0.42    |
| 24 hours later                              | 140 ± 20.6        | 155 ± 10.5   | 0.06    |
| Relative changes %                          | -17.6 ± 14.4      | -3.1 ± 13.2  | <0.001  |

**Diastolic blood pressure (mmHg±SD)**

| On admission                                 | 100.5 ± 16.2      | 90.5 ± 12.7  | 0.79    |
| 24 hours later                               | 90 ± 10.8         | 85 ± 9       | 0.67    |
| Relative changes %                           | -10.0 ± 17.8      | -5.6 ± 19.7  | 0.46    |

**Blood sugar, mean mg/dl ± SD**

| On admission                                 | 161.8 ± 57.6      | 112 ± 32.4   | <0.001  |
| 24 hours later                               | 147.6 ± 49.1      | 106.3 ± 24.5 | <0.001  |
| Relative changes %                           | -8.7 ± 20.5       | -5.4 ± 29.7  | 0.26    |

**Hematocrite % ± SD**

| On admission                                 | 41.0 ± 3.4        | 14.3 ± 4.7   | 0.75    |
| 24 hours later                               | 39.7 ± 3.9        | 39.5 ± 5.1   | 0.84    |
| Relative Changes %                           | -2.7 ± 8.4        | -4.8 ± 6.1   | 0.20    |
Table 2. Summary of the results (cont.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Progressive group</th>
<th>Stable group</th>
<th>P-Value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univariate</td>
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<tr>
<td><strong>Temperature</strong></td>
<td></td>
<td></td>
<td>Multivariate</td>
</tr>
<tr>
<td>Patients with fever on Admission, No (%)</td>
<td>2 (9.5%)</td>
<td>5 (12.2%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Patients developed fever 24 hours later, No (%)</td>
<td>8 (38.1%)</td>
<td>7 (17.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Radiological findings</strong></td>
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<td></td>
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</tr>
<tr>
<td>Mean time to first CT brain, mean hours ± SD</td>
<td>11 ± 2.1</td>
<td>14 ± 2.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Presence of focal hypodense area consistent with Neurological findings on C.T of admission (%)</td>
<td>8 (38.1%)</td>
<td>13 (31.7%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Presence of hyperdense MCA sign on CT brain of admission</td>
<td>8 (38.1%)</td>
<td>9 (22%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lentiform obscuration N0 (%)</td>
<td>9 (42.9%)</td>
<td>21(51.2%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Patients with ≥ 3 Co-existing silent ischemic lesion in MRI brain of admission, No (%)</td>
<td>13 (61.9%)</td>
<td>16 (39%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Size of infraction on diffusion weighted imaging (DWI) on admission, (Mean cm$^2$ ± SD)</td>
<td>5.8 ± 1.6</td>
<td>2.6 ± 1.4</td>
<td>0.01</td>
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<tr>
<td><strong>MRA of admission, No (%)</strong></td>
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<tr>
<td>Occluded MCA (absence of flow) No (%)</td>
<td>7 (33.3%)</td>
<td>8 (19.5%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Transcranial Doppler (TCD) on admission</strong></td>
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<tr>
<td>MCA no flow or asymmetric MCA flow signal, No (%)</td>
<td>15 (71.4%)</td>
<td>19 (46.3%)</td>
<td>0.01</td>
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<tr>
<td><strong>Carotid duplex findings on admission</strong></td>
<td></td>
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<tr>
<td>Ipsilateral ICA stenosis ≥50%, No (%)</td>
<td>3 cases (14.3%)</td>
<td>5 cases (12.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Presence of Soft plaque in the ipsilateral ICA, No (%)</td>
<td>2 cases (9.5%)</td>
<td>3 cases (7.3%)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Echocardiography findings</strong></td>
<td></td>
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<tr>
<td>Patients with atrial fibrillation (AF)</td>
<td>5 cases (23.8%)</td>
<td>8 cases (19.5%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Patients with one or more of other cardiac risk factors, No (%)</td>
<td>4 cases (19%)</td>
<td>7 cases (17%)</td>
<td>0.32</td>
</tr>
</tbody>
</table>
To identify those factors with an independent capacity to predict progression among the clinical profile obtained on admission, we used a logistic multiple regression model.

In brief, progress or stability was regarded as a dependent variable, whereas factors that demonstrated a significant difference in univariate analysis were regarded as independent variables. A value of $p < 0.05$ was considered significant.

**RESULTS**

This study included 62 patients, 21 (33.9%) had progressive infarction and 41 (66.1%) were classified into the stable (or improving) infarction group. Table (2) summarized the whole results of our study.

In progressive ischemic stroke patients, 13 patients (61.9%) were administered aspirin with low molecular weight heparin and 8 patients (38.1%) administered aspirin with heparin. However in patients with stable infarction, 24 patients (58.5%) were administered aspirin with low molecular weight heparin and 17 patients (41.5%) were administered aspirin with heparin. Other appropriate secondary preventive medication (e.g. dehydrating measures, statins, antihypertensive and hypoglycemic) standardized by our hospital stroke care pathway. There were no significant differences regarding the treatment.

Neurological impairment at presentation and on daily basis was assessed by clinical findings and NIHSS score. The score of NIHSS for all patients ranged between 2 and 28.

The mean NIHSS score of progressive infarction groups on admission (11.8±3.2) was significantly higher than NIHSS score of stable infarction (7.4±2.4) ($P<0.05$). About 32 patients (51.6%) of all patients had NIHSS score 7 or less on admission and 27 patients of them (87.5%) did not experience any clinical or NIHSS score deterioration [only 4 of them (12.5%) developed deterioration]. At same time 16 patients of all patients (25.8%) had NIHSS score of ≥15 on admissions and only 4 of them (25%) did not develop clinical or NIHSS score deterioration [12 of them (75%) develop deterioration]. Meanwhile 14 patients of all patients (22.6%) have NIHSS score more than 7 and less than 15 on admission and 9 of them (65.3%) did not develop clinical or NIHSS score deterioration [5 of them (35.7%) developed deterioration].

Accordingly about more than 75% of patients who had a NIHSS score of 7 or less on admission did not experience any clinical or NIHSS score deterioration. At same time very few patients with a base line NIHSS score of ≥15 (25% of them) did not develop clinical deteriorated or any new neurological signs.

**Factors Associated with Progression**

**Time from onset to admission**

The mean time ± Standard deviation (mean ± SD) from the onset to admission time was 9.4±6.1 hours for progressive group and 10.9±7.7 hours for stable group with no significant difference between both groups ($P>0.05$).

**Age and gender**

The mean age (±SD) of all patients was 58.5±8.2 years. The mean age (±SD) among progressive infarction group was 61±9.4 years while among stable infarction group was 56±8.0 years. There was no significant difference between the two groups as regard the mean age ($P>0.05$).

In progressive group 66.7% (14 patients) were ≥60 years old while in stable group only 41.5% (17 patients) were ≥60 years old. There was significant difference between the two groups as regard the percentage of patients with age ≥60 years with higher percentage of patients ≥60 years old among progressive group compared with stable group ($P<0.05$).

The men/women in progressive group was 15/6 (71.4% / 28.6%) while in stable group was 27/14 (65.9% / 34.1%). There was no significant difference between the two groups as regard sex distribution ($P>0.05$).
Hypertension
At admission 47 patients of total patients had past history of hypertension (most of them were on antihypertensive medications). In progressive group 15 patients (71.4%) & 19 patients in stable group (46.3%) were hypertensive.
There was a significant difference between the two groups as regards the history of hypertension with significant higher percentage of patients with history of hypertension among progressive group compared with stable group (P<0.05).
There was no significant difference between the two groups as regard the mean systolic & diastolic blood pressure (BP) on admission (P>0.05%). The mean systolic and diastolic BP among progressive group after 24 hours from admission were (140±20.6, 80±10.8 respectively) while among stable group were (155±10.5 & 85+9). There was a significant difference between two groups as regard mean systolic BP, 24 hours after admission with lower systolic BP among progressive group than among stable group. However there was no significant difference between two groups as regard mean diastolic BP, 24 hours after admission.
The relative change of mean systolic BP from admission to 24 hours after admission among progressive group (-17.6) was significantly lower than among stable group (-3.1) (P<0.001). However the relative changes of mean diastolic BP value from admission to 24 hours after admission showed no significant difference between the two groups (P>0.05). At the same time there was no significant change between the relative changed of mean systolic & diastolic BP from 24 hours to 48 hours after admission (P>0.05).

Diabetes mellitus
The percentage of patients with past history of diabetes mellitus among progressive group (11 patients, 52.4%) was significant higher than among stable group (9 patients, 22%) (P<0.01).
The mean blood sugar levels were significantly higher in the progressive group on admission & 24 hours after admission (161.8±57.6, 147.6±49.1 respectively) compared with the stable infarction group (112±32.4, 106.3±24.5 respectively) (P<0.001).
However there was no significant difference between the two groups regarding the relative changes of mean blood sugar level on admission & 24 hours after admission in each group (Table 2).

Haematocrit percentage
There was no significant difference regarding mean haematocrit percentage between the two groups on admission (progressive group 41.0±3.4, stable group 41.31±4.7) (P>0.05). The same was found regarding the haematocrit percentage 24 hours after admission (progressive group 39.7±3.9, stable group 39.5±5.1) (Table 2).
On the other hand there was no significant difference between the two groups as regard the percentage of patients presented with fever on admission (9.5% in progressive group and 12.2% in stable group) (P>0.05). However percentage of patients developed fever in progressive group 24 hours after admission (8 patients = 38.1%) was significantly higher compared with percentage of patients developed fever in stable group (7 patients = 17.1%) (P <0.05).
Past History of dyslipidemia, presence of cardiac abnormality including ischemic heart disease (IHD), atrial fibrillation (AF) or any cardiac events showed no significant difference between the two groups (P>0.05).
Among of previous mentioned clinical factors increased NIHSS score on admission, past history of diabetes mellitus on admission, significant systolic blood pressure reduction 24 hours after admission and high blood sugar on admission were demonstrated to be independent risk factors for progression by a logistic multiple regression analysis (Table 2).

Radiological results
All patients underwent C.T brain on admission. The meantime to the first C.T brain did not significantly differed between the two groups (11 hours ± 2.1 for progressive group and 14 hours ± 2.5 for stable group (P>0.05) (Table 2).
The frequency of presence of a focal hypodense lesion consistent with the neurological findings confirmed by C.T brain on admission did not significantly differ between the progressive (8 patients, 38.1%) and stable (13 patients, 31.7%) groups (P>0.05) (Table 2).

There was a significant difference between the two groups as regard presence of hypodense MCA sign on C.T of admission with higher percentage among progressive group (38.1%) in comparison to stable group (22%) (P<0.05) (Table2). However there was no significant difference between the two groups as regard the lentiform obscuration on C.T brain of admission (42.9% for progressive group and 51.2% for stable group) (P>0.05).

All patients undergo MRI brain with diffusion technique on admission. The size of the infarction was larger in the patients with progressive infarction (5.8 cm$^2$ ± 1.6) than in those with stable infarction (2.6 cm$^2$ ± 1.4) (P<0.01) (Table 2). Also the incidence of the co-existing silent ischemic lesions were significantly higher in progressive group of patients (61.9%) than in those with stable infarction (39%) (P<0.05) (Table 2).

MRA of all patients on admission showed a significant higher percentage of patients with flow void sign or occluded MCA among progressive infarction group (33.3%) than among those with stable infarction (19.5%) (P<0.05).

Meanwhile there was a significant difference between the two groups as regard the TCD study results with higher incidence of MCA occlusion and/or MCA flow asymmetry among patients with progressive infarction (15 patients = 71.4%) than in those with stable infarction (19 patients = 46.3%) (P <0.05) (Table 2).

There was no significant difference between the two groups as regard presence of significant ipsilateral ICA stenosis and presence of ICA soft plaque. At the same time there was no significant difference between the two groups as regard percentage of patients with AF or other cardiac risk factors.

### DISCUSSION

Some patients with MCA territory recent infarction show early progression of their neurological effects.

In current study we defined progressive stroke as progression of focal neurological deficits over the course of minutes or hours$^1$. Further because previous report suggested that the mechanism involved is different between those patients who deteriorate early after onset and those who deteriorate later, this study focused on progression between admission and the first 24 hours after admission. The time to presentation in this study doesn’t have difference between the two groups and it is ≤ 24 hours maximally in two groups.

Based on this definition the incidence of patients with early progression was 33.9%. The previous studies$^{15,21,22}$ have demonstrated that neurological deficits progressed after admission in as many as 8 to 62% of patients. Accordingly identifying & preventing or minimizing factors that leading to this progression will help in avoidance or minimizing this progression as early as possible.

The results in this current study demonstrated the influence of different factors on early progression of ischemic stroke. The percentage of patients with age ≥ 60 years old was significantly higher among progressive group (66.7%) than among stable group (41.5%).

Henon et al$^{23}$ and Macciocchi et al$^{24}$ Concluded that old age is one of the major factors that negatively influences the outcome for patients with ischemic stroke. This poor outcome with old age patients can be explained by higher frequency of secondary complications among elderly stroke patients and the high incidence of other systemic illnesses that precluded recovery. The one situation in which advanced age may be protective is in a setting of large infarction size causing mass effect. The likely explanation of this paradox is the protection afford by age related brain atrophy providing additional intracranial volume for space occupying edema$^{25}$.  

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Also presence of past history of hypertension and diabetes mellitus were associated with significant higher percentage of stroke progression. Krieger et al., Demchuk and Buchan, and Vicek et al. found the same results. This may be explained by associated systemic complication of hypertension and negative effects of long term hypertension and diabetes on cerebral perfusion.

Ahmed, and Kasner, evaluated the base line NIHSS score as early predictor of functional outcome after stroke. They concluded that the NIHSS score was the strongest predictor of outcome after acute stroke. In current study NIHSS score predicts the likelihood of a patient’s recovery after stroke. This study showed that 75% of patients who had a NIHSS score of 7 or less on admission did not experience any clinical or NIHSS score deterioration. At same time very few patients with a base line NIHSS score of ≥15 (25% of them) did not develop clinical deteriorated or any new neurological signs. Adams et al., found similar results as they found that a NIHSS score of ≥ 16 forecasted a high probability of death or severe disability whereas a score of less ≤ 6 forecasted a good recovery. At the same time DeGraba et al., confirmed that an initial score of 7 identified a dichotomy in early outcome. They found that patients with score ≤ 7 were 45% likely to be functionally normal 48 hours from symptoms onset compared with 2.5% of patients who were functionally normal at 48 hours with score above this cutoff.

Most patients have elevated blood pressure (BP) in the early phase after an acute ischemic stroke. The benefits of intervention by lowering the initial BP or waiting for spontaneous return to normal values remain debated. Our results clearly demonstrated the influence of blood pressure reduction on early neurological outcome. A significant systolic blood pressure reduction between admission and first 24 hours after admission was associated with progression of neurological deficit early after acute ischemic stroke. At the same time and in spite of absence of significant difference between relative reductions of diastolic blood pressure between the two groups the reduction of diastolic blood pressure was more among progressive ischemic MCA territory stroke group in comparison to group of stable (or improving) ischemic stroke. Yong, concluded that higher baseline SBP or DBP was associated with favorable outcome after stroke. Also Oliveira-Filho et al., concluded that blood pressure reduction in the first 24 hours of stroke onset is independently associated with poor outcome. The main result of their study was a strong, independent relationship of BP course to adverse outcome, with an almost twofold increased risk of poor outcome for every 10% decrease in the systolic BP over the first 24 hours. Zhu and Auer, concluded also that blood pressure reduction have shown a decrease in cerebral blood flow to the infarct area in patients with MCA ischemic stroke. Also our results are more or less in line with recently published data demonstrating worsening of neurological outcome after reduction of blood pressure, particularly diastolic blood pressure of more than 25% within the first 24 hours after ischemic acute stroke.

In many cases the hypertension that follows an ischemic stroke is transient, often lasting 24–48 hours. In one study the best prognosis was associated with a baseline systolic blood pressure of about 150 mmHg, whereas in another study the best prognosis was associated with a baseline systolic blood pressure of about 180 mmHg and the worst prognosis with a rapid fall of pressure. Despite these observations, the debate continues over whether such increases in blood pressure should be corrected early after stroke.

When deciding whether to give antihypertensive drugs to reduce the blood pressure after stroke, we should distinguish the early phase (the first 24–48 hours) from the late phase because of the rapid changes of cerebral blood flow autoregulation that occur after stroke. Because of the loss of autoregulation in the penumbra during the first 24–48 hours of acute ischemic stroke, the extent of cerebral perfusion depends on the perfusion pressure, and a fall in blood pressure during this critical time may
reduce cerebral perfusion, extend the ischemic area, induce irreversible damage and worsen the disabling consequences of the initial stroke. In contrast, in the later phase a smooth rate of blood pressure reduction is recommended, in order to reduce the risk of cerebral edema, hemorrhagic transformation, stroke recurrence and cardiovascular complications.

Given these uncertainties, the American Stroke Association and the European Stroke Initiative recommend that only patients with blood pressure values repeatedly above 220/120 mmHg should be given either labetalol or sodium nitroprusside, intravenously, unless there are other indications for antihypertensive therapy (congestive heart failure, myocardial infarction, aortic dissection). The blood pressure target during the acute phase of an ischemic stroke should not be a normal blood pressure but, rather, 180/105 mmHg in previously hypertensive patients and 160–180/90–100 mmHg in previously normotensive patients.

In patients who were not receiving antihypertensive treatment before the ischemic stroke and who have a baseline systolic pressure of 180–220 mmHg and a diastolic pressure below 120 mmHg, antihypertensive therapy should be deferred for the first 48 hours after the stroke, unless thrombolytic therapy is indicated. In patients who were already receiving oral antihypertensive therapy before the stroke and who have a baseline blood pressure within the above mentioned range, antihypertensive therapy should be given to avoid rebound hypertension, with the aim of maintaining a systolic pressure of 180–220 mmHg and a diastolic pressure below 120 mmHg. If the systolic pressure is higher than 220 mm Hg and the diastolic pressure higher than 120 mmHg, intravenous antihypertensive drugs are recommended to keep the blood pressure at about 180/100–105 mmHg. It is important to select rapidly reversible agents in case neurological signs and symptoms worsen with the blood pressure reduction.

Accordingly patients, families, emergency physicians and paramedics alike should be instructed to abstain from administering antihypertensive agents if stroke symptoms are present, until the diagnosis of stroke has been established and the existence of severe hypertension requiring treatment confirmed. In the acute phase of stroke they must resist the temptation to “catch up” on failed prevention by starting or potentiating antihypertensive therapy too early, since by this action they may unwittingly interfere with cerebral perfusion of the injured brain.

The present study suggests that presence of hyperglycemia on admission and persistence of hyperglycemia after admission are among the important factors that predict early progression of acute ischemic stroke. A heparinoid versus placebo study found that higher admission blood glucose levels are associated with a worse 3-month outcome independent of stroke severity, diabetes or other vascular risks. Similarly Nakamura et al. suggest that diabetes mellitus and severity of motor deficits on admission are both associated with early progression of motor deficits in acute motor lacunar infarcts. Hyperglycemia seems to produce its detrimental effects by causing a profound cellular acidosis. Acidosis is caused by excessive substrates production in the form of lactate during anaerobic glycolysis that occurs in hypoxic/ischemic tissue.

Body temperature also predicts and influences stroke outcome. In this study the percentage of patients developed fever 24 hours after admission in progressive group was significantly higher compared with patients developed fever in stable (or improving) group. Reith et al. concluded that elevated temperature (>37.5 °C) was an independent predictor of large infarct volume and higher neurological deficit or dependence when it occurred in the first 24 hours after stroke onset. Castillo et al., and Castillo et al., were found similar findings. One explanation for the detrimental effects of increased temperature is an increased concentration of excitotoxic neurotransmitters present.
Meanwhile the current study showed that the percentages of patients with hyperdense MCA sign on CT brain of admission (Fig. 1) and patients with co-existing silent ischemic lesion in MRI brain of admission were significantly higher among progressive group compared with stable group. Also the mean size of the new infarction in MRI brain of admission was significantly higher among progressive group compared with stable group. At the same time and inspite of absence of significant difference between the two groups regarding the presence of focal hypodense area consistent with the neurological findings, the percentage of presence of focal hypodense area consistent with the neurological findings was higher among progressive group (38.1%) in comparison to stable group (31.7%). This was inspite of nearly similar mean onset to the first CT brain (11±2.1 hours for progressive group and 14±2.5 hours for stable group). Among these radiological findings the mean size of the new infarction in MRI brain of admission was demonstrated to be independent risk factor for progression by a logistic multiple regression analysis (Table 2 and Fig. 1).

![Fig. (1): Unenhanced CTs showing (A) a left hyperdense middle cerebral artery sign (HMCAS) (arrow) and a calcification in the right MCA. (B1) Attenuation of the lentiform nucleus (ALN) sign (grade 1) in the left hemisphere (between arrows). Note the decrease in contrast of the lentiform nucleus but the respect of its limits. (B2) ALN sign (grade 2) with loss of precise delineation of the left lentiform nucleus (arrows). In addition, presence of a left posterior loss of the insular ribbon (LIR) (arrow heads) and edema with sulcus effacement involving the left temporal cortex. (C) Total LIR in the left hemisphere. A precise delineation between the gray and white matters is not possible (arrows).](image)

Many of the previous studies reported similar radiological results. Demchuk and Buchan, reported that the presence of hyperdense MCA sign seems to be a poor prognostic indicator, in particular when other early CT findings are present. This sign may suggest a large clot burden in the vessel with poor or no residual flow, making systemic thrombolysis therapies largely ineffective. Similarly Moulin et al., concluded that the presence of any two of the following—lentiform obscuration, insular ribbon sign, or hemispheric sulcal effacement—was associated with extended MCA infarct and poor outcome. Also Buttner et al., and von Kummer et al., reported that the presence of early CT findings of parenchymal hypodensity and sulcal effacement is associated with severe stroke and unfavorable functional outcome. The size of the hypodensity in particular correlates with mortality. Early ischemic changes affecting more than 50% of the MCA territory are associated with a mortality rate of 85%. MCA flow void sign or occluded MCA in MRA in this study was also among factors that
predict progression as the percentage of patients with flow void sign or occluded MCA in MRA on admission was significantly high in progressive group compared with stable group. Similarly Barber et al.\textsuperscript{9}, found that acute penumbral patterns (a perfusion-imaging (PI) lesion larger than the diffusion-weighted imaging (DWI) lesion) were present in 14 of 26 patients. Most of these patients (9 of 14) had no MCA flow, whereas all nonpenumbral patients (PI ≤ DWI lesion) had MCA flow. Penumbral-pattern patients with absent MCA flow in their study had greater DWI lesion expansion and worse clinical outcome. Moreover Wen et al\textsuperscript{49}, concluded also that the presence or absence of MRA flow provided independent prognostic information on clinical outcome.

Meanwhile the current study showed that MCA occlusion and/or MCA flow asymmetry was among the factors that associated with progression of MCA infarction. Similarly previous studies\textsuperscript{50,51} reported that severe neurologic deficits and large MCA territory ischemic infarctions have been associated with sonographic signs of MCA occlusion or decreased MCA flow velocities within 12 hours of stroke onset, whereas a patent MCA without reduced MCA flow velocities may be predictive of early clinical improvement.

The cardiac and carotid risk factors in this study were not among significant factors that predict early progression in progressive group. However many previous studies\textsuperscript{3,52} reported that atrial fibrillation is an important direct cause of ischemic stroke and a strong influence on outcome. Strokes in patients with atrial fibrillation are usually more severe, more disabling and associated with a higher mortality\textsuperscript{53}. More over Penado et al\textsuperscript{54} and Dhamoon et al\textsuperscript{55}, concluded that atrial fibrillation was an independent risk factor for stroke recurrence over a wide age range. At the same time Carotid duplex scanning performed soon after stroke onset provides diagnostic information. Baptista et al\textsuperscript{56}, provided evidence that anterior circulation stroke patients with severe (90% or greater) ipsilateral carotid stenosis or occlusion have a higher mortality rate (5.6%) than patients without ipsilateral stenosis (2.8%). Similarly\textsuperscript{57} Presence of arterial occlusion with combined TCD and carotid duplex scanning predicts poor outcome. The low number of patients in our study may explain our results regarding the carotid and cardiac risk factors for stroke progression.

Castillo et al\textsuperscript{41}, demonstrated that early neurological progression of acute ischemic stroke is associated with high concentrations of glutamate in the blood and CSF. Because an earlier report showed that glutamate was released in high concentrations in the penumbral cortex\textsuperscript{58}, the findings of Castillo et al\textsuperscript{41}, seem to suggest that the penumbral zone plays an important role in the progression of neurological deficits and that a change from ischemic penumbra to a complete infarct is associated with progression. From this point of view, deterioration in cerebral blood flow, which is a major cause of the change from ischemic penumbra to an infarct, may be associated with progression of neurological deficits. Among various factors that influence cerebral blood flow, a fall in blood pressure or elevation of hematocrit levels often causes a decrease in cerebral blood flow. Another report\textsuperscript{59} showing that a thrombotic tendency was enhanced in diabetic patients suggests the importance of local factors in the progression of motor deficits in diabetic patients.

Ischemic stroke is a heterogeneous disease with many factors influencing early progression and overall outcome. Clinicians must be knowledgeable regarding the relative importance of each of these factors to be able to offer realistic expectations for families of stroke victims. These factors must be considered when important treatment decisions such as thrombolysis are being contemplated. This knowledge at the earliest stages of stroke will greatly assist us in understanding ischemic stroke and ultimately in better treating this disease. Finally it seems that various factors combine to cause early progression of neurological deficits of ischemic stroke. To clarify fully the mechanism of early progression of neurological deficits, however, additional studies are essential.


المؤشر العربي

العوامل التي تنبؤ بحدوث تدهور مبكر في حالات الجلطة الدماغية

تنهار بعض حالات الجلطة الدماغية الحديثة وتزداد نسبة عجزها حتى بعد بدء العلاج الطبي ولكن من غير المعروف أي الحالات سوف تنهار وماذا تنهار؟ وعلى ذلك يهدف هذا البحث إلى دراسة العوامل المختلفة التي ربما تؤثر على التهاب الجلطة الدماغية. دلالات هذه الدراسة أن تنشر 62 مريض (32 رجل و30 امرأة) لعولمة مرة من جسم الجملة الدماغية في منطقة تلفون الدمسيس الألمنيوم على أن تكون العوامل التي تنبؤ بحدوث تدهور حالة الدماغية. وجدت الدراسة أن نسبة عجزهم في الأربعة والعشر من بداية العلاج والشهرين الأولى من بداية العلاج وجمعية أخرى تكون من 41 مريض تعادل حالاتهم بعلاج نفسي حذر في خلال نفس الفترة. وقد تم هذا التقييم على أساس عزم الألكيني البولي السهلية والинтерventions القائمة والد０ وتحديد أن عزم الألكيني البولي السهلية أن عزم الألكيني البولي السهلية كان له علاقة بالجهاز في كل المرضى بصفة يومية. وتم أيضاً مقارنة العوامل التي قام بالدراسة على حذف تدهور مبكر في مثل هذه الحالات.

وقد أوضحت الدراسة أن (أ) 33% (21 مريض) من كل المرضى يعانون من تنهور وازداد في نسبة العجز. كما أظهر أن نسبة شدة الجلطة من أهم عوامل التهاب حالات الدماغية. حيث وجد أن المرضى الذين كانت نسبة مقايس الجملة الدماغية السهولة للسيدة الدماغية فيهم أكثر من أو تساوي 15 أكثر عزم بحجة في الأربعة والعشر من بداية العلاج في حالاتهم. وان أكثر من 41 مريض ظلت في نفس الفئة. كما أوضح الدراسة أن هناك عدة عوامل أخرى قد تؤدي إلى تدهور مبكر حالات الجلطة الدماغية الحديثة ومصرع ذات دلالة إحصائية ومن هذه العوامل: (1) ازداد عمر المريض عند حدوث تدهور حالة الدماغية حيث كان المرضى ذوون عادة أكثر عزم ازداد العجز والإرباح في نسبة العجز. (2) وجود تاريخ مرضي واضح للمرض. (3) ازداد خطأ ضغط الدم بصورة واضحة في الأربعة والعشر من بداية العلاج. (4) ازداد خطأ ضغط الدم عند بداية العلاج بـ 24 ساعة. (5) ازداد خطأ ضغط الدم عند بداية العلاج. (6) وجود علامة تتحرك الألمنيوم السهلية في الصحة المخية والرئة. (7) في الصدر. (8) وجود علامة خفية عند الدماغ. (9) كانت عزم مباشرة على المريض. (10) وتحديد قسط في القطعة المخية والرئة، وظائف الدماغية. (11) وأخيراً وجود علامة صغرى في الدم. (12) والذين كاشحذت الدراسة أيضا أنها لم تكن لهذه العوامل الأولية ذكرها أن كشف نسبة عزم الألكيني البولي السهلية للسيدة الدماغية وان تكن عزم مباشرة على المريض. (13) وتشير الدراسة إلى تدهور مبكر في حالات الجلطة الدماغية الحديثة.

وقد استخلصت هذه الدراسة أن هناك عدة عوامل تعمل معًا على حدوث تدهور مبكر في حالات الجلطة الدماغية الحديثة. وان هذه العوامل المختلفة سوف تساعد الأطباء على التعامل الصحيح والدقوق مع هذه الحالات المختلفة وبالتالي علاج مرضى الجلطة الدماغية بصورة أفضل. تقلل من نسبة حدوث تدهور وازداد في نسبة عذر هؤلاء المرضى.