Multiparametric Approach Enhances Detection of Patients with Cerebral TIAs at Risk of Stroke: A Prospective Pilot Case Series

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Abstract

Background—Patients with transient ischemic attack (TIA) are generally clinically unstable, with fear of developing a handicapping stroke. Identification of those at highest and lowest risk of stroke in the first days and weeks after a TIA would allow appropriate use of worthy secondary prevention strategies.

Objective—Incorporation of a clinical scoring system, neurovascular imaging, and magnetic resonance-diffusion-weighted imaging (MR-DWI) to help predicting risk of developing an ischemic stroke following a TIA.

Subjects and methods—A prospective observational study was conducted on 25 patients with TIAs, 64% were females, and 26% were males, with a mean age of 57±10.36. Patients were assessed clinically and an ABCD² score was applied. Patients have undergone diffusion-weighted imaging (DWI), within 24 h from the event, and intra- and extracranial duplex study. Patients were followed up at intervals of one week, three months, six months, and one year.

Results—Six patients (24%) developed stroke on their follow-up, most of them (83.3%) had their strokes within the first three months and had an initial ABCD² score of ≥4. The development of stroke was associated with the presence of significant extra and/or intracranial vessel disease (P=0.006) and the presence of acute lesions on their DWI (P=0.035).

Conclusion—Incorporation of brain MR-DWIs and neurovascular imaging together with the ABCD² score improves prediction of ischemic stroke following TIA.

Keywords
ABCD² score; diffusion weighted image (DWI); neurovascular imaging; stroke risk; transient ischemic attack

INTRODUCTION

Recently, transient ischemic attack (TIA) is defined as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction [1]. In the past, TIAs were operationally defined as any focal cerebral ischemic event with symptoms lasting no more than 24 h [2]. However, this arbitrary time threshold was too broad because 30% to 50% of classically defined TIAs show brain injury on diffusion-weighted magnetic resonance (MR) imaging (MRI). Newer, neuroimaging informed, operational definitions of TIA was proposed as “a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction”[1]. Yet, with rare exceptions [3], the newer definitions have not been fully endorsed [4].

Patients with TIA are generally clinically unstable, with risk of having a stroke within 90 days after a TIA, half within the first two days [5]. Most studies have focused
on the clinical predictors of ischemic stroke following a TIA [6]. Some studies have discussed the implication of neurovascular imaging and the new brain imaging techniques in a separate fashion [7,8]. However, investigating the three parameters together will add new perspectives on prediction of ischemic stroke development after TIAs.

We aimed in this study to investigate the effect of DWI and neurovascular imaging on risk of recurrent TIA and stroke occurrence after TIA.

Another aim of the study is the correlation between the clinical characteristics of TIAs patients in the form of ABCD², neurovascular and brain parenchymal findings.

**SUBJECTS AND METHODS**

**Study design**

A prospective observational, pilot case series

**Study population**

We conducted our study on 25 consecutive transient ischemic attack (TIA) patients referred to Neurology Department, Kasr Al-Aini Hospital (Cairo University) from January 1, 2013 to January 1, 2014. The study was approved by the institutional ethical committee, and all patients provided informed consent.

TIA was defined as acute focal loss of cerebral or retinal functions with a presumed ischemic origin and with the focal neurologic event lasting less than 24 h [9].

All patients who fulfilled this definition with age above 45 years were eligible for inclusion in this study.

We excluded patients with established stroke on initial presentation, or patients with TIA mimics (as space occupying lesions, demyelinating brain diseases, hemiplegic migraine and epilepsy).

On enrollment, a standardized case report form was completed collecting demographic data, vascular risk factors, medical history, and examination findings. Clinical scales as ABCD² score and NIHSS was recorded. All patients underwent a standardized etiologic workup, including standard blood tests, 12-lead ECG, transthoracic echocardiography and Holter ECG when indicated, cervical carotid ultrasonography and transcranial Doppler ultrasonography, computed tomography (CT) scan, and MR-DWI imaging.

Subsequently, all relevant diagnostic testing was recorded, and an assessment of the presumed cause of the TIA and its duration was determined. Patients with clear high-risk features such as ABCD² score of ≥4 or persistent deficits suggestive of stroke defined as acute deficit of focal neurologic function with symptoms lasting more than 24 h, resulting from intracranial vascular ischemia [10] or crescendo TIA, or atrial fibrillation requiring anticoagulation were admitted to the hospital and their care was managed by the hospitalist team.

**Baseline vascular risk factors**

Hypertension (HTN) was defined as blood pressure ≥ 140/90 mmHg for ≥ 2 repeated measurements [11] or subject on anti-hypertensive medications. Diabetes mellitus was defined by repeated fasting plasma glucose ≥126 mg/dl [12] or if the patient is on antidiabetic measures. Dyslipidemia was defined as a history of abnormal lipid profile detected when total cholesterol level >220 mg/dl, HDL < 40 mg/dl, LDL cholesterol > 130 mg/dl, triglycerides > 150 mg/dl [13] or if the subject on lipid-lowering drugs or gave a history of established diagnosis of dyslipidemia. History of cigarette smoking was positive if subjects smoked ≥ 10 cigarette per day for > 10 years. Ischemic heart disease (IHD) was considered as evidenced by ECG, echocardiography, stress test or coronary angiography or if the patient was known to have IHD. History of previous TIAs or ischaemic strokes according to the definitions mentioned previously.

**Clinical scales**

ABCD² score—Determination of ABCD risk score was performed in a manner identical to that reported by the originators of this score. This six-point score incorporates age (>60 years=1 point), blood pressure (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg=1 point), clinical features (unilateral weakness=2 points; speech disturbance without weakness=1 point; other symptoms =0 points), diabetes (= 1point) and duration of symptoms (>60 minutes=2 points; 10 to 59 minutes=1 point; 0-10 minutes=0 points) [14].

NIHSS [15] for those with evident deficit by the time they were seen.

**Imaging:**

**A. Vascular Imaging**—All patients were subjected to Duplex ultrasonography for extra and intracranial vasculature at the Neurovascular Ultrasound Laboratory in the Neurology Department, Cairo University using Phillips HDI 5000 ultrasound equipment, within 24 h from the event.
Extracranial vessels Carotid duplex scanning was performed by qualified vascular operators using Philips HDI 5000 machines. A high-frequency (7–10 MHz) linear array transducer was employed to scan the carotid from the most proximal CCA to the ICA as far as the mandible permitted. The identified parameters and measures named: intima media thickness (IMT), the presence of carotid plaque, degree of carotid stenosis and occlusion. The measures and quantifications of extra-cranial carotid atherosclerosis were performed according to the internationally published data [16].

2. Transcranial color-coded Doppler ultrasonography (TCCS) technique Transcranial color-coded duplex ultrasonography was performed using a 2–4 MHz phased-array transducer through the following bone windows:
   - Temporal window to assess both right and left middle cerebral arteries (MCAs), anterior cerebral arteries (ACAs), posterior cerebral arteries (PCAs) as well as the intracranial part of internal carotid arteries (ICAs).
   - Suboccipital window to assess the basilar artery (BA) and intracranial right and left vertebral arteries (VAs) through the foramen magnum.

Diagnosis of intracranial stenosis interpreted according to the internationally published criteria [17].

B-Brain imaging
1. Computerized tomography (CT) of the brain—Done at presentation, to detect the presence of a recent infarction or the presence of an old one, exclude hemorrhagic stroke, and to confirm ischemic stroke diagnosis, describing infarction site, size, and distribution.

2. Magnetic resonance imaging (MRI) of the brain and diffusion-weighted image (DWI)—Done within the first 24 h. MRI was performed with the use of echo-planar imaging on (General Electric GE profile Excite open magnet, 1.5T). Multislice whole-brain DWI was performed with the following variables: 16 slices; repetition time, 8100 ms; echo time, 110 ms; slice thickness, 5 mm; gap, 2.5 mm; 128_128 matrix; and field of view, 24 cm. B values were 0 and 829 s/mm². Diffusion-weighted images were acquired in the x, y, and z directions and were processed to generate trace apparent diffusion coefficient maps.

MRI scans were read by an independent Neuro-radiologist. A DWI scan was considered positive if the scan revealed an area of hyperintensity on DWI and hypointensity on apparent diffusion coefficient maps relative to the normal brain.

Follow-up and clinical endpoint
Patients were followed for one year from the first event (during the first week, after three months, after six months, and till the end of one year). Clinical outcomes were determined by telephone and/or direct reassessment using a standardized parameters to provide evidence of development of any new vascular events (three clinical endpoints) (recurrent TIAs, stroke, vascular death), doctor visits, hospitalizations, and further treatments initiated since discharge. In addition, we were committed for strict control of all modifiable risk factor.

Statistical methods
Data were described in terms of range, mean ± standard deviation (± SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done by Mann–Whitney U-test for independent samples. For comparing categorical data, Chi square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Spearman rank correlation equation for non-normal variables. A probability value (P value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows

Results:
Base-line characteristics of the study group
The present study included 25 patients with TIAs; 16 (64%) were females. Their ages ranged from 45 to 80 years with a mean age of 57 ± 10.36 years. Hypertension was the main vascular risk factor in 17 (68%) cases.

Clinical characteristics of study participants, ABCD² Scores, Duplex and DWI findings are shown in (Table 1). Eight patients (32%) had their TIAs lasting <10 min, 10 (40%) had TIAs lasting between10 to 60 min, and seven (28%) had attacks lasting > 60 min.

ABCD² score and its relation with imaging studies
Six (24%) patients showed a low risk (0–3); 15(60%) had a moderate risk (4–5); and four (16%) showed high risk (6–7).
Increasing ABCD² scores was marginally associated with increasing grades of stenosis of the intra- and/or extracranial vessels evidenced by duplex examination. However, this difference did not reach statistical significance (P=0.06). Regarding, neuroimaging and the ABCD² scores showed a statistically significant difference in relation to the presence of positive findings on DWIs (P=0.035) (Table 2).

### Results of follow-up

Nine patients (36%) out of 25 developed recurrent TIAs and six patients (24%) developed ischemic stroke during the follow-up period. TIAs recurrence was associated with the presence of acute lesions on DWI (P=0.011), while no significant association was detected in relation to duplex findings (P=0.27) or ABCD² (P=0.6).

Regarding the six patients who developed ischemic stroke during the follow-up period, one patient had his stroke within the first week, four (66.7%) within the first three months and one (16.7%) after six months.

Development of ischemic stroke was not associated with higher ABCD² scores (P=0.27). On the other hand, the presence of high grade >50% stenosis in either extra or intracranial vasculature (P=0.006) and positive DWIs was associated with stroke occurrence (P=0.001) (Figs. 1a and b).

It was noted that the presence of more than one of the studied variables ABCD² ≥4, abnormal extra/intracranial duplex and DWI lesions were associated with stroke occurrence (P=0.016) but not TIA recurrence (Table 3).

### DISCUSSION

The current study shows a clear association between large vessel steno-occlusive disease, positive DWI lesions and the risk of future stroke development in patients with TIAs. Nevertheless, the ABCD² scores alone did not show positive association regarding stroke development.

In this cohort, most patients with high ABCD² (4–5) score had >50% stenosis either in the extra or intracranial vessels. Generally, there was a tendency for patients with higher ABCD² scores to have high grades of steno-
Forty nine years old female patient presented with cerebral TIA, ABCD² score = 6, MRI-DWI showed diffusion restriction at right high parietal area (a); extra-cranial carotid duplex revealed high grade > 50% stenosis at the right internal carotid artery (b).
The relation between large artery atherosclerosis and cerebral ischemia among Egyptians was extensively studied and published [28–31]. Findings from our study proves that the occurrence of stroke was associated with the presence of high grade >50% stenosis in either extra or intracranial vasculature, where five out of six patients who developed stroke had ≥50% stenosis in extra and/or intracranial duplex compared with those who did not develop stroke (3/19) (P=0.006). These findings are consistent with population-based cohorts [32,33] which found that large artery atherosclerosis (LAA) was an independent predictor of early risk of stroke, and in agreement with another study by Purroy et al., [34] showing that TIA patients with LAA had the highest risk of stroke at three months (20% vs. 5.7% in other etiologies); however, the predictor value of intracranial medium and small vessel disease was not addressed. In a study [35] which addressed stroke risk after transient ischemic attack among individuals with symptomatic intracranial artery stenosis, there was a higher 90-day risk of ischemic stroke in the arterial territory affected following TIA 6.9% compared to after stroke 4.7%. It concluded that prompt management of TIA in patients having intracranial stenosis, is recommended.

This points that combining both extra and intracranial vascular imaging may increase the predictive risk of stroke in TIA patients.

In our study, neither TIA recurrence nor stroke development was associated with high ABCD² scores. Although these results stand against other studies [37,38] which found that infarction, particularly on DWI, is associated with high early stroke risk after TIA, which emphasizes the ability of DWI to further identify patients at high early risk of stroke after TIA.

One study compared risk factors for stroke and TIA in patients initially presenting with presumed TIA, it concluded that risk factors for subsequent stroke and recurrent TIA are different. The authors suggested that inclusion of events due to causes other than thromboembolism (e.g., vasospasm) seemed a likely explanation for the difference in risk factor profiles for stroke and recurrent TIA [43]. Moreover, we found no evidence that

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**Table 3. TIA recurrence and stroke development in relation to individual vascular risk factors, ABCD² score, Duplex, and DWI results.**

<table>
<thead>
<tr>
<th>N=25</th>
<th>TIA recurrence</th>
<th>Stroke occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular risk factors</td>
<td>P=0.035</td>
<td>P=0.35</td>
</tr>
<tr>
<td>TIA recurrence</td>
<td>P=0.037</td>
<td>0.065</td>
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<tr>
<td>Occurrence of previous strokes (P=0.037)</td>
<td>P=0.05</td>
<td>P=0.05</td>
</tr>
<tr>
<td>Others</td>
<td>P=0.6</td>
<td>P=0.271</td>
</tr>
<tr>
<td>ABCD² score ≥4</td>
<td>P=0.011</td>
<td>P=0.001 *</td>
</tr>
<tr>
<td>Duplex results showing significant stenosis in extra/intracranial vasculature</td>
<td>P&gt; 0.05</td>
<td>P=0.035</td>
</tr>
<tr>
<td>DWI findings showing: acute lesion (s)</td>
<td>P=0.6</td>
<td>P=0.001 *</td>
</tr>
<tr>
<td>chronic lesion(s)</td>
<td>P&gt; 0.05</td>
<td>P=0.001 *</td>
</tr>
<tr>
<td>The presence of more than one variable</td>
<td>P=0.035</td>
<td>P=0.016 *</td>
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</table>

* Significant finding
those with multiple TIAs were at greater risk of subsequent stroke.

In this study, all the patients who developed stroke six out of 25 had two or more of the three stroke risk predictors: ABCD² score ≥4; significant extra/intracranial vessel disease; and positive DWIs, where five out of six had all the three predictors present together. Compared with patients without stroke where six out of 19 had two or more of the above-mentioned variables while 13 out of 19 had no positive variables (P=0.029). These findings are nearly similar to those of a study by Calvet et al., [23] in which TIA patients systematically underwent DWI-MRI and etiologic investigations, they reported that in addition to the ABCD² score, positive DWI and, to a lesser extent, large artery atherosclerosis (LAA) are independently associated with an increased early risk of stroke after TIA. They reported that patients with an ABCD² score ≥4, DWI lesions, and LAA had the highest early risk of stroke (18% at three months).

Therefore, the summation of those variables which detect vascular lesions as extra and intracranial duplex, DWI and the ABCD² score improves the predictive power of stroke development among patients presenting with TIAs. We find our results highly agree with the best evidence for stroke practice [44].

It is advisable to note that our study results should be taken with caution as it was a small case series and the statistical power to detect the associations was limited. We recommend a large scale multicenter prospective study to confirm our findings.

CONCLUSION

Although it is a small cohort data from our study showed an association between vascular lesions and positive MRI-DWI and prediction of stroke development in patients with symptoms of cerebral transient ischemic attacks, the coexistence of significant burden of large artery steno-occlusive disease, brain parenchymal lesions and high clinical scores in TIAs patients may detect patients at a very high risk for stroke, who could be targeted for more aggressive preventive intervention

REFERENCES


