TIA patients with higher ABCD3-I scores are prone to a higher incidence of intracranial stenosis, unstable carotid plaques and multiple-vessel involvement

Qiujian Yu, PhD
Wei Miao, PhD
Jianhong Han, MD

a Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, China
b Department of Neurology, Second Affiliated Hospital of Kunming Medical University, Kunming Medical University, Kunming, China

Correspondence to: Jianhong Han
E-mail: hanjh2kunyi@163.com

Summary

The ABCD3-I criteria have proved to be effective for use in regular clinical practice to assist in transient ischemic attack (TIA) risk stratification and treatment. In this prospective study we aimed to explore the relationships between risk stratification and arterial stenosis location, carotid plaque morphology and vessel involvement in 90 TIA patients, stratifying risk by ABCD3-I scores. Clinical variables such as total cholesterol, triglyceride, low-density lipoprotein cholesterol, glycosylated hemoglobin, homocysteine and high-sensitive C-reactive protein levels were recorded. The endpoint was subsequent stroke at seven-day follow-up. Ninety patients were divided into three risk groups on the basis of their ABCD3-I scores. The results revealed that patients with higher ABCD3-I scores showed a higher occurrence of intracranial stenosis (P < 0.05), less organized carotid plaques (P < 0.05) and multiple-vessel involvement (P < 0.05).

KEY WORDS: ABCD3-I score, intracranial stenosis, multiple-vessel involvement, transient ischemic attack.

Introduction

The traditional definition of transient ischemic attack (TIA) is time based. A TIA is a transient episode of neurological dysfunction caused by ischemia, which resolves in 24 hours without acute infarction. The scientific committee of the American Heart Association (AHA) proposed a new tissue-based definition of TIA, which emphasized that TIA is caused by an ischemic dysfunction of the focal brain, spinal cord or retina (Easton et al., 2009). TIA is referred to as mini-stroke. In addition, approximately 20% of TIA cases proceed to stroke (Rothwell and Warlow, 2005). Diffusion-weighted magnetic resonance imaging (DWI) is now considered to be an essential and optimal imaging technique for acute brain infarction detection. According to the AHA scientific committee, the finding of abnormalities on DWI scans confirms the presence of some form of brain ischemia. Furthermore, patients with neurological deficiency combined with few lesions on DWI scans have a higher risk of brain stroke than those without DWI abnormalities (Purroy et al., 2011; Prabhakaran et al., 2007).

Traditionally, TIA patients can be evaluated using ABCD scores with different risk stratifications. Age (A), blood pressure (B), clinical manifestation (C), and duration of the symptoms (D) are the classic components of the ABCD score (Tsivgoulis et al., 2006). More recently, however, diabetes, carotid stenosis and the clinical variable “dual TIA” (an earlier transient ischemic attack within in 7 days of the index event), as well as DWI findings, have been integrated into the ABCD scoring method to form a brand-new TIA risk stratification system: the ABCD3-I score (Merwick et al., 2010). An increasing amount of evidence has indicated that the ABCD3-I criteria enhance the predictive and risk classification of TIA patients with or without stroke (Mayer et al., 2018; Kelly et al., 2016). To date, few studies have focused on the type of the arterial lesion or the number of vessels involved in TIA.

This study has a prospective design, and its aim was to investigate the ABCD3-I criteria and their association with the incidence of intracranial and extracranial artery stenosis and different carotid lesion types in 90 TIA patients.

Materials and methods

Patient enrolment

This study was approved by the Committee on Medical Ethics of the Second Affiliated Hospital of Kunming Medical University. Informed consent was obtained from all participants.

Patients from this hospital were enrolled between December 2011 and February 2012. A TIA was defined as a transient episode of neurological deficit associated with an ischemic lesion (caused by focal brain, spinal cord or retinal ischemia) without acute infarction (American Heart Association & American Stroke, 2016). We treated all patients within 48 hours of the onset of symptoms, and excluded patients with a diagnosis other than TIA and/or a modified Rankin Scale score > 3, which...
means patients who still have mild to moderate neurological deficits. All patients were tested for fasting blood total cholesterol (CHO), total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), homocysteine (HCY), and high-sensitive C-reactive protein (CRP) levels.

**ABCD3-I score calculation**

Each patient’s ABCD3-I score (based on their age, blood pressure, clinical manifestations and neuroimaging results) was calculated prospectively within 48 hours of symptom onset. Positive DWI was defined as a DWI scan showing areas of high signal intensity, which represents acute ischemia. All were followed up for seven days to identify those with “dual TIA” as previously described (Kiyohara et al., 2014). Patients were then classified into three stratification groups: low risk (ABCD3-I score: 0-3), medium risk (ABCD3-I score: 4-7), and high risk (ABCD3-I score: 8-13).

**Computed tomography angiography (CTA) scanning**

In all patients, CTA scanning was performed within 72 hours of symptom onset using a Philips Brilliance 256 iCT (Philips Medical Systems, USA). Images were read by at least two radiologists before final reports were agreed and drawn up. According to the location of the arterial stenosis, the CTA results were divided into intracranial vascular stenosis and carotid vascular stenosis. More precisely, arterial stenosis < 50% was defined as mild vascular stenosis, arterial stenosis between 50-69% was defined as moderate vascular stenosis, and arterial stenosis > 70% was defined as severe vascular stenosis.

**Carotid ultrasonography (CUS)**

Carotid ultrasonography has been the preferred imaging technique for screening patients with suspected atherosclerotic cerebrovascular disease since the 1990s. It was performed in the patients within 72 hours of symptom onset using a B-mode ultrasound system (HITACHI HI VISION Avius, Tokyo, Japan). Patients were examined in the supine position with the head slightly extended in the opposite direction to the carotid artery being examined. Each carotid artery and segment was interrogated independently from continuous angles (anterior, lateral and posterior). Carotid intima-media thickness (CIMT) is defined as the distance between the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface. Carotid intimal thickening was deemed to be present if this distance was ≥ 1.0 mm. The entire carotid system was surveyed bilaterally for the presence of plaque, which was defined as a focal structure with a thickness 50% greater than the surrounding CIMT value. More specifically, plaque formations in the carotid artery were defined as soft when the echo within the plaque was lower than the echo of the artery wall, and as calcified when the echo in the plaque was close to or stronger than the echo of the wall (with or without acoustic shadow). The finding of both strong echo and low echo within the plaque denoted the presence of a mixed plaque formation. CUS was also used to determine the degree of carotid stenosis. All ultrasound measurements were performed by two experienced doctors, who were blinded to the CTA results.

**Blood CHO, TG, LDL-C, Hba1c, HCY and CRP levels**

Fasting blood HCY levels in all patients were measured using HPLC (high-performance liquid chromatography) fluoroscopy (Beckman, CA, USA) at a single center. In addition, fasting blood CHO, TG, LDL-C, HbA1c and CRP levels were assessed using an automatic biochemical analyzer (Hitachi 7080, Japan) the day after admission.

**Statistical analysis**

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL). The results were expressed as means ± SEM, except for demographic data (means ± SD). The patients’ blood levels of CHO, LDL-C, TG, HbA1c, HCY and CRP were analyzed in relation to three risk groups: low (ABCD3-I score: 0-3), medium (ABCD3-I score: 4-7) and high (ABCD3-I score: 8-13). The variables CIMT/plaque type, site of stenosis, and vessel involvement were analyzed in relation to two risk groups: low (ABCD3-I score: 0-3) and higher (ABCD3-I score: 4-13). Chi-square test and one-way analysis of variance were used to compare and exclude the interference of sex and age between the different risk groups stratified by ABCD3-I score. Multivariate analysis was used to compare CHO, TG, LDL-C, HbA1c, HCY and CRP levels between the three groups, and then perform all pairwise multiple comparisons. The Mann-Whitney U test was used to compare the numbers of cases with CIMT or the different plaque types detected by CUS, and with intracranial or extracranial stenosis, between the low-risk group and the higher-risk group (medium-risk plus high-risk group). The Kruskal-Wallis H test was used to compare the numbers of cases with single or multiple-vessel involvement between the three risk groups. This was followed by mean rank post-hoc multiple comparisons.

**Results**

**Study participants**

Table I gives detailed demographic data. The TIA patients were divided into three risk groups according to their ABCD3-I scores. Twenty-six patients were assigned to the low-risk group (ABCD3-I score: 0-3), 35 patients were assigned to the medium-risk group (ABCD3-I score: 4-7), and the remaining 29 patients were assigned to the high-risk group (ABCD3-I score: 8-13). Table I also shows the gender, age and CHO, TG, LDL-C, HbA1c, HCY and CRP levels of the patients in the different groups. No differences in gender or age emerged between the three groups (P > 0.05). In addition, no significant differences were found in CHO and LDL-C levels (P > 0.05) (Figure 1a, b). However, the TG,
HbA1c, HCY and CRP levels were found to differ significantly among the three groups (P < 0.05). Specifically, on multiple comparisons, the levels of TG in the high-risk group were significantly higher than those in the low-risk group (3.01 ± 0.85 mmol/L, n = 29 vs 1.80 ± 0.85 mmol/L, n = 26, P < 0.05) (Fig. 1c). The HbA1c levels were considerably augmented in the high-risk group compared with those in the low-risk group (6.08 ± 1.03%, n = 29 vs 5.41 ± 0.61%, n = 26, P < 0.05) (Fig. 1d). Moreover, compared with those in the low-risk group, the HCY levels were significantly higher in both the medium-risk and high-risk groups (11.21 ± 3.40 μmol/L, n = 26 vs 13.99 ± 4.36 μmol/L, n = 35 vs 15.30 ± 7.10 μmol/L, n = 29, P < 0.05) (Fig. 1e). Compared with the levels recorded in the high-risk group, the blood CRP levels were significantly lower in the low-risk and medium-risk groups (0.73 ± 0.95 mg/dL, n = 29 vs 0.20 ± 0.18 mg/dL, n = 26 vs 0.42 ± 0.98 mg/dL, n = 35, P < 0.05) (Figure 1f).

**ABCD3-I stratification and patients with single- or multiple-vessel involvement**

Single-vessel involvement was defined as present in patients who had stenosis of only one artery or CIMT, detected by either CTA orCUS. Instead, patients with stenosis of more than two arteries, detected by CTA or CUS, were considered affected by multiple-vessel involvement. Significant differences in the numbers of patients with single or multiple-vessel involvement were observed between the different ABCD3-I stratifications (P < 0.05). More precisely, more single-vessel involvement was found in the low- and medium-risk groups than in the high-risk group (n = 17 for an ABCD3-I score of 0–3 or n = 20 for an ABCD3-I score of 4–7, vs n = 6 for an ABCD3-I score of 8–13, P < 0.05). By contrast, the incidence of multiple-vessel involvement was significantly higher in the high-risk group than in the low- or medium-risk groups (n = 22 for an ABCD3-I score of 6–13 vs n = 13 for an ABCD3-I score of 0–3 or n = 12 for an ABCD3-I score of 4–7, P < 0.05) (Figure 2c).

**Discussion**

Sometimes called a mini-stroke, TIA is associated with a high risk of early stroke, with the incidence of stroke following TIA reported to be as high as 10–13% in epidemiological studies (Rothwell et al., 2005). Early diagnosis and treatment of TIA allow prompt intervention designed to prevent stroke and related conditions. TIA is also a vital marker for predicting events such as coronary disorders, cognitive impairment and stroke recurrence (Yang et al., 2010; Touze et al., 2005; Takahashi et al., 2009).
Stroke risk after TIA can be accurately predicted using clinical prediction scores such as the California and ABCD scores (ABCD, ABCD2, ABCD3 and ABCD3-I). More precisely, the ABCD2 score was shown to have good validity for stroke prediction 2, 7, 28 and 90 days after TIA in a study of 2,654 TIA patients (Merwick et al., 2010). The ABCD3-I score has been found to improve the predictive and risk classification of TIA patients with and without stroke. Recently measured in an independent validation sample of 5,273 patients from multiple stroke units, the ABCD3-I score was found to be highly predictive, with clinical presentation (C), symptom duration (D), and cerebral and carotid imaging (I) found to account for the information provided by the full scores (Knoflach et al., 2016).

The ABCD3-I score has a number of advantages; for example, it can be successfully validated, is easy to apply, and is likely to improve risk stratification after TIA, especially in secondary care settings. However, few studies of TIA patients have considered the type and location of the arterial lesion, and the number of vessels involved. Therefore, in this study, we explored these aspects, and also the results of multiple relevant blood tests.
In terms of the relationship between blood lipid levels and ABCD3-I score, the results of this cohort study of 90 patients with TIA show that TG is an independent risk factor associated with ABCD3-I stratification. An increasing amount of evidence has suggested that reducing blood lipid levels might prevent the occurrence of ischemic complications of TIA or carotid artery stenosis. Long and Yao (2016), in a study of 70 TIA patients, found that by monitoring and modulating their blood lipid indices, such as HDL-C, LDL-C and TG, with simvastatin, the incidence of cardiovascular events decreased considerably compared with that observed in controls (Long and Yao, 2016). This research followed experimental work by Takayama et al. (2014), who found that administration of a preoperative statin allowed patients’ LDL-C levels to be kept steady and controlled; this was found to be a significant therapy for reducing carotid artery stenosis-induced ischemic injuries (Takayama et al. 2014). In conclusion, blood lipid levels, especially of TG (but not LDL-C and CHO), may contribute to the occurrence of TIA and the stratification of a new score.

In this study, we observed a significantly higher HCY level in patients in the ABCD3-I-based high-risk versus low-risk group. It is commonly accepted that raised HCY is a risk factor for stroke (Sacco et al., 2004). The effect of HCY on endothelial dysfunction has been shown to be the mechanism by which it increases the risk of stroke (Hassan et al., 2004). More specifically, HCY may directly lead to an endothelial inflammatory response, which may result in endothelial damage via both atherogenic and prothrombotic pathways (Dardik et al., 2000). After measuring HCY levels in 307 hospitalized stroke or TIA patients, Sen et al. (2010) proposed a positive correlation between HCY and the occurrence of stroke or TIA, because HCY can accelerate the development of aortic arch atheroma (Sen et al., 2010). Another study focused on young patients (less than 55 years old) with stroke/TIA, and showed HCY to be a risk factor associated with vascular damage possibly mediated by elevated blood pressure (Sobol et al., 2005). HbA1c levels, which indicate the previous 2-3 months’ glucose levels, are regularly obtained as a marker of chronic hyperglycemia in the evaluation of known diabetic patients. In addition, the American Diabetes Association (2014) has recommended HbA1c measurement for the diagnosis of (pre)diabetes. On the basis of combined assessment of fasting plasma glucose, 2-hour postload glucose and HbA1c levels in TIA, stroke and intracerebral hemorrhage individuals, Fonville et al. (2013) performed a prospective study, and found that patients with increased HbA1c have a higher incidence of TIA or stroke (Fonville et al. 2013). In the present study, we found considerably increased HbA1c levels in the high-risk patient group compared with the low-risk group. This result supports the idea that HbA1c levels might be an independent risk factor for TIA. As an inflammatory mediator, CRP has been shown to be a sensitive predictor associated with cerebral ischemia. A case-control study found a dramatically higher level of CRP in TIA patients than in controls (Martinic-Popovic et al., 2014). Moreover, Corso et al. (2011) evaluated routine CRP levels in 194 TIA individuals and concluded that CRP assessment combined with ABCD2 score might be of greater benefit for predicting a higher risk of post-TIA ischemic stroke than ABCD2 evaluation alone (Corso et al., 2011). In the present study, we found a positive correlation between CRP and ABCD3-I score stratification.

In this study, CTA and CUS were used as two common approaches for the further assessment of TIA patients. The results demonstrated a higher incidence of intracranial stenosis and soft plaque formation in the group defined, by ABCD3-I score, to be at higher risk. In addition, multiple-vessel involvement was also greater than single-vessel involvement in the high-risk group. There are numerous case reports of arterial lesions in TIA or stroke; however, few cases have been correlated with intracranial stenosis. An investigation of 359 patients from two prospective studies has established that intracranial stenosis is a convincing independent indicator of stroke recurrence when patients are followed up for 90 days (33% risk of individuals with intracranial stenosis and 16.2% risk of those with extracranial stenosis) (Gulli et al., 2013). TIA patients with atherogenic dyslipidemia, such as reduced HDL-C and increased TG levels, showed a higher prevalence of intracranial stenosis and a high incidence of stroke recurrence (Sirimarco et al., 2011). These outcomes were very similar to our findings in this study, and we suggest that intracranial artery stenosis might be an independent contributor to TIA in the high-risk group stratified by ABCD3-I score.

Carotid ultrasonography provides details about morphological plaque formations in the carotid artery. In this study, we demonstrated that patients with higher risk, indicated by ABCD3-I score stratification, are prone to have a higher incidence of morphologically less-orga-

Table II - Numbers of patients with CIMT and different plaque types, stratified by ABCD3-I score.

<table>
<thead>
<tr>
<th>ABCD3-I score</th>
<th>CIMT n (%)</th>
<th>Soft plaque n (%)</th>
<th>Calcified plaque n (%)</th>
<th>Mixed plaque n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 (n=20)</td>
<td>9 (45.00)</td>
<td>5 (25.00)</td>
<td>5 (25.00)</td>
<td>1 (5.00)</td>
</tr>
<tr>
<td>4-13 (n=64)</td>
<td>13 (20.31)</td>
<td>22 (34.38)</td>
<td>15 (23.44)</td>
<td>14 (21.88)</td>
</tr>
</tbody>
</table>

Abbreviations: CIMT= carotid intima-media thickness; CUS=carotid ultrasonography

Table III - Numbers of patients with intracranial and extracranial stenosis, stratified by ABCD3-I score.

<table>
<thead>
<tr>
<th>ABCD3-I score</th>
<th>Intracranial stenosis n (%)</th>
<th>Extracranial stenosis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 (n=12)</td>
<td>5 (41.67)</td>
<td>7 (58.33)</td>
</tr>
<tr>
<td>4-13 (n=65)</td>
<td>49 (75.38)</td>
<td>16 (24.62)</td>
</tr>
</tbody>
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Abbreviation: CTA= computed tomography angiography
nized (soft) plaques. The same result was found by O’Holleran et al., who recruited 293 asymptomatic individuals and followed them for 46 months. They reached the conclusion that participants with morphologically soft plaques had the highest risk of TIA or stroke (O’Holleran et al., 1987). In a cross-sectional study, Gupta and colleagues (2014) found an apparent connection between soft plaque formation and ipsilateral ischemic events. Furthermore, they discovered that with every 1-mm increase in plaque thickness, there was a 2.7-fold increase in ischemic disease (Gupta et al., 2014).

Few studies have focused on the number of injured vessels involved in TIA or ischemic stroke processes. In the present study, we found that 46.81% of ABCD3-I-stratified high-risk patients had multiple-vessel involvement detected by CTA and CUS. This result was very similar to that reported by Pratap and Mafauzy (1993), who, using continuous-wave Doppler ultrasonography detection, found that 48% of recruited stroke patients showed multiple-vessel involvement (Pratap and Mafauzy 1993).

In summary, our results showed, first of all, that blood TG, HCY, CRP and HbA1c levels are four independent risk factors for TIA and are associated with risk stratifications based on ABCD3-I score. Importantly, patients in the higher-risk group stratified by ABCD3-I score have a higher incidence of intracranial artery stenosis, as well as morphologically less-organized plaque formations. Finally, we found that multiple-vessel involvement is a critical factor in TIA patients. Several aspects of our study could be improved: its follow-up duration (endpoint) was short, making further follow-up necessary in
order to better predict the prognosis of TIA after ABCD3-I assessment. Additionally, more subjects could be enrolled to increase the sample size, and thus lessen the bias between different risk groups. In conclusion, we explored multiple independent factors that are related to TIA using ABCD3-I assessment. It is worth noting that this study might provide a novel combination of factors for a new score for TIA patients.

References


