Journal of Neurological Sciences [Turkish] **33:(3)**# 50; 473-481, 2016
http://www.jns.dergisi.org/text.php3?id=993
Research Article

An Evaluation of ABCD² Scores, Atrial Fibrillation, Serum CRP, Fibrinogen and D-Dimer Levels as Diagnostic Predictors for Stroke In Patients Admitted to Emergency Department with the Diagnosis of Transient Ischemic Attack

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Summary

Introduction: This study aimed to define the roles of ABCD² score as well as other diagnostic parameters such as the presence of AF, serum fibrinogen, D-dimer and CRP levels as diagnostic predictors to determine the risk of stroke in patients diagnosed with TIA.
Materials and Methods: We performed a prospective study of 70 patients who were admitted to the emergency department at Ankara Training and Research Hospital with a diagnosis of TIA. Patients demographic data and vital signs were calculated and scores with ABCD². The blood samples for measuring CRP, D dimer and fibrinogen levels were collected. Patients were interviewed by telephone and stroke prognosis was learned after 3 months.
Results: Dysphasia (45%) and weakness (40%) were the most common presenting symptom. 52.9% of patients had moderate risk, and 12.9% had high stroke recurrence risk. 14.3% of patients have had a stroke within 3 months. AF has been detected of 10% (n:7) of all the patients and five of the seven (71.4%) patients with AF developed stroke ($p<0.05$). Only the CRP was targeted as possible blood predictors of stroke recurrence in TIA ($p=0.008$).
Conclusion: Our findings provide evidence that the ABCD² score may predict the recurrence of TIA and likelihood of having stroke after the diagnosis of TIA. Although the presence of AF, CRP, fibrinogen and D-dimer levels may be used in the diagnosis of stroke or TIA, combining the presence of AF and high-CRP levels can enhance the predictive value of ABCD² score to determine the risk of stroke.

Key words: TIA, ABCD², CRP, Fibrinogen, D-Dimer

Acil Servise Başvuran Geçici İskemik Atak (GİA) Tanısı Alan Hastalarda ABCD² Skorları İle Kan CRP, Fibrinojen, D-Dimer Düzeylerinin İnme Gelişme Riski Açısından Karşılaştırılması

Özet

Giriş: İnme için en önemli risk faktörlerinden biri de geçici iskemik ataklardır (GİA). Bu çalışma ile ABCD² skoru , koagülasyon belirteçleri yanı sıra atriyal fibrilasyon (AF) varlığını kullanarak GİA hastalarında erken dönemde inme riskini hesaplanamak amaçlanmıştır.
Materyal ve Metod: Ankara Eğitim ve Araştırma Hastanesi Acil Servise başvuran, GİA tanısı almış ve katılım için onam veren 70 ardışık hasta çalışmaya alındı. Hastaların anamnez, fizik muayene ve vital bulguları ile ABCD² skorları hesaplandı. Hastaların acil servis içinde tetkik ve tedavileri devam ederken CRP, fibrinojen, D-Dimer düzeyleri için kan alındı. Hastaların inme geçirip geçirmedikleri 3 ay sonra telefonla aranarak öğrenildi.

Bulgular: Konuşma bozukluğu (%45) ve güç kaybı (%40) en sık saptanan semptomlardı. İnme gelişme riski hastaların %52.9' unda orta iken, %12.9'unda yüksek saptandı. 3 ay içinde hastaların %14.3' ünde inme gelişti. Hastaların tamamı ele alındığın %10 (n:7)' unda AF saptandı ve bu AF saptanan yedi hastanın beşinde (%71.4) inme gelişti ($p<0.05$). Serum belirteçlerinden sadece CRP markerının inme geçirme durumuyla ilişkisi bulundu. ($p=0.008$).
Sonuç: Bulgularımız ABCD² skorlamasının GİA tanısı alanlarda; GİA tekrarı ve inme gelişme riski hakkında tahmin edilebilir kanıtlar sunduğu yönündedir. AF ve yüksek CRP, fibrinojen ve D-dimer seviyelerinin varlığı, inme veya GİA tanılarında kullanılabilmesine rağmen çalışmamızda sadece AF ve yüksek CRP seviyelerinin birlikteliğinin ABCD² skorunun prediktif değerini artırdığını göstermesine rağmen daha fazla çalışmalar ile bu bulguların teyid edilmesi gereklidir.

Anahtar Kelimeler: GİA, ABCD², CRP, Fibrinojen, D-Dimer

INTRODUCTION

Transient ischaemic attack (TIA) is defined as transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia without the evidence of acute stroke[11]. TIA has been regarded as a significant independent risk factor and the most useful warning sign of acute stroke[13,29]. The stroke risk within the first 3 months following TIA has been reported as 10-15%, and half of this occurring within the first 48 hours[17].

ABCD and ABCD² scores were developed to determine the risk of acute stroke among patients following the diagnosis of TIA[3,6,12,22,28,33,36]. However in clinical practice their role can be limited as diagnostic predictors. Some studies suggest using these tools in conjunction with other diagnostic facilities such as coagulation markers and magnetic resonance in order to enhance their diagnostic role[3,6,36].

C-reactive protein (CRP) leads to increased production of several adhesion molecules by activating the complement system[20,24,26]. Fibrinogen is the substrate of fibrin which is the end product of the complement system, whereas D-dimer is a parameter that indicates fibrin degradation[21,39]. Prior studies have shown that levels of D-dimer and CRP are increased in patients with acute stroke, particularly in patients with confirmed TIA compared to matched control subjects[8,20,23].

In our study we aimed to define the roles of ABCD² score as well as other diagnostic parameters such as the presence of AF, serum fibrinogen, D-dimer and CRP levels as diagnostic predictors to determine the risk of stroke in patients diagnosed with TIA.

MATERIAL AND METHODS

We performed a prospective study of 70 patients who were admitted to the emergency department at Ankara Training and Research Hospital with a diagnosis of TIA between January 1, 2010 and December 31, 2010. The approval of the Ethics Committee was obtained.

We included patients over 18 years of age, who were admitted to the emergency department within 24 hours from the onset of symptoms. Patients with symptoms lasting longer than 24 hours and who were pregnant were excluded. Informed consent was obtained from all patients. The patients who were prediagnosed with TIA were consulted with the neurology clinic, and those who were diagnosed with TIA by the neurology clinic were included in the study.

The blood samples were collected within two hours following the diagnosis. Serum CRP, D-dimer and fibrinogen levels were performed. Blood samples (4cc) were drawn into standard 0.5 ml tubes (Greiner

Bio-One, Germany) with 0.109 M tri-sodium citrate solution, and the plasma was separated by centrifugation at 3000 rpm for 10 minutes. Plasma was stored at -80^{0}C until the tests were done. Coagulation tests were performed using an ACL TOP device (Beckman Coulter, USA) calibrated on a daily basis, using well-matched kits. DD and fibrinogen values of the patients were evaluated using these devices. Even though the normal ranges of these values change with age, we have taken 180-320 mg/dL for fibrinogen and 0-253 ng/ml for DD as normal range. The blood samples used for CRP measurement were centrifuged at 1500-2000 rpm for 10 minutes. Then, the strained serum was analysed in an Afinion AS100 blood analyser (Oslo Norway) with appropriate kits. The reference range for CRP taken as 0-0.8 mg/DL.

All the patients had follow up visit at 3 months after the diagnosis of TIA. Clinical and radiological evaluation was carried out in neurology outpatient department in order to determine whether strokes have occurred. At this stage patients who failed to attend the follow up visit, who passed away within this 3 months period and patients whose records were not available were excluded from the analysis.

We used SPSS 16.0 software for data analysis. Descriptive statistics were performed to examine demographics and baseline characteristics. Man-Whitney U test was used to compare the stroke vs non-stroke group. Categorical variables were assessed using Fisher's exact and Pearson's test. ROC curve was used for calculating appropriate cut-off values. A value of $P < 0.05$ was accepted as statistically significant.

RESULTS

We identified seventy patients between January 1, 2010 and December 31, 2010. Thirty four (48.6%) patients were female with median age of 58 years (range: 18-91). Demographic and baseline characteristics are shown in Table 2. The ABCD² scores of the patients are shown in Table 1.

Dysphasia (45%) and weakness (40%) were the most common presenting symptoms (Table 2). Ten (14.3%) patients were diagnosed with stroke according to WHO definition. D-dimer was positive in 42.9% of the patients with median value of 0.5 (IQR: 0.91); CRP was positive in 31.4% of the patients with median value of 310 (IQR: 154) and fibrinogen was positive in 64.3% of the patients with median value of 285 (IQR: 233) (Table 2).

In patients with a diagnosis of stroke median ABCD² score was 4.5, the median D-dimer, CRP and fibrinogen levels were 314 ng/ml, 7.68 mg/dl and 295 mg/dL respectively. In patients without the diagnosis of stroke the median ABCD² score was 4, the median D-dimer, CRP and fibrinogen levels were 274 ng/ml, 0,5 mg/dl and 310 mg/dL respectively. ABCD² score and CRP levels were significantly higher in patients with a diagnosis of stroke ($p < 0.05$) (Table 3). Five out of seven (71.4%) patients with AF developed stroke ($p<0.05$) (Table 3).

Regarding the parameters which increase significantly in stroke, the cut off value for ABCD² was 5.5 with a sensitivity of 40%, and specificity of 96.7%; the cut off value for CRP was 4.225 with a sensitivity of 70% and specificity of 96.7%; sensitivity of AF was %71.4, and specificity was %92.1 (Figure 1, Table 4).

Table 1: The ABCD² scores

ABCD²	Age > 60 years	1
	Blood pressure increase (systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg)	1
	Unilateral weakness	2
	Speech impairment without weakness	1
	Duration of TIA (>10 -59 minutes)	1
	Duration of TIA (≥ 60 minutes)	2
	History of Diabetes	1

low risk: 0-3, high risk: ≥ 4

Table 2: Demographic informations related to the medical histories of the patients Patient Characteristics

(n = 70)

Age, (mean ± standard deviation)	58.9 ± 17.2
Systolic blood pressure, mm Hg (ort ± ss)	137.8 ± 22.8
Diastolic blood pressure, mm Hg (ort ± ss)	79.3 ± 11.5
Pulse	83.09 ± 10.35
Hypertension, n (%)	37 (52.9%)
Diabetes, n (%)	19 (27.1%)
Coronary artery disease, n (%)	12 (18.6%)
Clinical characteristics of symptoms, n (%):	
Dysphasia	32 (45%)
Weakness	28 (40%)
Amaurosis	10 (14.3%)
Facial paralysis	7 (10%)
Symptom duration, n (%):	
0-10 min	20 (28.6%)
10-59 min	23 (32.9%)
60 min and over	27 (38.6%)
D-dimer positive rate, n(%)	30 (42.9%)
CRP positive rate, n(%)	22 (31.4%)
Fibrinogen positive rate, n(%)	45 (64.3%)
D-dimer, median (IQR*)	0.5 (0.91)
CRP, median (IQR)	310 (154)
Fibrinogen, median (IQR)	285 (233)

*IQR: interquartile range

Table 3: Stroke of patients within 3 months a comparison of the value of ABCD², D-dimer, fibrinogen and CRP levels

		Experienced stroke Median (İQR)	Not experienced stroke Median (İQR)	P
ABCD²		4.5 (2)	4 (2)	0.015*
D-DIMER		314 (608)	274(235)	0.237*
FIBRINOGEN		295 (289)	310 (155)	0.620*
CRP		7.68 (17.25)	0.5 (0.41)	0.004*
AF	Yes, n(%)	5 (71.4%)	2 (28.6%)	
	No, n(%)	58 (92.1%)	5 (7.9%)	<0.001**

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Table 4: Cut-off patients, AUC values of Sensitivity and Specificity

	Cut-off	AUC	Sensitivity	Specificity
ABCD²	5.5	0.736	40	91.7
D-DIMER	305	0.618	60	56.7
FIBRINOGEN	349.5	0.549	50	71.7
CRP	4.225	0.788	70	967
AF			71.4	92.1

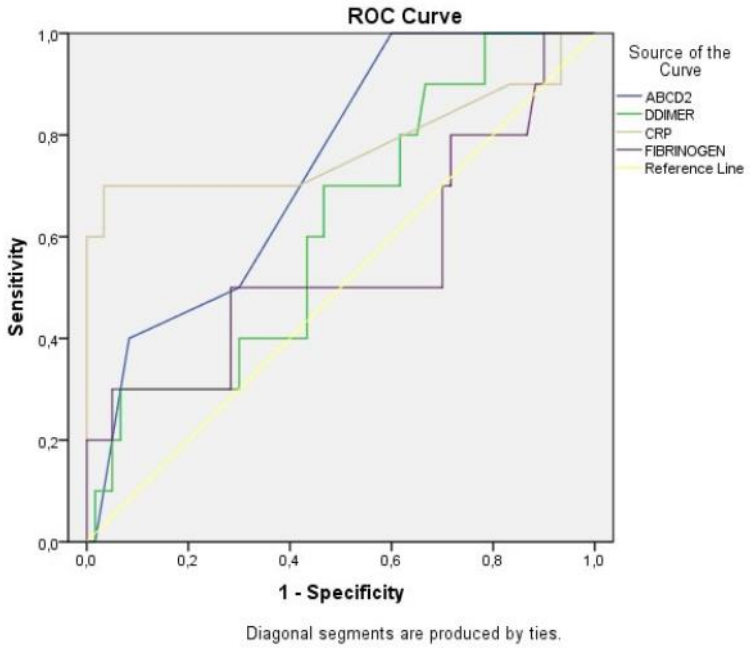

Figure 1: *Cut-off patients, AUC ROC curve of Sensitivity and Specificity values*

DISCUSSION

Early diagnosis of TIA can be challenging. Patients with migraine, seizure, syncope, subdural haematoma, intoxications, brain tumours and hypoglycemia can also present with similar symptoms[4,15,19,25]. Wu et al reported early risk of stroke in patients with TIA as 4% within two days, 8% in 30 days, and 9% for in 90 days[40]. In their prospective study, Giles et al reported the incidence of stroke as 11% within 7 days in patients with a diagnosis of TIA[16]. In our study we observed 14.3% risk of stroke in patients with a diagnosis of TIA. The difference in rates may vary mainly due to the difference in patients background such as presence of co-morbidities and AF and prescribed medications.

The use of some highly sensitive and specific parameters can guide clinicians in the diagnosis of cerebral ischaemia and also provide information on future risk of stroke[40]. ABCD score was first described in 2005, and subsequently modified to ABCD^2 including diabetes as a significant risk factor. ABCD^2 is a simple and efficient score that includes the main clinical features and risk factors of TIA and has been validated for prediction of short-term risk of ischaemic stroke after TIA[12,22,28,33]. The ABCD^2 score is a seven point summation of independently risk factors to predict the risk of stroke. These factors include age, clinical features such as motor impairment and speech disturbance, duration of symptoms, history of diabetes and hypertension. The rule identifies three strata of stroke risk after TIA; low risk (0–3 points), moderate risk (4–5 points) and high risk (6–7 points)[16]. Patients with a high score are classified as having high risk for early stroke[1,14,16]. Johnston et al. reported that the risk of developing stroke can be predicted by ABCD^2 in patients diagnosed with TIA[16]. In our study, which is consistent with the literature, we have also found that the risk of developing stroke increases as the ABCD^2 score. We think that the high value of AUC and high specificity of ABCD^2 supports its use in predicting the risk of developing stroke.

Biomarkers can be used in determining the existence of unstable atherosclerotic plaques and in risk classification[30]. CRP is a typical acute-phase protein, widely present in the serum and other body fluids and also significantly increases 100 times or more in cases of tissue injury, infection or inflammation[20,26]. It is also reported to be a potent predictor of vascular ischaemic events[30,32] and recurrence of these events[10,31]. This marker is released from the atherosclerotic plaque during the inflammatory activation in atherothrombotic diseases and has been shown to have direct role in atherogenesis[18]. It has been proven that CRP levels may also increase due to cerebral ischaemia and secondary complications after stroke[2]. CRP has been reported to be useful as a marker for inflammatory events in atherosclerotic events[38]. It has also been suggested to be useful in classification of risk in vascular diseases[20,26,27]. Although CRP has been found to be correlated with recurrent vascular diseases and high mortality rates, varying CRP levels have been measured in different studies[2,20,26,27,38,41]. In our study we found that CRP levels were high in 31.4% of the patients who developed TIA and CRP levels were higher in patients who developed stroke after the diagnosis of TIA when compared to the patients without the diagnosis of stroke in three months period. In addition, we think that the similarity of AUC value and specificity of CRP with ABCD^2 score suggest that it can be used in predicting the development of stroke in patients with TIA.

Fibrinogen is another acute phase reactant but leads to a lower level of acute phase response when compared to CRP and other reactants[20]. Several large-sample prospective studies[7,34] have shown that

people with high levels of fibrinogen have higher risk of stroke than those with low levels. It has been reported that fibrinogen levels have been found higher in atherothrombotic stroke patients when compared to cardioembolic stroke patients[37]. Increase of fibrinogen levels are associated with advancement of carotid stenosis and small vessel differentiations in brain imaging[7,34,37]. Dutch reported that the risk of stroke is increased in patients with fibrinogen levels above 3 g/dl, but they did not find a statistically significant relationship between fibrinogen levels and stroke[35]. In our study we found that fibrinogen levels were high in 64.3% of the patients who developed TIA but we did not observed any relationship between fibrinogen and development of stroke after the diagnosis of TIA. Although the availability of fibrinogen in predicting ischaemic stroke is unclear we suggest that it may be used in stratifying clinical conditions in terms of vascular risk.

Some observational studies have shown that D-dimer has significantly increased in stroke patients compared with healthy controls[21,39]. It has been reported D-dimer increases in vascular pathologies, especially in patients with acute stroke and TIA[21,23,39]. In our study, we observed high D-dimer levels in 42.9% of the patients, however we found no significant relationship between D-dimer levels and development of stroke. Therefore, we think it's usage as a predictor is still unclear.

AF has been used as a tool in predicting long term risk of stroke especially in patients with TIA[9]. In our study 10% of the patients had electrocardiogram proven AF. The Heparin in Acute Embolic Stroke Trial has shown that low molecular weight heparins decrease the risk of stroke in patients with TIA with AF[5]. In our study the risk of developing stroke was significantly higher in patients with AF. Our result suggests that including AF to ABCD² score may ensure a stronger predictive value.

Our findings provide evidence that the ABCD² score may predict the recurrence of TIA and likelihood of having stroke after the diagnosis of TIA. Although the presence of AF, CRP, fibrinogen and D-dimer levels may be used in the diagnosis of stroke or TIA, combining the presence of AF and CRP levels can enhance the predictive value of ABCD² score to determine the risk of stroke.

Limitations

Limitations of our study should be mentioned. The relatively small number of patients enrolled in our study but results can substantially influence the overall approach to patients with new diagnosis of TIA. Although all the study participants had CT brain performed which showed no acute abnormality, only half of the participants had diffusion weighted imaging (DWI) as the recruitment was done in emergency department. This is one of the most important limitation of our study as positive DWI lesions are one of the major predictors of recurrence following TIA[29]. Further studies involving bigger sample sizes are needed to confirm the predictive role of these diagnostic tools.

Conflict of Interest

The authors declare that there are no potential conflicts of interest

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Received by: 24 January 2016
Revised by: 06 August 2016
Accepted: 20 September 2016

The Online Journal of Neurological Sciences (Turkish) 1984-2016
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

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