

Original Article

The Diagnostic Value of Stweak in Acute Ischemic Stroke

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Background: Considering the critical role of early diagnosis and management of acute ischemic stroke (AIS), there is still a need for biomarkers that would reliably assist. The expected features of a reliable stroke biomarker should include rapid analysis, high specificity for brain damage, and availability in the emergency settings for early diagnosis as well as exclusion from other conditions that mimic AIS. Being a protein involved in the regulation of several biological functions, soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) could be a potential biomarker of AIS.

Aims: This study aimed to investigate the diagnostic value of sTWEAK in AIS patients, and to examine the relationship between ischemic area volume (IAV) determined at Diffusion-Weighted Magnetic Resonance Imaging (DWI) and sTWEAK.

Study Design: Prospective, case-control study.

Methods: Participants of this case-control prospective study were AIS patients and healthy volunteers. Information on age, sex, presence of chronic disease, neurological examination findings, times of presentation to the emergency department after AIS, sTWEAK levels, IAVs at DWI, and 6-month mortality rates after stroke were recorded. The results were analyzed on SPSS 22.0 software, and p values < 0.05 were considered as statistically significant.

Results: Thirty-six patients with AIS and 36 healthy volunteers were included in the study. A sTWEAK cut-off value of 995.5 pg/ml exhibited sensitivity of 80.5% and a positive predictive value of 82.5% with Area Under Curve: 0.84 (95% CI: 0.74-0.94; p < 0.001). The

mean sTWEAK levels were significantly higher in the AIS group ($1968.08 \pm 1441.99 \mu\text{g/L}$) than the control group ($704.81 \pm 291.72 \mu\text{g/L}$) ($p < 0.001$). No correlation was observed between sTWEAK levels, and IAV measured at DWI ($r: -0.008$; $p = 0.07$). The mean IAV was $505.68 \pm 381.10 \text{ mm}^3$ in the non-surviving patients and $60.96 \pm 80.89 \text{ mm}^3$ in the surviving patients ($p = 0.002$).

Conclusion: sTWEAK can be used in the diagnosis of AIS. However, it is inconclusive in estimating IAV and early mortality following AIS. IAV measured at DWI is a marker of poor prognosis and can be used in predicting early mortality.

INTRODUCTION

Stroke with its two types (ischemic or hemorrhagic) is the second leading cause of mortality and the principal cause of long-term disability worldwide (1). The majority of strokes are acute ischemic stroke (AIS). Stroke is generally presented with a sudden onset of acute neurologic symptoms. Early diagnosis at admission and prompt restoration of normal blood flow are the key elements that determine the course of stroke patients (2). Cranial and neurovascular imaging is mandatory for the confirmation of preliminary diagnosis and the selection of appropriate treatment strategies. The first step of current imaging practice for stroke is non-contrast Computed Tomography (CT) of the head (3). It can be beneficial in detecting ischemic stroke changes besides having an almost excellent accuracy for hemorrhagic stroke. Unfortunately, it is not very sensitive for minor ischemic strokes. On the other hand, Diffusion-Weighted Magnetic Resonance Imaging (DWI) can detect ischemic changes in the brain within minutes and show even small infarct areas (4, 5). Therefore, it is more precise than CT for detecting the exact boundaries of an ischemic area volume (IAV) and for the follow-up process.

Soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) is a growth regulator protein with weak apoptotic activity and a member of the tumor necrosis factor- α family. sTWEAK is involved in the regulation of several biological functions, including inflammatory cytokine release, cell growth, and angiogenesis induction, and particularly the stimulation of apoptosis (6). Fibroblast growth factor-inducible 14 (Fn14) is a type 1 transmembrane protein with a physiological affinity for sTWEAK, and it has been described as an sTWEAK receptor (7). Studies have shown that the protein sTWEAK and the receptor Fn14 are found in heart, kidney, endothelial and blood cells, as well as in astrocyte, microglial cells, and neurons of the central nervous system (8-11). Inta et al. showed that AIS patients had high levels of sTWEAK (11). However, no correlation was found between sTWEAK and IAV during acute stroke in a recent study (12).

The present study aims to determine sTWEAK levels in patients with AIS, to evaluate the relationship with IAV determined at DWI, and to investigate the early predictive value of sTWEAK for the prognosis of AIS.

MATERIALS AND METHODS

Study design

The prospective case-control study was conducted after the local institutional review board approval (No:2015-20/07). The patients with AIS with an onset time of stroke symptoms not exceeding 12 hours, presenting to the Emergency Department (ED) of the institution between 1 March 2016 and 1 January 2017, were included. The written informed consent forms were obtained from the patients.

Demographic data of the patients (age, sex, history, presence of chronic disease, and medications used), admission Glasgow Coma Scale (GCS), admission modified Rankin Scale (mRS) scores, laboratory results, sTWEAK levels, admission IAV at DWI and 6-month mRS were recorded. Only age, sex, and sTWEAK levels were recorded in the sex and age-matched control group.

Subjects with a history of stroke, disease capable of affecting sTWEAK levels (acute myocardial infarction, kidney, liver or heart failure), aged under 18 years or declining to take part, were excluded from the study. The exclusion criteria for the study group were also used for the control group.

The mortality and morbidity outcomes were classified as asymptomatic (mRS score of 0), mild sequela (mRS score of 1-2), moderate/severe sequela (mRS score of 3-5), and death (mRS score of 6) due to 6-month mRS (180 days) following hospital discharge. The patients were followed-up prospectively by face-to-face or telephone interviews.

Biochemical analysis

First, 10 cc blood specimens were collected and placed into biochemistry tubes. These were centrifuged for 6 min at 5000 rpm for serum separation. The sera obtained were then placed into Eppendorf tubes and stored at -80°C . The specimens were subsequently thawed simultaneously at room temperature when required for biochemical investigation. sTWEAK measurement was subsequently performed from serum specimens using a "Human TNFSF12/sTWEAK ELISA kit" (Boster Biological Technology, Pleasanton CA, USA) in line with the manufacturer's instructions. The results were expressed as "pg/ml". The Human TNFSF12/sTWEAK ELISA kit measurement range was 62.5-10000 pg/ml, sensitivity was < 10 pg/ml, intra-assay CV value was 5.4%, and inter-assay CV value was 6.4%.

Diffusion-Weighted Magnetic Resonance Imaging (DWI)

DWI was applied to patients presenting to the ED due to stroke within the first 12 hours of arrival using a 1.5 Tesla Philips Achieva (Philips Medical Systems, Best, Netherlands) device (with a b value of 0 and 1000 s/mm^2). Sequence duration was set at 43 sec. DWI sequence parameters were TR/TE, 7216/122.8; flip angle, 90° ; FOV 24×24 cm and matrix dimension 128×128 mm. Section thickness during imaging was 5 mm, the intersection interval was 1 mm, and an average of 20-24 axial sections was obtained from each participant. DWI images were evaluated by the same two radiologists, and IAV calculations were done according to the modified ellipsoid method developed by Sims et al. (13).

Statistical analysis

SPSS for Windows 25.0 (SPSS Inc., Chicago, IL, USA) software was employed for data analysis. Descriptive statistics were expressed as mean \pm standard deviation (SD). Power analysis was conducted for the independent groups by using t-test (Student's t-test; i.e., the parametric alternative of Mann-Whitney U test) in order to determine the sample size before the study. Results indicated that the study should be carried out with 72 subjects, with medium effect size, %80 power and a significance level of 0.05. Pearson's Chi-square and Fisher's exact were used in the analysis of categorical variables. Mann-Whitney U test was applied to assess the significant difference between two independent groups in case of non-normally distributed data. Correlations between variables were evaluated using Spearman's rho correlation analysis. sTWEAK sensitivity, specificity, positive and negative predictive values, and usefulness in the diagnosis of stroke and early prognosis were evaluated using ROC curve analysis. An error probability of 5% ($p < 0.05$) was regarded as statistically significant.

RESULTS

One hundred twelve stroke patients presented to the ED during the study period. Thirty-one of these were excluded due to presenting more than 12 hours after onset of stroke symptoms, seven due to hemorrhagic stroke, 13 due to the previous history of stroke, 20 due to comorbid diseases capable of affecting sTWEAK levels, and five patients due to unwillingness to take part in the study. Thus, the case-control study included 36 adult AIS patients and 36 healthy volunteers.

The mean ages of the patient and control group were 66.06 ± 14.59 (range: 23-94) and 66.1 ± 14.4 (range: 25-94) ($p = 0.980$), respectively, and 63.8% of both groups were men. Four in

five patients (80.6%) presented to the ED within the first 3 hours after the onset of AIS symptoms. Most of them presented with two neurological symptoms. The most common neurological examination findings were lateralizing neurological deficit, followed by lateralizing neurological deficit + speech disorder. Serum sTWEAK levels were significantly higher in the AIS group ($1968.08 \pm 1441.99 \mu\text{g/L}$) than in the control group ($704.81 \pm 291.72 \mu\text{g/L}$) ($p < 0.001$). The mean IAV in the AIS group was $159.78 \pm 263.11 \text{ mm}^3$ (Table 1). At ROC curve analysis, sTWEAK emerged as a valuable marker in the prediction of AIS [Area Under Curve (AUC): 0.84 (95% CI: 0.74-0.94; $p < 0.001$)], with a cut-off value of 995.5 pg/ml, exhibiting 77.8% sensitivity, 91.7% specificity, a positive predictive value of 90.3% and a negative predictive value of 80.5%. However, sTWEAK was of no value in predicting 6-month mortality in AIS patients [AUC: 0.55 (95% CI: 0.30-0.83; $p = 0.792$) (Figure 1).

No significant relation was determined between sTWEAK levels and IAV ($r = -0.008$; $p = 0.07$) or between sTWEAK levels and 6-month mRS ($r = -0.04$; $p = 0.65$). GCS and mRS had a significant correlation with IAV ($r = -0.66$ and 0.63 ; $p < 0.01$ and $p < 0.01$, respectively) in patients with AIS. Also admission GCS was related with 6-month mRS ($r = -0.81$; $p < 0.01$) (Table 2).

None of the patients underwent thrombectomy. Only nine patients in the AIS group were received tissue plasminogen activator (tPA). Mortality occurred in 22.2% of AIS patients during the first six months. GCS was significantly low, and IAV was significantly high in the non-surviving group, whereas sTWEAK levels did not differ between the surviving and non-surviving groups ($p = 0.648$) (Table 3).

DISCUSSION

A biomarker is any objectively evaluated parameter which reveals information about the diagnosis or course of a condition. The current diagnostic and prognostic biomarkers for AIS are based on imaging studies that might be unavailable for some patients or insufficient for minor cases. Imaging modalities also require physicians who are capable of evaluating them. The clinical practice of stroke is unfortunately short of objective, simple, easy to evaluate, and highly efficient biochemical biomarkers.

Several studies have been performed to investigate the rapid diagnosis of AIS and the prediction of neurological deficit or mortality. Some of the markers whose value in diagnosis and predicting mortality and prognosis have recently been investigated are glucose, iron, ferritin, homocysteine, insulin, P-selectin, matrix metalloproteinase-9, high-density lipoprotein cholesterol, platelets, C-reactive protein, glial fibrillary acidic protein, TNF- α , interleukin-6, and proenkephalin-A (14-19). Recently, sTWEAK has become a highly investigated protein, mainly due to its effect on apoptosis stimulation and inflammatory cytokine release (6-11). Literature shows that sTWEAK levels could be used as a marker of mortality and prognosis in patients with chronic kidney failure, non-ischemic heart failure and chronic stable heart failure (20-22). Moreover, sTWEAK levels in patients with ST-elevation myocardial infarction (STEMI) is significantly higher compared to both healthy controls and subjects with stable coronary artery disease (23). In their study comparing sTWEAK levels of patients with abdominal aortic aneurysm (AAA) with those of healthy controls, Martin-Ventura et al. reported an inverse correlation between low sTWEAK levels and aortic diameter. Therefore, they suggested that sTWEAK can be used in determining the diagnosis and prognosis of AAA (24). As for the potential of sTWEAK in central nervous system diseases, Inta et al. examined the correlation between AIS and sTWEAK and determined that sTWEAK and Fn14 levels were significantly higher in AIS patients presenting within 24 h compared to the control group. Although the high levels were correlated with post-stroke survival, no association was determined with IAV (11). In our study, sTWEAK levels in AIS

patients were significantly higher compared to healthy volunteers. Although this suggests that sTWEAK may have diagnostic value in AIS, we also determined that measuring sTWEAK levels was ineffective in terms of predicting mortality or prognosis.

For studies investigating serum biomarkers, the cut-off value is a crucial point. Filusch et al. reported a cut-off value of 306 pg/ml for sTWEAK in patients with pulmonary artery hypertension, while Chorianopoulos et al. calculated the cut-off value as 1286 pg/ml in STEMI (23, 25). We determined a cut-off value of 995.5 pg/ml for sTWEAK in AIS patients. We attribute the differences in cut-off values to the variety of the study groups and/or methodologies employed. The IAV at DWI is currently used as a guide for both mortality and estimation of functional outcomes (26).

IAV is another parameter investigated in studies focusing on AIS. Morita et al. showed a correlation between neurological outcomes and IAV measured 3-24 h after AIS. In comparison, Thijs et al. reported a correlation between neurological outcomes with survival and IAV 48 h after AIS and concluded that IAV measured after stroke was an independent marker of post-stroke outcomes (27, 28). In a study which was very similar to ours, Yilmaz et al. evaluated the relationship between sTWEAK, lesion size and the diagnostic value of sTWEAK in AIS cases. They concluded that sTWEAK could be a useful parameter for the diagnosis of acute stroke but did not correlate with IAV (12). In our study, 80.6% of patients presenting to the ED due to stroke were admitted to the hospital within 3 h of onset of symptoms, and DWI was performed within 12 h after the presentation. IAVs in patients who died within 6 months, in particular, were significantly higher than those of the surviving patients. This finding is parallel with other studies reporting that IAV is a guide to prognosis, and it correlates with early period survival.

Neurological scoring and laboratory results are two other variables, the effectiveness of which has been investigated in terms of survival and prognosis of stroke patients. However, there is no consensus regarding the efficacy of these variables. Lin et al. reported that a GCS score of 12 or less was a marker of early neurological worsening (29). Yilmaz et al. found that NIHSS score had a positive correlation with IAV of stroke cases (12). In our study, we determined that GCS of 11 or less at the time of presentation to the ED was related with increased risk of 6-month mortality in AIS patients. Hence we can suggest that low admission GCS following AIS is related to the patient's mortality and prognosis.

As mentioned before, many system pathologies might result in changes in sTWEAK levels. Also,

the etiology of AIS is highly related with kidney and liver diseases and cardiovascular problems (such as acute/chronic kidney disease, acute liver failure, arrhythmia, coronary artery disease, heart failure), each of which may lead to alteration in sTWEAK levels. In our study, the exclusion of the potential comorbidities associated with sTWEAK level alterations caused to decrease in the number of study patients. Another limitation for the current study might be the turnaround time of sTWEAK as the analysis of sTWEAK ELISA test generally takes approximately 2 hours with the current techniques.

CONCLUSION

sTWEAK may function as a useful biomarker in the diagnosis of AIS. However, sTWEAK measurement is ineffective in predicting IAV or early period mortality following AIS. Further studies are required for a better understanding of the relationship between the value of sTWEAK and AIS.

Conflict of interest: None.

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TABLE 1. Demographic data, sTWEAK levels and IAV results of the participants

	The AIS group	The control group
	mean \pm SD, min-max, (n)	mean \pm SD, min-max, (n)
Age (years)	66.06 \pm 14.59, 23-94 (n=36)	66.11 \pm 14.36, 25-94 (n=36)
Female	70.46 \pm 18.44, 23-94 (n=13)	70.62 \pm 18.02, 25-94 (n=13)
Male	63.57 \pm 11.62, 32-86 (n=23)	63.57 \pm 11.49, 32-84 (n=23)
Admission GCS	13.07 \pm 2.25 (8-15)	
6-month neurological outcomes		
Asymptomatic (mRS score=0)	30.6 %, (n=11)	
Mild sequelae (mRS score= 1-2)	36.1 % (n=13)	
Moderate/Severe sequelae (mRS score=3-5)	10.2 %, (n=4)	
Death (mRS=6)	11.1 %, (n=8)	
Time since onset of symptoms		
0-3 hours	80.6 %, (n=29)	
3-12 hours	19.4 %, (n=7)	
Number of deficits		
1	41.7 %, (n=15)	
2	44.4 %, (n=16)	
≥ 3	13.9 %, (n=5)	
sTWEAK (pg/ml)	1968.08 \pm 1441.99, 377-6632	704.81 \pm 291.72, 147-1515
IAV (mm³)	159.78 \pm 263.11, 174-947	

The categorical data were expressed as percentages, number. GCS; Glasgow Coma Scale, mRS; modified Rankin Scale, sTWEAK; Soluble tumor necrosis factor-like weak inducer of apoptosis, IAV; ischemic area volume.

TABLE 2. Bivariate correlations among GCS, 6-month mRS, sTWEAK and IAV

<i>Spearman rho</i>	Admission GCS	6-month mRS	sTWEAK	IAV
Admission GCS				
6-month mRS	-0.81*			
sTWEAK	0.07	-0.04		
IAV	-0.66*	0.63*	-0.04	
6-month mortality	-0.73**		0.08	0.52**

* p<0.05, **p<0.01. GCS; Glasgow Coma Scale, mRS; modified Rankin Scale. sTWEAK; Soluble tumor necrosis factor-like weak inducer of apoptosis, IAV; ischemic area volume.

TABLE 3. The 6-month mortality of AIS patients			
	6-month Prognosis		P*
	Surviving (n=28)	Non-surviving (n=8)	
	Mean±SD	Mean±SD	
GCS	14 ± 1.52	9.63 ± 0.74	0.000
sTWEAK (pg/ml)	1813.61 ± 1141.33	2508.75 ± 2223.22	0.648
IAV (mm³)	60.96 ± 80.89	505.68 ± 381.10	0.002

*p values represent results for the Mann-Whitney U test. GCS; Glasgow Coma Scale, sTWEAK; Soluble tumor necrosis factor-like weak inducer of apoptosis, IAV; ischemic area volume.

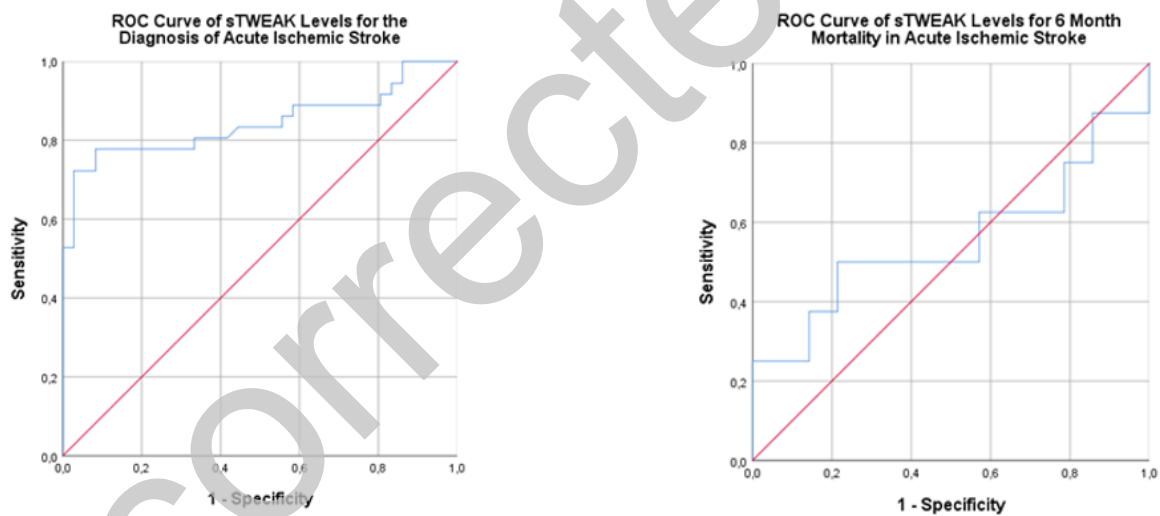


FIG. 1. ROC curves of sTWEAK levels for the diagnosis of acute ischemic stroke and 6-month mortality in acute ischemic stroke.