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Change of serum levels of thioredoxin in patients with severe traumatic brain injury

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ABSTRACT

Background: Thioredoxin (TRX), a potent anti-oxidant, is released during inflammation and oxidative stress. The purpose of this study was to establish the relationship between serum TRX concentrations and trauma severity and outcome in severe traumatic brain injury (STBI).
Methods: We determined serum TRX concentrations in 112 patients and 112 controls. Multivariate analyses were performed to analyze the predictive factors of 1-week mortality, 6-month mortality and 6-month unfavorable outcome. The predictive values were investigated under receiver operating characteristic curves.
Results: Serum TRX concentrations were markedly higher in patients than in controls (19.1 ± 7.8 ng/ml vs. 8.0 ± 2.3 ng/ml, $P < 0.001$). There was a significant negative association between serum TRX concentrations and Glasgow coma scale (GCS) scores ($r = -0.543$, $P < 0.001$). Increased TRX was identified as an independent prognostic marker of 1-week mortality [Odds ratio (OR), 1.220; 95% confidence interval (CI), 1.101–1.367; $P < 0.001$], 6-month mortality (OR, 1.201; 95% CI, 1.097–1.324; $P < 0.001$) and 6-month unfavorable outcome (OR, 1.189; 95% CI, 1.090–1.311; $P < 0.001$). TRX concentrations improved area under curve of GCS scores for 6-month unfavorable outcome, but not for 1-week mortality and 6-month mortality.
Conclusions: Increased serum TRX concentration, associated highly with trauma severity and poor outcome, might be a novel prognostic marker in patients with STBI.

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1. Introduction

Oxidative stress reaction is one of the most popular mechanisms in the secondary brain injury after traumatic brain injury (TBI) [1–3]. Oxidative stress, resulting from an imbalance in the production of reactive oxygen species and the anti-oxidative defenses that maintain a cellular redox state, is proposed to be an important factor leading to oxidative damage in brain tissues and consequently contributing to mortality or neurological dysfunction after TBI [4–6]. The determination of oxidative stress in TBI would be very significant for a better understanding of TBI pathophysiology and for identifying subgroups of patients at the risk of poor prognosis. Blood biomarkers of oxidative stress have been investigated broadly in recent years [7–10].

Thioredoxin (TRX), a ubiquitous, 12.5 kDa intracellular thiol protein, is identified as a potent anti-oxidant which regulates inflammation, cell growth and apoptosis [11,12]. TRX is released during oxidative stress and inflammation, and subsequently its circulating concentrations are increased in many diseases including sepsis, post-cardiac arrest syndrome, acute myocardial infarction and malignant neoplasms, in which TRX has close relation to the severity and prognosis [13–17], suggesting that TRX might be an oxidative stress marker. Recently, the close association of increased serum TRX with the clinical severity, infarct volume and short-term functional outcome were demonstrated in patients with acute ischemic stroke [18], indicating TRX as a possible novel prognostic marker in neurological diseases.

2. Methods

2.1. Design and subjects

A prospective, observational study of a consecutive series of patients with severe TBI at our hospital between January 2011 and January 2014 was performed. Severe TBI was defined as Glasgow Coma Scale (GCS) score lower than 9 points. Patients with Injury Severity Score in non-cranial aspects higher than 9 points, time from trauma to admission more than 6 h, pregnancy, infectious diseases, immunological diseases, use of immunosuppressant, fever within recent 1 month before head trauma, an increased white blood cell count, positive chest X-ray, <18 y, previous severe head trauma, neurological disease including ischemic or hemorrhagic stroke, use of antiplatelet or anticoagulant medication and presence of other prior systemic diseases such as diabetes mellitus, hypertension, uremia, liver cirrhosis, malignancy and chronic heart or lung disease were excluded from the study.

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The control group consisted of healthy volunteers who came to our hospital for healthy examination during the period of July 2013 to January 2014 and were checked for the absence of chronic or acute illness by questionnaire and medical examination. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of our hospital. Written informed consent from the subjects or from their legal guardians was obtained.

2.2. Assessment

The following information was recorded for each patient: age, gender, blood pressure, time from trauma to admission, GCS score, traumatic subarachnoid hemorrhage, abnormal cisterns, midline shift >5 mm, pupil dilation and brain lesion according to Marshall computed tomography classification [19]. Radiological procedures were completed according to the neuroradiology department protocol. The investigative group comprised a neurosurgeon and a radiologist and they were blinded to clinical information. Clinical outcomes were evaluated with 1-week mortality, 6-month mortality and 6-month unfavorable outcome. Unfavorable outcome was defined as Glasgow outcome scale score of 1–3 [20–22]. For follow-up, we used structure telephone interviews performed by 1 doctor, blinded to clinical information.

2.3. Immunological analysis

The blood was drawn from cubital vein at admission in the patients and at study entry in the controls. After centrifugation, aliquots of the samples were immediately stored −80 °C before assay. Measurements of TRX were performed in duplicate samples with a commercially available sensitive enzyme-linked immunosorbent assay (Redox Biosciences, Kyoto, Japan). Patients exhibiting hemolysis were excluded due to the high intracellular concentration of TRX, which will bias assessment [11]. All determinations were performed by laboratory technicians blinded to all clinical data.

2.4. Statistical methods

The normality of data distribution was assessed by the Kolmogorovor–Smirnov test or Shapiro–Wilk test. The results were reported as counts (percentage) for the categorical variables, mean ± SD if normally distributed and median (the upper and lower quartiles) if not normally distributed for the continuous variables. Linear relationships between GCS scores and TRX concentrations were examined using Spearman's correlation coefficient.

Initial univariate analysis was done to assess the statistical significance of the intergroup observed difference with Student *t* test or Mann–Whitney U-test for the continuous variables and χ^2 test or Fisher exact test for the categorical variables as appropriate. All parameters that were found to be significant in the univariate analysis were further analyzed using multivariate regression to identify those parameters that retained significant while accounting for all relevant variables. The odds ratio values and 95% confidence intervals were calculated and reported.

Receiver operating curves (ROCs) were generated to determine cut-off values for optimal prognostic predictive sensitivities and specificities. The area under curves (AUCs) and 95% CI were calculated and reported based on the ROC curves. In a combined logistic-regression model, the additive benefit of TRX concentrations to GCS scores was estimated. All data were analyzed using SPSS 19. and MedCalc ver 9.6.4.0 Statistical significance was defined as a $P < 0.05$.

3. Results

3.1. Subjects' characteristics

Initially, 149 patients were assessed. 37 patients were excluded because of the following reasons. 3 patients had Injury Severity Score in non-cranial aspects >9 points; 4 patients, time from trauma to admission >6 h; 1 patient, pregnancy; 2 patients, infectious diseases; 2 patients, immunological diseases; 1 patient, use of immunosuppressant; 2 patients, fever within recent 1 month before head trauma; 3 patients, an increased white blood cell count; 2 patients, positive chest X-ray; 1 patient, < 18 y; 2 patients, previous severe head trauma; 4 patients, neurological disease including ischemic or hemorrhagic stroke; 3 patients, use of antiplatelet or anticoagulant medication; 7 patients, presence of other prior systemic diseases such as diabetes mellitus, hypertension, uremia, liver cirrhosis, malignancy and chronic heart or lung disease. This study finally included 112 STBI patients and 112 healthy controls. There were not statistical significances in intergroup differences of gender and age. In this group of STBI patients, median initial postresuscitation GCS scores were 5 (4–7) (range, 3–8); 52 patients (46.4%) had unreactive pupils on admission; 55 patients (49.1%), CT classification 5 or 6; 53 patients (47.3%), abnormal cisterns on initial CT scan; 57 patients (50.9%), midline shift >5 mm on initial CT scan; 65 patients (58.0%), presence of traumatic subarachnoid hemorrhage on initial CT scan; 61 patients (54.5%), intracranial surgery in 1st 24 h.

3.2. The change of serum TRX concentrations and their association with GCS scores

The admission serum TRX concentrations were significantly increased in all patients (19.1 ± 7.8 ng/ml), compared with healthy controls (8.0 ± 2.3 ng/ml, $P < 0.001$). We found that the serum TRX concentrations reflected the head trauma severity. Concentrations of TRX increased with increasing severity of head trauma as defined by the GCS score. There was a significant negative association between serum TRX concentrations and GCS scores ($r = -0.543$, $P < 0.001$) in Fig. 1.

3.3. 1-week mortality prediction

Fifteen patients (13.4%) deceased within 1 week after head trauma. In Table 1, non-survivors had higher serum TRX concentrations than survivors. When the variables the univariate analysis found significant were introduced into the logistic model, GCS scores (OR, 0.299; 95% CI, 0.102–0.774; $P < 0.001$) and serum TRX concentrations (OR, 1.220; 95% CI, 1.101–1.367; $P < 0.001$) were identified as the independent predictors for 1-week mortality of patients.

A ROC curve identified that an admission serum TRX concentration > 21.7 ng/ml predicted 1-week mortality of patients

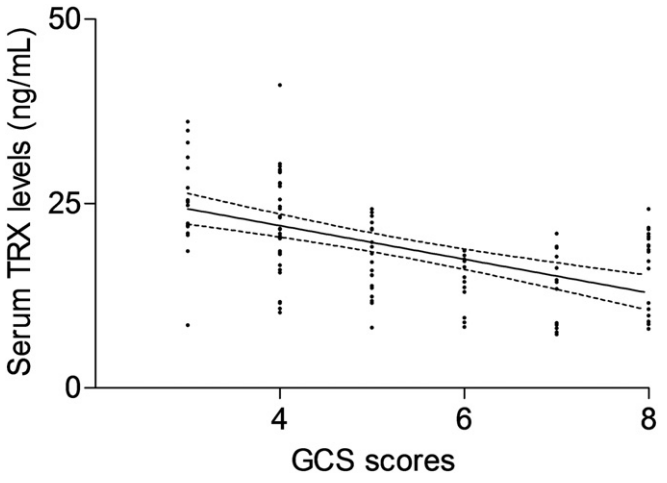

Fig. 1. The association of serum thioredoxin (TRX) levels and Glasgow coma scale (GCS) scores.

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