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Peripheral glutamate and TNF-α levels in patients with intracerebral hemorrhage: Their prognostic values and interactions toward the formation of the edemal volume

Vladimir Rendevski[a,*], Boris Aleksovski[b], Dragan Stojanov[c,d], Vasko Aleksovski[e], Ana Mihajlovska Rendevska[f], Milena Kolevska[b], Kiro Stojanoski[b], Icko Gjorgoski[b]

[a] University Clinic for Neurosurgery, Medical Faculty, "Ss. Cyril and Methodius" University, 1000 Skopje, Macedonia
[b] Faculty of Natural Sciences and Mathematics, "Ss. Cyril and Methodius" University, 1000 Skopje, Macedonia
[c] Faculty of Medicine, University of Niš, 18101 Niš, Serbia
[d] Center of Radiology, Clinical Center Niš, 18101 Niš, Serbia
[e] University Clinic for Neurology, Medical Faculty, "Ss. Cyril and Methodius" University, 1000 Skopje, Macedonia
[f] University Clinic for Radiology, Belgradska bb, 1000 Skopje, Macedonia

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ABSTRACT

Objective: We aimed to evaluate the prognostic values, contribution and interactions of the peripheral blood plasma glutamate and tumor-necrosis factor-α (TNF-α) levels toward the formation of the perifocal edema in patients with intracerebral hemorrhage (ICH).
Methods: Fifty patients with ICH and fifty healthy controls were included in the study. The peripheral markers were detected by high-sensitivity ELISA.
Results: A highly significant differences in plasma glutamate and TNF-α levels with good separation of their values was detected between patients and healthy controls. The two variables correlated with the severity of the symptoms and the initial volume of the ICH at admission. Both peripheral glutamate and TNF-α levels at admission were estimated as significant predictors for the formation of the perifocal edema five days after ICH; nevertheless, it was shown that they independently contribute to the development of the edema, without effects of interaction and regardless the localization of the ICH.
Conclusions: Our results support the idea for the significance of glutamate and TNF-α as peripheral markers for excitotoxicity and inflammation in ICH patients. The developed multiple regression model for prediction of the development of the edema could be beneficial in decision making between conservative treatment and surgical intervention in the clinical practice.

* *Corresponding author at*: Medical Faculty, "Ss. Cyril and Methodius" University, University Clinic for Neurosurgery, Vodnjanska 17, 1000 Skopje, Macedonia.
E-mail address: vladimirrendevski@yahoo.com (V. Rendevski).
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1. Introduction

Intracerebral hemorrhage (ICH) accounts for 10–15% of strokes [1]. It is the deadliest subtype of stroke associated with worse neurological outcome when compared to the ischemic stroke, with mortality rate of 37–52% after 30 days [2] and in-hospital mortality of 40% [3].

The biggest neurological deterioration after ICH occurs due to the formation of the perihematomal edema, a proven significant predictor for bad neurological outcome [4]. The long-standing dilemma whether patients should be treated with conservative treatment or surgical intervention was a matter of subject years ago [5]; nevertheless, the results from the international STICH study have shown no overall benefit from early surgery when compared to the initial conservative treatment [6], leaving the clinicians with the same problem of decision making without any obvious direction. Therefore, the search for a molecular marker that could predict the formation of the edema is a major challenge, because these patients can be treated in advance with potent anti-edematous therapy or early craniotomy, thus preventing neurological deteriorations and future bad outcome.

In the last several years, the focus of the interests for intervention in ICH has slowly shifted from the acute to the post-hemorrhagic phase [7]. Several animal models for experimental ICH have been developed [8,9], and the pre-clinical studies using these models have revealed that the secondary brain injury after ICH is mainly triggered by inflammatory mechanisms and formation of peri-hematomal edema [10–12]. All of these studies have reported increased levels of pro-inflammatory mediators immediately after the bleeding [13,14], with the tumor necrosis factor-α (TNF-α) being argued as one of the major constituents of this process [7]. On the other side, contrary to the ischemic stroke, the contribution of excitotoxicity in the development of brain injury after ICH has not been well defined [15]. Several studies have shown higher glutamate levels in the brain of experimental animals with induced ICH [16] and in the perihematomal area in patients with deep ICH [17], suggesting that excitotoxicity may also contribute to the secondary brain injury. However, their interaction with the other primary mechanisms of brain injury has not been studied in details.

A vast number of pre-clinical studies have shown the effect of TNF-α on the secondary brain injury in animal models of ICH, but however detailed clinical studies that evaluate their role in patients are very rare. An increased variability of the blood–brain barrier (BBB) has been reported after ICH [18], leading to the hypothesis that the excitotoxic and pro-inflammatory mediators can transfer from the brain in the blood and be detected peripherally. The fact that plasma glutamate concentration can reflect the released glutamate levels from the brain tissue in patients with ischemic stroke [19] supports this hypothesis.

The aim of the present study is to evaluate the role of peripheral plasma glutamate and TNF-α levels as biomarkers for ICH, in respect to the anatomic localization of ICH, the hemispheric side, the symptom severity and the initial volume of ICH, and moreover, to examine the prognostic role and possible interactions of these variables on the development of the volume of the edema five days after ICH.

2. Methods

2.1. Subjects and study design

We have included 50 patients with acute, primary, supratentorial ICH, recruited from the University clinics of Neurosurgery and Neurology and 50 healthy controls in the period from 01.01.2014 to 31.10.2016. The study was approved by the Ethical committee and all subjects have given informed consent.

For the purposes of the initial screening, all subjects were called for a short conversation and their medical history as well as basic demographic characteristics were recorded in a medical questionnaire. The inclusion criteria for entering the study were absence of any medical history or other neurological, neurodegenerative or psychiatric disorders, as well as absence of any medical history of cardiovascular, pulmonary, renal and hepatic diseases, coagulopathies and any inflammatory conditions or immune diseases that could influence TNF-α levels. The time interval between the onset of ICH and the admission was less than 24 h in all patients. A detailed neurological examination was performed on every patient by a team of experienced neurologist and neurosurgeon. The severity of the symptoms was estimated according to the Canadian Stroke Scale (CSS).

Controls underwent detailed interview to exclude presence of current or any past history of neurological, neurodegenerative and mental diseases. Healthy controls were selected to match patients according to gender and age, so that the effects of these variables are excluded (Table 1).

2.2. Radiological analyses

Two CT scans were performed on all patients: at admission and five days after ICH. The volume of the hematoma was measured by performing transversal slices with slice thickness of 3.5–10 mm. The calculations of the volume of the hematoma and the edema were performed according to the ABC/2 formula, as described before [20]. Several patients had irregular ICH volume and in this case, we have used the calculator for irregular volumes [21,22]. The edema was defined as the most hypodense area immediately surrounding the ICH and more hypodense than the corresponding area in the contralateral hemisphere, according to the present recommendations [23] and it was determined by subtracting the volume of the ICH from that of the total lesion, as performed in the previous studies [24,25] (given as supplementary material).

2.3. Biochemical analyses

At admission, blood was collected in the morning (after overnight fasting) in EDTA-anticoagulated tubes. The tubes were centrifuged at 3,000 rpm, 15 min at +4 °C. The obtained blood plasma was aliquoted and stored at −80 °C till further analyses. The quantitative detection of glutamate and TNF-α was performed using the ELISA kits from Abnova (Glutamate ELISA Kit, KA1909) and Quantikine (Human TNF-alpha Quantikine ELISA Kit, DTA00C), according to the manufac-

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