Involvement of Peripheral Unit of Serotonin Energetic System in Brain Lesions of Different Types

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Abstract: The paper presents findings of the quantitative studies of blood serum serotonin in patients in acute period of inflammatory and traumatic brain injuries. The study involved 72 patients with acute traumatic injury (45 patients with brain contusion and 27 with concussion) and 44 patients with tick-borne encephalitis (TBE) at the height of the disease (35 patients with non-paralytic and 9 with paralytic forms). The control group consisted of 15 healthy individuals. The peripheral blood serum serotonin was measured by enzyme-linked immunosorbent assay. Its concentration in patients with brain contusion was 288.63±57.88 ng/ml, which was significantly (p=0.049) higher than in patients with brain concussion and in healthy individuals. Average serum level of serotonin in TBE patients regardless of clinical form of the disease, was 97.2±57.1 ng/ml, significantly lower than in healthy persons (p=0.003). In more severe paralytic form the quantitative serum serotonin levels were significantly lower than in non-paralytic one. Thus, the study of blood serum concentration of serotonin in traumatic and infectious processes allows to define and predict the severity of brain damage.

Key words: Serotonin • Injury and concussion • Tick-borne encephalitis

INTRODUCTION

Despite the recent advances of the modern neurology, the search into the objective evaluation criteria of the brain matter lesions in certain diseases of the nervous system retains its topicality. Currently, there are no accurate differential diagnostic clinical and neuroimaging criteria of brain concussion (BC) and brain contusion (BCT) in the acute period of the closed brain injury (CBI) [1]. Moreover, in the first days the severity and the prognosis of such CHS diseases as stroke and tick-borne encephalitis (TBE) cannot be identified either [2, 3]. In TBE the general infectious syndrome predominates while neurologic manifestations can develop later. Consequently, in particular diseases of the nervous system clinical symptoms do not always reflect the actual severity of the brain and/or the spinal cord lesions. This can explain the fact that clinical outcomes, particularly unfavorable ones, become predictable and apparent far not in the first days of the disease. All this makes actual the search for markers of the severity of pathological CNS changes aimed at the early diagnosis and an appropriate timely treatment.

Nervous tissue involvement in the pathological process is frequently associated with the logical development of neurotransmitter imbalance on the part of the actively functioning systems of the brain, i.e. the serotoenergetic ones [4-11]. A. Adell et al. assume that the content of serotonin in the peripheral blood plasma reflects its concentration in the extracellular space of the brain (including the synaptic space) [12].

Genetic studies have shown that the structure of the platelet and cerebral serotonin transporter is encoded by the same gene [13]. The identity of platelet receptors and serotonergic neurons has provided the basis for the theory of the similarity of two systems: "Platelets - Plasma" and "Presynaptic terminals - Extracellular fluid" [2, 13, 14]. These facts also testify that humoral unit presents as the accessible and adequate model of the investigation of the serotonin system of CNS. According
to V.I. Skvortsova et al., low concentration of serotonin and its metabolites in the blood and liquor of patients may be both the result of the serotonergic system inhibition and, on the contrary, reflect compensatory inhibition of serotonin synthesis due to excessive enforcement of the serotonergic transmission in the brain [2]. To measure the serotonin concentration a number of modern biochemical and immunochemical methods which have substituted insufficiently sensitive colorimetric test are being used presently. They include high-performance fluorometric and gas chromatography with various types of detection as well as radioimmunoassay and enzyme immunoassay techniques. In most studies serotonin concentration is measured with chromatography methods which are accurate and highly sensitive but expensive and demand highly qualified staff and this limits their practical application. The emergence of a new enzyme immunoassay technique not less sensitive and specific comparing with the routine tests [15] has provided the possibility to measure serotonin concentration utilizing the already available instrumentation base and the professional staff experience.

IFA detection of serotonin presents some peculiarities because the specific high affinity antibody can be obtained only to molecules of acylated derivatives of neurotransmitter. Thus, before the examination the samples are to be subjected to the additional stage of extraction, acylation and hydrolysis. The introduction of improved versions of the technique opens the perspective of its large-scale introduction into the laboratory diagnosis.

**Purpose:** The investigation was aimed at quantitative studies of serotonin in the sera of patients in the acute period of traumatic (craniocerebral trauma) and inflammatory brain damage (TBE).

**MATERIAL AND METHODS**

45 patients with traumatic injuries in the form of brain contusion were studied. Among them 17 individuals had mild brain contusion and 28 patients had moderate brain contusion. For comparative analysis 27 patients with brain concussion were evaluated. Besides 44 patients with TBE at the height of the disease were studied, 35 having non-paralytic TBE form (19 patients with febrile form, 16 with meningeal form) and 9 patients with paralytic (focal) TBE form. The control group for the total of examined patients included 15 healthy subjects matched for sex and age. The study of humoral serotonin levels in the serum of peripheral blood was performed using the solid phase enzyme immunoassay method with “Serotonin ELISA” kit. A 5 ml of morning fasting venous blood sample was collected into the plastic tube. It was centrifuged at 1000 r/min during 10 min. The separated serum sample was kept in eppendorfs at 20°C until the diagnosis was established. The intensity of the color response was measured at the 450 nm wave length. The amount of serotonin in the sample was estimated with the calibration curve and expressed in ng/ml.

**Statistical Analysis:** Was performed using the software package STATISTICA 6.0 and the descriptive statistics (selective mean (M) and mean square deviation (σ)) non-parametric methods (comparison of independent groups using Mann-Whitney test). Dependency analysis was performed with Spearman’s rank correlation coefficient (r). At p<0.05 differences were considered statistically significant.

**RESULTS AND DISCUSSION**

Estimation of the quantitative indices of serum serotonin in patients with moderate brain injury revealed considerable trends. Concentration of serum serotonin in BCT group was 288.6±57.9 ng/ml which significantly (p=0.049) surpasses indices in BC group and healthy individuals. Blood serum serotonin concentration in BC group was 148.9±59.6 ng/ml and did not differ (p<0.05) from the control group (187.2±28.9 ng/ml). In group with moderate BCT the target neuromediator indices elevated up to 331.8±77.1 ng/ml and were higher (p=0.029) than in BC group. Correlation analysis showed relationship of serum serotonin and CBI type (r=0.35, p=0.02).

Therefore, BSS quantitative indices may serve as the diagnostic markers of the BI severity degree and be applied in the differential diagnosis of BC and BCT (patent on invention No 2440581 “Method of differential diagnosis of brain concussion and brain contusion”).

Quantitative studies of blood serum serotonin at the height of TBE revealed a significant decrease in this indicator compared with the control values. Regardless of the clinical form of the disease mean BSS was 97.2±57.1 ng/ml, that is significantly lower than in healthy persons (p=0.003). A more detailed analysis of the BSS concentration in the studied groups allowed to establish its reduction during the first days of the disease in paralytic (focal) form: 45.7±23.6 ng/ml compared with 115.6±54.4 ng/ml in non-paralytic form (p=0.015). Comparison of blood serum serotonin concentration in patients with different forms of TBE at the height of the disease showed significant differences between focal and
feverish (p=0.006), as well as focal and meningeal forms (p=0.048). A statistically significant difference between severe and less severe non-paralytic forms of TBE has enabled us to substantiate the possibility of application of this parameter as a prognostic indicator for early assessment of the infection course.

CONCLUSION

The obtained findings show the involvement of peripheral humoral serotonin system in neurological diseases. However, in traumatic and infectious processes multidirectional changes in this system are recorded.

In the first day of traumatic lesions activation of the serotonin system is observed, which might suggest the participation of serotonin in the processes associated with aseptic inflammation and reparation. On the contrary, in TBE deficiency of serotonergic system is noted, which is probably due to its active involvement in the pathogenic processes already in the incubation period and by the time of the onset of its first clinical manifestations its breakdown occurs. It has been previously shown that on the basis of serum concentrations of serotonin the severity of brain damage and degree of CNS involvement, to administer an adequate therapy and to reduce the number of complications. The concept of the place and role of lesions of serotonergic mediation in the pathogenesis of cerebral damage in different mechanisms needs to be further developed.

REFERENCES