Study of Endothelin-1 in Acute Ischemic Stroke

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Endothelins (ETs) are potent vasoconstrictor and may play a role in the pathophysiology of several cardiovascular diseases. Endothelin-mediated vasoconstriction may enhance ischemic neuronal damage. The study aimed to find out whether the plasma ET-1 levels may serve as marker of early ischemic stroke. Plasma ET-1 levels were tested in 20 patients with acute ischemic stroke, mean age 63.7 ± 5.03 years, 12 men and 8 women, within 24 hours of stroke onset as compared to 10 sex- and age-matched control subjects; only the patients with normal CT-scan at admission were included in the study. Plasma ET-1 was measured by ELISA. The results were statistically analyzed by Student test and a p < 0.05 (95% CI) was considered statistically significant. ET-1 levels in patients with hemiplegia and normal CT-scan at admission were significantly higher as compared to control group (0.0910 ± 0.0256 pg/mL vs. 0.0490 ± 0.0185 pg/mL, p < 0.0001) (95% CI). Ischemic stroke is associated with acute and marked increased levels of ET-1 in plasma. This may reflect enhanced production by damaged endothelial cells within the infarcted lesion. ET-1 may be used as additional marker of cerebral ischemia in selected cases to distinguish between the onset of an ischemic stroke and other non-vascular diseases presenting similar symptoms.

Key words: endothelin-1 (ET-1), early ischemic stroke.

The endothelial cells synthetize many active substances in order to maintain the potency of the blood vessels and the fluidity of blood, including endothelin-1 (ET-1).

In healthy humans, levels of ET-1 measured by radioimmunoassay of plasma have been estimated to range from 0.26 to 5 ng/L. However, the concentrations of ET-1 are likely to be much higher at the interface of the endothelin and smooth muscle (because of the small volume of distribution) than in the blood stream [1].

ET-1 is the most active pressor substance yet discovered [2–4].

Cerebral arterial endothelial cells may produce ET-1 [5].

Current interventions for ischemic stroke being time dependent, the stroke diagnosis must be quick.

The research of new biomarkers may help in the evaluation of patients with potential ischemic stroke [6] [7].

The study aimed to find out whether the plasma ET-1 levels may serve as marker of early ischemic stroke.

MATERIAL AND METHODS

Plasma ET-1 levels were tested in 20 patients with acute ischemic stroke, mean age 63.7 ± 5.03 years, 12 men and 8 women, within 24 hours of stroke onset as compared to 19 sex- and age-matched control subjects.

At each sampling, the patients underwent a complete neurological evaluation. All stroke risk factors were recorded, an array of laboratory tests were performed, and computer tomography (CT) was performed and subsequently, only the patients with normal CT-scan at admission were included in the study.

Exclusion criteria were: intracerebral hemorrhage, hemorrhagic infarction, brain tumor, demyelinating disease, vascular headache, acute or chronic infection, inflammatory disease of the central nervous system (CNS), systemic metabolic disease, or systemic vasculitis.

Plasma ET-1 was measured by ELISA [8].

The results were statistically analyzed by Student t test and a p<0.05 (95% CI) was considered statistically significant.

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For all eligible patients the informed consent was given for the use of their blood in this study. The research received approval by the ethical committee of the institution.

RESULTS

ET-1 levels in patients with hemiplegia and normal CT-scan at admission were significantly higher as compared to control group (0.0910 ± 0.0256 pg/mL vs. 0.0490 ± 0.0185 pg/mL, p < 0.0001) (95% CI).

DISCUSSION

ET-1 induces a vasoconstrictor effect on blood vessels of the brain, regional blood flow and cerebral microvasculature, fact demonstrated in the choroid plexus of the rabbit [9] and in the large cerebral arteries of cats [10]. This vasoconstriction effect on cerebral microvessels is dose-dependent in response to ET-1 but not ET-3 [11] and last for 24 to 2 hours [12][13].

Some authors have observed that ET-mediated vasoconstriction aggravated the ischemic effect of an existing cerebral lesion and was associated with an increased ET-1 concentration in brain tissue and plasma [14–16].

The ET-1-mediated ischemic effect and the neurodestructive mechanism could be revealed by specific ET-receptor blocking [17–19] as well as by N-methyl-D-aspartate antagonists [20].

It was found a factor that decreases ET-1 levels in the endothelial cell microvessels, and is released from cultured astrocytes. Astrocytes may be also involved in a regulatory loop of ET-1 production. At the level of the blood-brain-barrier (BBB) [21], ET-1 and ET-3 were both detected in astrocytes after focal or global ischemia, specially in damaged hippocampal tissue [22].

In animal models studies it was shown that administration of ET-1 into the CSF is followed by severe vasospasm lasting for up to 72 hours [12][13].

Intraventricular administration of ET-1 reduced cerebral blood flow and led to the development of brain infarction [23]. Injection of ET-1 into the lateral ventricles of rats induced hypometabolism of various brain structures [24]; this effect could be completely reversed by intraventricular ET-1 receptor antagonist [17].

In serum of patients with acute vascular headache [25] and in patients with subarachnoid hemorrhage [26–30] increased ET-1 concentrations have been demonstrated.

In patients with ischemic stroke plasma ET-1 levels were examined at various stages after the event and were found to be elevated [31–35].

We have observed significantly higher plasma ET-1 levels in patients with hemiplegia at the onset of acute ischemic stroke.

It was demonstrated the elevation of ET level in neural tissue after focal ischemia and in the extracellular fluid in global ischemia [36].

Some authors have observed that ET-1 concentration in the plasma is correlated with the clinical status on admission and the final outcome, but not with the size of infarction [32][37].

It was found a discrepancy between the normal ET level in patients with ischemic stroke found by some researches and the high level of ET observed by other studies, the explanation may be the very early stage of measurement in the first group [38][39].

The ET-1 levels were significantly higher in the CSF of patients with large cortical infarcts compared with smaller subcortical lesions [38].

Patients with mitral stenosis and history of cerebral thromboembolism did not present elevated levels of plasma ET-1 [40].

In a group of patients after 1 year of follow-up after ischemic stroke plasma ET-1 levels were higher in patients with cardioembolic disease when compared with patients with small- and large vessel disease [34].

ET-1 causes vasoconstriction if applied from the adventiceal side [41], so explaining the mechanism of such reaction.

In patients with alteration of BBB, ET-1 may have access also to the vascular smooth muscle cells and thus induce an additional contraction mechanism. New trends in stroke therapy are administration of combined ET-A and ET-B blockers for protection against the development of stroke [42–48].

CONCLUSIONS

Ischemic stroke is associated with acute and marked increased levels of ET-1 in the plasma.

This may reflect enhanced production by damaged endothelial cells within the infarcted lesion.

ET-1 may be used as additional marker of cerebral ischemia in selected cases to differentiate between the onset of an ischemic stroke and other non-vascular diseases presenting similar symptoms.
Endotelinele sunt vasoconstrictoare puternice și pot prezenta un rol în fiziopatologia unor boli cardiovasculare. Vasoconstricția mediată de endotelină poate agrava leziunea neuronală ischemică. Studiul a urmărit dacă nivelurile plasmatice ale ET-1 pot fi utilizate ca marker ale stroke-ului ischemic la debut. Au fost testate nivelurile plasmatice ale ET-1 la 20 pacienți cu stroke ischemic acut, vârsta medie 63,7 ± 5,03 ani, 12 bărbați și 8 femei, în primele 24 ore de la debut comparativ cu 10 martori cu vârstă și sex asemănătoare; au fost inclusi în studiu numai pacienții cu CT scan normal la internare. Probele de sânge au fost analizate cu ELISA. Rezultatele au fost prelucrate statistic prin testul t, un p < 0.05 (95% CI) a fost considerat semnificativ statistic. Nivelurile ET-1 la pacienții cu hemiplegie și CT scan normal la internare au fost semnificativ mai mari comparativ cu ale martorilor (0,0910 ± 0,0256 pg/ml vs. 0,0490 ± 0,0185 pg/ml, p < 0.0001) (95% CI). Stroke-ul ischemic este asociat cu creșterea marcată și acută a nivelurilor plasmatice ale ET-1. Aceasta poate reflecta creșterea producției de către celulele endoteliale afectate în leziunea de infarct. ET-1 poate fi utilizat ca marker suplimentar al ischemiei cerebrale la cazuri selectate pentru a deosebi debutul unui stroke ischemic de alte afecțiuni nevasculare cu simptome similare.

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