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Oxidative stress and serum hepcidin levels in pati

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Introduction

Oxidative stress plays an important role in neuronal injuries caused by cerebral ischemia. It is well established that free iron increases significantly during ischemia and is responsible for oxidative damage in the brain. Many mechanisms are involved in ischemia-induced brain injuries, such as oxidative stress (1,2), increased intracellular calcium concentration (3,4), inflammation (5), and elevated excitatory amino acids (6). Iron, the most abundant trace metal in the brain, is also believed to play a critical role in neuronal injuries caused by oxidative stress in ischemia, although the exact mechanism is not understood. Increased levels of free iron and ferritin have been observed in ischemic brain (7). Elevated hypoxia inducible factor 1 (HIF-1) expression causes high secretion of hepcidin (8,9). Elevated serum hepcidin levels leads to internalization and degradation of the only known intracellular iron exporter ferroportin (10). Increased hepcidin levels causes iron retention in macrophages, hepatocytes and duodenal enterocytes (11). New studies suggests that feroportin is also expressed in the brain and might play a role in iron export from nerve cells (12). In the brain, iron homeostasis depends on both iron uptake by the cells and iron export from the cell.

Materials and Methods

For a period of one year we determined serum hepcidin levels using ELISA assay in 80 samples; average age 54.7 ± 9.5. Samples were taken from 40 patients with acute ischemic stroke, diagnosed in "Aleksandrovska" hospital, Dept. of Neurology. Their results were compared to 40 age matched controls.

We measure serum iron levels, ferritin and CRP. Pearson's coefficient and Student's t-test were used for evaluation of correlation and statistical significance. We quantify hepcidin levels using verified ELISA method (13). For iron quantification we used AAS (Perkin Elmer) and for serum ferritin levels – ECLIA method (Roche Diagnostics). CRP was measured by using nephelometry (Siemens).

Patients were signing the informed consent according to the Declaration of Helsinki (Directive 2001/20 / EC).

Results

We found statistically significant differences in serum hepcidin levels between measured groups: patients with acute ischemic stroke: 88.3 ± 21.3 μg/L and control group 19.2 ± 4.3 μg/L ($P < 0.001$) (Figure 1). Serum hepcidin levels were established in the previous study (14). Serum ferritin levels showed significant differences between the groups: control group: 152.6 ± 53.5 μg/L vs. ischemic stroke group 335.4 ± 53.5 μg/L ($P < 0.001$) (Figure 2).

Serum iron levels were increased in patients with ischemic stroke: 47.0 ± 5.6 μmol/L to 19.9 ± 4.8 μmol/L ($P < 0.001$). As there was a presence of inflammation in patients with ischemic stroke, their serum CRP levels were increased, compared to the control group: 29.3 ± 9.5mg/L to 1.7 ± 1.4 mg/L ($P < 0.001$).

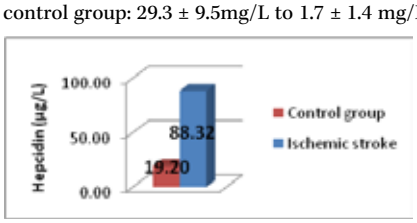

Figure 1. Measured serum hepcidin levels

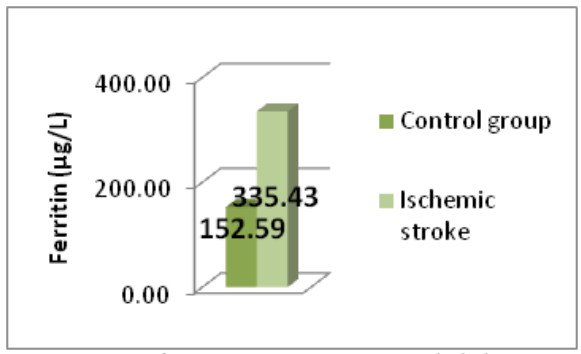

Figure 2. Serum ferritin concentrations in included groups

Discussion

Functional studies have demonstrated that hepcidin is the central regulator of systemic iron homeostasis by regulating feroportin, the only protein known to release iron from cells (11). Ischemia-reperfusion increases hepcidin expression and down-regulates feroportin expression in the cerebral cortex and the hippocampus (15).

It is known that inflammation up-regulates hepcidin expression and that cytokines are a major mediator of the inflammatory response. HIF-1 is one of the factors activated in early ischemia that can induce vascular endothelial growth factor, erythropoietin, etc. (16). Previous studies have shown that iron chelators, can reduce injury caused by cardiac ischemia and reperfusion (17) and cerebral ischemia (18).

In our study we found high serum hepcidin levels, elevated CRP, iron and ferritin concentrations in patients with ischemic stroke.

Conclusion

Recently, there are two pathways that contribute to iron overload in ischemic brain tissues as outlined. A) Ischemia increases the expression of cytokines that up-regulates hepcidin by the JAK/STAT3 pathway, which causes iron accumulation. And B) Ischemia up-regulates the HIF-1α level, which leads to iron accumulation in the ischemic tissues.

Our results indicate that serum hepcidin plays an important role for iron overload in cerebral ischemia.

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