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Study on the correlation between HO-1 level and white matter lesions of cerebral small vessel encephalopathy

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Abstract: OBJECTIVE: Heme oxygenase (HO), a cytoprotective agent has become an ideal and participates in the neuroprotection of various neurological diseases. The purpose of this study is to investigate whether plasma heme oxygenase-1 (HO-1) has role in cerebral small vessel disease (CSVD). METHODS: In this study, there were 147 patients prospectively included with CSVD who were admitted to the three departments of neurology from March 2018 to April 2019, and obtained baseline data, clinical scores, imaging Fazekas scores, and peripheral blood samples of the patients for analysis. According to the patient's Fazekas score, Fazekas<2 is defined as WMH (-), and Fazekas≥2 is defined as WMH (+) to study the relationship between plasma HO-1 concentration and the degree of white matter lesions. RESULTS: The difference in plasma HO-1 between WMH (+) and WMH (-) patients was not statistically significant (p = 0.082). CONCLUSION: There is no significant correlation between the level of HO-1 and the degree of white matter lesions.
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Keywords: Cerebral small vessel disease; Biomarker; Cognition; White matter hyperintensity

1. Introduction

CSVD is a highly prevalent disease, which is related to age and is closely related to stroke, cognitive, emotional disorders, gait instability, and aging. Mostly, CSVD is diagnosed by magnetic resonance imaging (MRI) of the brain. Its main features are white matter hyperintensity (WMH), lacunar cerebral infarction, perivascular space enlargement (PVS), new small subcortical infarction, and Brain microhemorrhage (Akila and Uma Maheswari, 2019).

Heme oxygenase-1 (HO-1) is considered to be the main protein involved in disease oxidation and inflammation. HO-1 exerts its antioxidant function by regulating the level of pro-oxidant heme in cells, or by by-products such as carbon monoxide (CO) and biliverdin (BV) (Maines, M.D. and P.E. Gibbs, 2005). HO-1 induction occurs in both neuronal and non-neuronal brain cells. However, Astrocytes show a stronger HO-1 response than neurons (Chen, J, 2014). Although the beneficial effects of HO-1 induction have been reported in many cells and tissues. More and more evidences show that the increase of HO-1 expression may lead to the progression of many neurological diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), and brain aging Process, etc. (Liu, Z., et al., 2017; Wael Al-Shelfa, et al, 2017; Mohamed Mohamed Ahmed Ebada, et al, 2018).

2. Materials and methods

The inclusion criteria are 1) Age older than 20 years; 2) The following imaging findings include: new subcortical lacunar infarction, which may be in a vasculogenic space, enlarged perivascular space, cerebral microhemorrhage, and possibly a blood vessel. The origin of the white matter of the brain is demyelinated and the atrophy of brain. If the patient meets any of the following criteria, it will be excluded from the study: 1) Cervical and intracranial vascular examination (TCD / MRV / DSA) recommend neck or intracranial stenosis> 50% (MRA recommends stenosis> 70 %); 2) Intoxication, metabolic or tumor-related encephalopathy; 3) Infection, proposed multiple sclerosis, optic nerve, and spinal cord spectrum disease; 4) Intracranial space occupation; 5) Cerebrovascular malformation/cerebral aneurysm; 6) Combined with serious diseases affecting the life cycle; 7) Unable to complete the MRI examination; 8) Refusal to participate in the study.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All patients participating in the study or their legal representatives signed written informed consent.

Clinical information collection

We collected baseline data, examination data, and peripheral blood samples of the patients. MRI was performed using 3.0T magnets weighing T1 and T2, and the flow recovery sequence (FLAIR) was used at the beginning and end of the study. According to the MRI results, Fazekas score was performed. Patients with Fazekas score ≥ 2 were classified as heavy burden in the WMH group, denoted as WMH (+), and patients with Fazekas score <2 were classified as low burden in the WMH group, denoted as WMH (-). According to the manufacturer's instructions, an enzyme-linked immunosorbent assay (ELISA) method was used to measure plasma HO-1 levels. The samples were prevented from freezing and thawing repeatedly and set a repeating hole for each sample, perform repeated measurements, and use the average value for statistical analysis to reduce experimental errors. All HO-1 analyses were performed at Zhengzhou University School of Medicine.

Statistical analysis

Use SPSS 24.0 to perform statistical analysis on the data. Chi-square test is used to test qualitative variables, such as gender, smoking, alcohol consumption, and group differences in past disease history. Student's t-test is used to analyze the difference between age and BMI. Non-parametric tests are used to analyze differences in education level, glomerular filtration rate, homocysteine, and plasma HO-1 levels. All statistical analyses were performed using two-sided inspections. A P value of less than 0.05 is considered statistically significant (test level $\alpha<0.05$).

3. Result

The average age of the WMH (-) group was 55.49±10.84 years, and males accounted for 50.67% of the participants. The average age of the WMH (+) group was 60.57±9.28 years, and males accounted for 51.39% of the participants. WMH (+) group age and blood homocysteine levels were lower than WMH (-) group, the difference was statistically significant ($p<0.05$). The level of glomerular filtration rate in WMH (+) group was higher than that in WMH (-) group, the difference was statistically significant ($p<0.05$). There was no statistically significant difference in the levels of HO-1 between the two groups ($p<0.05$) (Table).

Table: Baseline data for recruiting CSVD patients

	WMH (-) (n=75)	WMH (+) (n=72)	p
Age	55.49±10.84	60.57±9.28	**0.003***
Male	38（50.67）	37（51.39）	0.930
BMI, kg/m2	24.97±2.82	25.49±3.00	0.272
Length of education	12（9,12）	9（6,12）	0.103
Smoking	11（14.67）	12（16.67）	0.739
Drinking	19（25.33）	17（23.61）	0.808
Hypertension	41（54.67）	43（59.72）	0.536
Hyperlipidemia	25（33.33）	35（48.61）	0.060
Diabetes	20（26.67）	21（29.17）	0.735
Coronary Heart Disease	10（13.33）	7（9.72）	0.494
Glomerular filtration rate	97.96（91.80,104.17）	93.05（86.13,98.56）	**0.002***
Homocysteine	15.23（12.86,17.29）	15.85（14.05,20.70）	**0.028***
Plasma HO-1 levels	0.700（0.50,1.07）	0.60（0.46,0.88）	0.082

4. Discussion

HO degrades the heme group into carbon monoxide (CO), free ferrous iron (Fe2+) and biliverdin (Keyse, S. and R. Tyrrell,1989; Maines, M., 1988). Through the activity of biliverdin reductase (BVR), biliverdin is converted into bilirubin, which can scavenge hydroxyl free radicals, singlet oxygen and superoxide anion (Dudnik, L. and N. Khrapova,1988) and prevent protein and lipid peroxidation (He, M., et al.,2015), then it exerts powerful antioxidant (Stocker, R., et al., 1987), anti-apoptotic (Loboda, A., A. Jozkowicz, and J. Dulak, 2015) and anti-inflammatory activity (Loboda, A., et al.,2016).

In addition, the neuroprotective effect of HO-1 may not only be attributed to its antioxidant and anti-inflammatory activities, but also the enhanced production of neurotrophic factors. The overexpression of HO-1 induced by adenovirus in the substantia nigra regulates the production of

brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) in dopaminergic neurons and glial cells, respectively (Hung, S., et al., 2008). Studies have shown that the downstream products of HO-1 are involved in the regulation of BDNF and GDNF expression in neurons and astrocytes (Mancuso, C., et al., 2008; Qi, D., et al., 2014). Studies have shown that HO-1 activity seems to be important for demyelination. HO-1 knockout mice showed demyelination, paralysis and increased mortality.

The results of this study show that HO-1 does not correlate with white matter lesions in patients with CSVD. This may be because the up-regulation of HO-1 is related to extensive neuronal damage and degeneration (Syapin, P., 2008), neurons and glial cells, as well as in the cerebral cortex and hippocampus. The immunoreactivity of HO-1 gradually increases between the ages of 3 and 84 (Hirose, W., K. Ikematsu, and R. Tsuda, 2003). Studies have shown that HO-1 immunoreactivity in neurons and temporal cortex cannot be detected in non-dementia patients (Schipper, H., S. Cissé, and E. Stopa, 1995).

This study still has certain limitations: this study is a prospective study, due to time constraints, the sample size is not large enough.

In the next study, the sample size should be expanded. Long-term follow-up and face-to-face interviews will be conducted for further study of influencing of plasma HO-1 on the prognosis of CSVD patients.

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