Analyzing the neuropsychological characteristics and changes in serum markers of patients with chronic cerebral circulation insufficiency

Jianhua Tang[1], Yuqing Zhen[1], Ling Yu[1], Cui Lv[1], Juan Zheng[1], Hui Liang[1]*

[1]Department of Neurology, Yantaishan Hospital, Yantai, China

Study conducted at the Department of Neurology, Yantaishan Hospital, Yantai, China

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***Correspondence:**
Department of Neurology,
Yantaishan Hospital
Address: No. 91 Jiefang Road
Yantai, Shandong – China
Postal code: 264401
lianghui_aikan@163.com

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Summary

Objective: To investigate the neuropsychological characteristics and changes in CRP, S100B, MBP, HSP-7, and NSE in serum.
Method: Sixty-six (66) patients treated in our hospital as CCCI group were chosen for our study, and 90 patients with depression were selected as the depression group. The patients in both groups were examined with CT perfusion, depression, anxiety and cognition evaluation. Their serum CRP, S100B, MBP, HSP-70 and NSE levels were detected. Neuropsychological and serum markers characteristics were compared.
Results: The CBF and CBV in bilateral basal ganglia, frontal lobes, greater oval center, brain stem, and left and right regions of occipital lobes of the patients in CCCI group were significantly lower than in the depression group. The HAMD and HAMA scores of CCCI group patients were significantly lower than in the depression group; CCCI group performed better regarding attention, memory, abstract terms and delayed recall. CCCI also had significantly higher total scores than the depression group. Serum CRP, S100B, MBP, HSP-70 and NSE levels in CCCI group were significantly higher than in the depression group. The differences reach statistical significance ($p<0.05$).
Conclusion: CCCI patients who are accompanied by minor depressive disorder have different degrees of cognitive impairment and experience a significant rise in serum CRP, S100B, MBP, HSP-70 and NSE.

Keywords: Neuropsychology. Biomarkers. Cerebrovascular Circulation.

Introduction

Chronic cerebral circulation insufficiency (CCCI) is cerebral vascular stenosis or hypoperfusion in patients induced by multiple factors. It can cause the cerebral blood flow to be incapable of satisfying the basic physiological demands.[1-3] Its existence has been one of the most controversial issues in this field because this disease has no specific clinical manifestations and there is no reliable diagnosis method for it.[4-6] However, a large number of clinical experiences have demonstrated that such patients often experience the clinical manifestations of repeated dizziness and head heaviness, which are accompanied by emotional abnormalities such as anxiety-depression of varying degrees, with a very high possibility of acute stroke and cognitive impairment. During recent years, in order to find an accurate method to diagnose CCCI, the changes in the level of serum markers have drawn wide attention from scholars.[7,8] Therefore, our study reviewed the CCCI patients admitted in our hospital from April 2013 to April 2015 and analyzed their psychological characteristics as well as serum markers.

Method

General materials

A total of 66 CCCI patients visited our hospital for treatment from April 2013 to April 2015, meeting the diagnosis criteria: (1) aged over 60 years; (2) with the risk factors of cerebrovascular diseases; (3) with a course of chronic diseases for over half a year; (4) with subjective symptoms such as obvious dizziness and head heaviness; (5) cerebral arterial vascular stenosis displayed by MRA/DSA examinations. In the CCCI group, the number of male and female patients was 42 and 24, respectively, aged 60 to 79 years with a mean of 68.31±5.24 years. Additionally, 55-year old individuals

with depression who sought our hospital during the same period were selected and included as a control group, with the clinical manifestations of similar dizziness and vertigo. The control group had 25 males and 20 females aged 61 to 78 years with a mean of 67.32±4.27 years.

Study methods

CT spiral perfusion examination: all patients underwent cerebral CT perfusion imaging examination within one week after their admissions. The examination was performed with a 64-layer spiral CT machine (Brilliance from Phillips Company). Using the canthomeatal line as the baseline, the conventional cross section scan with a layer thickness of 5 mm and a layer spacing of 5 mm was first performed, and then CT perfusion imaging was performed with basal ganglia plane as the center and a coverage area of 40 mm (layer thickness 5 mm × 8 layers). By means of high-pressure syringe, a bolus injection of 50 mL non-ion contrast medium (ultravist 300 mg/mL) was performed at the rate of 4 mm/s via the hand dorsum vein. In the meantime, dynamic scan (matrix 512 × 512, scan field 24 × 24 mm, tube voltage 120 kV, tube current 80 mA) was performed continuously for 50 seconds, the re-acquired 152 dynamic images were transmitted to the workstation, and Brain perfusion software was used for further processing. The planes at the basal ganglia and corona radiata areas of the CCCI patients were selected as the planes of interest, and a method of hand drawing of the region of interest (ROI) was adopted to observe the following regions: bilateral basal ganglia, frontal lobes, greater oval center, brain stem and occipital lobes. Parameters such as cerebral blood flow, cerebral blood volume, mean transit time (MTT) and time-to-peak (TTP) were measured. Generally, each site was measured for three times to ensure that the size of ROI selected each time was reasonably consistent. Both qualitative and quantitative methods were adopted to evaluate the computed tomography perfusion imaging (CTPI) parameters, i.e. a qualitative evaluation on whether the left and right cerebral perfusion was symmetric on the TTP and MTT pseudocolor images: with the measured values in the control group as the yardstick, if the absolute value of CTPI parameters of each ROI in CCCI group exceeded 95% confidence interval of the absolute values in the control group, that was considered as perfusion abnormality.

In the next morning following admission, 5 mL of venous fasting blood were extracted as detection samples, then they were centrifuged, and finally the supernatant was saved and stored at -80°C. Radioimmune turbidimetric method was used to measure the C-reactive protein (CRP) levels of the patients in the two groups after admission and after the treatment, and the enzyme linked immunosorbent assay was used to determine the S100 calcium-binding protein B (S100B), myelin basic protein (MBP), heat shock protein 70 (HSP-70) and neuron-specific enolase (NSE) contents in plasma.

Grade indexes

Status evaluation: the Hamilton's Depression Scale (HAMD) and Anxiety Scale (HAMA) were used to evaluate the patient's depression and anxiety status after admission and after treatment.

Cognitive function evaluation: the Montreal Cognitive Assessment (MoCA) scale was used to determine the patient's cognitive functions after admission and after treatment, the scale is mainly used to explore eight aspects of cognitive functions, such as visual space, executive capacity, naming, ability to concentrate mentally and language. The test generally lasts 8 to 10 minutes. A higher score means stronger cognitive abilities.

Statistical methods

SPSS 15 software was used for data processing, the enumeration data were shown in the form of absolute numbers and frequencies, t and χ^2 methods were used for the test. $p<0.05$ means the difference was of statistical significance.

Results

CT perfusion parameters in the left and right encephalic regions

As is shown in Figure 1, the cerebral blood flow (CBF) and cerebral blood volume (CBV) in bilateral basal ganglia, frontal lobes, greater oval center, brain stem, and left and right regions of occipital lobes of the patients in CCCI group were significantly lower than those seen in the depression group. The comparison generated a significant difference ($p<0.05$ or $p<0.01$), and the inter-group comparison did not generate an obvious difference in MTT and TTP ($p>0.05$).

Depression and anxiety evaluation

As shown in Table 1, the HAMD and HAMA scores of patients in the CCCI group were significantly lower than those of the depression group, and the comparison generated a significant difference ($p<0.05$). The proportions of patients with possible depression and anxiety in the CCCI group were significantly higher than that of the depression group, but the proportion of patients with confirmed depression and anxiety and obvious depression and anxiety was significantly lower than that of depression group, and the comparison generated a significant difference ($p<0.05$).

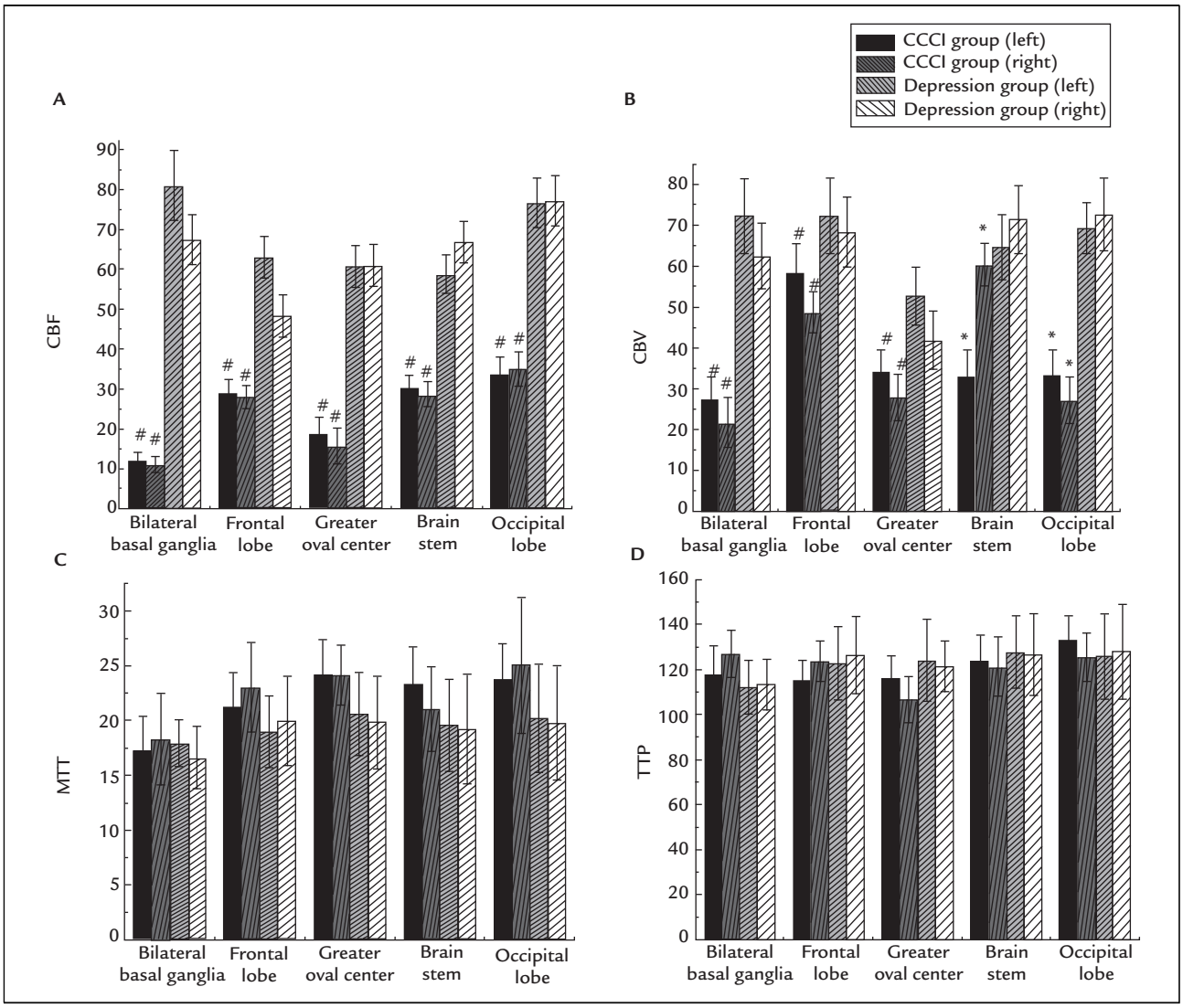

FIGURE 1 Comparison between CCCI group and depression group in terms of the patient's perfusion parameters of left and right encephalic regions when compared with the depression group. *p<0.05; #p<0.01.

CCCI: chronic cerebral circulation insufficiency; CBF: cerebral blood flow; CBV: cerebral blood volume; MTT: mean transit time; TTP: time-to-peak.

TABLE 1 Comparison between CCCI group and depression group in terms of anxiety-depression.

Group	Depression					Anxiety				
	HAMD score	Normal	Possible depression	Confirmed depression	Serious depression	HAMA score	No anxiety	Possible anxiety	Confirmed anxiety	Obvious anxiety
CCCI group (n=66)	23.22±5.27	8 (12.12)	36 (54.55)	19 (28.79)	3 (4.55)	17.32±4.29	14 (21.21)	32 (48.48)	13 (19.70)	7 (10.61)
Depression group (n=55)	33.21±5.32	0 (0)	10 (18.18)	29 (52.73)	16 (29.09)	26.32±5.21	5 (9.09)	11 (20.00)	26 (47.27)	13 (23.64)
t/χ^2	7.833	-	4.486	5.874	3.76	4.844	4.456	5.477	6.685	4.466
p	0.009	-	0.013	0.017	0.028	0.012	0.015	0.013	0.024	0.034

CCCI: chronic cerebral circulation insufficiency; HAMD: Hamilton's Depression Scale; HAMA: Anxiety Scale (HAMA).

Cognitive evaluation

As shown in Table 2, the scores for visual space, executive capacity, ability to focus, memory, abstraction ability, delayed recall and the total scores of the patients in the CCCI group were significantly lower than those in the depression group, and the comparison generated a significant difference ($p<0.05$).

Plasma CRP, S100B, MBP, HSP-70 and NSE levels

As shown in Figure 2, the levels of CRP, S100B, MBP, HSP-70 and NSE in serum of the patients in the CCCI group were significantly higher than those of the depression group, and the comparison generated a significant difference ($p<0.05$).

Discussion

In 1990, a scholar from Japan first proposed the concept of chronic cerebral circulation insufficiency, which refers to a phenomenon of overall blood flow decrease that occurs in the brain instead of the focal ischemic lesions.[5] Studies have revealed that the primary reason for CCCI occurrence is as follows: atherosclerosis leads to the occurrence of vascular plaques and stenosis, so that the cerebral blood flow decreases. When it decreases to a certain threshold value, the local perfusion will also decrease, causing clinical manifestations such as dizziness and head heaviness, which are usually considered to be the early manifestations of cerebral infarction.[9-12] As there is no specific manifestation for CCCI clinical symptoms and imaging characteristics, early accurate diagnosis is one of the difficulties in the treatment of this disease. Currently, domestic and foreign studies show that the early manifestations of many patients with chronic cerebral functional insufficiency are experiencing an increase in memory loss and emotional disorders, which is similar to neurosis such as depression and accompanied by mild cognitive disorder. Therefore, the studies on the neuropsychological characteristics of CCCI patients have drawn wide attention from scholars during the recent years.[13]

The results of our study revealed that 87.88% of the patients in the CCCI group have anxiety issues and 78.78% of the patients concomitantly suffer from the psychological conditions of depression. Comparison between the CCCI group and the depression patients shows that the proportion of patients with possible depression and anxiety in the CCCI group was significantly higher than that of the depression group, but the proportion of patients with confirmed depression and anxiety and obvious depression and anxiety was significantly lower than that of the depression group. It is also found that the HAMD and HAMA scores of the patients in the CCCI group were significantly lower than those seen in the depression group. The results indicated that the majority of the CCCI patients concomitantly suffer from depression, but the depression is mild and there is no specific report on the incidence rate of depression among CCCI patients. Secondly, in our study, the MoCA scale was used to evaluate the cognitive functions of the patients in the two groups. The results indicated that the scores for visual space, executive capacity, ability to focus attention, memory, abstraction and delayed recall and the total scores of the patients in the CCCI group were significantly lower than those in the depression group. The result also indicated that the cognitive functions of the patients in the CCCI patients decreased significantly. The decrease in the cognitive functions of the patients in the CCCI patients has drawn wide attention. Animal experiment studies showed that chronic cerebral ischemia will cause serious damages to the neurons of hippocampal CA1 area of rats while the hippocampal neurons are the key links that influence the cognitive abilities such as memory and learning, which can properly explain the decrease in the cognitive functions of the

TABLE 2 Comparison between CCCI group and depression group in terms of MoCA score.

Item	Full score	CCCI group (n=66)	Depression group (n=50)	t	p
Visual space and executive capacity	5	4.39±0.26	4.54±0.31	5.967	0.028
Naming	3	2.23±0.17	2.41±0.27	0.876	0.142
Ability to concentrate mentally and memory	6	4.34±1.01	5.12±0.57	2.837	0.037
Language	3	2.42±0.31	2.68±0.18	0.412	0.052
Abstraction	2	1.17±0.25	1.52±0.17	3.076	0.026
Delayed recall	5	2.57±0.83	3.78±0.54	6.983	0.017
Orientation	6	5.73±0.11	5.76±0.07	0.928	0.219
Total score	30	22.27±3.56	25.27±3.13	4.976	0.026

CCCI: chronic cerebral circulation insufficiency; MoCA score: Montreal Cognitive Assessment score.

CCCI patients. Studies revealed that basal nuclei areas and greater oval centers are rich in a large number of neurons and fibers closely associated with cognitive functions such as learning and memory.[14-17] By means of multi-layer spiral CT examination, our study found that the CBF and CBV in bilateral basal ganglia, frontal lobes, greater oval center, brain stem, and left and right regions of occipital lobes of the patients in CCCI group were significantly lower than those seen in the depression group, which leads to decrease in the cognitive functions of the CCCI patients.

Change in blood markers is also one of the most important manifestations of chronic cerebral ischemic diseases.[18,19] In our study, the research of all indices in blood indicated that CRP, S100B, MBP, HSP-70 and NSE in the blood of patients in the CCCI group had a significant increase compared with the depression group. CRP level is one of the commonest markers for body inflammatory reactions during the clinical application. A large number of studies revealed that increased levels of CRP in plasma of patients with chronic cerebral ischemia are closely as-

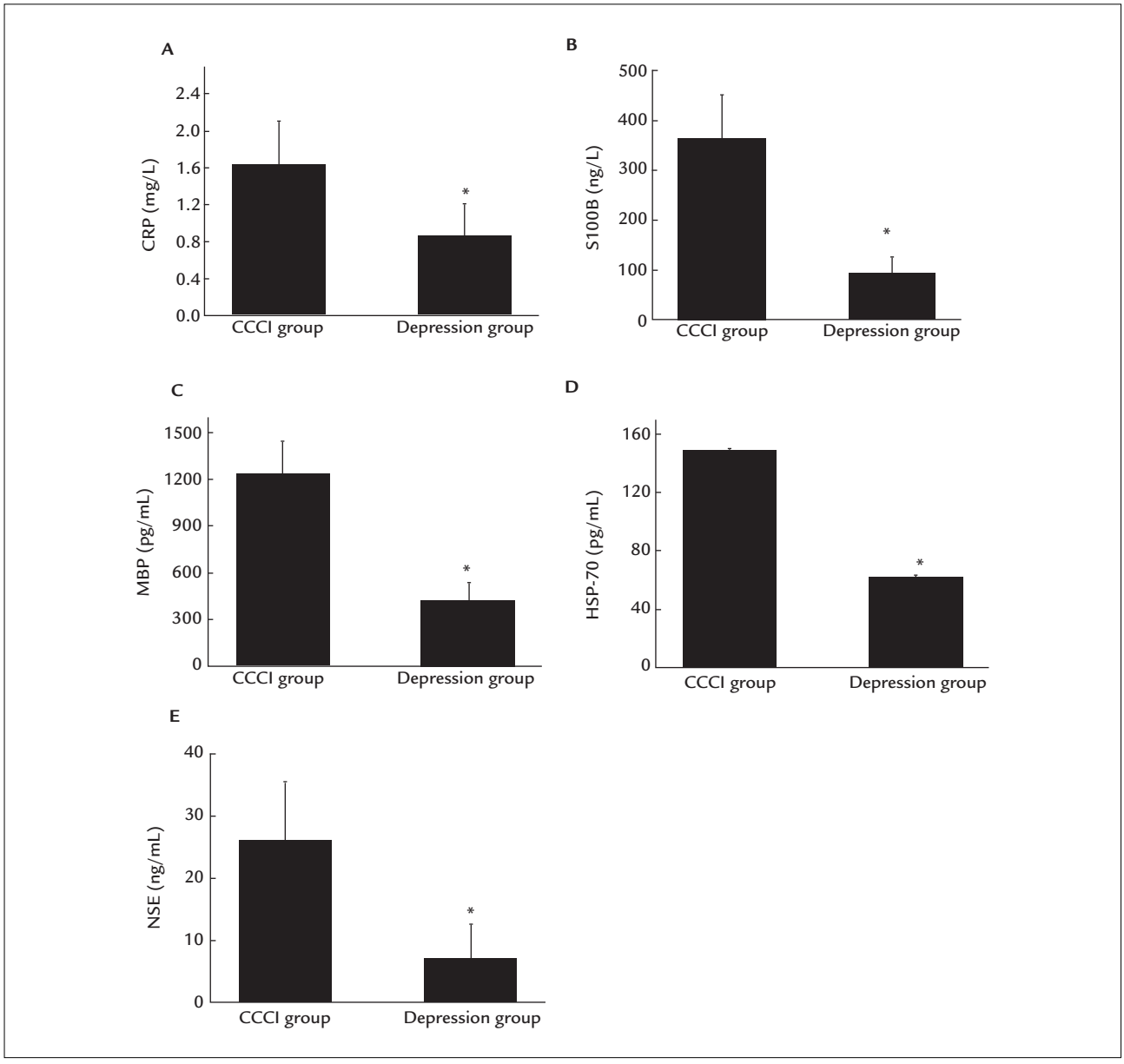

FIGURE 2 Comparison the levels of CRP, S100B, MBP, HSP-70 and NSE between the CCCI group and depression group. Data are presented as mean + SD. *p<0.05 versus CCCI group.

CCCI: chronic cerebral circulation insufficiency; CRP: C-reactive protein; MBP: myelin basic protein; HSP-70: heat shock protein 70; NSE: neuron-specific enolase.

sociated with the degree of injuries in brain cells. And it can further aggravate the injuries of cerebral vascular endothelial cells and aggravate patient conditions.[20] NSE is a type of specific enolase present in the cerebral neurons and endocrine cells and participates in the glycolysis process. Cerebral blood supply insufficiency will lead to functional disorder and structural injuries in neuron serous membrane. As a result, NSE will be released from the damaged cell membrane and enter the cerebrospinal fluid, passing through the disrupted blood-brain barrier and entering the blood circulation, further leading to an increase in the level of NSE in blood. S100B and MBP are present in the colloid and oligodendrocytes in the central nervous system. Their abundance can somewhat reflect the degree of damages of colloid and oligodendrocytes and is closely associated with the damages in cognitive functions.[21] NSE, S100B and MBP are often used to evaluate whether the damages occur to neurons, colloid and oligodendrocytes in the cerebral tissues. They can also be used to evaluate severity because they are important serum markers of cognitive function. Studies revealed that HSP-70 is a type of stress protein closely associated with patient cognitive functions, and HSP-70 can improve neurocyte tolerance and activate the anti-apoptosis route under the stress status so that the damaged neurocytes in the brain can be protected. Therefore, in the case of cerebral blood supply insufficiency in the human body, the HSP-20 level will be greatly increased to lower the neurocyte injuries.[17] As shown in the above results, in the case of the occurrence of CCCI, the CRP, S100B, MBP, HSP-70 and NSE will experience significant changes, and these can be used as important indices for the diagnosis of this disease.

To sum up, CCCI patients often concomitantly suffer from mild depression and cognitive injuries of varying degrees, the CRP, S100B, MBP, HSP-70 and NSE in serum will increase significantly, and the diagnosis of CCCI can be made according to the neuropsychological characteristics and the changes in serum markers.

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