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ORIGINAL ARTICLE

The predictive value of serum p-CREB level on secondary cognitive impairment in patients with mild-to-moderate craniocerebral trauma

Chenyang Han[1] · Yi Yang[1] · Shuiliang Ruan[2] · Li Guo[3] · Xiaoling Zhang[4] · Qiaobing Guan[4]

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Abstract

The study was designed to investigate the predictive value of phosphorylated CAMP response element binding protein (p-CREB) level in peripheral blood on secondary cognitive impairment in patients with mild-to-moderate craniocerebral trauma. A total of 107 patients with mild-to-moderate craniocerebral trauma were selected, who were admitted to the Second Affiliated Hospital of College of Jiaxing from January 2016 to January 2017. Of them, 30 patients were diagnosed with secondary mild cognitive impairment (MCI) during follow-up, who were assigned to the experimental group. The remaining 77 subjects were assigned to the control group, without significant cognitive impairment. The clinical data of patients were compared between two groups, and the clinical data of patients with different p-CREB levels were compared. Logistic regression analysis was used to investigate the risks of MCI in patients with different p-CREB levels. Moreover, multiple linear regression analysis was employed to assess the influencing factors of scores of Mini-Mental State Examination (MMSE) on patients with secondary MCI. The following pathophysiologic factors, including age, rescuing time, the proportion of hypertension, trauma severity score (AIS-ISS), and serum total cholesterol (TC) were significantly higher in patients in the experimental group compared to those in the control group (all $P < 0.05$). The serum level of p-CREB ranged from 0.127 to 1.852 ng/ml. Afterwards, the serum levels of p-CREB of patients were divided into four quartiles. The first, second, third, and fourth quartile groups were 0.127–0.548 ng/ml, 0.549–0.982 ng/ml, 0.983–1.412 ng/ml, and 1.413–1.852 ng/ml, respectively. As the level of p-CREB increased, age, rescuing time, the proportion of hypertension, and AIS-ISS gradually decreased, with statistical significance (all $P < 0.05$). Univariate and multivariate logistic regression analyses demonstrated that the risk of secondary MCI of patients in the first quartile was 1.21 and 1.58 times of the fourth quarter, respectively. Multivariate linear regression analysis showed that age, rescuing time, AIS-ISS, and serum p-CREB level were independent influencing factors of MMSE score in secondary MCI patients. For each increase of 0.1 ng/ml in serum p-CREB level, the MMSE score increased by 0.382 in MCI patients. Serum p-CREB level was an independent risk factor of secondary MCI in patients with mild-to-moderate craniocerebral trauma, whose level was significantly correlated with the injured degree of cognitive impairment. The level of p-CREB is also age-related, and younger patients have a higher level.

Keywords Cognitive impairment · p-CREB · Craniocerebral trauma · Secondary

✉ Xiaoling Zhang
wt198805@126.com

✉ Qiaobing Guan
wasd911@126.com

Chenyang Han
691513770@qq.com

Yi Yang
13736196736@163.com

Shuiliang Ruan
ruanguan@hotmail.com

Li Guo
13429401897@163.com

[1] Department of Pharmacy, The Second Affiliated Hospital of Jiaxing University, Jiaxing 314000, China

[2] Department of neurosurgery, The Second Affiliated Hospital of Jiaxing University, Jiaxing 314000, China

[3] Department of Center Laboratory, The Second Affiliated Hospital of Jiaxing University, Jiaxing 314000, China

[4] Department of Neurology, The Second Affiliated Hospital of Jiaxing University, Jiaxing 314000, China

Introduction

Craniocerebral trauma is a group of mechanical damage, with serious conditions, rapid progression, high mortality, and disability rate. According to epidemiological data in 2010 in China, craniocerebral trauma is a relatively common type of surgery, with an incidence of > 100/100,000, of which, mild and moderate craniocerebral trauma accounts for about 80% of the total group [1].

Cognitive impairment is a complication that occurs after craniocerebral trauma, which is characterized by long duration, and clinical manifestations were perception disorder, memory disorder, and thinking disorder. It can be divided into two stages: mild cognitive impairment (MCI) and dementia [2]. The external attack on brain tissue results in damage of brain tissue structure, nerve damage, and loss of the original function. The daily performance of patients includes decreased work and life ability, declined cognition, and understanding [3]. Due to occult onset of secondary MCI and atypical progression, MCI is often neglected in clinical practice. Once MCI deteriorates into the stage of dementia, the daily living ability of patients would be seriously affected. In view of the abovementioned damage of MCI, how to conveniently select sensitive and specific risk factors of MCI is of great significance in predicting the occurrence of MCI. However, there is no sensitive or specific biochemical indicator in clinic at present. In recent years, CAMP response element binding protein has been detected as a member of nuclear transcription factor family. It is whose basic region of C-terminal can bind to DNA and leucine zipper structure for dimerization. Its active structure, phosphorylated CREB (p-CREB), plays a crucial role in a variety of pathophysiologic processes, such as learning and memory and synaptic plasticity. p-CREB can integrate calcium, growth factor, and cAMP, which affect the survival and growth of neurons [4, 5]. In animal experiments, the level of p-CREB in the brain tissue has been confirmed to be closely correlated with the cognitive ethology of rats, and the formation of long-term memory relies on the mediation of p-CREB signaling [6]. In this study, we investigated the potential influencing factors of secondary MCI in patients with mild-to-moderate craniocerebral trauma. We aimed to understand whether p-CREB harbored predictive value for MCI, hoping to reveal the pathogenesis of MCI and to improve the prediction and diagnosis of MCI, which would provide theoretical basis for improving the prognosis of patients with craniocerebral trauma.

Materials and methods

Subjects

It was a prospective, serial cohort study, enrolling 112 patients with mild-to-moderate craniocerebral trauma who were admitted to the Second Affiliated Hospital of College of Jiaxing from January 2016 to January 2017. These patients were followed up from July 2016 to December 2017 to confirm the associated prognosis. The end point events of follow-up were secondary MCI or without MCI within 1 year after discharge from the hospital. Patients who developed MCI were assigned to the experimental group, while those without MCI were assigned to the control group. All patients were treated surgically, without anesthesia. Because of mild-to-moderate craniocerebral trauma, the patients were treated in the routine ward.

The grade of craniocerebral trauma Craniocerebral trauma was graded according to the Head and Neck Section of the Concise Trauma Scoring (AIS-ISS) [7], where 1 for mild trauma and 2 for moderate trauma.

The diagnostic criteria of MCI The diagnostic criteria of MCI were in accordance with "China Consensus on Prevention and Treatment of Cognitive Impairment" published in 2006 [8], which were listed as follows: (1) memory impairment is the main complaint, which is confirmed by insider or the patient himself. (2) The daily living ability is not affected. (3) The patient does not meet the standard of dementia. (4) The rest of brain function degenerative diseases are excluded, such as disturbance of consciousness, delirium, and aphasia. After MCI diagnosis, the degree of cognitive impairment of the patient was quantitatively evaluated by the Mini-Mental State Examination (MMSE). The total score of the scale was 30 points, and the MMSE scores of MCI patients were generally of or over 24 points.

Exclusion criteria

(1) Patients with confirmed cognitive impairment and undergoing relevant physical therapy or drug treatment. (2) Patients with low educational level (illiterate). (3) Patients suffering from mental illness and receiving drugs to interfere with mental state for a long time. (4) Patients combined with stroke, brain tumors, liver and kidney dysfunction, and other diseases. (5) Patients addicted to alcoholism and abuse of narcotic drugs for a long time. (6) Patients who cannot be communicated properly due to communication and visual disorders.

Removal criteria

Patients enrolled in the study were removed from the observation cohort in the following conditions. (1) Incomplete data of patient and follow-up. (2) All kinds of stroke and brain trauma occurred again during the follow-up. (3) Lost or incomplete follow-up data. (4) Other factors affecting the disease, which disturbed the results.

Collection of data

A total of 112 eligible patients with craniocerebral trauma were enrolled according to inclusion and exclusion criteria. Among them, 63 were injured in traffic accidents, 28 were injured in impact lesion, and 21 were injured in falls. During follow-up, two patients were removed from the observation cohort due to a secondary hemorrhagic stroke, one patient lost contact, and two patients were lost to follow-up. The overall rate of lost to follow-up was 4.46%, and the bias of this study was controllable. The final number of enrolled patients in the study was 107. Of them, 30 patients developed secondary MCI (experiment group), 77 patients were not accompanied with significant cognitive impairment (control group).

The enrolled data of the observation cohort included (1) type of trauma, rescuing time (from the trauma to being treated at hospital); (2) general condition, personal history, and related past history; (3) laboratory examinations and serum p-CREB levels at discharge; and (4) all kinds of trauma application score: the Abbreviated Injury Scale (AIS-ISS), acute physiology and chronic health evaluation-II (APACHE-II, and Glasgow Coma Scale (GCS).

The study was approved by the Ethics Committee of the Second Affiliated Hospital of College of Jiaxing. Written informed consent and follow-up consent were signed by patients or their family at first admission.

Statistical analysis

SPSS 21.0 statistical software was used for analysis. The measurement data of normal distribution were expressed as mean ± standard deviation ($\overline{x} \pm s$). Two sets of independent samples *t* test or one-way ANOVA were used for comparison among groups (LSD *t* test was used for further comparison). Enumeration data were shown as percentage, which was compared by χ^2 test. Univariate and multivariate logistic regression analyses were employed to assess the risks of secondary MCI in patients with different levels of p-CREB and different independent variables. Multivariate linear regression analysis was utilized to investigate the effect of p-CREB level on MMSE score at follow-up. A $P < 0.05$ was considered as statistical significance.

Results

The comparison of clinical data of patients in experiment group and control group

The age, rescuing time, the proportion of hypertension, AIS-ISS, serum total cholesterol TC), and p-CREB of patients in the experiment group were significantly higher compared to those in the control group (all $P < 0.05$, shown in Table 1)

The comparison of clinical data of patients with different p-CREB levels

The level of p-CREB ranged from 0.127 to 1.852 ng/ml, which was further divided into four quartiles. The first, second, third, and fourth quartile groups were 0.127–0.548 ng/ml, 0.549–0.982 ng/ml, 0.983–1.412 ng/ml, and 1.413–1.852 ng/ml, respectively. Univariate analysis demonstrated that the age, rescuing time, the proportion of hypertension, and AIS-ISS were statistically different in patients with different p-CREB levels (all $P < 0.05$). As the level of p-CREB increased, age, rescuing time, the proportion of hypertension, and AIS-ISS gradually decreased, with statistical significance ($P < 0.05$). However, the TC was not statistically significant in patients with different levels of p-CREB ($P > 0.05$). Results are shown in Table 2.

The risk of secondary MCI in patients with different p-CREB levels

The existence of secondary MCI was taken as dependent variable; univariate and multivariate logistic regression analyses were used to assess the effect of independent variables, such as p-CREB level on it: (1) model I was a univariate logistic regression analysis, which demonstrated that risk of secondary MCI in the first quarter was 1.58 times higher than that of the fourth quarter, with statistical significance ($P < 0.05$). (2) model II was a multivariate logistic regression analysis after correcting independent variable, TC level, which showed that the risk of secondary MCI gradually decreased and the risk of secondary MCI in the first quartile group was 1.28 times of that in the fourth quartile, with statistical significance ($P < 0.05$). (3) model III was a multivariate logistic regression analysis after correcting age, rescuing time, history of hypertension, and AIS-ISS, which suggested that the risk of secondary MCI was further reduced, but the risk of secondary MCI in the first quartile was still 1.21 times higher than that in the fourth quartile, with statistical significance ($P < 0.05$). The results were shown in Table 3

The influencing factor of scores of MMSE scale in patients with secondary MCI

The scores MMSE scale of patients with secondary MCI ($N = 30$) at follow-up were taken as dependent variables; the age, rescuing time, proportion of hypertension, AIS-ISS, TC level, and p-CREB of patients were taken as independent variables; multivariate linear regression analysis was used. As a result, the final regression model consisted of age, rescuing time, AIS-ISS, and p-CREB level. The regression equation was $Y = 13.851 - 0.079X_1 - 0.711X_2 - 1.214X_4 - 0.354X_6$. For each increase of 0.1 ng/ml in serum p-CREB level before discharge, the MMSE score increased by 0.382. The results are shown in Table 4.

Table 1 The comparison of clinical data of patients in experiment group and control group

Items	Control group ($n = 77$)	Experiment group ($n = 30$)	χ^2/t value	P value
Male (number)	45(58.44%)	16(53.33%)	0.641	0.281
Age (years)	45.15 ± 11.33	62.21 ± 14.21	6.542	0.002
BMI (kg/m^2)	21.22 ± 4.21	23.24 ± 3.84	0.487	0.254
Type of trauma				
Cerebral contusion and laceration (number)	18 (23.37%)	6 (20%)	1.281	0.182
Epidural hematoma (number)	15 (19.48%)	6 (20%)	1.141	0.224
Subarachnoid hemorrhage (number)	16 (20.78%)	7 (23.33%)	1.574	0.412
Fracture of skull (number)	28 (36.36%)	11 (36.67%)	1.254	0.241
Rescuing time (hour)	1.21 ± 0.35	2.54 ± 1.05	3.241	0.018
Smoking (number)	22 (28.57%)	9 (30.0%)	0.181	0.227
Alcoholism (number)	10 (12.99%)	4 (13.33%)	1.421	0.304
Hyperlipidemia (number)	20 (25.97%)	8 (26.67%)	1.251	0.258
Hypertension (number)	17 (22.10%)	12 (40.0%)	3.571	0.008
Diabetes mellitus (number)	7 (9.10%)	4 (13.30%)	0.852	0.106
AIS-ISS (point)	13.24 ± 3.57	18.41 ± 4.10	4.521	0.012
APACHE-II (point)	26.34 ± 8.54	28.08 ± 9.57	1.741	0.187
GCS (point)	13.25 ± 1.87	12.87 ± 2.08	1.320	0.207
MAP (mmHg)	112.87 ± 21.24	107.25 ± 20.25	0.852	0.241
APN (μg/ml)	5.27 ± 1.57	4.89 ± 1.47	1.121	0.152
TC (mmol/l)	5.87 ± 1.44	7.85 ± 1.64	4.142	0.018
LDL-C (mmol/l)	4.12 ± 1.22	4.01 ± 1.51	1.852	0.178
HDL-C (mmol/l)	0.88 ± 0.22	0.79 ± 0.18	0.952	0.221
TG (mmol/L)	3.66 ± 0.87	3.15 ± 1.10	0.785	0.182
HbAlc (%)	5.21 ± 1.29	5.87 ± 0.88	0.121	0.316
CysC (μg/ml)	3.40 ± 1.24	3.88 ± 1.10	0.182	0.387
p-CREB (ng/ml)	1.21 ± 0.21	0.65 ± 0.14	5.774	0.003

BMI, body mass index; *AIS-ISS*, the Abbreviated Injury Scale trauma severity score; *APACHE-II*, acute physiology and chronic health score II; *GCS*, Glasgow Coma Scale; *MAP*, mean arterial pressure: *TC*, total cholesterol; *LDL-C*, low-density lipoprotein; *HDL-C*, high-density lipoprotein; *TG*, triglyceride; *HbAlc*, glycosylated hemoglobin; *APN*, adiponectin; *CysC*, serum cystatin C; *p-CREB*, CAMP response element binding protein

Discussion

Pre-judgment and identification of MCI after craniocerebral trauma and timely intervention play a significant role in the diagnosis and treatment of MCI, delaying the pathological progression of MCI and improving relevant prognosis in clinics. However, the current clinical treatment focuses on the treatment of craniocerebral trauma, while there is insufficient knowledge about secondary MCI, which basically stayed at the theoretical level [9]. Hence, it is of great significance to predict the occurrence of MCI.

CREB, a protein monomer consisted of 341 amino acids, mainly contains kinase-inducing region at C-terminal, basic region at N-terminal, and leucine zipper motif [10]. CREB is

Table 2 The comparison of clinical data of patients with different p-CREB levels

Groups	Age (year)	Rescuing time (hour)	Hypertension (yes/no)	AIS-ISS	TC (mmol/l)
The first quartile group	65.21 ± 9.12	2.52 ± 0.82	13/30	19.35 ± 4.52	6.87 ± 1.57
The second quartile group	52.31 ± 10.21	1.89 ± 0.71	10/28	16.32 ± 3.87	5.38 ± 1.27
The third quartile group	48.52 ± 11.22	1.61 ± 0.68	5/26	14.22 ± 4.10	4.87 ± 1.54
The fourth quartile group	40.24 ± 10.32	1.08 ± 0.47	3/23	12.18 ± 3.97	4.64 ± 1.21
F/χ^2	6.854	1.024	2.987	4.011	1.877
P value	0.000	0.032	0.018	0.014	0.088

Except TC, P values < 0.05 in comparison of any two of the remaining items. *TC*, total cholesterol; *AIS-ISS*, trauma severity score

Table 3 Risk models of secondary MCI in patients with different quartiles of p-CREB levels

Groups	Model I		Model II		Model III	
	OR value (95% CI)	*P* value	OR value (95% CI)	*P* value	OR value (95% CI)	*P* value
The first quartile group	1.00	–	1.00	–	1.00	–
The second quartile group	1.19(1.08–1.33)	0.007	1.11(0.98–1.20)	0.021	1.08(0.90–1.11)	0.181
The third quartile group	1.28(1.19–1.49)	0.006	1.30(1.20–1.41)	0.005	1.12(0.10–1.23)	0.062
The fourth quartile group	1.50(1.30–1.61)	0.000	1.38(1.31–1.48)	0.001	1.24(1.11–1.38)	0.012

P-CREB, phosphorylated cAMP response element binding protein; *MCI*, mild cognitive impairment; *OR*, odds ratio

widely distributed in the cerebral cortex and hippocampus. The CREB in the brain cortex is positively expressed in the neurons of molecular layer, astrocytes of granular layer, and cells of pyramidal cell layer; CREB in hippocampus is mainly distributed in granulosa cell layer of dentate gyrus, followed by CA3 area and CA1 [11]. CREB is dephosphorylated at rest, whereas CREB is phosphorylated to become active p-CREB after cell activation [12].

In the CREB study, Hayward found that external stimuli could promote the formation of p-CREB, activate the intracellular protein kinase cascade, and induce the expression of target genes to trigger long-term effects and promote memory formation [13]. In central-hippocampal formation, the main role of p-CREB is associated with the formation of new neurons, synaptic plasticity, and long-term memory, and p-CREB can activate gene expression that is closely related to long-term memory [14]. Multiple experiments have confirmed that decreased activity of p-CREB can inhibit the formation of long-term memory. Memory is generally declined in cognitive impairment. Therefore, from this perspective, p-CREB has a close relationship with cognitive impairment.

Accompanied by increased age, varying degrees of underlying disease, continuous decline of metabolism during aging, and changes in vascular elasticity, in the case of delayed rescue after craniocerebral trauma, a large number of inflammatory cytokines may lead to further damage of endothelial cells of arteries and aggravate the insufficiency of blood supply to the nerve cells, which decreases the repair capacity of damaged neurons. With prolonged course of craniocerebral trauma, organic damage can directly damage nerve cells and lead to nerve conduction disorders of thinking activities and affect cognitive function by interrupting the contact of cortex and subcortical area [15]. During this process, various pathological factors contribute to the increased permeability of the blood-brain barrier, resulting in the exudation of p-CREB. The serum level of p-CREB can reflect the level of p-CREB in the brain. In this study, sample data were prospectively and serially collected, followed by 1-year follow-up to screen patients with secondary MCI after craniocerebral trauma. In addition, based on the degree of dementia using MMSE scale, the relevant results were obtained after statistical analysis. (1) Logistic regression analysis demonstrated that the risk of secondary MCI in patients in the first quartile group was 1.21 and 1.58 times higher than those in the fourth quartile group, indicating that the level of p-CREB was an independent risk factor for secondary MCI within 1 year after mild-to-moderate craniocerebral trauma, and patients with lower levels of p-CREB were more likely to experience MCI. (2) Multivariate linear regression analysis showed that patients with higher levels of p-CREB harbored a lower degree of secondary MCI. The final regression model consisted of age, rescuing time, AIS-ISS, and p-CREB level. For each increase of 0.1 ng/ml in serum p-CREB level before discharge, the MMSE score increased by 0.382. (3) The level of p-CREB is higher in young patients, which indicates that the level of p-CREB has a certain relationship with age.

Table 4 Multivariate linear regression analysis on the influencing factor of scores of MMSE scale in patients with secondary MCI

Factor	*B*	*β* value	*t* value	*P* value	VIF
age (X_1)	− 0.079	− 0.214	− 3.121	0.018	2.214
Rescuing time (X_2)	− 0.077	− 0.141	− 3.162	0.021	1.401
History of hypertension (X_3)	− 0.311	− 0.150	− 2.140	0.080	1.820
AIS-ISS (X_4)	− 1.214	− 0.241	− 4.121	0.014	2.214
TC (X_5)	− 0.211	− 0.314	− 1.021	0.152	2.087
P-CREB (X_6)	− 0.354	− 0.541	− 3.128	0.017	3.054

B, regression coefficient; *TC*, total cholesterol; *p-CREB*, phosphorylated cAMP response element binding protein; *AIS-ISS*, trauma severity score; *MCI*, mild cognitive impairment; *MMSE*, Mini-Mental State Examination; *VIF*, multiple collinear factors

Collectively, in this study, we demonstrated that serum level of p-CREB was an independent risk factor for secondary MCI after craniocerebral trauma, and patients with higher levels of p-CREB had a lower probability of suffering from MCI. The level of p-CREB was correlated with age. Anyhow, prolonged investigative time and larger sample size are necessary for confirmed conclusions.

Compliance with ethical standards

Ethical standards This study conforms to the relevant ethical regulations, and the research program and process are approved by the Ethics Committee. All patients voluntarily participated and signed the informed consent.

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