Article

Baigui Zhou[1]
Kun Mu[1]
Xuzhou Yu[2]
Xiaoying Shi[3,*]

Serum Levels and Clinical Significance of NSE, BDNF and CNTF in Patients with Cancer-associated Ischemic Stroke Complicated with Post-stroke Depression

[1]Department of Neurology, Zhejiang Jinhua Guangfu Oncology Hospital, 321000 Jinhua, Zhejiang, China
[2]Department of Respiratory Oncology, Zhejiang Jinhua Guangfu Oncology Hospital, 321000 Jinhua, Zhejiang, China
[3]Department of Emergency, Zhejiang Jinhua Guangfu Oncology Hospital, 321000 Jinhua, Zhejiang, China

Abstract

Background: The incidence of post-stroke depression (PSD) may be higher in patients with cancer-associated ischemic stroke (CAIS). The pathogenesis of PSD is mainly related to the emotional injury of stroke and the inability of neurons to effectively repair. This study aims to explore the clinical significance of serum neuron-specific enolase (NSE), brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) expression levels in CAIS patients.

Methods: Clinical data of 106 patients with CAIS admitted to Jinhua Guangfu Oncology Hospital from January 2012 to December 2022 were retrospectively analyzed. Serum levels of NSE, BDNF and CNTF were measured in all patients after admission. Depression screening was performed by Hamilton Depression Scale-17 (HAMD-17) three months after intravenous thrombolysis. Patients with HAMD-17 score >7 were included in the PSD group (n = 44), and patients with HAMD-17 score ≤7 were included in the non-PSD group (n = 62). The general data and serum levels of NSE, BDNF and CNTF were compared between the two groups. According to HAMD-17 scores, patients in PSD group were further divided into mild depression group (8–16 points), moderate depression group (17–23 points) and severe depression group (≥24 points), and the serum levels of NSE, BDNF and CNTF were compared among the three groups. Pearson's correlation test was used to analyze the correlation between HAMD-17 scores and serum NSE, BDNF and CNTF levels in PSD patients. Logistic regression model was used to determine the influencing factors of PSD in CAIS patients. Receiver operating characteristic (ROC) curve was plotted to analyze the predictive efficacy of serum NSE, BDNF, CNTF and their combination on PSD.

Results: Among 106 CAIS patients, the incidence of PSD was 41.51% (44 cases), including 19 patients with mild PSD (43.18%), 14 patients with moderate PSD (31.82%), and 11 patients with severe PSD (25.00%). There were statistically significant differences in negative life events and complications after thrombolytic therapy between PSD and non-PSD patients ($p < 0.05$). The serum NSE level in PSD group was significantly higher than that in non-PSD group, and the serum BDNF and CNTF levels were notably lower than those in non-PSD group (all $p < 0.001$). The serum levels of NSE, BDNF and CNTF in patients with different severity of PSD were statistically significant (all $p < 0.001$). HAMD-17 scores in PSD patients were positively correlated with serum NSE levels ($r = 0.676$, $p < 0.001$) and negatively correlated with serum BDNF and CNTF levels ($r = –0.661$, $p < 0.001$; $r = –0.401$, $p = 0.007$, respectively). By binary logistic regression analysis, the levels of serum NSE, BDNF and CNTF were independent influencing factors for PSD in CAIS patients, among which NSE was a risk factor (odds ratio (OR) >1, $p < 0.05$), BDNF and CNTF were protective factors (OR <1, $p < 0.05$).

Conclusion: This study reveals for the first time that the levels of serum NSE, BDNF and CNTF are closely related to the occurrence and development of PSD in CAIS patients. In clinical CAIS patients with abnormal changes in the above indicators, in addition to anti-tumor treatment

*Corresponding author details: Xiaoying Shi, Department of Emergency, Zhejiang Jinhua Guangfu Oncology Hospital, 321000 Jinhua, Zhejiang, China. Email: shixiaoying0579@163.com

and improvement of neurological deficit symptoms, attention should also be paid to the symptoms of psychological disorders.

Keywords

cancer-associated ischemic stroke; post-stroke depression; NSE; BDNF; CNTF

Introduction

Malignant tumor and stroke are two major types of chronic diseases that endanger human life and health [1,2]. Cancer and stroke are closely linked to each other given the traditional cerebrovascular risk factors in cancer patients. Cancer-associated ischemic stroke (CAIS) represents a variant of stroke caused directly or indirectly by cancer [3,4]. CAIS is characterized by a systemic thromboembolism caused by coagulation disorders related to cancer [5]. At present, the main pathogenesis of CAIS may be related to the hypercoagulable state mediated by cancer, the direct effect of cancer cells and the anti-tumor related treatment [6].

Post-stroke depression (PSD) is the main manifestation of emotional disorders, which is a common complication in stroke patients. The major symptoms of PSD include insomnia, anxiety, sadness and disappointment, reduced speech, slow thinking, loss of appetite, and even suicidal thoughts, all of which exert severe impact on prognosis and quality of life. Patients with PSD pose a substantial burden to the family and society [7–9]. Studies have found that nearly one-third of stroke survivors will experience depressive symptoms [10], and in recent years, with the increasing incidence of malignant tumors and stroke, the incidence of PSD has also increased significantly. For patients with CAIS who have both cancer and stroke, the disease burden, socioeconomic burden, and risk of prognostic death may be greatly increased, potentially accompanied by a higher incidence of PSD. Therefore, early identification of depressive symptoms and proposed targeted intervention plans are the key to the prevention and control of PSD.

Unfortunately, missed diagnosis and misdiagnosis of PSD are very common due to the hidden onset of PSD, the lack of typical symptoms and manifestations, the lack of unified diagnostic standards and diagnosis and treatment guidelines, and the low level of clinical attention to psychological disorders. At present, there is no special diagnosis and treatment method for PSD, and depression rating scale is mainly used for depression screening and antidepressant drugs are used for treatment. However, interpretation of the depression rating scale is susceptible to strong subjectivity, rendering the diagnosis and treatment difficult. Therefore, it is necessary to identify better clinical indicators to help guide the prevention and treatment of PSD. At present, the pathogenesis of PSD has not been fully revealed. Some scholars have pointed out that the pathogenesis of PSD is closely related to the emotional injury of stroke and the inability of neurons to effectively repair [11–13].

Neuron-specific enolase (NSE), brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) all have neuronal trophic functions, which are mostly centered on the repair of injured nerves. NSE is specifically expressed in neurons and neuroendocrine cells. Under pathological conditions, the injured nerve cells in stroke patients drive an increased production of NSE, which further aggravates neurovascular injury in the brain [14], although some studies reported no correlation between NES and PSD. It has been found that serum BDNF levels are significantly reduced in both patients with major depression and animal models of depression [15], but the mechanism of action is still unclear. As a neurocytokine almost exclusively expressed in the nervous system, CNTF level increases following a brain injury. A study suggested that CNTF may affect the emotional behavior of animals by regulating neurotransmission [16], indicating that CNTF level is of great significance for the evaluation of PSD. However, reports on the influencing factors of PSD in CAIS patients have been scarce. Thus, this study aimed to retrospectively analyze the clinical data of 106 CAIS patients, compare the expression levels of serum NSE, BDNF and CNTF between different categories of patients, and analyze the efficacy of serum NSE, BDNF and CNTF and their combination in predicting PSD. The findings of this study will provide a new direction for the prevention and early diagnosis of PSD in CAIS patients.

Materials and Methods

Study Participants

Clinical data of 106 patients with CAIS admitted to Jinhua Guangfu Oncology Hospital from January 2012 to December 2022 were collected and retrospectively analyzed. The samples included 62 males and 44 females, with an age range of 50–75 years and an average of 63.46 ± 7.07 years. There were 33 cases of lung cancer, 25 cases of colorectal cancer, 17 cases of pancreatic cancer, 14 cases of urinary system tumors, 11 cases of breast cancer, and 6 cases of ovarian cancer, 68 cases on the left side of the le-

sion, 31 cases on the right side, and 7 cases on both sides. There were 20 cases of diabetes mellitus, 25 cases of hyperlipidemia and 16 cases of coronary heart disease.

Inclusion Criteria

Patients fulfilling the criteria below were included in this study:

(a) meeting the diagnostic criteria for stroke [17], and diagnosed with malignant tumor within three months before the diagnosis of stroke;

(b) manifesting stroke onset for the first time (the time between stroke occurrence and enrollment was less than 14 days);

(c) within the age range of 18–75 years (both inclusive);

(d) having received thrombolytic surgery with intravenous alteplase;

(e) having not received antidepressant treatment;

(f) being conscious and manifesting high level of awareness, coupled with normal communication skills (including ability to read and understand Chinese);

(g) having been screened for depression subjected to determination of serum NSE, BDNF, CNTF levels three months after intravenous thrombolysis;

(h) having complete clinical data.

Exclusion Criteria

Patients with the following characteristics were excluded from the study:

(a) having tumors in the heart, liver, kidney, hematopoietic system and nervous system;

(b) having neurological diseases;

(c) having depression history or family history of mental illness;

(d) having mental disorders caused by drugs, drug abuse, alcohol abuse, etc.;

(e) having previous history of major head trauma and intracranial surgery;

(f) having cognitive dysfunction and speech dysfunction;

(g) alcohol- and/or drug-dependent.

Methods

Depression Screening

Patients with CAIS were screened for depression using the Hamilton Depression Scale-17 (HAMD-17) [18] three months after intravenous thrombolysis. Patients with HAMD-17 score >7 were classified as depressed and included in the PSD group (n = 44), whereas those with HAMD-17 score ≤7 were classified as not depressed and included in the non-PSD group (n = 62) [19,20]. Patients in the PSD group were further stratified, according to the HAMD-17 scores, into mild depression (8–16 points), moderate depression (17–23 points), and severe depression subgroups (≥24 points).

Data Collection and Biochemical Indicator Determination

Baseline and clinical characteristics of the patients were collected. These characteristics include gender, age, body mass index, place of residence, educational level, systolic blood pressure, diastolic blood pressure, lesion site, diabetes mellitus, hyperlipidemia, coronary heart disease, smoking history, drinking history, negative life events (refer to social stressors causing pain and distress in the subjects, including serious illness and death of relatives in the preceding three months, separation, divorce, job loss, unemployment or retirement, natural or man-made disasters, financial hardship, family tension, etc.), post-thrombolytic complications (including cerebral hemorrhage, digestive tract hemorrhage, hemorrhage in other organs, asthma, rash, ischemia reperfusion injury, etc.).

To determine serum levels of NSE, BDNF, CNTF, 10 mL of venous blood was drawn from each patient in the morning of the next day after fasting for 12 hours. The blood specimens were centrifuged at 3000 r/min for 5 min at room temperature. Serum was then obtained and stored in the refrigerator at –20 °C. Serum levels of NSE, BDNF and CNTF were detected using enzyme-linked immunosorbent assay (ELISA) kits acquired from Shanghai Enzyme-Linked Biotechnology Co., Ltd. (Shanghai, China), with the serial numbers ML-EA-A05120, ml-E3786 and mlC9112-1, respectively.

Statistical Analysis

The normality of data distribution was tested using Kolmogorov–Smirnov test. Continuous variables were presented as mean ± standard deviation (SD), and their data were analyzed using independent samples *t*-test for comparison between two groups, and one-way analysis of variance (ANOVA) for comparison between multiple groups. *LSD* test was used for two comparisons between groups. Categorical variables were expressed as [*n* (%)], and χ^2 test was used for comparison. Pearson's correlation test was used to analyze the correlation between HAMD-17 scores and serum NSE, BDNF and CNTF levels in PSD patients. Logistic regression model was used to identify the influencing factors of PSD in CAIS patients. Receiver operating characteristic (ROC) curve was plotted to analyze the efficacy of serum NSE, BDNF, CNTF and their combination on PSD. Statistical significance was set at a p-value < 0.05. Data were analyzed using SPSS 27.0 software (IBM, Armonk, NY, USA).

Results

Depression in CAIS Patients

Forty-four out of 106 patients with CAIS were complicated with PSD, with an average HAMD-17 score of 19.39 ± 7.51, while 62 patients were not found to experience PSD, displaying an average HAMD-17 score of 3.11 ± 1.87. Among the 44 patients with PSD, 19 patients had mild PSD (43.18%), 14 had moderate PSD (31.82%), and 11 had severe PSD (25.00%), with average HAMD-17 scores of 12.26 ± 3.59, 21.50 ± 2.10, and 29.00 ± 3.00 points, respectively.

Comparison of Baseline and Clinical Characteristics between PSD Group and Non-PSD Group

There were no significant differences in gender, age, body mass index, residence, education level, lesion site, systolic blood pressure, diastolic blood pressure, diabetes, hyperlipidemia, coronary heart disease, smoking history and drinking history between PSD and non-PSD groups ($p > 0.05$). There was a statistically significant difference ($p < 0.05$) between the two groups in terms of negative life events and incidence of complications after thrombolysis, as detailed in Table 1.

Comparison of Serum NSE, BDNF, and CNTF Levels between PSD Group and Non-PSD Group

The serum level of NSE in the PSD group was higher than that in the non-PSD group ($t = 4.401$, $p < 0.001$), while the serum BDNF and CNTF levels were lower than those in the non-PSD group ($t = 4.571$ and 5.422, respectively, all $p < 0.001$), as detailed in Table 2.

Comparison of Serum NSE, BDNF, and CNTF Levels in Patients with PSD of the Same Severity

The serum levels of NSE, BDNF, and CNTF in PSD patients with different severity levels were compared. Our analysis revealed that the differences were statistically significant ($F = 19.959$, 16.398, 7.603, all $p < 0.001$), as detailed in Table 3.

Correlation Analysis between HAMD-17 Scores and Serum NSE, BDNF, CNTF Levels in PSD Patients

The HAMD-17 scores of PSD patients were positively correlated with serum NSE levels ($p < 0.001$), and negatively correlated with serum BDNF and CNTF levels ($p < 0.001$ and $p = 0.007$, respectively), as detailed in Table 4.

Determination of Factors Influencing PSD Occurrence in CAIS Patients

Using the occurrence of PSD in CAIS patients as the dependent variable (yes = 1, no = 0), and statistically significant differences in negative life events (yes = 1, no = 0), post thrombolytic complications (yes = 1, no = 0), serum NSE (actual value), BDNF (actual value), and CNTF (actual value) levels in Tables 1,2 as independent variables, the binary logistic regression model was included. The significant threshold value was set to $p < 0.05$. The analysis revealed that serum levels of NSE, BDNF, and CNTF were independent factors ($p < 0.05$) influencing the occurrence of PSD in CAIS patients, with NSE as the risk factor (odds ratio (OR) >1, $p < 0.05$) and BDNF and CNTF as protective factors (OR <1, $p < 0.05$), as detailed in Table 5.

Predictive Efficacy of Serum NSE, BDNF, and CNTF Levels for PSD Occurrence in CAIS Patients

When NSE level ≥3.315 μg/L, the area under the curve (AUC) for predicting PSD occurrence in CAIS patients was 0.729, coupled with a sensitivity of 0.682 and a specificity of 0.661. When BDNF ≤16.600 ng/L, the AUC was 0.751, with a sensitivity of 0.750 and a speci-

Table 1. Comparison of baseline and clinical characteristics between PSD group and non-PSD group.

Factor	PSD group (n = 44)	Non-PSD group (n = 62)	t/χ^2 value	p-value
Gender [n (%)]			0.011	0.916
Male	26 (59.09)	36 (58.06)		
Female	18 (40.91)	26 (41.94)		
Age (year)	63.48 ± 6.59	63.45 ± 7.45	0.018	0.985
Body mass index (kg/m^2)	22.70 ± 3.64	23.40 ± 3.63	0.976	0.331
Lesion site [n (%)]			5.159	0.076
Left side	23 (52.27)	45 (72.58)		
Right side	18 (40.91)	13 (20.97)		
Bilateral	3 (6.82)	4 (6.45)		
Area of residence [n (%)]			0.095	0.758
Urban	30 (68.18)	44 (70.97)		
Rural	14 (31.82)	18 (29.03)		
Educational level [n (%)]			0.533	0.766
Primary school and below	14 (31.82)	19 (30.65)		
Junior/High school	20 (45.45)	32 (51.61)		
College or above	10 (22.73)	11 (17.74)		
Systolic blood pressure (mmHg)	123.02 ± 13.55	122.92 ± 11.14	0.043	0.966
Diastolic blood pressure (mmHg)	93.05 ± 14.92	89.18 ± 13.33	1.401	0.164
Diabetes [n (%)]			0.124	0.725
Yes	9 (20.45)	11 (17.74)		
No	35 (79.55)	51 (82.26)		
Hyperlipidemia [n (%)]			0.568	0.451
Yes	12 (27.27)	13 (20.97)		
No	32 (72.73)	49 (79.03)		
Coronary heart disease [n (%)]			0.039	0.844
Yes	7 (15.91)	9 (14.52)		
No	37 (84.09)	53 (85.48)		
Smoking history [n (%)]			0.140	0.708
Yes	15 (34.09)	19 (30.65)		
No	29 (65.91)	43 (69.35)		
Drinking history [n (%)]			0.193	0.660
Yes	16 (36.36)	20 (32.26)		
No	28 (63.64)	42 (67.74)		
Negative life events [n (%)]			10.600	0.001
Yes	29 (65.91)	21 (33.87)		
No	15 (34.09)	41 (66.13)		
Complications after thrombolysis [n (%)]			5.603	0.018
Yes	13 (29.55)	7 (11.29)		
No	31 (70.45)	55 (88.78)		

PSD, post-stroke depression.

ficity of 0.645. When CNTF ≤18.700 ng/L, the AUC was 0.767, coupled with a sensitivity of 0.818 and a specificity of 0.629. For the combined assessment of these biochemical indicators, the AUC was 0.827, with a sensitivity of 0.818 and a specificity of 0.710, as detailed in Table 6 and Fig. 1.

Discussion

In this retrospective study, we found that 44 out of 106 CAIS patients developed PSD within three months, with an incidence rate of 41.51%. Further comparison revealed that there were significant differences in lesion sites, negative life events, and incidence of post-thrombolytic com-

Table 2. Comparison of serum NSE, BDNF, and CNTF levels between PSD group and non-PSD group.

Factor	PSD group (n = 44)	Non-PSD group (n = 62)	t-value	p-value
NSE (μg/L)	7.35 ± 2.99	5.06 ± 2.36	4.401	<0.001
BDNF (ng/L)	14.87 ± 4.86	19.18 ± 4.73	4.571	<0.001
CNTF (ng/L)	13.59 ± 3.17	17.50 ± 3.96	5.422	<0.001

Abbreviations: BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; NSE, neuron-specific enolase; PSD, post-stroke depression.

Table 3. Comparison of serum NSE, BDNF, and CNTF levels in patients with PSD of different severity levels.

Factor	Mild PSD (n = 19)	Moderate PSD (n = 14)	Severe PSD (n = 11)	F-value	p-value
NSE (μg/L)	5.48 ± 2.15	7.25 ± 2.30*	10.69 ± 2.06*#	19.959	<0.001
BDNF (ng/L)	17.99 ± 4.96	14.49 ± 2.55*	13.80 ± 3.49*#	16.398	<0.001
CNTF (ng/L)	10.69 ± 2.06	9.97 ± 1.91	10.91 ± 2.29*#	7.603	<0.001

Notes: *$p < 0.05$ compared with mild PSD subgroup; #$p < 0.05$ compared with moderate PSD group.

Abbreviations: BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; NSE, neuron-specific enolase; PSD, post-stroke depression.

Table 4. Correlation between HAMD-17 scores and serum NSE, BDNF, CNTF levels in PSD patients.

Factor	HAMD-17 (points)	
	r-value	p-value
NSE (μg/L)	0.676	<0.001
BDNF (ng/L)	–0.661	<0.001
CNTF (ng/L)	–0.401	0.007

Abbreviations: BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; HAMD-17, Hamilton Depression Scale-17; NSE, neuron-specific enolase.

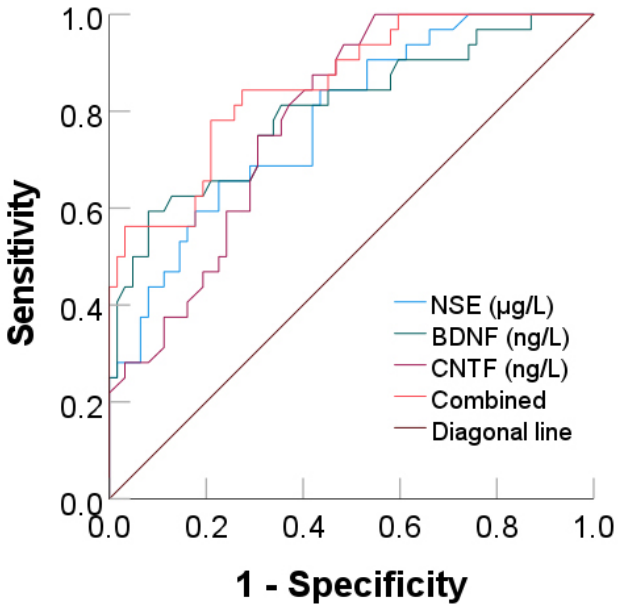

Fig. 1. Receiver operating characteristic (ROC) curve of serum NSE, BDNF, and CNTF levels for predicting PSD occurrence in cancer-associated ischemic stroke (CAIS) patients.

plications between the PSD group and the non-PSD group. However, the logistic regression analysis demonstrated that these factors were not independent influencing factors for the occurrence of PSD in CAIS patients. The serum levels of NSE, BDNF, and CNTF, which are closely related to the occurrence and severity of PSD, were determined to be independent influencing factors in this respect. In addition, measuring the serum levels of these three biochemical parameters was found to possess better predictive power for the occurrence of PSD in CAIS patients within three months.

At present, the research conclusions on the incidence rate of PSD are different. For instance, Guo *et al.* [21] pointed out that the incidence rate of PSD in stroke patients within two years varies from 11% to 41%. In another study, Avadhani *et al.* [22] reported that 111 out of 308 stroke survivors (36%) on day 180 had PSD after conducting a depression screening. A retrospective analysis of clinical and imaging data from 130 young patients with cerebral hemorrhage aged 16–49 found that the incidence of PSD was 23.1% (30/130) [23]. Stern-Nezer *et al.* [24] pointed

Table 5. Logistic regression analysis of the influencing factors of PSD in CAIS patients.

Variable	β	SE	Wald χ^2	*p*-value	OR	95% CI
Negative life events	0.085	0.110	0.593	0.441	1.088	0.877–1.350
Post-thrombolytic complications	0.764	0.698	1.199	0.274	2.146	0.547–8.424
NSE (μg/L)	1.502	0.567	7.015	0.008	4.492	1.478–13.656
BDNF (ng/L)	–0.129	0.061	4.519	0.034	0.879	0.780–0.990
CNTF (ng/L)	–0.248	0.079	9.886	0.002	0.780	0.669–0.911
Constant	3.826	1.789	4.575	0.032	45.898	

Abbreviations: BDNF, brain-derived neurotrophic factor; CI, confidence interval; CNTF, ciliary neurotrophic factor; CAIS, cancer-associated ischemic stroke; NSE, neuron-specific enolase; OR, odds ratio; SE, standard error.

Table 6. Efficacy of serum NSE, BDNF, and CNTF levels for predicting PSD occurrence in CAIS patients.

Variable	AUC	*p*-value	Cut-off	Sensitivity	Specificity	Youden index	95% CI
NSE (μg/L)	0.729	<0.001	3.315	0.682	0.661	0.343	0.634–0.824
BDNF (ng/L)	0.751	<0.001	16.600	0.750	0.645	0.395	0.655–0.847
CNTF (ng/L)	0.767	<0.001	18.700	0.818	0.629	0.447	0.679–0.855
Combined	0.827	<0.001	-	0.818	0.710	0.528	0.751–0.903

Abbreviations: AUC, area under the curve; BDNF, brain-derived neurotrophic factor; CI, confidence interval; CNTF, ciliary neurotrophic factor; NSE, neuron-specific enolase.

out that the one-year prevalence of PSD in 89 patients with spontaneous cerebral hemorrhage was 15%, while Christensen *et al.* [25] found that among 657 patients with cerebral hemorrhage, 596 survived within three months after onset, with 20% of patients experiencing PSD. In this study, 44 out of 106 CAIS patients developed PSD, accounting for 41.51%, which is at a relatively high level. The reasons for this may be related to sample size, age, race, and duration of depression assessment. In addition, the patients included in this study are CAIS patients, not just stroke patients. CAIS patients not only face stress events caused by diagnosed cancer, but also experience physical image damage caused by adverse reactions to radiotherapy and chemotherapy, and bear high treatment costs. In addition, they are worried about disease recurrence, which further increases the risk of PSD.

NSE is a unique acidic protease in neuroendocrine cells and neurons, mainly present in tissues and cells but with a low content in serum, which can fully reflect neuronal damage [26]. Several studies have established an association between serum NSE levels and prognosis of stroke patients. Gao *et al.* [27] pointed out that patients with acute ischemic stroke and hypertension with high baseline NSE have poorer prognosis. Kurakina *et al.* [28], on the other hand, found that the plasma NSE levels in ischemic stroke patients were correlated with the severity of neurological symptoms, indicating the potential role of NSE in predicting the recovery of motor function in patients after onset. A retrospective analysis on stroke patients with acute anterior circulation occlusion revealed that elevated NSE levels can serve as an independent influencing factor for symptomatic intracranial hemorrhage [29]. However, none of these published studies had reported the correlations between serum NSE levels and PSD. To the best of our knowledge, this study is the first to explore the clinical significance of serum NSE levels in patients with CAIS combined with PSD. We discovered that the serum NSE level was higher in the PSD group than in the non-PSD group, increasing with the severity of depression. The author analyzed that the reasons for this may be as follows: when the body is in a healthy state, NSE can catalyze 2-phosphoglycyrrhetinic acid, causing it to break down and produce enol phosphopyruvate, thereby regulating the glycolysis process of brain tissue and fully protecting nerve tissue. In CAIS patients, nerve cells in the body are damaged, and NSE factors can penetrate the blood-brain barrier and be released into the brain, spinal cord, and blood circulation, leading to an increase in serum NSE levels, causing neurological function and free radical damage, brain cell apoptosis, and possibly exacerbating the degree of brain neurovascular damage through pathways such as inducing oxidative stress damage and impaired enzyme synthesis. Schmidt *et al.* [30] conducted a comparative study on 31 patients with severe depression and 32 healthy individuals, confirming that elevated cerebrospinal fluid NSE levels are one of the pathogenic factors for severe depression.

Synthesized in the cell bodies of neurons and glial cells, BDNF represents the most abundant neurotrophic fac-

tor in the body. As a key signaling molecule in the development of the nervous system, BDNF can play many key functions in the central nervous system and is closely related to the survival, growth, and differentiation of neurons. BDNF is associated with many mental disorders, including schizophrenia [31], intellectual disabilities [32], and autism [33]. In recent years, research has found that BDNF is also closely associated with the occurrence and development of PSD [34]. It has been found that the BDNF/TrkB signaling pathway in the hippocampus of PSD rats became less active [35]. Consistent with the results of this study, Qiu *et al.* [36] reported a negative correlation between BDNF levels and HAMD-17 scores in patients affected by mild stroke. It is important to highlight the difference in disease type between our study and Qiu *et al.*'s [36] research. This study [36] also delineated the mechanism by which BDNF participates in the occurrence and development of PSD: (1) The hypoxic environment caused by stroke may downregulate the expression of BDNF in the brain, affecting the formation of hippocampal neurons, leading to the occurrence of PSD. Some patients who express lower levels of BDNF before the onset of stroke are more vulnerable to depressive symptoms. (2) BDNF interacts with several neurotransmitters, including serotonin and glutamate, which are associated with the underlying mechanisms of depression.

CNTF is produced and released by a large number of glial cells in the central nervous system, and is a neurotrophic factor along with BDNF. It is mainly distributed in the cerebral cortex, olfactory bulb, and subcortical area of the cerebellum. After binding with CNTF receptors, it has the function of nourishing the central and surrounding neurons. If neural network damage occurs, neurons can enhance the function of producing and secreting CNTF through axonal reversal, repairing and regenerating damaged nerves [37]. In addition, CNTF has a synergistic effect with other neurotrophic factors in repairing damaged nerves [38]. Through animal experiments, Peruga *et al.* [39] found that endogenous CNTF plays an important role in the structural maintenance of hippocampal function, and proposed that it has a significant impact on emotional behavior regulation such as anxiety and depression. Jia *et al.* [16] pointed out that CNTF can affect depressive like behavior in adult mice. However, Shpak *et al.* [40] studied 72 patients with focal epilepsy and did not find any correlation between their CNTF levels and the occurrence of depression, which may be due to the different types of diseases in the patients. This study found that CNTF, similar to NSE and BDNF, can serve as independent predictor of PSD in CAIS patients, and its expression level is closely related to the severity of PSD in patients. Chronic and persistent high secretion of corticotropin releasing hormone (CRH) during stress is an important factor in the etiology of stress-related diseases. A previous study reported that the activation of CRH hypothalamic neurons can trigger the release of CNTF [41], proving that hippocampal neuronal damage and reduced regeneration may be important pathological foundations of depressive behavior in rats.

The current study is limited by several shortcomings. (a) The sample size and representativeness of the study are limited, which may cause information bias to a certain extent. Further expansion of the sample size is needed for research and confirmation. (b) There are many influencing factors for the occurrence of PSD in CAIS patients. Although this study comprehensively considered some factors, the range of variables is still limited, and the possibility of other potential factors cannot be ruled out. (c) The individual characteristics of patients were not separately statistically analyzed, and serum levels of NSE, BDNF, and CNTF may also be related to the patient's weight, physical fitness, etc. (d) This study used the HAMD-17 scale for evaluating depression status. As the scale is a subjective assessment at the level of consciousness, there may be some deviations from the objective situation. (e) Due to the limitation of follow-up time, the screening time for depression in patients in this study was 3 months after intravenous thrombolysis, and the follow-up time will be further extended in the future. (f) In addition, this study did not explore the severity of the patient's disease and whether they received treatment. These factors will be included in the future to further verify the conclusions of this study.

Conclusion

This study reveals for the first time that serum levels of NSE, BDNF, and CNTF are independent influencing factors of PSD in CAIS patients, providing a basis for clinical prevention and treatment of PSD in CAIS. The author believes that in clinical practice, for CAIS patients with abnormal changes in serum cytokines such as NSE, BDNF, CNTF, etc., anti-tumor treatment and improvement of neurological deficits should be carried out, attention should be paid to their psychological disorders, and timely detection and active treatment measures should be taken to reduce the risk of PSD in CAIS patients.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

BGZ, XYS and KM designed the research study. BGZ and XZY performed the research. XYS and KM provided help and advice on the ELISA experiments. BGZ and XZY analyzed the data. All authors contributed to the drafting or important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The data for this study comes from Guangfu Oncology Hospital after approval by the Institutional Ethical Committee (Approval NO.: 2022-001). Informed consent was obtained from all subjects, in line with the provisions of the Declaration of Helsinki on ethics.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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