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ORIGINAL RESEARCH

Higher Concentration of Adrenocorticotropic Hormone Predicts Post-Stroke Depression

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Background: Post-stroke depression (PSD) is the most common neuropsychiatric complication after stroke, seriously affecting the quality of survivors' life. As one of the important causes of PSD, neuroendocrine mechanism has been widely studied in recent years. The main objective of this study was to investigate the relationship between adrenocorticotropic hormone (ACTH) on admission and PSD at 3 months.

Methods: This is a hospital-based prospective cohort study, which was conducted at three independent hospitals (Tongji Hospital, Wuhan First Hospital and Wuhan Central Hospital) between August 2018 and June 2019. A total of 768 ischemic stroke patients were finally eligible for analysis and categorized into equal tertiles according to the distribution of ACTH and the number of patients. The χ^2-test, Mann–Whitney *U*-test and Kruskal–Wallis test were used to check for statistical significance. And restricted cubic spline (RCS) regression model was used to explore the non-linear relationship between continuous ACTH levels and PSD at 3 months.

Results: The optimal cut-off points of ACTH were as follows: (T1) 0.32–20.55 pg/mL, (T2) 20.56–39.79 pg/mL, (T3) 39.80–143.40 pg/mL. A total of 305 patients (39.7%) were diagnosed as PSD at 3 months follow-up. Significant differences were found between the PSD and non-PSD groups in ACTH concentration (P = 0.001). After adjustment for all conventional confounders, the odds ratios of PSD were 1.735 (95% CI = 1.176–2.560, P = 0.005) for the highest tertile of ACTH and 1.496 (95% CI = 1.019–2.194, P = 0.040) for the middle tertile of ACTH, as compared with the lowest tertile. In multiple-adjusted RCS regression, continuous ACTH showed saturation effect relation with PSD risk after 31.02 pg/mL (P for nonlinear = 0.0143).

Conclusion: Higher ACTH level on admission is a significant and independent biomarker to predict the development of PSD at 3 months follow-up. Besides, saturation effect was revealed even if the underlying mechanism is unclear. For stroke patients, doctors should pay attention to the baseline ACTH for screening high-risk PSD in clinical practice.

Keywords: neuroendocrinology, HPA axis, adrenocorticotropic hormone, post-stroke depression, restricted cubic spline, saturation effect

Introduction

PSD is the most common mental illness after stroke, which significantly increases the disability rate, recurrence rate and mortality rate of stroke; seriously harms the quality of life of stroke survivors; and brings great pain and distress to patients and their families.[1–3] According to a new review, PSD incidence was highest especially within 3 months after the acute event and the cumulative incidence of PSD was up to 52% within 5 years of stroke.[4] There are many hypotheses about the pathogenesis of PSD, but the biological mechanisms remain unclear. Neuroendocrine disorders,[5,6] especially hypothalamic-pituitary-adrenal (HPA) axis dysfunction,[7] which is considered as a potential pathogenesis of PSD, has been aroused the concern of researchers and become a hot topic in recent years.

Hypothalamus, pituitary gland and adrenal cortex together form a complex neuroendocrine system, clinically known as the HPA axis. Corticosterone release hormone (CRH) secreted by the hypothalamus stimulates the pituitary gland to

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secrete ACTH, which in turn stimulates the adrenal cortex to secrete glucocorticoid (cortisol in human, corticosterone in rodents). Eventually, glucocorticoid is secreted into the blood and binds to specific receptors in multiple target tissues, exerting a powerful physiological effect.[8] The activated HPA axis not only regulates homeostasis,[9] stress response[10] but also has a profound effect on emotional regulation.[11]

There are numerous studies on the relationship between HPA axis and mental illness. Previous studies have shown that patients suffering from generalized anxiety or major depression, manifested as high concentrations of CRH and exacerbated response to ACTH.[12,13] It has also been suggested that elevated cortisol may be responsible for the emergence of psychotic symptoms in severe major depressive disorder.[14–16] One study has shown that patients with psychotic major depression had higher cortisol levels throughout the afternoon compared to non-psychotic depressed or healthy subjects.[17] Other empirical evidence suggested that the HPA axis played a key role in perinatal psychiatric disorders.[18,19] Elevated cortisol levels in the second and third trimesters have been linked to prenatal depressive symptoms.[18,20] A meta-analysis showed that women with major depression or anxiety disorders were blunted in responding to cortisol stress,[21] and increased cortisol arousal often predicted increased vulnerability to depression.[22] In addition, one study demonstrated that cortisol levels were an important mediator between childhood trauma and depressive symptoms.[23] Yue et al wrote in their article: Many successful antidepressant treatments of depressive disorders using a variety of different antidepressant treatments are linked to the HPA axis.[24]

Thus, considering that the HPA axis played such an important role in mental illness and ACTH has proven to be an effective predictor of generalized anxiety or major depression, we hypothesized that the ACTH may also predict PSD. Further elucidation of the relationship between ACTH and PSD may ultimately lead to specific targeted treatments. The objective of our research today is to explore the association between ACTH on admission and PSD at 3 months.

Materials and Methods

Study Design and Subjects

As a multicenter prospective cohort study (Registration number: ChiCTR-ROC-17013993), our research was conducted at three independent hospitals (Tongji Hospital, Wuhan First Hospital and Wuhan Central Hospital) between August 2018 and June 2019. All patients involved in this study or their family members gave written informed consents according to the Declaration of Helsinki. The approval of the study for experiments was obtained from the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (Approved No. of ethics committee: TJ-IRB20171108). A total of 1060 patients first-ever diagnosed stroke, including ischemic as well as hemorrhagic stroke, were consecutively enrolled and 768 patients were finally eligible for the research (Figure 1).

Inclusion and Exclusion Criteria

The inclusion criteria of this study were as follows: 1) ages 18 years and over; 2) admitted to hospital within 7 days after stroke onset, including ischemic as well as hemorrhagic stroke;and 3) stroke was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scans.

Exclusion criteria were as follows: 1) brain dysfunction caused by other non-vascular causes (such as primary brain tumor, brain metastasis, subdural hematoma, post-seizure paralysis, brain trauma, etc.); 2) the history of dementia, depression and other mental illness; 3) aphasia, blindness, deafness and cognitive dysfunction [Mini-mental State Examination (MMSE)<17]; 4) transient ischemic attack (TIA) and subarachnoid hemorrhage; and 5) unable to complete the follow-up.

Data Collection

A standardized questionnaire was used upon admission to collect detailed information about each patient's demographic and medical history, including age, sex, height, weight, sleep time, educational level, smoking history, drinking history, physical activity, hypertension, diabetes mellitus, hyperlipidemia and history of coronary heart disease (CHD).

Blood samples were obtained from the medial cubital vein at fasting in the early morning of the second day (within 24 hours of admission). The concentrations of fasting C-peptide (FCP), adrenocorticotropic hormone (ACTH), cortisol,

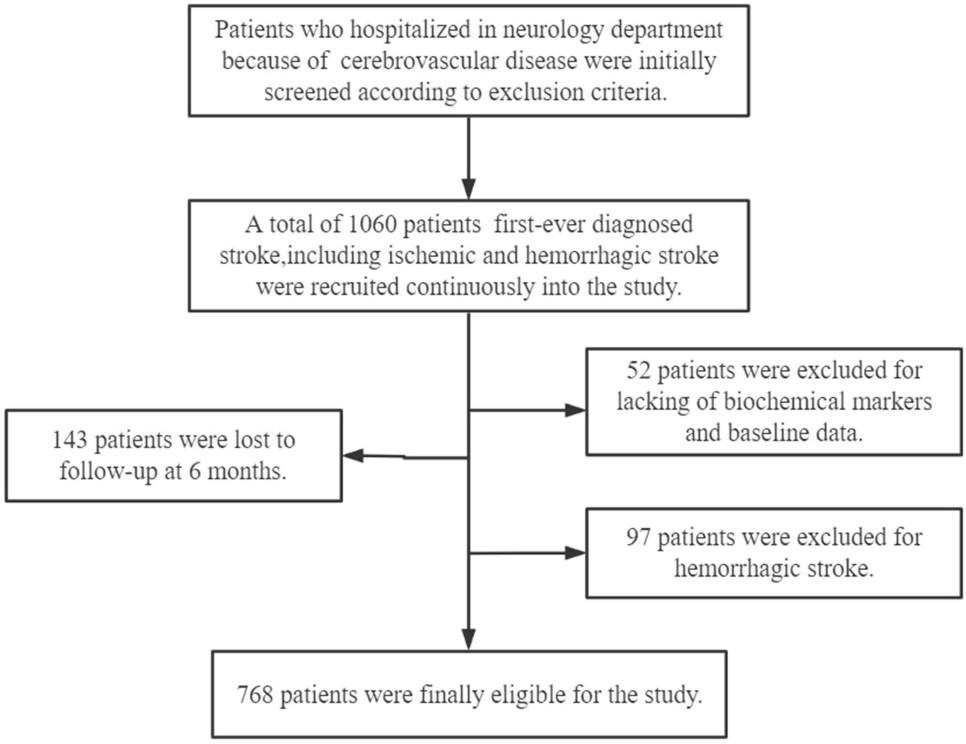

Figure 1 The enrollment flow chart of this study.

total WBC count (WBC) and neutrophil count (NEU) were measured in clinical laboratory of Tongji Hospital. FCP, ACTH and cortisol were measured by Abbott chemiluminescence, Roche electro-chemiluminescence immunoassay and Beckman DXI chemiluminescence, respectively. WBC and NEU were measured by fluorescence staining flow cytometry. The inflammatory factors, including interleukin (IL-1β, IL-6, IL-10, IL-18), tumor necrosis factor (TNF-α), interferon (IFN-γ) as well as brain-derived neurotrophic factor (BDNF) were measured using a solid-phase sandwich enzyme-linked immunosorbent assay kit (CUSABIO, China) according to the manufacturer's specifications in Kind star Company, Wuhan, which was a nationwide comprehensive clinical medical testing agency. To minimize assay variance, all samples were analyzed on the same day in duplicate in a random order by a technician blind to the clinical diagnoses; the intra-assay coefficients were <5%.[25]

The National Institutes of Health Stroke Scale (NIHSS), Barthel index (BI), modified Rankin scale (mRS) were evaluated immediately after admission. The 17-item Hamilton Rating Scale for Depression (HAMD-17) had been proved to have good reliability and validity in Chinese population,[26] which therefore was used to measure the severity of depressive symptoms at 3 and 6 months after ischemic stroke onset. This paper only presents the data analysis results of 3 months. All psychological evaluations were performed by two experienced psychiatrists who were blinded to other clinical and laboratory findings after receiving standardized training. The HAMD-17 was mainly administered in the form of face-to-face interviews in the hospital. For a small number of patients who could not come to the hospital, HAMD-17 was evaluated in the form of WeChat video and phone. Participants who met DSM-V diagnostic criteria (depression caused by another medical condition) along with HAMD-17 score >7 were diagnosed as PSD.

Statistical Analysis

Continuous variables were presented as medians [interquartile range (IQR)] because of skewed distribution while categorical variables were expressed as frequencies (percentages).

Patients were classified into two groups by HAMD-17 scores and three groups by ACTH tertiles. Group differences were assessed by χ^2 tests for categorical variables and nonparametric Mann–Whitney *U*-test/Kruskal–Wallis test for

continuous variables. The associations between ACTH levels and 3 months PSD were investigated with multivariate-adjusted binary logistic regression models, which using a backward stepwise method with input of variables if p-value <0.05 and backward elimination if p-value >0.05.[27] The lowest tertile (0.32–20.55) was defined as the reference group. After adjusting for traditional confounders and main baseline variables related to PSD (which were explicitly listed in great detail in Table 1), the odds ratios (ORs) and their 95% confidence intervals (CIs) were obtained.[28]

In addition, RCS regression model was conducted to provide more precise estimates and examine the shape of the associations between ACTH as a continuous measure and 3 months PSD. The reference point for ACTH was the median (11.20 pg/mL) of the reference group (the lowest tertile), and the OR was adjusted for all confounding variables (the same variables as model 3 in Table 1).[29] To balance best fit and overfitting in the spline, the number of knots, between three and seven, was chosen as the lowest value for the Akaike information criterion.[30]

Overall, a two-sided value of p<0.05 was considered statistically significant. Data analysis were performed with Statistical Program for Social Sciences (SPSS) statistical software (version 25, Chicago, IL, USA) and R version 4.0.3. The R packages "rms" and "ggplot2" were applied.

Results

Baseline Characteristics of Patients in Non-PSD Group and PSD Group

In total, 768 patients with acute ischemic stroke were consecutively recruited in this study. Of all these potential subjects, 305 (39.7%) developed PSD at 3 months after ischemic stroke onset. Table 2 shows a comparison of baseline information between the non-PSD and PSD groups. The PSD group had a higher proportion of female (p = 0.009), lower proportion of physical activity (p = 0.002), higher NIHSS score (p < 0.001), lower BI score (p < 0.001), higher m *RS* score (p < 0.001). As for serum biochemicals, the PSD group showed higher level of fasting C-peptide (p=0.011), higher level of ACTH (p=0.001), higher white blood cell count (p=0.001), higher neutrophil count (p=0.001) and higher level of IL.6 (p=0.016).

Characteristics of All Patients in ACTH Tertiles

Of the 768 patients, 22.4% were female and 77.6% were male. The mean age of them was 59 years (Table 3). All participants were divided into three subgroups according to tertiles of ACTH levels, which ensured the most categories with adequate number of patients per subgroups[28] between the range of 0.32 and 143.40pg/mL (T1, 255 patients; T2, 257 patients; T3, 256 patients). The cut-off values for this stratification on the ACTH level into tertiles were as follows: (T1) 0.32–20.55pg/mL, (T2) 20.56–39.79pg/mL, and (T3) 39.80–143.40pg/mL. Table 3 summarized the characteristics of the patients by the tertiles of ACTH. Compared to patients with lower ACTH, those with higher ACTH were more likely to be younger (p=0.001); had lower proportions of female (p<0.001) and hypertension (p=0.027); had higher proportions of drinking (p=0.019); had higher scores of NIHSS (p=0.004), m *RS* (p<0.001) and HAMD at 3 months (p<0.001).

Association Between the Level of ACTH and PSD at 3 Months

In Table 1, unadjusted and multivariate-adjusted binary logistic regression models were used to estimate the association between the level of ACTH and PSD at 3 months. In unadjusted binary logistic regression model, with the lowest tertile of

Table 1 Multivariate Adjusted Odds Ratios for the Association Between ACTH Levels and PSD at 3 months

ACTH (pg/mL)	Unadjusted Model		Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
		0.004		0.005		0.005		0.017
T1, n=255	1 (Reference)	…	1 (Reference)	…	1 (Reference)	…	1 (Reference)	
T2, n=257	1.717 (1.196–2.464)	0.003	1.660 (1.147–2.401)	0.007	1.660 (1.147–2.401)	0.007	1.496 (1.019–2.194)	0.040
T3, n=256	1.701 (1.185–2.443)	0.004	1.790 (1.230–2.605)	0.002	1.790 (1.230–2.605)	0.002	1.735 (1.176–2.560)	0.005

Notes: Reference OR (1.000) is the lowest level of ACTH for PSD. Model 1: adjusted for age, sex, BMI, sleep time, education levels, smoking, drinking and physical activity. Model 2: adjusted for covariates from model 1 and further adjusted for hypertension, diabetes mellitus, hyperlipidemia and coronary artery disease. Model 3: adjusted for covariates from model 2 and further adjusted for baseline NIHSS, BI and mRS.

Abbreviations: OR, odds ratio; CI, confidence level; PSD, post-stroke depression.

Table 2 Baseline Characteristics of Patients without and with PSD at 3 Months

Parameter	Non-PSD (N=463) 60.3%	PSD (N=305) 39.7%	*p*-value
Demographic information			
Age, median (IQR)	59 (51,66)	60 (52,66)	0.878
Female, n (%)	89 (19.2)	83 (27.2)	0.009*
BMI, median (IQR)	24 (22,27)	24 (22,27)	0.403
Sleep (<5 h)	257 (55.5)	190 (62.3)	0.062
Education level, n (%)			
Primary school and below	113 (24.4)	108 (35.4)	0.003*
Junior middle school	147 (31.7)	89 (29.2)	
Senior high/Polytechnic school	117 (25.3)	73 (23.9)	
Bachelor/senior college and above	86 (18.6)	35 (11.5)	
Smoking, n (%)	218 (47.1)	127 (41.6)	0.138
Drinking, n (%)	208 (44.9)	127 (41.6)	0.369
Physical activity, n (%)	200 (43.2)	98 (32.1)	0.002*
Hypertension, n (%)	278 (60.0)	184 (60.3)	0.937
Diabetes mellitus, n (%)	130 (28.1)	86 (28.2)	0.971
Hyperlipemia, n (%)	120 (25.9)	90 (29.5)	0.275
CHD, n (%)	43 (9.3)	39 (12.8)	0.124
Serum biochemicals			
Fasting C-peptide, median (IQR)	1.93 (1.08,2.57)	1.99 (1.42,2.63)	0.011*
ACTH, median (IQR)	27.30 (13.75,43.50)	32.80 (19.80,47.80)	0.001*
Cortical, median (IQR)	12.95 (10.41,15.59)	13.30 (10.70,16.20)	0.058
WBC, median (IQR)	6.54 (5.43,7.98)	7.06 (5.85,8.75)	0.001*
NEU, median (IQR)	4.04 (3.25,5.37)	4.54 (3.45,6.11)	0.001*
IL.1β, median (IQR)	72.50 (28.05,170.84)	67.32 (29.42,164.61)	0.605
IL.6, median (IQR)	4.34 (1.83,9.86)	6.01 (2.29,11.66)	0.016*
IL.10, median (IQR)	9.03 (2.96,23.92)	9.16 (3.59,26.68)	0.925
IL.18, median (IQR)	1993.37 (982.30,4668.82)	1930.84 (826.86,4608.17)	0.373
TNF.α, median (IQR)	39.66 (22.52,58.97)	39.38 (20.74,58.54)	0.499
IFN.γ, median (IQR)	4.50 (1.65,8.54)	5.37 (2.03,9.72)	0.072
BDNF, median (IQR)	3.79 (2.15,8.31)	3.43 (2.13,6.74)	0.176
Clinical characteristics			
NIHSS, median (IQR)	2 (1,4)	4 (2,7)	<0.001*
BI, median (IQR)	100 (75,100)	80 (40,100)	<0.001*
mRS, median (IQR)	1 (1,3)	3 (1,4)	<0.001*

Notes: *Statistically significant at p < 0.05 level, two-sided.

Abbreviations: PSD, post-stroke depression; IQR, interquartile range; BMI, body mass index; CHD, cronary heart disease, ACTH, adrenocorticotropic hormone; WBC, white blood count; NEU, neutrophil count; IL, interleukin; TNF-α, tumor necrosis factor-α; IFN, interferon; BDNF, brain-derived neurotrophic factor; NIHSS, The National Institutes of Health Stroke Scale; BI, Barthel Index; mRS, modified Rankin Scale.

ACTH taken as the reference, both highest and middle tertile of ACTH were independent risk predictor of PSD with an unadjusted OR of 1.701 (95% CI=1.185–2.443, P=0.004) and 1.717 (95% CI=1.196–2.464, P= 0.003), respectively. After adjusting for confounders including age, sex, BMI, education levels, sleep time, physical activity, smoking, drinking, hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, baseline NIHSS, mRS and BI scores, the highest tertile of ACTH was remained significant independently associated with the prevalence of PSD (model 1: OR = 1.790, 95% CI = 1.230–2.605, P=0.002; model 2: OR = 1.790, 95% CI = 1.230–2.605, P=0.002; model 3: OR = 1.735, 95% CI = 1.176–2.560, P=0.005). Similar results were found in the middle tertile of ACTH (model 1: OR = 1.660, 95% CI = 1.147–2.401, P=0.007; model 2: OR = 1.660, 95% CI = 1.147–2.401, P=0.007; model 3: OR =1.496, 95% CI = 1.019–2.194, P=0.040).

Furthermore, RCS regression model was used to confirm the non-linear relationship between continuous ACTH levels and PSD at 3 months (P for nonlinear=0.0143, Figure 2). The RCS curve showed that there was saturation effect relation between ACTH and the OR value of PSD at 3 months. When the level of ACTH <31.02pg/mL, OR value showed an

Table 3 Characteristics of Patients with Ischemic Stroke According to ACTH Tertiles

Parameter	All Patients	ACTH Tertiles			*p*-value
		Tertile 1, n=255	Tertile 2, n=257	Tertile 3, n=256	
		(0.32–20.55)	(20.56–39.79)	(39.80–143.40)	
Demographic information					
Age, median (IQR)	59 (52,66)	61 (54,68)	57 (51,67)	57 (51,64)	0.001*
Female, n (%)	172 (22.4)	73 (28.6)	64 (24.9)	35 (13.7)	<0.001*
BMI, median (IQR)	24 (22,27)	24 (22,26)	24 (22,27)	24 (23,27)	0.411
Sleep (<5 h)	447 (58.2)	162 (63.5)	147 (57.2)	138 (53.9)	0.081
Education level, n (%)					
Primary school and below	221 (28.8)	63 (24.7)	85 (33.1)	73 (28.5)	0.025*
Junior middle school	236 (30.7)	67 (26.3)	78 (30.4)	91 (35.5)	
Senior high/Polytechnic school	190 (24.7)	74 (29.0)	56 (21.8)	60 (23.4)	
Bachelor/senior college and above	121 (15.8)	51 (20.0)	38 (14.8)	32 (12.5)	
Smoking, n (%)	345 (44.9)	111 (43.5)	107 (41.6)	127 (49.6)	0.166
Drinking, n (%)	335 (43.6)	96 (37.6)	111 (43.2)	128 (50.0)	0.019*
Physical activity, n (%)	298 (38.8)	103 (40.4)	88 (34.2)	107 (41.8)	0.175
Hypertension, n (%)	462 (60.2)	164 (64.3)	161 (62.6)	137 (53.5)	0.027*
Diabetes mellitus, n (%)	216 (28.1)	72 (28.2)	73 (28.4)	71 (27.7)	0.985
Hyperlipemia, n (%)	210 (27.3)	76 (29.8)	61 (23.7)	73 (28.5)	0.267
CHD, n (%)	82 (10.7)	34 (13.3)	23 (8.9)	25 (9.8)	0.233
Serum biochemicals					
Fasting C-peptide, median (IQR)	1.95 (1.26,2.60)	1.96 (0.99,2.76)	1.99 (1.43,2.61)	1.91 (1.28,2.54)	0.464
ACTH, median (IQR)	29.90 (16.61,44.50)	11.20 (6.27,16.60)	29.90 (24.80,34.70)	54.15 (44.50,68.38)	<0.001*
Cortical, median (IQR)	13.09 (10.50,15.80)	11.79 (8.58,14.59)	12.90 (10.90,15.50)	14.30 (11.73,16.88)	<0.001*
WBC, median (IQR)	6.76 (5.56,8.31)	7.16 (5.68,8.73)	6.79 (5.68,8.25)	6.35 (5.34,7.84)	<0.001*
NEU, median (IQR)	4.23 (3.30,5.64)	4.66 (3.53,6.18)	4.32 (3.45,5.61)	3.91 (3.03,5.15)	<0.001*
IL.1β, median (IQR)	69.87 (28.78,167.74)	92.45 (39.11,203.68)	73.61 (27.66,169.52)	57.35 (23.66,149.34)	0.004*
IL.6, median (IQR)	5.12 (2.04,10.41)	4.20 (1.92,10.12)	5.36 (2.14,10.94)	5.39 (2.05,10.26)	0.686
IL.10, median (IQR)	9.04 (3.26,24.52)	9.92 (3.44,40.69)	9.05 (4.09,21.38)	8.65 (2.27,19.66)	0.208
IL.18, median (IQR)	1966.20 (955.19,4639,56)	1901.16 (956.33,4426.81)	1959.33 (918.77,4802.31)	2015.05 (976.01,4913.12)	0.821
TNF.α, median (IQR)	39.60 (21.78,58.73)	41.05 (23.20,63.26)	41.26 (22.75,58.95)	36.73 (20.05,56.04)	0.223
IFN.γ, median (IQR)	4.61 (1.79,8.82)	4.70 (1.79,9.72)	4.42 (1.66,8.69)	4.78 (1.91,7.84)	0.287
BDNF, median (IQR)	3.62 (2.14,7.64)	3.92 (2.37,7.96)	3.39 (1.97,8.05)	3.53 (2.11,7.17)	0.340
Clinical characteristics					
NIHSS, median (IQR)	3 (1,5)	2 (1,5)	3 (1,6)	3 (1,5)	0.004*
BI, median (IQR)	95 (60,100)	95 (65,100)	85 (55,100)	95 (60,100)	0.040*
mRS, median (IQR)	2 (1,4)	1 (1,3)	2 (1,4)	2 (1,4)	<0.001*
3 months HAMD, median (IQR)	6 (3,10)	5 (1,8)	7 (3,11)	6 (3,11)	<0.001*
6 months HAMD, median (IQR)	6 (3,9)	5 (3,9)	6 (3,9)	6 (3,9)	0.136

Notes: *Statistically significant at $p < 0.05$ level, two-sided.
Abbreviations: ACTH, adrenocorticotropic hormone; IQR, interquartile range, BMI, body mass index; CHD, coronary heart disease; NIHSS, The National Institutes of Health Stroke Scale; BI, Barthel Index; mRS, modified Rankin Scale.

obvious growth trend. However, when ACTH >31.02pg/mL, as the ACTH concentration increases gradually, OR value did not change significantly.

Discussions

In this multicenter prospective cohort study, we aimed to explore the association between ACTH and the development of PSD outcome. The final results suggested that higher ACTH level on admission is a significant and independent

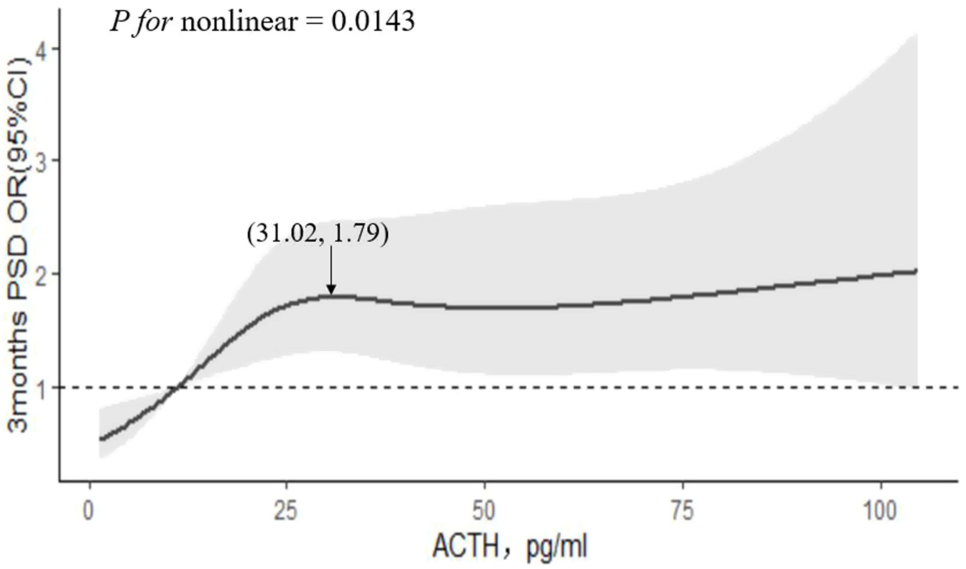

Figure 2 Association of ACTH levels on admission with risk of PSD at 3 months' follow-up. Odds ratios and 95% confidence intervals derived from RCS regression. Odds ratios were estimated using logistic regression model, adjusting for the same variables as model 3 in Table 1.

biomarker to predict the development of PSD at 3 months' follow-up. In addition, we found that there was saturation effect relation between continuous ACTH and the risk of PSD at 3 months. To a certain extent, our findings provide useful evidence for the neuroendocrine mechanism of PSD.

A total of 39.7% of acute ischemic stroke patients were diagnosed as PSD at 3 months in this study, which is similar to the incidence reported in previous studies.[31,32] Our results suggested that female and those who are physically inactive are at higher risk for PSD, which were consistent with previous studies.[33,34] Our results also demonstrated that patients with PSD had significantly increased stroke severity and worse functional outcome, which was the same as other studies.[35,36] A reasonable explanation of this phenomenon might be that PSD patients were more likely exposed to high-risk health behaviors such as sedentary lifestyle, smoking and nonadherence to secondary prevention measures.[28] As shown in Table 2, PSD patients had higher fasting C-peptide levels. The underlying mechanism might be that high levels of fasting C-peptide reflect insulin resistance and disrupted glucose metabolism, which contributes to depression.[31] Furthermore, previous studies have confirmed that neutrophil count[25] as well as IL.6[37] were involved in the development of PSD and our study came to the same conclusion.

In recent years, psychiatrists have become increasingly interested in the relationship between HPA axis and depression. Nevertheless, as for HPA axis disorder and depression, which is the cause and which is the effect, there is no unified conclusion at present. Some studies suggested that HPA axis disorder is the consequence or an epiphenomenon of depression. For example, a study showed that depressed patients present with increased cortisol levels and attenuated immune responses.[38] Another study also described that depressed patients have increased circulating levels of proinflammatory cytokines, which can further stimulate the HPA axis and cortisol.[39] A reasonable explanation is that anxiety and depression patients are often accompanied by sleep disorders,[40] which can trigger vascular inflammation to a certain extent,[41,42] and then lead to the increase in peroxides, free radicals and glucocorticoids in the body, and the excessive activation of cytokines, and eventually develop into endocrine disorders. Other studies, however, take the opposite view. Pariante et al[8] described the relationship between HPA axis hyperactivity and depression graphically as a chicken–egg relationship, insisting that HPA axis disorder is a risk factor predisposing to the development of depression. A widely accepted potential mechanism was outlined as follows. The HPA axis is a primary stress system in the human body, which is sensitive to both acute and chronic stress.[10,43] As an important mediator, glucocorticoid regulates stress responses through the negative feedback regulation of the HPA axis by binding to the glucocorticoid receptor (GR).[8,44] Under pathological conditions, the impairment of the GR-mediated negative feedback system of the HPA axis results in constant HPA axis hyperactivity and chronically high glucocorticoid levels, leading to the development of

depressive disorders.[45–47] Besides, the hippocampus and the prefrontal cortex are involved in the negative feedback regulation of the HPA axis and in the pathogenesis of depression.[47–49] Furthermore, increased inflammation as another important biological finding in major depression is often associated with hyperactivity of the HPA axis, although the underlying molecular and clinical mechanisms are still unclear.[50] IL-6, a widely studied pro-inflammatory cytokine, has been found to be a factor associated with major depressive disorder and increased IL-6 activity may cause depression through activation of HPA axis or influence of the neurotransmitter metabolism.[51] Carvalho et al also described increased plasma IL-6 and increased plasma cortisol levels in the same depressed individuals,[52] which further confirmed the notion that increased inflammation and cortisol hypersecretion are indeed coexistent and related biological abnormalities.

Considering there are many similarities between the pathogenesis of depression and PSD, it is reasonable to deem that there is a close link between hyperactivity of HPA axis and PSD. Our data show that as ACTH levels go up, so do cortisol levels and pro-inflammatory cytokine IL-6 levels (Table 3), which was consistent with previous studies.[50–52] It seems that our study supports the latter conclusion because the risk of PSD at 3 months increases with ACTH levels on admission (Table 1 and Figure 2). However, we did not measure ACTH dynamically at follow-up, so we were unable to understand the serum ACTH levels of patients after the onset of PSD. We therefore fail to know whether PSD will further affect ACTH. A reasonable hypothesis is that HPA axis disorder and PSD influence each other, cause and effect each other, leading to vicious cycle, but the specific mechanism still needs further study.

Strengths and Limitations

The main advantage of this study is that it is a prospective cohort study, which enhances the credibility of etiological inferences. In addition, the sample size of the study was large enough and we adjusted many confounders in different models to make the results more referential. Furthermore, compared with microRNAs, ACTH, as a common objective biomarker, is more readily available. Finally, though further studies are still needed to confirm the association between the ACTH level on admission and the risk of PSD at 3 months, our study results revealed the saturation effect between them.

However, this study had several limitations. First of all, patients with dysarthria, aphasia or other diseases were excluded, and these excluded patients might be suffered from depressive symptoms. This might cause a selection bias, resulting in a lower rate of PSD than actual data. Moreover, the loss rate of follow-up may reduce statistical power of the analyses. Another limitation is the sex imbalance in our study population, with female accounting for only 22.4%, which is caused by the fact that the number of male stroke patients in the Neurology department of Tongji Hospital is far more than that of female. Therefore, more studies are needed to explore the relationship between ACTH and PSD in other populations with adequate number of women and other geographic populations.

Conclusions

Higher ACTH level on admission is a significant and independent biomarker to predict the development of PSD at 3 months' follow-up. Further investigations are needed to clarify the underlying mechanism of saturation effect relation between continuous ACTH and PSD. For Chinese elderly stroke patients, doctors should pay attention to the baseline ACTH for screening high-risk PSD in clinical practice.

Abbreviations

PSD, post-stroke depression; HPA, hypothalamic pituitary adrenal; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone; GR, glucocorticoid receptor; HAMD-17, 17-item Hamilton Rating Scale for Depression; TNF-α, tumor necrosis factor-α; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CHD, coronary heart disease; WBC, white blood count; NEU, neutrophil count; IL, interleukin; IFN, interferon; NIHSS, The National Institutes of Health Stroke Scale; BI, Barthel Index; mRS, modified Rankin Scale; RCS, restricted cubic spline.

Data Sharing Statement

The database used in the current study are available from the corresponding authors on reasonable request.

Ethics Approval and Consent to Participate

All patients involved in this study or their family members gave written informed consents according to the Declaration of Helsinki. The approval of the study for experiments was obtained from the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (Approved No. of ethics committee: TJ-IRB20171108).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. SZ and ZZ had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Disclosure

The authors report no conflicts of interest for this work nor concerning the materials or methods used in this study nor the findings specified in this paper.

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