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Correlation between serum parathyroid hormone-associated protein concentration and acute ischemic stroke

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Abstract: Objective To investigate the correlation between serum Parathyroid hormone-related protein (PTHrP) and acute ischemic stroke (AIS). Methods from October 2020 to March 2021, 134 patients with AIS and 34 healthy individuals were enrolled. Serum PTHrP concentration was measured by enzyme-linked immunosorbent assay (ELISA) and subgroup analysis was performed according to Trial of Org 10 172 in acute stroke treatment (TOAST) classification. The severity of AIS was assessed by the National Institutes of Health stroke scale (NIHSS) score and the volume of cerebral infarction was assessed based on head magnetic resonance imaging. The correlation of serum PTHrP concentration with various indicators was analyzed. The 90-day functional prognosis of patients was assessed by the modified Rankin scale. Patients were divided into favorable outcomes group and unfavorable outcomes group and the difference in serum PTHrP concentration between the two groups was compared. Whether serum PTHrP was associated with AIS prognosis was analyzed by Logistic regression.Results The serum PTHrP concentration in AIS group was higher than that in the control group (P=0.000), and the serum PTHrP concentrations of the three common etiological subtypes, LAA, CE and SAO, were higher than those in the control group (all P<0.01). The AUC for distinguishing AIS patients and healthy control by serum PTHrP concentration was 0.751(P<0.0001). The serum PTHrP concentration in the AIS group was associated with the cumulative smoking volume (r=0.201, P=0.021) and APTT (r=-0.188, p=0.034). Serum PTHrP was not associated with TOAST classification (P=0.091), NIHSS score and cerebral infarction volume (all P>0.05), and there was no significant difference in serum PTHrP concentration between the favorable outcomes group and unfavorable outcomes group (P> 0.05). Univariate logistic regression showed that serum PTHrP concentration was not a prognostic factor of AIS [OR=1.000 95% CI (0.999, 1.002) P=0.678]. Conclusion Serum PTHrP concentration was significantly increased in AIS patients. Serum PTHrP might be ancillary for early identification of AIS. Serum PTHrP concentration correlated with cumulative smoking volume and APTT in AIS patients, and could possibly be used to assess the true smoking volume of patients and analyze coagulation function. However, serum PTHrP concentration was not associated with TOAST classification, NIHSS score, cerebral infarction volume and 90-day prognosis, which meant it cannot be used to evaluated the etiology, severity and prognosis of AIS patients.

Keywords: Parathyroid hormone-related protein; Acute ischemic stroke; Serum; Correlation.

1. Introduction

Acute ischemic stroke (AIS) refers to the necrosis of brain tissue caused by a sudden interruption of the blood supply to the brain. AIS is more common in middle-aged and elderly people, and it develops rapidly, with high disability rate and high mortality rate, which has brought a heavy burden to families and society . Therefore, improving the diagnosis and treatment level of AIS is an important goal of medical development. Exploring the correlation between substances and AIS from basic and clinical aspects can help to further expand the pathophysiological mechanism of AIS, discover new therapeutic targets, and provide new ideas for drug intervention.

Parathyroid hormone-related protein (PTHrP) is a protein expressed in systemic tissues, partially homologous to parathyroid hormone (PTH), is a calcium regulator of cells, a cascade of peripheral tissue inflammation, and a physiological smooth muscle relaxant. Animal experiments showed that the expression of local PTHrP increased after cerebral infarction in rats, and that PTHrP perfusion in vivo cranial window could expand the blood vessels of the pia mater microcirculation, and ventricular bolus injection of PTHrP could reduce the volume of infarction in rats, all of which showed that PTHrP may have the effect of dilating blood vessels and increasing cerebral blood flow after AIS . In addition, there is evidence that PTHrP also acts as an inflammatory mediator after brain injury , and it can reduce excitotoxicity by reducing calcium influx [5, 6]. Basic studies have shown that PTHrP is associated with AIS and may be a protective factor for AIS. However, there is currently a lack of clinical research on the correlation between serum PTHrP and AIS, and the clinical application value of serum PTHrP to AIS remains to be discovered.

This study aims to explore the expression of PTHrP in the serum of AIS patients, and analyze the correlation between serum PTHrP and the etiological classification, severity, infarction volume and prognosis of AIS, so as to provide a new theoretical basis for the diagnosis and treatment of AIS.

2. Information and methodology

2.1. Study population

From October 2020 to March 2021, 134 patients with AIS admitted to the Department of Neurology of the First Affiliated Hospital of Chongqing Medical University were enrolled in the AIS group. The inclusion criteria were: 1) the first diagnosis of AIS, which was based on the Chinese

Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018; 2) Onset within 72 hours. The exclusion criteria were: 1) intracranial hemorrhage; 2) transient ischemic attack; 3) previous stroke history; 4) degenerative diseases of the nervous system; 5) brain tumors; 6) Severe liver and kidney function damage; 7) lack of brain MRI. During the same time period, after matching sex and age, 34 healthy people who underwent physical examinations at the hospital were included as a control group.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (approval number: 2020-593), and all participants signed informed consent.

2.2. Serum PTHrP test

The AIS group and the control group were drawn 5ml of cubital venous blood at the time of admission and physical examination, respectively, to detect PTHrP. The specific operation process is: the blood sample is centrifuged at 3000 rpm for 5 minutes, and the serum is stored at -80 °C until the measurement. The enzyme-linked immunosorbent assay (ELISA) kit (Kanglang, Shanghai, China) was used to quantitatively detect PTHrP in serum in ng/ml.

2.3. Clinical data collection

The sex, age, body mass index (BMI), history of hypertension, diabetes, hyperlipidemia, smoking, and alcohol consumption were collected from both groups, and fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), and low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), homocysteine (HCY), white blood cell (WBC), and N-terminal pro-B-type precursor natriuretic peptide (NT-proBNP), D-dimer (D-D), prothrombin time (PT), and activated partial thromboplastin time (APTT) were collected.

In the AIS group, patients were divided into 5 categories according to the Trial of Org 10 172 in acute stroke treatment (TOAST) classification, including large artery atherosclerosis (LAA), cardio-embolism (CE), small artery occlusion, SAO), stroke of other determined cause (SOC), stroke of undetermined cause (SUC). The National Institutes of Health stroke scale (NIHSS) score was collected on admission to evaluate the severity of the neurological impairment of the patients. The total score was 42, and those with a score of less than 5 were classified into the mild group. 5-15 points are classified as moderate group, and more than 15 points are classified as severe group. The volume of cerebral infarction was collected according to brain MRI in cm3. Patients with less than 5 cm3 were classified as small infarction group, and 5-15 cm3 were classified as medium infarction group, and those greater than 15 cm3 were classified as large infarction group. The functional prognosis of the AIS group at 90 days after onset was evaluated by the Modified Rankin Scale (mRS) , which used 0~6 points to describe seven different outcomes from asymptomatic to death. 0-2 points were classified as good prognosis group and 3-6 points were classified as poor prognosis group. This process is done through outpatient follow-up or telephone follow-up. The assessment of TOAST classification, NIHSS score, infarct volume, and mRS was done independently by two experienced neurologists, and if there were differences, the final results were obtained after discussion between the two physicians.

2.4. Statistical processing

The number of categorical variable was shown as cases (percentage) [n(%)]. The Shapiro-Wilk test was used to distinguish whether continuous variables were normal distribution. Continuous variables with normal distributions were represented by mean ± standard deviation ($\bar{x} \pm s$), and continuous variables with nonnormal distributions were represented by median and interquartile range [M(Q1,Q3)]. The $\chi 2$ test was used to determine whether there was a statistical difference between the two groups of categorical variables. For continuous variables, the Mann-Whitney U test was used to compare the differences between the two groups of nonnormal distribution indicators. The t-test was used to compare the differences of normal distribution indicators between two groups, and the Kruskal-Wallis H test was used to compare the differences of nonnormal distribution indicators of multiple groups. For variables that are not normally distributed, Spearman rank correlation is used to determine the correlation between two variables. The Receiver Operating Characteristic (ROC) curve was used to evaluate the ability of PTHrP to distinguish between AIS and healthy groups. A logistic regression model was used to analyze the influence of variables on prognosis. SPSS 23 was used to complete the statistics, and the $P<0.05$ was statistically significant.

3. Results

3.1. Comparison of clinical data between AIS and control groups

This is shown in Table 1. There was no significant difference in sex and age between the two groups ($P>0.05$). BMI, proportion of hyperlipidemia, smoking history and drink history, lipid profile, PT and APTT were not statistically significant between the two groups ($P>0.05$). In the AIS group, the proportions of hypertension and diabetes were higher than those in the control group (all $P<0.05$), and FBG, HCY, WBC, NT-proBNP and D-D were higher than those in the control group (all $P<0.05$).

3.2. Comparison of serum PTHrP concentrations between the AIS group and the control group

The study showed that the serum PTHrP concentration in the AIS group was significantly higher than that in the control group [1754.20 (1569.20, 2055.30) pg/ml vs 1555.00 (1389.70, 1721.40) pg/ml, $P=0.000$], as shown in Figure 1.

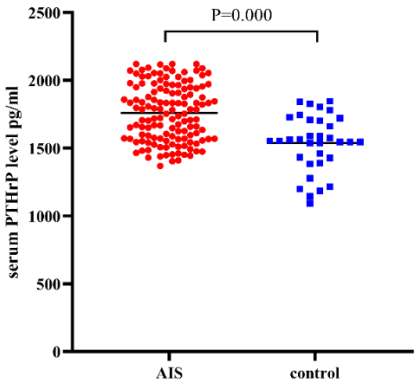

Fig. 1 Comparison of serum PTHrP concentration between AIS group and control group

3.3. The effectiveness of serum PTHrP concentration for differentiating AIS from healthy people

Based on ROC curves, we evaluated the effectiveness of serum PTHrP concentration for early identification of AIS. The area under curve (AUC) was 0.751 [95% CI (0.6627, 0.8386), P<0.0001], and the optimal cut-off value was 1781 pg/ml, where the sensitivity was 50.38% and the specificity was 87.10%, as shown in Figure 2.

3.4. Subgroup analysis of serum PTHrP concentration etiology in the AIS group

The result is shown in Table 2. The serum PTHrP concentration in patients with LAA, CE, SAO and SUC subtype AIS was still significantly higher than that in the control group (all P<0.01), while the serum PTHrP concentration in patients with SOC subtype was not significantly different from that in the control group. The difference in serum PTHrP concentration of these five subtypes was compared by Kruskal-Wallis H test, and the difference was not statistically significant (P=0.091).

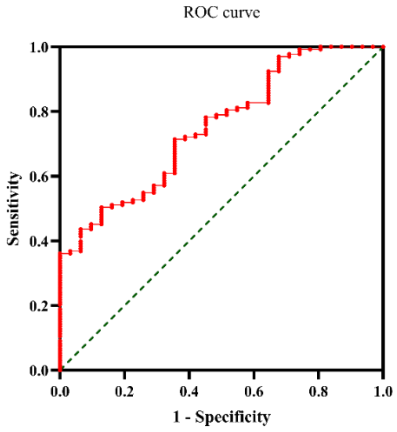

Fig. 2 Serum PTHrP concentrations distinguish between ROC curves for AIS and healthy people

Table 1. Baseline and clinical data [n (%),$\bar{x} \pm s$, M (Q1, Q3)]

	AIS group(n=134)	Control group(n=34)	Test statistics	*P value*
Sex, male	77(57.46%)	20(58.82%)	0.021[a]	0.886
Age, year	66.50(57.00, 75.00)	63.50(52.75, 76.00)	-0.849[b]	0.396
BMI, kg/m^2	24.48±3.58	23.53±2.61	1.306[c]	0.193
Hypertension	104(77.61%)	9(26.47%)	32.210[a]	0.000
Diabetes	48(35.82%)	5(14.71%)	5.599[a]	0.018
Hyperlipidemia	71(52.99%)	18(52.94%)	<0.001[a]	0.996
Smoking history	58(43.28%)	9(26.47%)	3.197[a]	0.074
Drink history	31(23.13%)	3(8.82%)	2.611[a]	0.106
FBG, mmol/L	6.10(5.25, 8.80)	5.30(4.80, 5.80)	-3.953[b]	0.000
TC, mmol/L	4.43±1.04	4.58±1.15	-0.662[c]	0.509
TG, mmol/L	1.23(0.96, 1.79)	1.29(0.93, 1.93)	-0.022[b]	0.982
LDL-c, mmol/L	2.62(2.07, 3.33)	2.82(2.10, 3.54)	-0.506[b]	0.613
HDL-c, mmol/L	1.14(0.96, 1.30)	1.08(0.88, 1.34)	-1.204[b]	0.229
HCY, μmol/L	15.97(11.98, 21.10)	12.03(10.04, 15.08)	-3.946[b]	0.000
WBC, ×10^9/L	7.96(6.51, 10.38)	6.02(5.15, 6.68)	-4.976[b]	0.000
NT-proBNP, ng/L	180.50(56.00, 787.25)	111.47(36.00, 311.00)	-3.136[b]	0.002
D-D, mg/L	0.61(0.28, 1.32)	0.26(0.15, 0.51)	-4.133[b]	0.000
PT, s	11.55(10.90, 12.30)	11.75(11.123, 12.40)	-0.609[b]	0.542
APTT, s	26.20(24.63, 27.90)	27.20(25.95, 28.45)	-1.876[b]	0.061
NIHSS score	4.00(2.00, 9.00)	-	-	-
Infarction olume, m^3	1.50(0.21-13.46)	-	-	-

Note: a represents the value of $\chi 2$, b represents the value of Z, c represents the value of t, and - indicates none of this

Table 2. Aetiological subgroup analysis of serum PTHrP concentration in the AIS group [n (%), M (Q1, Q3)]

	n(%)	Serum PTHrP level pg/ml	*Z value*	*P value*
LAA	62(46.27%)	1787.55 (1575.90, 1958.30)	-4.140	0.000
CE	25(18.66%)	1788.42 (1543.50, 2014.80)	-3.189	0.001
SAO	39(29.10%)	1712.90 (1569.60, 1861.35)	-3.221	0.001
SSUC	4(2.98%)	1567.10(1465.10, 1769.60)	-0.363	0.717
	4(2.98%)	2028.90(1837.05, 2101.88)	-3.007	0.003
H value		8.011		
P value		0.091		

Note: - indicates that there is no such content

3.5. Relationship between serum PTHrP concentration and severity of neurological deficit and volume of cerebral infarction

The severity of neurological defects in the AIS group is shown in Table 3. Serum PTHrP concentration in the severe group is higher than that in the mild and moderate groups, but the H-test shows no significant difference in PTHrP concentration between the three groups (P>0.05). The infarction volume grouping of the AIS group is shown in Table 4, and the H test showed no significant difference in PTHrP concentration between the three groups (P>0.05).

3.6. Relationship between serum PTHrP concentration and AIS prognosis

The prognostic grouping is shown in Table 5. There was no significant difference in serum PTHrP concentration between the favorable outcome group and the unfavorable outcome group (P>0.05). Univariate logistic regression analysis showed that serum PTHrP concentration was independent of prognosis [OR=1.000 95%CI (0.999,1.002) P=0.678].

Table 3. Relationship between serum PTHrP concentration and severity of neurological deficits in AIS group [n(%), M(Q1,Q3)]

	n(%)	NIHSS score	Serum PTHrP level pg/ml	H value	P value
Mild group	74(55.22%)	2.00(1.00, 3.00)	1737.00(1562.20, 1931.90)	2.892	0.235
Moderate group	39(29.10%)	8.00(5.00, 11.00)	1723.10(1573.40, 1948.60)		
Severe group	21(15.67%)	19.00(17.00, 21.00)	1834.00(1599.15, 2072.20)		

Table 4. Relationship between serum PTHrP concentration and cerebral infarction volume in AIS group [n(%), M(Q1,Q3)]

	n (%)	Infarction volume cm3	serum PTHrP levels pg/ml	H value	P value
Small infarction group	89(66.42%)	0.36(0.04, 1.53)	1768.05(1568.80, 1942.15)	1.877	0.391
medium infarction group	14(10.45%)	9.97(7.50, 12.89)	1690.75(1611.18, 1804.05)		
large infarction group	31(23.13%)	76.38(32.22, 189.43)	1855.60(1567.30, 2031.40)		

Table 5. Relationship between serum PTHrP concentration and AIS prognosis [n(%), M(Q1,Q3)]

	n(%)	90-day mRS score	Serum PTHrP level pg/ml	Z value	P value
Favorable outcome group	78(58.21%)	1.00(0.00, 2.00)	1784.10(1555.85, 1956.75)	-0.538	0.591
Favorable outcome group	56(41.79%)	4.00(3.00, 6.00)	1752.50(1597.53, 1936.53)		

3.7. Correlation of serum PTHrP concentration with various indexes in the AIS group

The results showed that the serum PTHrP level of AIS patients with a history of smoking was higher than that of AIS patients without smoking history [1829.55 (1652.10, 1965.58) pg/ml vs. 1674.30 (1527.80, 1948.60) pg/ml, P=0.015]. The relationship between cumulative smoking volume and serum PTHrP was further analyzed, and the results showed that serum PTHrP concentration and cumulative smoking volume (in "year * stick", If a subject smoked for 20 years and 20 sticks of cigarette per day, the cumulative smoking volume was 20×20 year * stick) were positively correlated (r=0.201, P=0.021, Spearman rank correlation), as shown in Figure 2. The results showed that APTT was negatively correlated with serum PTHrP levels in the AIS group (r=-0.188, p=0.034, Spearman rank correlation), as shown in Figure 4.

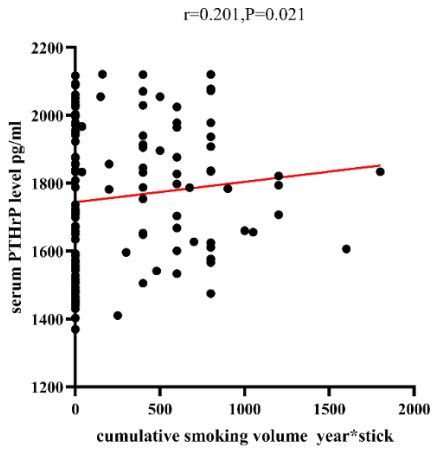

Fig. 3 Correlation between serum PTHrP concentration and cumulative smoking volume

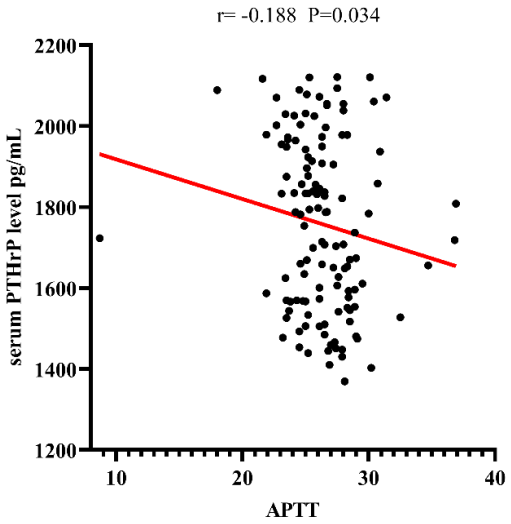

Fig. 4 Correlation between serum PTHrP concentration and APTT

The results showed that serum PTHrP levels were not associated with gender, age, BMI, hypertension, diabetes, hyperlipidemia, history of alcohol consumption, FBG, lipid indexes, HCY, WBC, NT-proBNP, D-D, and PT (all P>0.05).

4. Discussion

AIS is cerebral ischemic necrosis caused by disruption of blood flow, and the pathophysiological mechanism includes ischemic cascades such as energy metabolism disorders, excitatory neurotransmitter release, and inflammation. Using drugs to actively intervene in the key links contributes to favorable outcome of patients. Basic studies have found that PTHrP plays a protective role in multiple links after AIS, and it can act on multiple targets, which has the potential to become the research direction of AIS neuroprotective drugs.

Therefore, we explore the expression of serum PTHrP in AIS patients and analyze its correlation with multiple aspects of AIS, so as to provide a theoretical basis for the application of PTHrP in clinical practice.

Studies have shown that PTHrP may play a role in dilating blood vessels and increasing cerebral blood flow in cerebral ischemia. In the rat model of permanent unilateral middle cerebral artery occlusion, the immunoreactivity of PTHrP in infarcted local vascular endothelial cells increased. By the perfusion of PTHrP through living cranial window, the diameter of pia mater arterioles was increased by 30%, which is equivalent to a 3-fold increase in blood flow. By ventricle injection of PTHrP, the volume of cerebral infarction was reduced, especially the cortical infarction reduced by nearly 50%. Other studies have shown that in the central nervous system, PTHrP may be a cascade of brain inflammation. Funk et al. found through a rat brain injury model that the expression of PTHrP in astrocytes increased after brain injury, and the application of tumor necrosis factor (TNF) to cultured astrocytes could induce PTHrP expression with dose-dependent effect, which suggested that PTHrP after brain injury may be TNF-induced, just as PTHrP is induced in peripheral inflammation[4, 11]. In vitro cell experiments found that PTHrP and TNF induced the expression of IL-6, which had neuroprotective effect. It was found that PTHrP gene knockout mice and PTHrP gene knockout embryo mixed cerebral cortical cultures were twice as sensitive to kainic acid-induced excitotoxicity than control components, and PTHrP addition was found to have a protective effect on kainic acid toxicity in PTHrP gene knockout cultures. Further studies found that PTHrP could reduce the influx of L-VSCC Ca2+ into cultured mouse neuroblastoma cells, which suggested that PTHrP may reduce Ca inflow through L-type voltage-sensitive calcium channels, protecting nerve cells from excitotoxicity. The targets of PTHrP with increased expression of post-infarction brain tissue may also include 1) participating in reducing calcium influx in nerve cells and reducing excitotoxicity. 2) stimulating capillariesis, which may be related to the formation of new blood vessels after infarction. 3) participating in raising blood pressure and increasing cerebral perfusion volume, according to the basis that ventricular injection of PTHrP increased the mean arterial pressure in rats.

First of all, our data showed that the serum PTHrP level in the AIS group was significantly higher than that in the control group, and the serum PTHrP concentrations of the three common AIS subtypes, namely LAA, CE and SAO, were higher than those in the control group, indicating that AIS can increase the serum PTHrP concentration, which is consistent with previous studies, that is, PTHrP can be expressed in brain tissue after infarction, mainly from two sources: 1) increased expression of PTHrP in infarct local vascular endothelial cells, as a dilator of local blood vessels to compensately increase blood flow; 2) increased expression of PTHrP by astrocytes, possibly as an inflammatory mediator to induce neuroprotective IL-6 and inhibit glial cell proliferation to enhance synaptic regeneration after nerve cell injury. Kushnir's study showed that human cerebrospinal fluid PTHrP was 51 times higher than serum PTHrP, suggesting that central nervous system PTHrP may be an important source of serum PTHrP, which supported that increased cerebrospinal fluid PTHrP entered the bloodstream through the blood-cerebrospinal fluid barrier, resulting in increased serum PTHrP. Our results clinically supported the conclusion that PTHrP is a compensatory endogenous protective factor after AIS.

We used the ROC curve to evaluate the ability of serum PTHrP concentration to distinguish between AIS and normal control, and the results showed that the AUC was 0.751, and when the cut-off point was 1781pg/ml, the best efficacy was obtained, with a sensitivity of 50.38% and a specificity of 87.10%. This result preliminarily suggested that serum PTHrP might have auxiliary value for early clinical identification of AIS.

TOAST classification is the most commonly used clinical typing method for the etiology of AIS, which is beneficial to guide treatment and secondary prevention, here we analyzed the correlation between serum PTHrP and TOAST classification, and the results showed that the difference in serum PTHrP concentration of the five subtypes was not statistically significant, indicating that serum PTHrP has no value in guiding the classification of AIS etiology.

We explored the relationship between serum PTHrP and respectively NIHSS score at admission and cerebral infarction volume. The results showed that there was no significant change in serum PTHrP concentration with the increase of NIHSS score and infarction volume in different subgroups. We further explored the relationship between serum PTHrP concentration and the 90-day functional prognosis of AIS patients. The results showed that there was no significant difference between the favorable outcome group and the unfavorable outcome group, and univariate logistic regression showed that serum PTHrP was not related to prognosis. In this regard, we analyzed as follows (in terms of cerebral infarction volume analysis alone, because NIHSS score and infarction volume are highly correlated, r=0.617, P=0.000): 1) The larger the volume of cerebral infarction in AIS patients, the more vascular endothelial cells and astrocytes expressing PTHrP. Cerebrospinal fluid is the extracellular fluid of brain tissue, and is in direct contact with cerebral vascular endothelial cells and glial cells and continuously exchanges substances. Therefore, we hypothesized that as the infarction volume increased, the more PTHrP the cerebrospinal fluid increased. However, due to the presence of the blood cerebrospinal fluid barrier, PTHrP concentration will change significantly when transferred from cerebrospinal fluid to the blood as a macromolecular peptide[16, 17]. Moreover, various pathophysiological changes in the peripheral periphery after stroke, such as infection and stress, could lead to fluctuations in serum PTHrP. In addition, whether free PTHrP binded to other substances in serum is still unclear. The reasons above made the changes of serum PTHrP in AIS patients have many interfering factors, which could not accurately reflect the changes of cerebrospinal fluid PTHrP. 2) Results suggested that serum PTHrP concentrations cannot be used to assess the prognosis of patients with AIS. PTHrP can significantly reduce the volume of cerebral infarction by ventricle bolus injection in rats, and has demonstrated its effectiveness as an exogenous drug for human AIS. However, due to the presence of the blood-cerebrospinal fluid barrier and peripheral interference, the effect of PTHrP as an endogenous protective factor of AIS on patient prognosis could not be determined by serum testing.

Finally, this study explored the correlation between serum PTHrP and various indicators, and the results showed that the serum PTHrP of patients with a history of smoking in the AIS group was higher than that of patients without smoking history, and the serum PTHrP concentration of patients was

positively correlated with the cumulative smoking volume, which was consistent with the two basic studies [19, 20]. The mechanism may be that smoking leads to increased expression of PTHrP in ventricular and coronary endothelial cells [19, 20]. The clinical observation of smoking associated with serum PTHrP contributes to the use of PTHrP, such as assessing the true amount of smoking of AIS patients. In addition, this study found that serum PTHrP concentrations in AIS patients were inversely correlated with APTT, which may be related to the effect of PTHrP in increasing serum calcium. The results of this study showed that serum PTHrP was positively correlated with serum calcium, while APTT was negatively correlated with serum calcium (data not shown). The specific mechanism was that calcium ions as an electrolyte necessary for the coagulation process, and their elevation could accelerate coagulation, resulting in a decrease in APTT. This helps partly explain the early clotting increase in AIS patients。

Our study still had limitations: 1) the confounding factors in the control and AIS groups were not fully matched, which may have led to error in the results; 2) The serum PTHrP concentration was only measured at one time point, and the change of serum PTHrP after AIS could not be dynamically observed; 3) The concentration of cerebrospinal fluid PTHrP was not measured, and the changes of post-infarction brain PTHrP could not be explored more directly; 4) The sample size is small, and it is a single-center study, which has errors.

5. Conclusion

In summary, our study was the first to explore the correlation between serum PTHrP concentration and AIS from a clinical perspective. The results showed that the serum PTHrP concentration in the AIS group was significantly higher than that in the control group. Serum PTHrP might be ancillary for early identification of AIS. Serum PTHrP concentrations in the AIS group correlated with cumulative smoking volume and APTT, and might be useful to assess true amount of smoking and analyze coagulation function. However, serum PTHrP concentrations are not associated with TOAST classification, NIHSS score, cerebral infarction volume, and 90-day prognosis, which means it cannot be used to assess the etiology, severity, and prognosis of patients with AIS.

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