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THE PREDICTIVE VALUE OF SERUM PAF-AH AND VISININ-LIKE PROTEIN 1 FOR POOR PROGNOSIS IN PATIENTS WITH HYPERTENSIVE INTRACEREBRAL HEMORRHAGE

PREDIKTIVNA VREDNOST SERUMSKOG PAF-AH I PROTEINA SLIČNOG VIZININU 1 ZA LOŠU PROGNOZU KOD PACIJENATA SA INTRACEREBRALNIM KRVARENJEM USLED HIPERTENZIJE

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Summary

Background: o determine if serum levels of retinoid protein-like protein 1 (VILIP-1), Platelet-Activating Factor Acetylhydrolase (PAF-AH), and 8-hydroxydeoxyguanosine (8-OHDG) are prognostic of a poor prognosis in patients with hypertensive intracerebral haemorrhage.
Methods: The 194 patients in the cerebral haemorrhage group were hospitalised with hypertensive cerebral haemorrhage between January 2022 and January 2024. Forty-five healthy individuals who underwent concurrent physical examinations at the hospital were selected to form the healthy control group. To observe the differences in the levels of serum PAF-AH, VILIP-1 and 8-OHDG, the relationship with the amount of intracerebral haemorrhage, the severity of intracerebral haemorrhage and poor prognosis, and how effectively it predicts the bad outcome of patients suffering from hypertensive intracerebral haemorrhage.

Kratak sadržaj

Uvod: Cilj je bio da se utvrdi da li su serumski nivoi proteina sličnog retinoidnom proteinu 1 (VILIP-1), acetilhidrolaze faktora aktivacije trombocita (PAF-AH) i 8-hidroksideoksigvanozina (8-OHDG) prognostički pokazatelji loše prognoze kod pacijenata sa hipertenzivnim intracerebralnim krvarenjem.
Metode: U grupi pacijenata sa cerebralnim krvarenjem bilo je 194 pacijenta hospitalizovana sa hipertenzivnim cerebralnim krvarenjem između januara 2022. i januara 2024. Četrdeset pet zdravih osoba koje su u isto vreme obavljale sistematske preglede u bolnici odabrano je za kontrolnu grupu. Posmatrane su razlike u nivoima seruma PAF-AH, VILIP-1 i 8-OHDG, njihova povezanost sa količinom intracerebralnog krvarenja, te inom neurološkog oštećenja i lošom prognozom, kao i efikasnost predikcije nepovoljnog ishoda kod pacijenata sa hipertenzivnim intracerebralnim krvarenjem.

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Results: Serum PAF-AH, VILIP-1, and 8-OHDG levels were substantially greater in the brain haemorrhage group than in the healthy control group (P<0.05). The levels of serum PAF-AH, VILIP-1 and 8-OHDG in the cerebral haemorrhage group increased with the increase of the amount of cerebral haemorrhage and the severity of nerve defect, and patients with poor prognoses had significantly greater serum levels of PAF-AH, VILIP-1, and 8-OHDG than patients with excellent prognoses (P<0.05). The levels of serum PAF-AH, VILIP-1 and 8-OHDG have high value in predicting the poor prognosis of patients with cerebral haemorrhage. The combined detection's area under the curve (AUC) was 0.925, its sensitivity was 95.4%, and its specificity was 71.2%. The AUCs of the three indicators, determined independently, did not differ significantly (P>0.05).
Conclusions: PAF-AH, VILIP-1 and 8-OHDG are involved in the occurrence and development process of hypertensive intracerebral haemorrhage. The increase in their levels is associated with a poor prognosis. Combined detection is helpful to improve the predictive efficacy of poor prognosis in patients with hypertensive intracerebral haemorrhage.

Keywords: hypertension, cerebral haemorrhage, optoprotein-like protein 1, 8-hydroxydeoxyguanosine, platelet-activating factor acetylhydrolase

Rezultati: Nivoi seruma PAF-AH, VILIP-1 i 8-OHDG bili su značajno viši u grupi sa cerebralnim krvarenjem nego u kontrolnoj grupi zdravih osoba (P<0,05). Nivoi seruma PAF-AH, VILIP-1 i 8-OHDG u grupi sa cerebralnim krvarenjem povećavali su se sa povećanjem količine krvarenja i te ine neurološkog deficita, a pacijenti sa lošom prognozom imali su značajno više nivoe ovih markera nego pacijenti sa povoljnijom prognozom (P<0,05). Nivoi seruma PAF-AH, VILIP-1 i 8-OHDG imaju visoku vrednost u predikciji loše prognoze kod pacijenata sa cerebralnim krvarenjem. Površina ispod krive (AUC) za kombinovanu detekciju je iznosila 0,925, senzitivnost 95,4%, a specifičnost 71,2%. AUC vrednosti za tri indikatora, određene pojedinačno, se nisu značajno razlikovale (P>0,05).
Zaključak: PAF-AH, VILIP-1 i 8-OHDG učestvuju u procesu nastanka i razvoja hipertenzivnog intracerebralnog krvarenja. Povećanje njihovih nivoa povezano je sa lošom prognozom. Kombinovana detekcija doprinosi poboljšanju efikasnosti predviđanja lošeg ishoda kod pacijenata sa hipertenzivnim intracerebralnim krvarenjem.

Ključne reči: hipertenzija, cerebralno krvarenje, optoproteinu sličan protein 1, 8-hidroksideoksiguanozin, acetilhidrolaza faktora aktivacije trombocita

Introduction

Cerebral haemorrhage is the most serious complication of hypertension, characterised by a high disability rate, high incidence rate and poor prognosis (1). Survivors still have the possibility of experiencing cerebral haemorrhage and cerebral infarction again, and their prognosis is even worse than that of simple cerebral infarction (2–4). Therefore, early monitoring of hypertensive intracerebral haemorrhage has significant clinical value for disease diagnosis and prognosis improvement (5). The main pathological changes in patients with hypertensive intracerebral haemorrhage are hyaline or fibrous lesions in the walls of small arteries, leading to local haemorrhage, necrosis, and the formation of microaneurysms (6–8).

An inflammatory marker, Platelet-Activating Factor Acetylhydrolase (PAF-AH), contributes to the inflammatory response in blood vessels and is crucial for the development of atherosclerosis (9). It is also an indicator reflecting the degree of brain injury. Whether it has predictive value for the prognosis of cerebral haemorrhage remains unclear. 8-hydroxydeoxyguanosine (8-OHDG) is a recognised marker of oxidative stress that directly participates in the DNA damage process in nerve cells and plays a significant role in the occurrence and development of neurological diseases and brain injuries (10–12). VILIP-1 is a calcium-sensing protein of the nervous system, mainly regulating the calcium ion channels and signalling pathways of neurons (13). It is highly expressed in brain tissue injury and participates in the pathophysiological process (14).

All three indicators are related to nerve injury. It is speculated that all three are involved in the pathogenesis of cerebral haemorrhage; their usefulness in determining the prognosis of patients with cerebral haemorrhage is yet unknown (15). This study found that individuals with hypertensive intracerebral haemorrhage had blood levels of PAF-AH, VILIP-1, and 8-OHDG. It also noted the clinical utility of these levels in assessing the prognosis of these patients.

Materials and Methods

General information

For the cerebral haemorrhage group, a total of 194 patients – 110 men and 84 women – with hypertensive cerebral haemorrhage who were diagnosed and treated at our hospital between January 2022 and January 2024 were chosen. With an average age of 67.35±2.66 years, the age ranged from 52 to 74 years. Head CT and/or MRI were performed on all patients. Based on the amount of intracranial haemorrhage, patients were divided into three groups: 76 cases with minor haemorrhage (less than 15 mL), 80 cases with medium haemorrhage (15–30 mL), and 38 cases with significant haemorrhage (more than 30 mL). According to the National Institutes of Health Stroke Scale score, the patients were divided into the mild group (<5 points; 68 cases), the moderate group (5–15 points; 82 cases), and the severe group (>15 points; 44 cases).

Inclusion criteria: First admission for cerebral haemorrhage; Elevated blood pressure in the past or

upon admission; The estimated survival time exceeds three months. Admitted to the hospital within 24 hours of onset. Exclusion criteria: Secondary cerebral haemorrhage; Cerebral infarction; Cerebral vascular malformations or combined intracranial tumours; Combined with haematological diseases and immune system diseases; Dysfunction of vital organs such as the heart, liver and kidneys; Combined brain herniation; Died during emergency treatment; The follow-up data is incomplete. Ninety healthy individuals who underwent physical examinations in our hospital during the same period were selected and included in the healthy control group, including 56 males and 34 females. The age ranged from 50 to 77 years old, with an average of (66.85±4.29) years old. General data, including age and gender, did not show a statistically significant difference between the two groups ($P>0.05$), and they were equivalent.

Treatment methods

After admission, the patient should complete relevant examinations. Based on the condition, the appropriate treatment plan should be selected. For patients with surgical indications, small-bone-window hematoma evacuation surgery should be performed. Postoperatively, symptomatic treatments such as nerve nutrition, hemostasis, prevention of vascular spasm, electrolyte supplementation and nutritional support were routinely provided.

Collection of blood samples and specimen testing

After the patient was admitted to the hospital and during the physical examination of healthy individuals, approximately 5 mL of venous blood from the elbow was collected. The blood was centrifuged at 1,600×g for 10 minutes using a centrifuge with a 9 cm radius. The supernatant was placed in a refrigerator at -70 °C for testing. The levels of serum PAF-AH, VILIP-1 and 8-OHDG were determined by enzyme-linked immunosorbent assay. The kits were purchased from Wuhan Saipei Biotechnology Co., Ltd. and operated strictly in accordance with the instructions.

Follow-up analysis

After 3 months of treatment, the Glasgow Outcome Scale was used for scoring: 1 point for death, 2 points for vegetative state, 3 points for severe disability and inability to take care of oneself, 4 points for moderate disability and partial self-care of life, and 5 points for mild neurological dysfunction with no significant impact on daily life. A score of 1 to 3 indicates a poor-prognosis group, while a score of 4 to 5 indicates a good-prognosis group.

Laboratory testing reagents and equipment

The serum biomarker detection items involved in this study include Platelet-Activating Factor Acetylhydrolase (PAF-AH), cone protein-like protein-1 (VILIP-1), and 8-hydroxydeoxyguanosine (8-OHDG). The specific information on the reagent kits used, primary reagents, and key instruments and equipment is as follows:

Detection of serum PAF-AH concentration:

Detection method: Enzyme-Linked Immunosorbent Assay (ELISA)

Kit: Human Platelet-Activating Factor Acetylhydrolase (PAF-AH) ELISA Kit

Manufacturer: Wuhan Huamei Bioengineering Co., LTD. (Cloud-Clone Corp., CCC)

Item no. SEA753Hu

(2) Detection of serum VILIP-1 concentration:

Detection method: Enzyme-Linked Immunosorbent Assay (ELISA)

Kit: Human Cone Protein-like Protein 1 (VILIP-1) ELISA Kit

Manufacturer: Wuhan Huamei Bioengineering Co., LTD. (Cloud-Clone Corp., CCC)

Item no. SEC824Hu

(3) Detection of serum 8-OHDG concentration:

Detection method: Competitive Enzyme-Linked Immunosorbent Assay (ELISA)

Kit: 8-hydroxyDeoxyguanosine (8-OHDG) ELISA Kit

Manufacturer: Cayman Chemical Company

Item no. 58100-1-KIT

Observation indicators

To assess the variations in serum PAF-AH, VILIP-1, and 8-OHDG levels between hypertensive intracerebral haemorrhage patients and the healthy control group, analyse the relationship between the levels of PAF-AH, VILIP-1 and 8-OHDG and the amount of intracerebral haemorrhage, the severity of intracerebral haemorrhage and poor prognosis, as well as their value in predicting the poor prognosis of patients with hypertensive intracerebral haemorrhage.

Statistical processing

The statistical program SPSS 20.0 was used to handle and analyse the data. The measurement values that fit the normal distribution were expressed using $\bar{x}\pm s$. For two-group comparisons, the t-test was used. Pairwise comparisons between groups were

conducted using the LSD-t test, whereas multiple-group comparisons were performed using analysis of variance. The χ^2 test was used to compare groups, and the results were presented as percentages or counts. Binary Logistic regression was used to construct the equation of the combined detection index. The receiver operating characteristic (ROC) curve was used to evaluate the predictive efficacy of serum PAF-AH, VILIP-1, and 8-OHDG for the poor prognosis of patients with cerebral haemorrhage.

Results

Comparison of serum PAF-AH, VILIP-1 and 8-OHDG levels between the two groups

The levels of serum PAF-AH, VILIP-1 and 8-OHDG in the cerebral haemorrhage group were significantly higher than those in the healthy control group (P<0.05). See *Table I*.

Serum PAF-AH, VILIP-1, and 8-OHDG levels were significantly higher in the hypertensive cerebral haemorrhage group than in the healthy control group; this difference was statistically significant (P<0.05). The distribution of the three indicators in the case group generally shifted upward, suggesting that the inflammatory response, neuronal damage, and oxidative stress were enhanced. This can effectively distinguish patients from healthy people and provide a biological basis for disease identification and subsequent risk stratification.

Serum PAF-AH, VILIP-1, and 8-OHDG levels in patients with varying degrees of brain bleeding

Both the moderate haemorrhage group and the small haemorrhage group had significantly lower blood levels of VILIP-1, 8-OHDG, and PAF-AH than the major haemorrhage group (P<0.05). Still, the moderate haemorrhage group had substantially higher levels than the small haemorrhage group (see *Table II*).

Stratified analysis by bleeding amount showed that Serum PAF-AH, VILIP-1, and 8-OHDG levels rose gradually in patients with minor, moderate, and severe bleeding; these increases were significant between groups (P<0.05) and were positively associated with hematoma volume. The three biomarkers could sensitively reflect the bleeding burden and the degree of brain tissue damage, which were helpful for assessing disease severity and determining the risk of adverse outcomes.

Comparison of serum PAF-AH, VILIP-1 and 8-OHDG levels in patients with different severity degrees of cerebral haemorrhage

The levels of PAF-AH, VILIP-1 and 8-OHDG in the severe group were significantly higher than those in the moderate group and the mild group (P<0.05), and the moderate group was considerably higher than the mild group (P<0.05) (see *Table III*).

Table I Comparison of the two groups' serum levels of VILIP-1, 8-OHDG, and PAF-AH.

Group	n	PAF-AH (μg/L)	VILIP-1 (μg/L)	8-OHDG (pg/mL)
Hemorrhagic stroke group	194	158.76±31.68	0.87±0.23	45.89±8.14
Healthy control group	90	88.85±16.42	0.46±0.09	22.29±3.15
t		17.298	16.359	24.863
P		<0.001	<0.001	<0.001

Table II Comparison of serum PAF-AH, VILIP-1, and 8-OHDG levels in patients with different amounts of cerebral haemorrhage.

Group	n	PAF-AH (μg/L)	VILIP-1 (μg/L)	8-OHDG (pg/mL)
Small bleeding group	76	129.62±15.48	0.68±0.16	39.64±5.75
Moderate bleeding group	80	171.83±19.25	0.93±0.15	48.25±6.67
Massive bleeding group	38	189.75±29.37	1.15±0.26	53.43±6.15
F		69.489	63.106	36.158
P		<0.001	<0.001	<0.001

Table III Comparison of serum PAF-AH, VILIP-1, and 8-OHDG levels in patients with different degrees of cerebral haemorrhage.

Group	n	PAF-AH (μg/L)	VILIP-1 (μg/L)	8-OHDG (pg/mL)
Mild group	68	127.59±15.11	0.67±0.08	39.12±5.85
Moderate group	82	170.47±17.16	0.91±0.12	48.14±5.77
Severe group	44	185.25±32.96	1.07±0.25	52.18±7.88
F		60.408	53.563	32.985
P		<0.001	<0.001	<0.001

Table IV Comparison of serum PAF-AH, VILIP-1, and 8-OHDG levels in patients with different prognoses.

Group	n	PAF-AH (μg/L)	VILIP-1 (μg/L)	8-OHDG (pg/mL)
Good prognosis group	76	151.77±27.47	0.80±0.17	44.24±7.52
Poor prognosis group	21	184.24±33.39	1.05±0.27	51.79±7.82
t		4.571	3.992	4,035
P		<0.001	0.001	<0.001

Table V Value of serum PAF-AH, VILIP-1, and 8-OHDG levels in predicting poor prognosis in patients with cerebral haemorrhage.

Item	Truncated value	Sensitivity (%)	Specificity (%)	AUC	95%CI
PAF-AH	168.88 μg/L	76.1	76.5	0.789	0.695~0.868
VILIP-1	0.89 μg/L	85.2	65.2	0.794	0.697~0.869
8-OHDG	49.92 pg/mL	71.7	81.1	0.763	0.662~0.845
PAF-AH+VILIP-1+8-OHDG	–	95.4	71.6	0.926	0.853~0.969

Based on the stratification of neurological deficit severity (mild, moderate, and severe), the levels of serum PAF-AH, VILIP-1, and 8-OHDG increased stepwise with increasing severity. The severe group had the highest values, followed by the moderate group, and the mild group had the lowest. There was a statistically significant difference between the groups ($P<0.05$). The three were significantly positively correlated with the neurological deficit score and hematoma volume, and the linear trend test was also significant, suggesting that the inflammatory response, neuronal damage, and oxidative stress were simultaneously enhanced as the disease progressed.

Serum PAF-AH, VILIP-1, and 8-OHDG levels in patients with various prognostic factors

Following follow-up, 152 cases were in the good-prognosis group and 42 in the poor-prognosis group. Serum PAF-AH, VILIP-1, and 8-OHDG levels were considerably greater in the group with a bad prognosis than in the group with a good prognosis ($P<0.05$) (see *Table IV*).

Serum levels of VILIP-1, 8-OHDG, and PAF-AH were significantly lower in patients with a favourable prognosis ($P<0.05$). The three indicators in the poor-prognosis group increased overall. They were consistent with a greater bleeding burden and more severe neurological deficits, suggesting that the increase in inflammatory response, neuronal damage and oxidative stress levels was closely related to adverse outcomes. The analysis of receiver operating characteris-

tics further indicated that the combined detection of the three had a high recognition efficiency for poor prognosis (AUC=0.925), with a sensitivity of 95.4% and a specificity of 71.2%, significantly superior to individual indicators, supporting its application in clinical prognosis assessment and risk stratification.

The value of serum PAF-AH, VILIP-1 and 8-OHDG levels in predicting poor prognosis in patients with cerebral haemorrhage

To determine if patients with cerebral haemorrhage had a bad prognosis, binary logistic regression analysis was used. The equation Y=0.05×XPAF-AH+5.89×XVILIP-1+0.17×X8-OHDG-21.38 was obtained as the combined detection index. The combined detection's specificity was 71.2% and its sensitivity was 95.6%. Its area under the curve (AUC), which was 0.925, was noticeably greater than that of the independently identified PAF-AH (Z=2.492, P=0.018), VILIP-1 (Z=2.242, P=0.027), and 8-OHDG (Z=2.435, P=0.016). However, the comparison of AUC among the three indicators detected separately showed no statistically significant difference (P>0.05) (see *Table V*).

Discussion

If patients with cerebral haemorrhage do not receive effective treatment in the early stage, it can lead to irreversible damage to brain tissue and brain death (16). Early assessment of the condition and prognosis helps guide clinical treatment of such patients, improving survival and reducing disability (17–19). According to a multivariate analysis, the degree of neurological function impairment, age, bleeding volume, and grade of hypertension were risk factors for a poor outcome of intracerebral haemorrhage caused by hypertension (20). The traditional monitoring methods, such as brain MRI, CT, blood pressure grading, bleeding volume assessment, and functional scoring, cannot provide a comprehensive assessment of patients, are poorly repeatable, and some examinations are expensive, which, to some extent, limits their application (21). Serological indicators, due to their convenient specimen collection and the ability to be repeatedly monitored, can better guide clinical diagnosis and treatment (22).

This study demonstrates that the cerebral haemorrhage group's serum PAF-AH level is noticeably greater than the healthy control group's, and it increases with the increase of the amount of cerebral haemorrhage and the severity of nerve injury (23). This indicates that PAF-AH is involved in the occurrence and development of cerebral haemorrhage and is related to the damage of brain nerve function. Existing studies have confirmed that PAF-AH primarily promotes vascular amyloid deposition and the development of arteriosclerosis (24). When acute cerebral infarction occurs, PAF-AH levels increase, mediating the local inflammatory response in cerebral blood vessels and triggering a cascade of amplification in related inflammatory response pathways (25–27). It causes inflammatory cells to release large amounts of inflammatory mediators, such as interleukins and platelet-derived cytokines, thereby aggravating damage to brain tissue (28–30). Moreover, when serum PAF-AH was 168.89 μg/L, it had a high predictive value for a poor prognosis within 3 months in patients with cerebral haemorrhage. Treating stroke patients with PAF-AH-specific inhibitors can significantly reduce serum PAF-AH levels and improve the clinical symptoms and prognosis of stroke (31).

The brain haemorrhage group's serum VILIP-1 level is noticeably greater, and it increases with the increase of cerebral haemorrhage volume and the severity of nerve injury, indicating that there is a certain connection between serum VILIP-1 and cerebral haemorrhage disease (32). VILIP-1 is a specific marker of brain neuron injury, is richly expressed in brain neurons, and can regulate neuronal signalling pathways and calcium ion channels. VILIP-1 causes brain tissue damage mainly by phosphorylating tubulin, leading to the deposition of β-amyloid protein 1–42 in the brain. The main manifestations are inflammatory responses and ischemic and hypoxic injuries. The level of VILIP-1 is closely associated with short-term neurological prognosis. When brain tissue is damaged, a large amount of VILIP-1 is released and can cross the damaged blood-brain barrier, leading to an increase in VILIP-1 levels in peripheral blood (33).

The group experiencing cerebral haemorrhage had a considerably higher serum 8-OHDG level than the healthy control group, and this level increased with increasing cerebral haemorrhage volume and the severity of nerve injury, indicating that serum 8-OHDG is an essential indicator of cerebral haemorrhage severity. 8-OHDG is a marker of endogenous and exogenous DNA oxidative damage (34). As a product of oxidative modification, it is cleaved by specific repair enzymes and excreted in urine. The mechanism by which 8-OHDG causes brain tissue damage is that under oxidative stress conditions, a large amount of oxygen free radicals are produced, which leads to the generation of a large number of apoptosis-inducing factors, resulting in apoptosis of nerve cells, inhibition of nerve fiber regeneration, loss of neuronal function, progressive aggravation of neurological deficits, and eventually disability (35). This study demonstrates that the serum 8-OHDG level was substantially greater in the brain haemorrhage group with a poor prognosis than in the group with a good prognosis. Moreover, when the serum 8-OHDG level was 49.96 pg/mL, the sensitivity was 71.5%, the specificity was 81.8%, and the AUC was 0.765, indicating that serum 8-OHDG is an essential indicator for predicting the prognosis of cerebral haemorrhage.

Existing studies have shown that serum 8-OHDG levels are closely related to the prognosis of ischemic stroke, while there are still relatively few studies on hemorrhagic stroke. This study shows that the combined detection of serum PAF-AH, VILIP-1 and 8-OHDG has a higher efficacy in predicting the poor prognosis of patients with cerebral haemorrhage, which is significantly better than the individual indicators PAF-AH, VILIP-1 and 8-OHDG. This suggests that there may be some complementarity among the three indicators, and the interaction mechanism warrants further study.

Conclusion

PAF-AH, VILIP-1 and 8-OHDG are involved in the occurrence and development of hypertensive intracerebral haemorrhage. Their elevated levels are associated with poor prognosis. Combined detection is helpful to improve the predictive efficacy of poor prognosis of hypertensive intracerebral haemorrhage.

Authors' contribution

Yaqiang Bai and Man Wei contributed equally to this work and are regarded as co-first authors.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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