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Case Control Study

Changes and significance of serum ubiquitin carboxyl-terminal hydrolase L1 and glial fibrillary acidic protein in patients with glioma

INTRODUCTION

Brain glioma is an extremely common type of intracranial malignant tumor that deteriorates, grows rapidly and causes severe neurological impairment. Due to the poor sensitivity of brain gliomas to radiotherapy, they are mainly managed by surgical resection. However, some gliomas are large in size or close to important neural tissues and are difficult to completely remove intraoperatively. Therefore, the recurrence rate of brain gliomas after surgery is high[1,2]. Early prediction of postoperative prognosis in patients with gliomas is of great importance in clinical practice. Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) is a cysteine hydrolase that regulates the cell cycle, is involved in apoptosis and inflammatory responses, is present at high levels in the brain, and is regarded as a biomarker of brain injury[3]. Glial fibrillary acidic protein (GFAP) is a specific indicator of astrocytes and involved in neurological damage and lesions[4]. In this study, we evaluated changes in serum UCH-L1 and GFAP levels in patients with glioma before and after surgery. We also assessed the relationship between the two indicators and analyzed data of the patients' clinicopathological characteristics and postoperative recurrence. We also aimed to determine the values of UCH-L1 and GFAP for predicting glioma recurrence.

MATERIALS AND METHODS

Participants

A total of 91 patients with gliomas who underwent surgery in the hospital between June 2018 and June 2021 were enrolled in the glioma group. The control group included 60 healthy volunteers during the same period.

Patients with glioma

The inclusion criteria comprised patients: who were treated surgically; with glioma that was clearly detected by postoperative pathological examination; who underwent no radiotherapy before surgery; and with complete clinical case data. Patients with: acromegaly, hepatitis, and other diseases; severe defects in vital organ function; severe complications, and postoperative death; or other malignant tumors were excluded from the study.

The control group

The age and sex ratios in the control group were similar to those in the glioma group: both groups underwent physical examination and had no previous history of tumors, intracranial lesions, or brain injury.

Methods

All patients with gliomas were surgically treated, and 5 mL of peripheral venous blood was collected from these patients with glioma before and 3 d after surgery. In the control group, venous blood was collected during fasting in the early morning on day two after enrollment.

Blood samples were immediately centrifuged at 3000 rpm for 15 min. The liquid supernatant was separated and stored at -80°C for later use. Serum GFAP and UCH-L1 Levels were detected by ABC-ELISA, and kits were purchased from Rapid Bio, USA. The experimental procedure was performed in strict accordance with the relevant kit standards.

Study aims

(1) To compare UCH-L1 and GFAP levels between the glioma and control groups; (2) To analyze data of preoperative serum UCH-L1 and GFAP levels in patients with gliomas with different clinicopathological features; and (3) The patients were followed up until February 2022 to record the preoperative recurrence of glioma and compare serum UCH-L1 and GFAP levels between the recurring and non-recurring patients. A receiver operating characteristic (ROC) curve was drawn. Furthermore, the values of preoperative and postoperative serum UCH-L1 and GFAP levels for predicting postoperative glioma recurrence were analyzed.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0. The measurement data was presented as mean ± SD. The independent samples *t* test was used for mean comparison between the two groups. The mean data before and after treatment were analyzed using the paired *t* test, and the count data were conveyed by case. The χ^2 test was used to compare the two groups. ROC curves were drawn (Figure 1). In addition, the best critical value was calculated by the Youden index formula to evaluate the efficacy of preoperative and postoperative serum UCH-L1 and GFAP levels in predicting postoperative glioma recurrence. *P* value < 0.05 was considered statistically significant.

RESULTS

Comparison of serum UCH-L1 and GFAP levels between the glioma and control groups

UCH-L1 and GFAP levels in the patients with glioma decreased significantly 3 d after surgery compared with their pre-therapy levels ($P < 0.05$). However, the UCH-L1 and GFAP levels in the glioma group were significantly higher than those in the control group before and after surgery ($P < 0.05$, Table 1).

Analysis of the relationship between preoperative serum UCH-L1 and GFAP levels and clinicopathological characteristics in patients with glioma

There were no significant differences in the preoperative serum UCH-L1 and GFAP levels in patients with brain glioma with respect to sex, age, pathological type, tumor location, or number of lesions ($P > 0.05$, Table 2). The UCH-L1 and GFAP levels in the patients with WHO grade I-II tumors were lower than those in the participants with grade III-IV tumors. Additionally, the UCH-L1 and GFAP levels in the patients with tumor diameters ≤ 5 cm were lower than those in the participants with tumor diameters > 5 cm.

Comparison of UCH-L1 and GFAP levels in patients with glioma recurrence and those without recurrence before and after surgery

All patients were followed up until February 2022. A total of 22 patients with gliomas experienced recurrence. The preoperative and 3 d postoperative serum UCH-L1 and GFAP levels were significantly higher in the recurrence group compared with the non-recurrence group ($P < 0.05$, Table 3).

The value of UCH-L1 and GFAP levels for predicting postoperative recurrence of glioma

The AUC of the preoperative serum UCH-L1 and GFAP levels for predicting postoperative glioma recurrence were 0.785 and 0.775, respectively (Table 4). The efficacy of UCH-L1 and GFAP levels 3 d after surgery in predicting postoperative glioma recurrence was slightly lower than their preoperative levels.

DISCUSSION

Glioma is a tumor caused by glial cell lesions originating from the ectoderm of the nervous system with an incidence of approximately 5/100000. Owing to the lack of specific tumor markers related to gliomas, imaging examinations such as brain computed tomography or magnetic resonance imaging are the main methods for the clinical assessment of changes and treatment effects during the course of glioma. However, imaging examinations are particularly lagging behind clinical treatment and prognostic determination[5,6]. Therefore, finding more sensitive indicators that reflect treatment

effect and prognosis in patients with glioma as soon as possible was one of the aims of the current study.

UCH-L1 is a member of the ubiquitin protease system family, which mainly consists of 223 amino acids, and is abundant in the brain. It is involved in cell proliferation, differentiation, apoptosis, and other physiological processes *via* the ubiquitin pathway. In addition, UCH-L1 has been shown to be relevant to brain nervous system development, brain tumors, and brain injury[7,8]. Studies have shown that[9] after acute cerebral infarction, a large amount of UCH-L1 could be released from damaged nerve cells and penetrate the blood-brain barrier into the blood circulation. Therefore, serum UCH-L1 levels were elevated in patients with cerebral infarction. Wang *et al*[10] found that serum UCH-L1 Levels had good clinical value for reflecting the degree of brain injury and prognosis in patients with severe craniocerebral injury. Elevated levels of UCH-L1 in the cerebrospinal fluid and peripheral blood have become effective indicators of the severity of central nervous cell damage.

This study revealed that the preoperative serum UCH-L1 levels in patients with glioma were notably higher than those in the control group. Furthermore, UCH-L1 Levels in patients with gliomas significantly decreased after surgical treatment. However, the postoperative UCH-L1 level was also higher than that in healthy controls. This may be related to the fact that under compression by glioma, part of the brain nerve tissue could have been damaged, which in turn released a large amount of UCH-L1, leading to an increase in serum UCH-L1 Levels. Subsequently, the glioma was removed to relieve the compressed brain tissues and decrease the release of UCH-L1 from damaged nerve cells.

The WHO classifies gliomas into grades I–IV, with grades I–II as low-grade and those of III–IV as high-grade gliomas. This study demonstrated that UCH-L1 Levels in the patients with WHO grade III-IVI-II tumors were higher than those in those with grade I-II tumors. Additionally, the UCH-L1 Level was greater in the patients with a tumor diameter > 5 cm than in those with diameter ≤ 5 cm. It has been suggested that serum UCH-L1 Levels reflected development of glioma.

GFAP is a cytoskeletal protein that maintains the morphological and structural stability of astrocytes and determines the degree of astrocyte response to injury[11]. Some studies have shown that after central nervous system damage, astrocytes were abnormally active, manifesting as rapid synthesis and secretion of GFAP, and the addition of GFAP-positive astrocytes could further promote astrocyte mitosis. Some studies have found[12] that positive GFAP expression in astrocytes adjacent to the cerebral cortex significantly increased after brain injury. Feng *et al*[13] found that an increase in GFAP levels in patients with severe craniocerebral injury after surgery was a risk factor for poor prognosis, which had a certain value in promoting postoperative survival. Wang *et al*[14] found that serum GFAP levels were elevated in asphyxiated preterm infants with brain injury and serum GFAP had some value in the diagnosis of brain injury and could be used as a marker for central nervous system injury and prognosis.

We found that the preoperative serum GFAP levels in the patients with glioma were higher than those in the control group. After surgery, the serum GFAP levels in these patients with gliomas decreased. However, this level was higher than that observed in healthy controls. In addition, the serum GFAP levels in the patients with WHO grade III-IVI-II tumors were dramatically higher than those in the participants with grade I-II tumors. The serum GFAP level in the patients with tumor diameter > 5 cm was higher than that in those with diameter ≤ 5 cm. It has been suggested that serum GFAP was valuable in predicting the occurrence and development of gliomas.

In the early stages of glioma, patients do not exhibit specific clinical manifestations. However, by the time the disease is diagnosed, glioma is mostly advanced, with a large tumor size involving important functional brain nerve areas[15-17]. In addition, distinguishing the boundary between the tumor and normal brain tissue becomes difficult, making complete removal of the tumor challenging and resulting in residual tumor tissue, which is considered the main reason for postoperative recurrence[18-20]. In this study, among the 91 patients with glioma, 22 experienced recurrence after surgery. In addition, the UCH-L1 and GFAP levels were higher in the recurrence group than that in the non-recurrence group before and 3 d after surgery. This

indicated that serum UCH-L1 and GFAP levels had the potential to reflect postoperative glioma recurrence. By plotting ROC curves, we found that the efficacy of both preoperative UCH-L1 and GFAP levels in predicting postoperative glioma recurrence was slightly higher than that 3 d after surgery. However, limited by the study design, we did not discuss the optimal time points for serum UCH-L1 and GFAP levels to predict postoperative glioma recurrence. This study also did not consider the specific mechanisms of action of these two indicators of gliomas, which warrants further research.

CONCLUSION

The UCH-L1 and GFAP levels abnormally increased in patients with gliomas. Although the levels of these two indices decreased after the surgical treatment, they remained higher than those in the control group. Both serum UCH-L1 and GFAP levels may specifically reflect the development and postoperative recurrence of glioma. These two markers could be used as potential indicators of recurrence and prognosis in patients with postoperative glioma.

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Figure Legends

Figure 1 Receiver operating characteristic curve of serum ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels for predicting postoperative recurrence of glioma. UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

Table 1 Comparison of serum ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels between the glioma and control groups

Group	*n*	Time	UCH-L1 (pg/mL)	GFAP (ng/L)
Glioma group	91	Preoperative	96.89 ± 17.15[a]	16.69 ± 2.16[a]
		3 d after surgery	72.15 ± 12.33[a,d]	7.53 ± 1.74[a,d]
Control group	60		60.17 ± 10.78	1.16 ± 0.25

[a]$P < 0.05$ *vs* the control group.

[d]$P < 0.05$ *vs* the glioma group three days after surgery. UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

Table 2 Analysis of the relationship between preoperative serum ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels and clinicopathological characteristics in the patients with glioma

Clinicopathological features	UCH-L1 (pg/mL)	GFAP (ng/L)
Gender		
Male (*n* = 49)	95.89 ± 16.79	16.58 ± 2.14
Female (*n* = 42)	98.05 ± 17.69	16.82 ± 2.20
t value	0.597	0.515
P value	0.552	0.608
Age (yr)		
< 40 (*n* =44)	99.78 ± 18.42	17.03 ± 2.29
≥ 40 (*n* =47)	94.19 ± 15.58	16.37 ± 2.01
t value	1.566	1.483
P value	0.121	0.141
Pathological type		
Glioblastoma (*n* =76)	98.12 ± 17.14	16.84 ± 2.16
Medulloblastoma (*n* =15)	90.65 ± 16.35	15.92 ± 2.04

t value	1.554	1.512
P value	0.124	0.134
Tumor location		
Frontal lobe (*n* =41)	95.28 ± 16.24	16.50 ± 2.09
Temporal lobe (*n* =39)	99.14 ± 17.59	16.97 ± 2.21
Other locations (*n* =11)	94.93 ± 19.56	16.39 ± 2.29
F value	0.582	0.592
P value	0.561	0.555
Tumor grade		
WHO I-II grade (*n* =33)	78.89 ± 5.05	14.39 ± 0.84
WHO III-IV grade (*n* =58)	107.13 ± 12.48	18.01 ± 1.47
t value	12.402	12.900
P value	< 0.000	< 0.001
Tumor diameter		
≤ 5 cm (*n* =19)	75.23 ± 3.04	13.80 ± 0.59
> 5 cm (*n* =72)	102.61 ± 14.55	17.45 ± 1.73
t value	8.123	9.006
P value	< 0.001	< 0.001
Number of lesions		
Single (*n* =70)	97.57 ± 17.70	16.77 ± 2.25
Multiple (*n* =21)	94.63 ± 15.37	16.43 ± 1.84
t value	0.685	0.619
P value	0.495	0.537

WHO: World Health Organization; UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

Table 3 Comparison of ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels in patients with glioma recurrence and those without recurrence before and after surgery

Time	UCH-L1(pg/mL)	GFAP (ng/L)
Recurrence group (n = 22)		
Preoperative	120.44 ± 6.41	19.59 ± 0.57
3 d after surgery	88.01 ± 2.44	10.00 ± 0.46
t value	37.398	289.806
P value	< 0.001	< 0.001
Non-recurrence group (n = 69)		
Preoperative	89.38 ± 11.83	15.76 ± 1.58
3 d after surgery	67.09 ± 9.60	6.74 ± 1.16
t value	78.571	172.100
P value	< 0.001	< 0.001
Preoperative comparison of the two groups		
t value	11.749	11.118
P value	< 0.001	< 0.001
Comparison of the two groups at 3 d after surgery		
t value	10.086	12.791
P value	< 0.001	< 0.001

UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

Table 4 The value of ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels for predicting postoperative recurrence of glioma

Indicator	Critical value	AUC	95%CI	*P* value	Sensitivity (%)	Specificity (%)
Preoperative UCH-L1	103.85	0.785	0.670-0.901	< 0.001	68.2	81.2
3 d after surgery UCH-L1	85.61	0.646	0.507-0.785	0.040	63.6	62.3
Preoperative GFAP	18.70	0.775	0.651-0.898	< 0.001	63.6	88.4
3 d after surgery GFAP	8.58	0.648	0.508-0.787	0.038	59.1	75.4

AUC: Area under the curve; UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

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