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What Happens to Serum Levels of Visinin-Like Protein-1, Caveolin-1 and Neuron-Specific Enolase after Supratentorial Glioma Resection: A Pilot Study

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ABSTRACT

AIM: To observe changes in the serum levels of visinin-like protein-1 (VILIP-1), caveolin-1 (Cav-1) and neuron-specific enolase (NSE) after glioma resection.

MATERIAL and METHODS: Consecutive 14 glioma patients with different histologic grade and 14 age and gender-matched healthy subjects were included in this pilot study. From the patients serum samples were taken in preoperative and on day 2 and 10 of postoperative periods. Healthy subjects provided serum sample once. The serum changes of three proteins were evaluated by ELISA. The results were compared between preoperative and postoperative periods and between patients and controls.

RESULTS: Preoperative serum levels of VILIP-1 (p=0.008) and Cav-1 (p=0.012) were significantly higher in the patients. Mean serum levels of VILIP-1 (p=0.002) and Cav-1 (p=0.013) again were significantly higher than those of the controls. NSE did not show significant changes compared to controls in none of the periods. There was a steady decline regarding all three molecules from preoperative to postoperative day 10. However, statistical comparisons did not reveal any significant difference with respect the decline in any molecule. Significant positive correlation was detected between preoperative serum levels of VILIP-1 and Cav-1 (p=0.00001) in the patients and the controls (p=0.0000).

CONCLUSION: This pilot study suggested that Cav-1 and particularly VILIP-1 may be used as a valuable serum biomarker for follow-up and for early detection of recurrence in high-grade gliomas. Future studies including larger cohort of patients with homogeneous group of glioma is required.

KEYWORDS: Caveolin-1, Glioma, Neuron-specific enolase, Resection, Visinin-like protein-1

ABBREVIATIONS: Cav-1: Caveolin-1, **CNS:** Central nervous system, **ELISA:** Enzyme-linked immuno sorbent assay, **GBM:** Glioblastome multiforme, **MRI:** Magnetic resonance imaging, **NSE:** Neuron-specific enolase, **ODG:** Oligodendroglioma, **SPSS:** Statistical program for social sciences, **VILIP-1:** Visinin-like protein-1

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INTRODUCTION

Glial tumors are common brain tumors. The median survival of patients with high-grade gliomas, such as grade-IV astrocytoma (also known as glioblastoma multiforme [GBM]), is less than 15 months despite maximal surgical resection plus radiotherapy and chemotherapy. Owing to the high recurrence rate and poor outcomes with the current treatment modalities, the development of targeted therapeutic strategies for these tumors is a key imperative. Elucidating the molecular mechanism(s) underlying the development of gliomas is the first step toward the development of targeted therapies. Furthermore, the identification of reliable biomarkers of gliomas in serum or cerebrospinal fluid may help understand the underlying molecular mechanisms. Additionally, these markers may be used as an index for early detection of recurrence, especially in high-grade gliomas such as GBM.

Several biomarkers have been studied in cancer patients (1,5,19); however, no studies have investigated the serum levels of neuron-specific enolase (NSE), visinin-like protein-1 (VILIP-1), and caveolin-1 (Cav-1) before and after glioma resection. NSE is a well-known biomarker of neuronal injury (13). It is an isoenzyme of the glycolytic enzyme enolase that is highly expressed in neurons (4,5). Serum levels of NSE were shown to be associated with neuronal injury in head trauma (4,5). Furthermore, NSE is a useful biomarker for prognostic assessment and follow-up of patients with small cell lung cancer (1) and neuroblastoma (22), strongly correlating with tumor burden. Currently, there is a paucity of data related to serum levels of NSE in patients with glioma. A pilot study found no association between serum level of NSE and survival outcomes in patients with glioma (20). Visinin-like protein-1 (VILIP-1) is highly expressed in the central nervous system (CNS) and plays a major role in cell signaling and differentiation (7,12). This biomarker was originally studied in stroke (17) and traumatic brain injury (6). In a study, expression of VILIP-1 in a human neuroblastoma cell line was found to be associated with proliferation and invasion (21); however, there is no data regarding VILIP-1 expression in glioma. Caveolin-1 (Cav-1) is an integral membrane protein that regulates cell cycle progression, cell proliferation, and death (14). Cav-1 is also expressed in vessels in the CNS and protects the blood-brain barrier (10). It has been the focus of interest in several types of cancers including brain tumors (14). The tissue levels of Cav-1 may depend on the tumor stage with low levels detected at early stages (15). This molecule is believed to play a role in angiogenesis, metastasis, chemo- and radiotherapy resistance, and thus may play a major role in survival (14). A report revealed non-significant expression of Cav-1 in astrocytoma compared to normal brain tissue, but a higher expression level was observed later stages and this result was corroborated by findings of higher Cav-1 RNA levels in GBM (2,9). However, due to the paucity of published data on oligodendroglioma (ODG) models, Cav-1 expression in ODG is not well characterized (14).

The aim of this pilot study was to assess the serum levels of VILIP-1, Cav-1, and NSE after resection of supratentorial glioma and to identify the molecule that should be the subject of future studies in gliomas.

MATERIAL and METHODS

Local Ethics Committee of Cerrahpasa Medical Faculty approved this study (Date: 18.01.2023; Approval No: 590766).

Study Population

The study population comprised a consecutive series of 14 adult patients (age >18 years) who underwent surgical resection of a pathologically-proven supratentorial glioma (patient group) and 14 age- and sex-matched healthy subjects (control group). All patients were operated during the year 2022 and underwent their first glioma surgery. None of the patients received chemotherapy and/or radiotherapy before surgery. Our patient group had different types of gliomas with different stages of the disease. None of the patients showed co-morbidity. The extent of tumor resection was determined based on postoperative magnetic resonance imaging (MRI). Three types of resections were performed in this series. FLAIR and contrast-enhanced T_1-weighted postoperative MRI images were used to determine the extent of resection in low- and high-grade gliomas, respectively. Total, subtotal, and gross total resections were defined as no residual tumor, resection of tumor up to 90 %, and resection of tumor > 90 %, respectively.

Biochemical Analyses

Venous blood samples were obtained from all patients at three time points. The first sample was obtained before surgery during venous blood sampling for routine preoperative laboratory analyses. The second and third blood samples were obtained on postoperative day 2 and day 10 (at the time of suture removal), respectively. The controls provided a venous blood sample only once. All blood samples were centrifuged at 1,500 rpm for 10 minutes. Hemolysed samples were excluded to avoid potential false higher levels of NSE. After centrifugation, serum samples were stored at – 80 °C until biochemical analysis.

Levels of VILIP-1 (Elabscience Biotechnology Inc, USA), Cav-1 (Elabscience Biotechnology Inc, USA), and NSE (DRG Instruments GMbH, Germany) were determined by using a double-antibody sandwich human Enzyme-linked Immuno Sorbent Assay (ELISA) kit. The results were expressed as ng/mL.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 for Windows. Parametric variables were presented as mean ± standard deviation. Depending on data distribution, the Chi-square test and Mann-Whitney U-test were used for the assessment of between-group differences. Correlation analysis was performed using the Pearson correlation coefficient. Two-tailed p values < 0.05 were considered indicative of statistical significance.

RESULTS

Clinical Characteristics

Table I summarizes the demographic characteristics of the study population. There was no significant difference between patients and controls with respect to mean age (p=0.12) or gender distribution (p=0.58). The majority of the patients had seizures and the majority of the tumors were on the left side. The frontal lobe was the most common tumor location followed by the temporo-insular region. Depending on the preoperative MRI, total surgical resection was performed in most of the tumors. The histopathological diagnosis was astrocytoma grade-IV (GBM) in five patients, astrocytoma grade-II in three, astrocytoma grade-III in two, ODG grade-II in two, ODG grade-III in one, and ganglioglioma in one patient.

Biochemical Analysis

The serum levels of each molecule in each patient and control are presented in Table II. Overall, the serum level of each molecule in the majority of patients tended to decline during the postoperative period and this decline was remarkable on postoperative day 10, irrespective of the extent of tumor resection. Of note, the preoperative serum levels of VILIP-1, Cav-1, and NSE were remarkably higher in one patient with grade-II ODG compared to one patient with grade-III ODG.

Statistical results of group comparisons are presented in Table III and Figure 1. Preoperative mean levels of each molecule were higher in patients compared to the controls. Preoperative serum levels of VILIP-1 (p=0.008) and Cav-1 (p=0.012) were significantly higher in patients compared to controls. However, the between-group difference in preoperative NSE level was not statistically significant. The mean serum levels of VILIP-1 (p=0.002) and Cav-1 (p=0.013) on postoperative day 2 were also significantly higher than those in the control group, while the difference in NSE level was not statistically significant. On postoperative day 10, none of the molecules were significantly higher in patients than controls. Of note, differences in VILIP-1 level were remarkable compared to Cav-1 and NSE levels. As shown in Figure 1, there was a steady decline in the levels of all three molecules from preoperative to postoperative day 10. However, there was no significant difference with respect to the decline in any molecule. This may be due to the limited number of patients included in this pilot study.

A significant positive correlation was observed between preoperative serum levels of VILIP-1 and CaV-1 in patients (p=0.00001) and controls (p=0.0000). On day 10 of surgery, a significant positive correlation was observed between VILIP-1 and Cav-1 levels (p=0.004) but there was a negative correlation between VILIP-1 and NSE levels. Interestingly there was no positive or negative correlation among the three molecules on postoperative day 2.

DISCUSSION

In this pilot study, preoperative serum levels of VILIP-1 and Cav-1 in patients with glioma were significantly higher than those in controls. However, the NSE level was not significantly different between patients and controls. Likewise, serum levels of VILIP-1 and Cav-1 on postoperative day 2 were also significantly higher in patients compared to controls. On postoperative day 10, none of the molecules showed significantly higher serum levels compared to controls,

Table I: Summary of Some Clinical Parameters of the Patients and Controls

Variable	Patients (n=14)	Controls (n=14)	p-value
Age (mean ± SD; years)	44.35 ± 17.1	34.07 ± 11.6	0.12
Gender (M/F)	10/4	8/6	0.58
Preoperative seizure (yes/no)	12/2		
Lateralization (right/left)	4/10		
Localization			
Temporo-insular	5		
Frontal	6		
Parietal	1		
Fronto-parietal	1		
Temporo-parietal	1		
Resection			
Total	8		
Subtotal	3		
Gross total	3		

***F:** Female; **M:** Male; **SD:** Standard deviation.*

Table II: Values (ng/ml) of the Molecules Studied in Each Individual of the Patients and Controls

No	Pathology	˚VILIP-1	˚Cav-1	˚NSE	¶VILIP-1	¶Cav-1	¶NSE	ɣVILIP-1	ɣCav-1	ɣNSE
1	ODG-II	14.10	12.93	27.20	17.31	9.96	8.29	16	7.24	7.38
2	Astcyt-II	14.85	12.14	14.30	19.82	13.18	13.36	14.30	6.81	6.37
3	GG-I	16.03	12.76	2.22	14.97	8.18	3	18.56	12.22	6.58
4	Astcyt-III	21.69	17.79	11.76	16.17	10.32	6	12.02	8.45	16.03
5	Astcyt-IV	6.80	4.26	8.40	7.39	5.75	9.32	7.39	5.35	6.37
6	ODG-II	20.75	14.93	3.94	14.80	12.17	2.58	16.14	15.29	6.11
7	Astcyt-IV	6.26	3.94	14.80	4.75	5.03	8.35	4.46	4.55	11.76
8	Astcyt-II	20.96	12.81	32.61	16.84	12.45	26.90	16.84	12.45	26.90
9	Astcyt-III	25.54	20.42	25.59	16.19	10.55	32.73	15.96	13.43	6.74
10	Astcyt-IV	23.05	17.91	88.13	22.27	10.37	16.70	18.04	4.69	11.49
11	Astcyt-II	4.30	3.60	9.10	12.25	9.83	44.08	1.93	2.11	13.47
12	ODG-III	1.88	3.10	6.48	3.24	10.95	37.44	0.37	1.40	46.84
13	Astcyt-IV	14.11	12.24	8.94	13.51	9.34	16.59	4.25	8.27	43.42
14	Astcyt-IV	20.96	13.48	15.75	11.28	15.33	18.40	13.64	9.98	18.74
Controls										
1		4.61	5.77	12.04						
2		4.74	8.60	14.13						
3		13.04	12	7.81						
4		1.88	2.45	13.30						
5		2.15	2.57	11.76						
6		5.82	3.66	8.13						
7		3.17	2.72	9.21						
8		7.13	7.13	4.68						
9		8.99	8.01	14.47						
10		15.29	13.47	8.67						
11		12.15	10.42	12.31						
12		10.25	7.67	51.17						
13		7.80	8.14	17.72						
14		2.62	2.40	15.36						

Astcyt: *Astrocytoma,* ***Cav-1:*** *Caveolin-1,* ***GG:*** *Ganglioglioma,* ***NSE:*** *Neuron-specific enolase,* ***ODG:*** *Oligodendroglioma,* ***VILIP-1:*** *Visinin-like protein-1. ˚Preoperative values, ¶Post-operative values at 48th hour, ɣPost-operative values on day 10.*

Table III: Summary of Statistical Analysis of Serum Mean (± SD) Levels of the Molecules (ng/ml) Studied

Parameter	Patients (n = 14)	Controls (n = 14)	p-value
Pre-VILIP-1	15.09 ± 7.6	7.11 ± 4.31	**0.008**
Pre-Cav-1	11.59 ± 5.7	6.78 ± 3.6	**0.012**
Pre-NSE	19.23 ± 21.7	14.34 ± 11.1	0.80
Post-VILIP-1 (48th hour)	13.62 ± 5.4		**0.002**
Post-Cav-1 (48th hour)	10.24 ± 2.7		**0.013**
Post-NSE (48th hour)	17.41 ± 13.1		0.58
Post-VILIP-1 (10th day)	11.42 ± 6.3		0.06
Post-Cav-1 (10th day)	8.01 ± 4.2		0.52
Post-NSE (10th day)	16.3 ± 13.6		0.69

Cav-1: *Caveolin-1;* ***NSE:*** *Neuron-specific enolase;* ***Post:*** *Postoperative;* ***Pre:*** *Preoperative;* ***SD:*** *Standard deviation;* ***VILIP-1:*** *Visinin-like protein-1.*

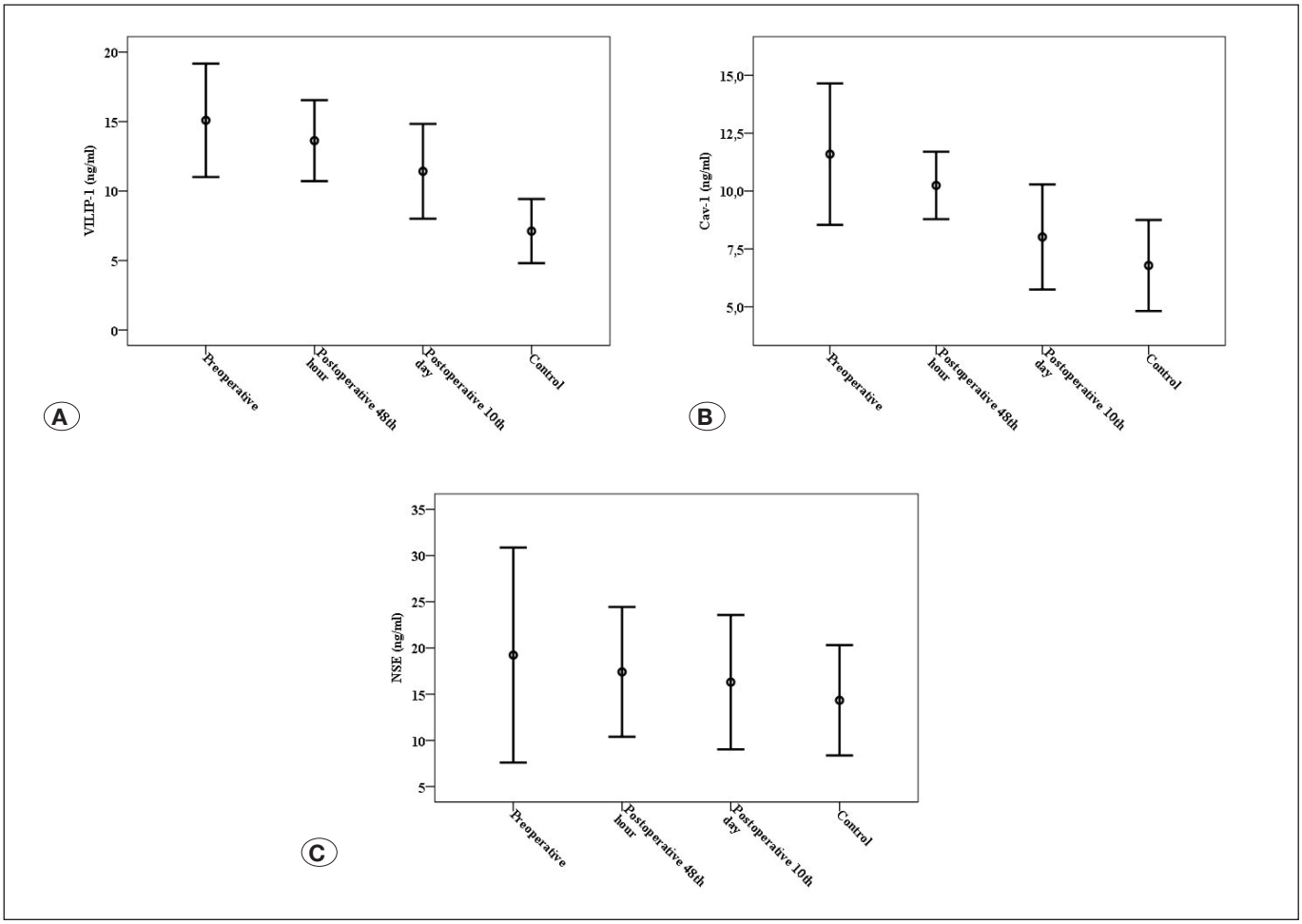

Figure 1: Graph showing a comparison of serum levels of VILIP-1 **(A)**, Cav-1 **(B)** and NSE **(C)** in patients and controls. Circles represent the means ± standard errors of the means and bars denote the range of values. The differences in the levels of VILIp-1 (p=0.008) and Cav-1 (p=0.012) were statistically significant compared to controls. However, no significant difference was found regarding NSE (p=0.80). Moreover, decrease form the preoperative to postoperative period for each molecule did not reach significant level (p>0.05).

although the mean serum level of each molecule was higher in patients. Interestingly, there was no significant differences between groups with respect to NSE level at all three time points. Furthermore, serum levels of VILIP-1 and Cav-1 showed significant positive correlations during the preoperative period and on postoperative day 10 in patients. There was a steady decline in mean serum levels of each molecule from the preoperative to postoperative period, but this decline was not significant. This was likely attributable to the small number of glioma patients included in this study. Moreover, NSE is a specific marker of neuronal injury rather than glial cells, which may explain the non-significant difference in NSE level between patients and controls. Our preliminary findings suggest that Cav-1 and especially VILIP-1 might be a valuable serum biomarker of glial injury and recurrence in glioma. Further studies should examine the longitudinal dynamics of serum Cav-1 and especially VILIP-1 in a homogeneous group of gliomas.

In a pilot study of 20 patients with different types and pathological stages of glioma, serum S-100B rather than NSE was associated with shorter survival. The authors concluded that NSE might not be a valuable prognostic marker in glioma (20). The paucity of data regarding serum NSE status in glioma patients makes it difficult to compare our results with the current literature. Among the three proteins studied here, Cav-1 has been widely studied in glioma (14). In a study, the tissue expression pattern of Cav-1 in glioma showed a significant association with histologic grade (3). In addition to glioma tissues, Cav-1 levels were evaluated in exosomes from the plasma of patients with GBM. The results demonstrated enriched Cav-1 exosomes from patients compared to control plasma (11). A recent tissue study including patients with glioma identified Cav-1 as an important regulator of glioma proliferation and vasculogenic mimicry, and its role in glioma development and progression (8). Our results are consistent with those of the above-cited studies as serum levels of Cav-1 in our patient group were significantly higher than those in controls. In the published literature, Cav-1 expression has largely been studied in GBM, while its expression in ODG is not well characterized. In a study, Cav-1 expression in ODG was correlated with grade, shorter survival, and poor prognosis (16). It should be noted that Cav-1 expression in ODG is variable and no consensus has been reached thus far. Thus, current literature should be interpreted carefully and results reported so far need to be validated in a larger series of patients with ODG. In our study, serum Cav-1 level in a patient with ODG-III was lower than that in the other two patients with ODG-II. The sample size of ODG patients was too small to draw any definitive conclusions.

Serum or tissue levels of VILIP-1 in glioma have not been reported in contemporary literature. Serum levels of VILIP-1 have been studied in patients with traumatic brain injury and stroke (6, 17). In a study, serum levels of VILIP-1 were correlated with seizure-induced neuronal injury in patients with epilepsy (18). In a literature search, we found a study showing tissue expression of VILIP-1 in patients with neuroblastoma using quantitative reverse transcriptase-polymerase chain reaction. The VILIP-1 mRNA was significantly higher in the invasive cell subpopulation compared to that in the less invasive cell subpopulation. The study suggested that VILIP-1 might play an important role in neuroblastoma metastasis (21). The current literature has no information regarding VILIP-1 expression in glioma, which makes it very difficult to discuss our results. In our study, serum VILIP-1 levels were significantly higher in both the preoperative period and on postoperative day 2 in patients compared to controls. On postoperative day 10, the serum levels in patients were still remarkably higher. These findings suggest that serum VILIP-1 level may be a more valuable biomarker compared to Cav-1 for the follow-up of patients with glioma.

Limitations

The small number of glioma patients is the foremost limitation of this study. Secondly, our study included a heterogeneous group of gliomas with different histologic grades. However, this was a pilot study which may serve as a prelude to larger studies enrolling a homogeneous group of gliomas.

CONCLUSION

This study investigating longitudinal dynamics of serum VILIP-1, Cav-1, and NSE levels suggested that Cav-1 and VILIP-1 may be valuable serum biomarkers for early detection of recurrence in high-grade gliomas during follow-up. However, the results should be interpreted with caution as this was a small-scale pilot study involving a heterogeneous group of gliomas with different grades. Future studies should include a larger cohort of homogeneous groups of glioma and the longitudinal serum dynamics of the proteins studied here should be evaluated at different time points after surgery. Currently, we are planning to analyze the longitudinal dynamics of serum VILIP-1 and Cav-1 levels in patients with high-grade gliomas by serial blood sampling during the preoperative period and at different time points after surgery.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: All authors in this study disclose that there is no any financial and personal relationships with other people or organizations that could inappropriately influence (bias) work and there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: TT, RK
Data collection: AK, EV
Analysis and interpretation of results: MI, IT, BBI
Draft manuscript preparation: RK
Critical revision of the article: TT, RK
Other (study supervision, fundings, materials, etc...): TT, TK
All authors (RK, AK, EV, MI, IT, BBI, TK, TT) reviewed the results and approved the final version of the manuscript.

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