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An Investigation into the Relationship of Sur1-Trpm4 Receptor with Peritumoral Edema in High-Grade Glial Tumors

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ABSTRACT

AIM: To investigate the presence of Sur1-Trpm4 receptors in high-grade glial tumors, and their relationship with edema volumes in preoperative magnetic resonance imaging (MRI) sequences.

MATERIAL and METHODS: MRI sections were extracted from T1-weighted (T1W) and T2-weighted (T2W) sequences and fluid-attenuated inversion recovery (FLAIR) images. After that, T1W 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequences were taken with and without contrast medium. Tumor and peritumoral edema volumes were calculated in cubic centimeters. Sur1-Trpm4 receptors were studied by immunohistochemical examination of tissue samples. Relationships between data were analyzed using Spearman's correlation coefficient.

RESULTS: In the immunohistochemical examinations, 58% of the samples from patients with high-grade glial tumors were positive for Sur1 and 74% were positive for Trpm4. The volume of tumors was correlated with the volume of peritumoral edema.

CONCLUSION: The presence of the Sur1-Trpm4 receptor complex in high-grade glial tumors was confirmed. Further preclinical or clinical studies are required to identify and validate the role of Sur1-Trpm4 in glial tumor subgroups.

KEYWORDS: Brain tumor, Cerebral edema, Glial tumor, Glioblastoma, Sur1-Trpm4

INTRODUCTION

Cerebral edema is increased water content in the brain parenchyma. It is a common cause of mortality and morbidity in patients with high-grade glial tumors and other pathologies of the central nervous system (CNS) (9,20). Peritumoral edema can worsen glioblastomas, metastatic tumors, and various benign intracranial tumors, regardless of mass volume. It can also cause herniation, especially in glioblastomas (21,29,40). Glioblastomas are the most common primary CNS tumor, accounting for about half of all primary intracranial tumors.

Vasogenic or cytotoxic processes may contribute to the volume of peritumoral edema. The extent of edema is the result of a complex dynamic interaction between glioma cells, neuroglial cells, endothelial cells, and microglial cells. Vasogenic edema is caused by a loss of function and increased permeability of the blood-brain barrier (BBB). Cytotoxic edema, on the other hand, is caused by a cellular metabolism disorder than interferes with cell membrane transport mechanisms (23). In glioblastomas, the edema is typically vasogenic. However, the molecular processes in the etiopathogenesis of cerebral edema and the resultant neurological damage render the

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distinction between cytotoxic and vasogenic edema somewhat redundant. Both the BBB and cell membrane transport mechanisms can be affected by glial cells through mediators such as vascular endothelial growth factor, prostaglandin E2/ prostaglandin F2 alpha, cyclooxygenase 2, and nitric oxide synthase (7). The increased accumulation of extracellular fluid becomes a separate lesion that impairs hemostasis in the parenchymal tissue. There is an increase in intracranial pressure, which causes a decrease in cerebral perfusion pressure and cerebral blood flow. This may result in herniation, ischemia, or death. Cerebral edema can also facilitate tumoral invasion through the loss of peritumoral tissue (20,40). However, the clinical symptoms of tumor-related cerebral edema depend on the size and location of the tumor.

In patients with glial tumors, the volume of peritumoral edema is measured using magnetic resonance imaging (MRI). Contrast material is administered intravenously (IV) and the presence or absence of contrast enhancement in the components of the tumor is assessed**.** The glial tumor is identified by contrast enhancement on T1-weighted images (T1W) after administration of a gadolinium-based contrast agent. The peritumoral edema in glioblastomas has a high signal on T2-weighted/ fluid attenuation inversion recovery (T2W/ FLAIR) images (37). Abnormality surrounding the enhanced solid lesion image is defined as peritumoral edema. However, this area may also contain diffuse-uncontrasted tumor cells. As there is no single magnetic resonance (MR) sequence able to differentiate between vasogenic edema and tumor cell infiltration, combinations of MRI sequences are used to achieve this (9). Diffuse, non-enhanced areas of tumor infiltration within the peritumoral edema can be calculated by an apparent diffusion coefficient gradient or FLAIR identification of areas with higher cell density (19).

Current medical treatment of cerebral edema can be either targeted or non-targeted. OSM-0205, mannitol, diuretics, hypertonic saline, anesthesia/ sedation, and glucocorticoids are non-targeted treatment modalities (9,11). Targeted therapies address the dysfunctions in neurovascular intercellular signaling involved in cerebral edema.

The Sur1-Trpm4 receptor channel complex is found on the surface of neurons, astrocytes, oligodendrocytes, and microvascular endothelial cells (7). Sur1 is a membrane protein that interacts with pore-forming Kir6.2 subunits to create adenosine triphosphate (ATP)-sensitive K^+ channels. This channel belongs to a large family of ATP-binding cassette transporters. Trpm4 is an ATP/Ca^{2+}-sensitive nonselective cation channel. Sur1 interactions with Trpm4 are referred to as Sur1-Trpm4 channels. These are known to contribute to cytotoxic edema the formation of vasogenic edema, and BBB breakdown. While Sur1 is constitutively expressed, Trpm4 is not normally present in brain tissue (22). Previous studies have shown that Sur1-Trpm4 plays an important role in ischemic and hemorrhagic strokes, traumatic brain and spinal cord injuries, and spontaneous subarachnoid hemorrhages (SAH) (6,7,33,42). Moreover, the administration of Sur1-Trpm4 receptor antagonists after CNS injuries has been shown to have neuroprotective effects and to reduce cerebral edema (6,31). In this study, we searched for the presence of Sur1-Trpm4 receptors in the pathological tissue excised from high-grade glial tumors and compared their expression levels with preoperative edema volumes.

MATERIAL and METHODS

Study Design

This retrospective study was approved by our institutional ethics committee (54022451-050.05.04), and was conducted in accordance with the tenets of the 2013 revision of the Declaration of Helsinki. The data used in this study were collected from our hospital's medical records. The demographic and clinical information of the 50 patients included is summarized in Table I. Inclusion criteria were adults (≥18 years) with newly diagnosed and histologically-proven grade 4 glioblastoma multiforme (using the World Health Organization [WHO], 2016 grading system) treated between May 2017 and October 2020. Patients who were using glucocorticoids or oral antidiabetic medication before the primary MRI; who underwent neuronavigation-assisted brain biopsy; who had recurrent glial tumors, gliomas affecting both hemispheres, or brain stem gliomas; who were receiving radiotherapy; or who had active or chronic infections were excluded from this study.

Volumetric Assessment

All radiological samples were evaluated and assessed in the presence of a single radiologist. Preoperative MRI was performed using the Magnetom Avanto 1.5T system (Siemens, Munich, Germany) using a head coil. The MRI protocol included T1-weighted (T1W) imaging with a repetition time (TR)/echo time (TE) of 475/10 ms, T2W imaging sequences in the axial and sagittal planes with TR/TE of 4870/87 ms, and FLAIR imaging in the axial and coronal planes with TR/ TE/inversion-time (TI) of 9000/87/2500 ms and 5-mm-thick sections. Thereafter, T1W 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequences with and without contrast medium (gadolinium-diethylenetriamine pentaacetic acid, 0.1 mmol/kg, IV), with TR/TE/TI of 12.5/5/450 ms, were applied.

The volume of each patient's brain mass and the volume of their edema on the T2W, FLAIR, diffusion, and post-contrast MP-RAGE images were measured using version VB30A_ HF06 of the syngo.via console (Siemens, Germany) and the MIP Thin, ROI freehand, VOI freehang and Create VOI, and VRT Thin stages programs (Figure 1). The mass volume was measured on the T2W, diffusion, and post-contrast MP-RAGE sequences, and both the mass and edema were measured on the FLAIR sequences.

Immunohistochemistry

All of the histopathological specimens were evaluated and diagnosed by a single pathologist. For the purposes of this study, formalin-fixed, paraffin-embedded tissue blocks were obtained from the Department of Pathology archives, and hematoxylin-eosin (H&E)-staining was performed for specimen reevaluation and block selection. We mounted 4-µm-thick

sections on poly-L-lysine-coated slides and deparaffinized and hydrated them through graded alcohol to water. The sections were stained with rabbit polyclonal antibody against SUR1 (Invitrogen, Fisher Scientific, Göteborg, Sweden; catalog no: PA5-59947; 1/100 titer) and mouse monoclonal antibody against Trpm4 (Novus Biologicals, Englewood, CO, USA; catalog no: NBP1-48036; 1/100 titer; clone OTI10H5) following the protocol of Ventana Medical Systems. The

Table I: Clinicopathological and Imaging Characteristics of High-Grade Glial Tumors

Variable	**Total Sample (n=50)**		
Gender, n (%)			
Male	24 (48)		
Female	26 (52)		
Age		**n**	**(%)**
Mean: 49.6 (min: 18–max:79, SD±14.7)	≤ 60 years	24	48.0
	≥60 - ≤70 years	18	36.0
	>70 years	8	16.0
Location		**n**	**(%)**
Right Hemisphere; 16 (32%) Left Hemisphere; 34(68 %)	Temporal Lobe	34	68.0
	Frontal Lobe	20	40.0
	Parietal Lobe	11	22.0
	Talamic	2	4.0
Immunohistochemistry			
Sur1	non = 21 (42%) weak= 20 (40%) moderate= 9 (18%) severe= 0 (0%)		
Trpm4	non = 13 (26%) weak= 23 (46%) moderate= 14 (28%) severe= 0 (0%)		
Ki-67 index (%)	29.14 (min:5-max:80;SD:±16.77)		
Number of Mitosis	19.24 (min:1-max:70; SD:±13.60)		
ATRX Mutation	Yes: 7		
	No: 43		
IDH Mutation	Yes: 14	n=7 [Astrocytoma, IDH-mutant (Grade 4)] n=7 (Anaplastic Oligodendroglioma)	
	No: 36	(Wilde Type)	
Radiological Assessment			
Enhancing Tumor Volume (cm^3) T1 sequence	54.97 (min:1.20-max:157; SD ± 39.22)		
Tumor Volume (cm^3) T2 sequence	49.98 (min:5.50-max:150; SD ± 40.351)		
Total Volume (Tm+edema cm^3) FLAIR	126.15 (min:19-max:280; SD ± 74.90)		
Diffusion-Restricted Tumor Volume (cm^3)	51.92 (min:0.00-max:170; SD ± 46.1)		

SD: *Standard deviation.*

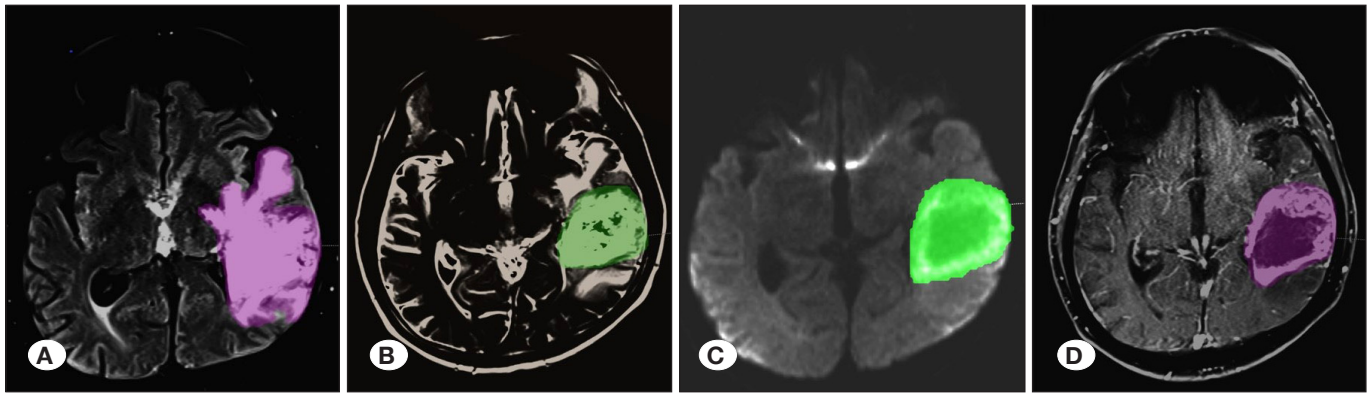

Figure 1: Magnetic resonance images from a two-dimensional volumetric assessment of glioblastoma in the left temporal lobe. A region of interest was created in the axial section of the MRI and screenshots were taken of the edematous segment of the glioblastoma. **A)** FLAIR imaging (masked with red) showing a mass and edema. **B)** T2 imaging (masked with green) of the lesion mass. **C)** Diffusion imaging (masked with green) of the lesion mass. **D)** T1 3D (MP-RAGE) post-contrast imaging, (masked with red) of the lesion mass. **FLAIR:** Fluid-attenuated inversion recovery; **MRI:** Magnetic resonance imaging; **MP-RAGE:** Magnetization-prepared rapid gradient echo.

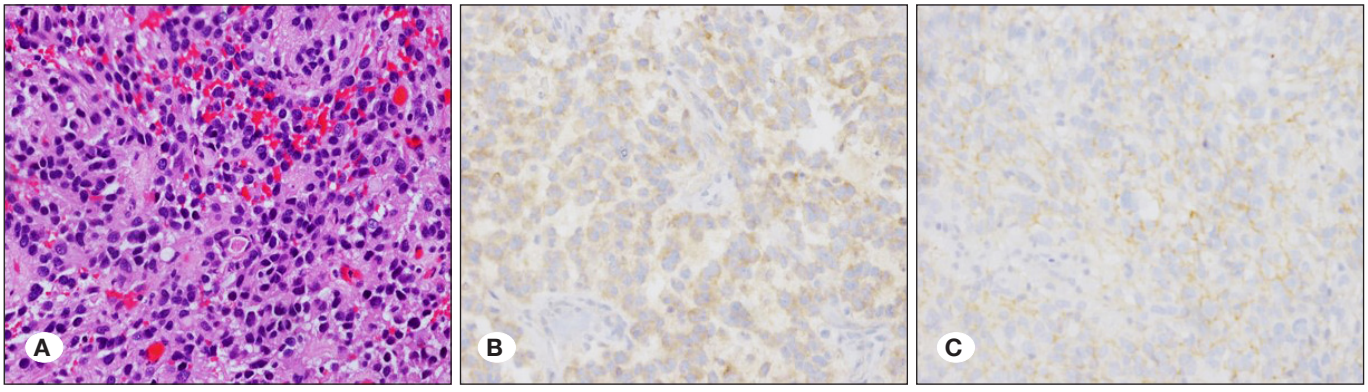

Figure 2: Immunohistochemically stained glioblastomas. H-scores were assigned to the staining intensity seen in the tumors assessed in this study. These were: 0 (none), 1 (weak), 2 (moderate), or 3 (severe). **A)** WHO grade H&E-stained tumor. **B)** Cytoplasmic and membranous granular stained and Sur1 stained tumor. **C)** Cytoplasmic and membranous granular stained and Trpm4 stained tumor. All at x200 magnification. **H&E:** hematoxylin and eosin; **WHO:** World Health Organization.

staining was performed on a Ventana BenchMark Ultra (Ventana Medical Systems, Inc., Tucson, AZ, USA). The slides were then reviewed using a Nikon Eclipse Ci-E microscope (Nikon Corp., Tokyo, Japan) at various magnifications. The staining patterns of Sur1 and Trpm4 antibodies in the selected tumor areas were evaluated as cytoplasmic (Figure 2). The proportions of tumor cells detected were graded 1 for <25%, 2 for 25–75%, and 3 for >75%. The staining intensities were graded as 0 (none), 1 (weak), 2 (moderate), or 3 (severe). These were combined into histochemical (H)-scores for the extent and intensity of staining. H-scores of 1–4 were regarded as low expression and scores of 5–9 as high expression (10). We later looked for correlations between these results and peritumoral edema volumes.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Armonk, NY, USA). This software was also used to create graphical presentations of the data. The data were described as medians and interquartile ranges or r frequencies and percentages. The relationships between the variables were analyzed using Spearman's correlation coefficient. A p-value of <0.05 was considered statistically significant.

RESULTS

The patients meeting the inclusion criteria in the study period comprised 26 (52%) females and 14 (28%) males, with a mean age of 49.62 (18–79) years. In our cohort, 52% were >60 years of age at the time of diagnosis. These age and sex distributions roughly corresponded to those in previous studies of this patient demographic. The tumors were predominantly located within the temporal lobe (n=20; 40%), followed by the frontal lobe (n=17; 34%), parietal lobe (n=11; 22%), and the left thalamus (n=2; 4%). The hemispheric distribution of our patients' tumors was 32% (16/50) in the right hemisphere and 68% (34/50) in the left hemisphere (Table I).

Immunohistochemical Results

Among the samples from our cohort, 42% (n=21) showed no Sur1 staining, 40% (n=20) showed weak staining, and 18% (n=9) showed moderate staining. None of the samples showed intense/severe Sur1 staining.

For Trpm4, 26% (n=13) of the samples showed no staining, 46% (n=23) showed weak staining, and 28% (n=14) showed moderate staining. None of the samples showed intense/severe Trpm4 staining.

The mean Ki-67 index was 29.14 (±16.77; 5-80) and the mean mitotic rate was 19.24 (±13.60; 1-70). ATRX mutations were identified in seven patients and IDH mutations in 14 patients (Table I).

Volumetric Results

On T1-weighted imaging, the mean tumor volume with contrast enhancement was 54.97 (±39.22) cm^3 (1.20–157 cm^3). On T2-weighted imaging, the mean tumor volume was 49.98 (±40.35) cm^3 (5.50–50 cm^3). The mean tumor and edema volume measured on the FLAIR sequences was 126.15 (±74.90) cm^3 (19–280 cm^3) and the mean tumor volume restricting diffusion was 51.92 (±46.1) cm^3 (12:00–170 cm^3) (Table I).

Correlation Analysis

Weak positive correlations were found between Trpm4 and Ki-67 (r=0.37; p=0.008), between Trpm4 and mitotic rate (r=0.31; p=0.0029), and between Sur1 and Ki-67 (r=0.306; p=0.031). There was no significant correlation between Sur1 and the mitotic rate (r=0.267; p=0.061). A moderate positive correlation was found between Sur1 and Trpm4 (r=0.41; p=0.003).

There were strong positive correlations between the total lesion volume on FLAIR (VF) and the mass lesion volume on T2 (MLVT2) (r=0.754; p<0.001), between VF and contrast-enhanced mass volume on T1 (CEMVT1) (r=0.781; p<0.001), between MLVT2 and MVM-DWI (r=0.854; p<0.001), and between CEMVT1 and MVM-DWI (r=0.845; p<0.001). There were moderately strong positive correlations between VF and mass volume measurement by diffusion-weighted imaging (MVM-DWI) (r=0.715; p<0.001), and between MLVT2 and CEMVT1 (r=0.939; p<0.001) (Table II).

There was no significant relationship between Trpm4 and VF (r=0.044; p=0.762) or between MLVT2, CEMVT1, and MVM-DWI (Figure 3). Moreover, when the Sur1 MR parameters were compared, no significant relationships were found between VF, MLVT2, CEMVT1, and MVM-DWI (Tables II, Figure 4).

Table II: Results of a Spearman's Correlation Coefficient Analysis of Glial Tumor Characteristics. Significant p-values are Shown in Bold Type

		VF	MLTV2	CEMTV1	MVM-DWI	Ki 67	Mitosis	Trpm 4 h	surh
VF	Correlation	1.000	0.754"	0.781"	0.715"	0.091	0.011	-0.044	0.076
	Coefficient (r)								
	p-value		**<0.001**	**<0.001**	**<0.001**	0.530	0.942	0.762	0.600
MLTV2	Correlation			0.939"	0.854"	-0.010	0.020	0.052	0.158
	Coefficient (r)								
	p-value			**<0.001**	**<0.001**	0.947	0.892	0.719	0.274
CEMTV1	Correlation			1.000	0.845"	-0.039	-0.025	0.011	0.177
	Coefficient (r)								
	p-value				**<0.001**	0.787	0.862	0.939	0.22
MVM-DWI	Correlation				1.000	0.022	0.049	0.028	0.021
	Coefficient (r)								
	p-value					0.878	0.736	0.847	0.887
Ki 67	Correlation					1.000	0.718"	0.370"	0.306"
	Coefficient (r)								
	p-value						**<0.001**	**0.008**	**0.031**
Mitosis	Correlation						1.000	0.310"	0.267
	Coefficient (r)								
	p-value							**0.029**	**0.061**
Trpm 4 h	Correlation							1.000	0.410"
	Coefficient (r)								
	p-value								0.003
Sur 1 h	Correlation								1.000
	Coefficient (r)								
	p-value								

CEMVT1: *Contrast-enhanced mass volume on T1 (cm^3);* ***MLVT2:*** *Mass lesion volume on T2;* ***MVM-DWI:*** *Mass volume measurement by diffusion-weighted imaging (cm^3);* ***VF:*** *Total lesion volume on FLAIR (cm^3).*

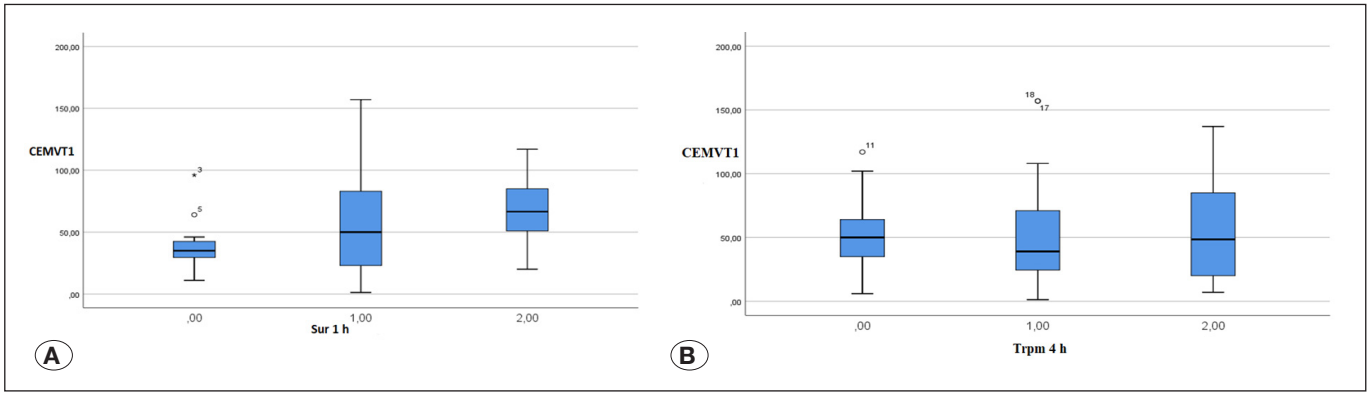

Figure 3: The intensity of Sur1 and Trpm4 staining of glial tumors. Stain intensity was graded as 0 (none), 1 (weak), 2 (moderate), or 3 (severe). **A)** Staining intensity distribution between VF and Sur1. **B)** Staining intensity distribution between VF and Trpm4. **VF:** total lesion volume on FLAIR (cm^3).

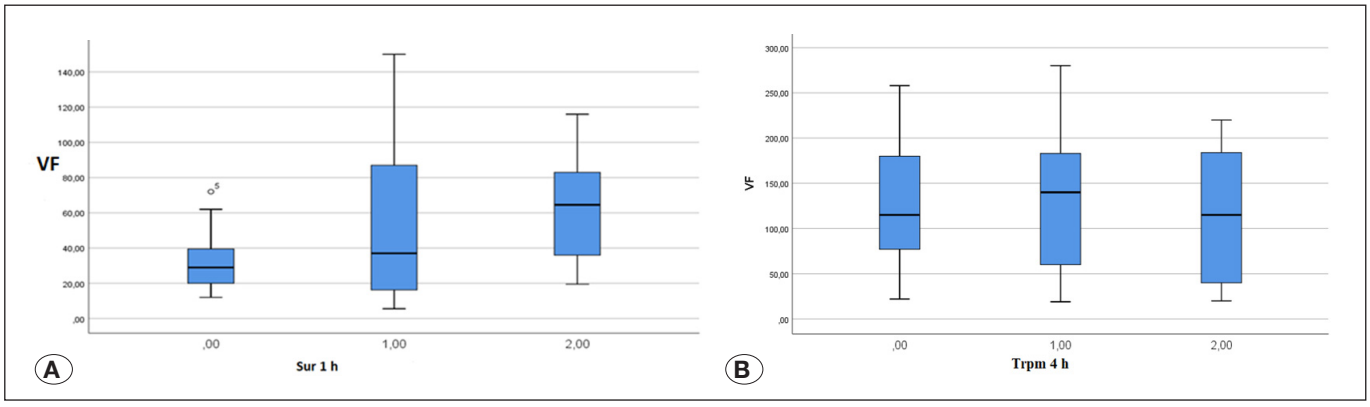

Figure 4: Distribution of Sur1 and Trpm4 staining intensity in glial tumors. Stain intensity was graded as 0 (none), 1 (weak), 2 (moderate), or 3 (severe). **A)** Distribution between CEMTV1 and Sur 1. **B)** Distribution between CEMTV1 and Trpm4. **CEMVT1:** Contrast-enhanced mass volume on T1 (cm^3).

DISCUSSION

When peritumoral edema occurs with glial tumors, it is generally vasogenic. The disruption of microvascular circulation causes extravasation of plasma fluid and its proteins, increasing the interstitial pressure (9,20). This edema significantly increases the patient's morbidity and mortality risks (20). The Sur1 receptor, together with the Trpm4 channels it regulates, was discovered 20 years ago and is known as the Sur1–Trpm4 ion channel complex (14). It has since been found on the membrane surfaces of neurons, astrocytes, oligodendrocytes, and microvascular endothelial cells (9). Studies in molecular biology have identified the two-channel subunits of the complex (24,32), its biophysical and molecular properties (24,30,35), and some of the transcription mechanisms responsible for its *de novo* pathological upregulation (34). The co-expression of Sur1-Trpm4 causes upregulation of perivascular tumor necrosis factor, extravasation of serum immunoglobulin G, and associated inflammation in necrotic endothelial cells (22). These increase extravasated serum proteins, microglia cell levels, and abnormal BBB permeability (7,9).

Sur1-Trpm4 plays a role in the etiology of vasogenic edema and its upregulation is involved in the pathogenesis of several neural injuries, including stroke and spinal cord damage (7,9,14). The Sur and Trpm families are both next-generation membrane proteins known to regulate the behavior of cancer cells (18).

Sur1 is a member of the ATP-binding cassette transporter superfamily and, alone, has no known function. Sur1 is encoded by the ABCC8 gene (18,33), the mRNA expression of which is an independent prognostic indicator for glioma. It can also predict chemosensitivity (44). Previous studies have found various levels of Sur1 expression in both pediatric and adult brain tumors (38). In the present study, 58% of the grade 4 glial tumors analyzed were positive for Sur1 following immunohistochemical staining. This result was compatible with the findings of previous research (12). The existing literature has demonstrated the upregulation of Sur1 (with or without Trpm4) in stroke, traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, spinal cord injury, encephalomyelitis, CNS metastases, cardiac arrest, hepatic failure, and even cerebral malaria (9,14,25).

Trpm4 is a member of a large protein superfamily consisting of 28 cation channels. The members of this family are

permeable to divalent cations, such as Ca^{2+} (22). A few of the Trpm channels contribute to glioma invasion by inducing Ca^{2+} signaling, migration processes, and cytoskeleton changes. Studies have shown a relationship between the expression of Trpm channels in glioblastoma and the probability of survival (1,12). A study found the genetic expression of Trpm channels, especially Trpm2, Trpm3, Trpm7, and Trpm8, in patients with glioblastomas to be significantly higher than in a healthy control group (1). In the present study, Trpm4 was found in 74% of our immunohistochemical stains. The Trpm4 channels play important roles in prostate cancer, diffuse large B-cell lymphoma, pancreatic, colorectal, hepatic, urinary bladder, breast, and endometrial cancers (3). Human cervical-uterine cancer-derived cell lines have been shown to display high Trpm4 mRNA levels and Trpm4 channel amplification (12). In light of the research discussed above, Trpm4 channels have been suggested as potential targets for anti-cancer treatment (3). We found varying levels of Trpm4 channel expression in high-grade glial tumors**.**

We found a moderately significant relationship between Sur1 and Trpm4 (r=0.41; p=0.003). The unique form of Sur1-Trpm4 is not usually present in brain tissue. Rather, *de novo* upregulation of Sur1-Trpm4 occurs following the onset of certain brain pathologies (4,41), including subarachnoid hemorrhage, ischemic stroke, and spinal cord injury. Our study adds high-grade glial tumors to this list.

Glial tumor types and subtypes vary in their cellular proliferation potential (8). Although molecular studies are beginning to replace classical approaches to the study of pathological diagnostic processes, the mitotic rate is still the main determinant of proliferation potential as an increase in the mitotic rate is indicative of an increase in proliferation potential and, thus, a poorer prognosis. The mitotic index is a simple count of the number of mitotic figures visible in the 10x magnification field after H&E tissue staining (4,8). In our study, no statistical relationship was found between Sur 1 and the number of mitoses. (r=0.267; p=0.061). On the other hand, a weak significant correlation was found between Trpm4 and mitosis (r=0.31; p=0.0029). The Ki-67 index has been used for many years in malignant tissue examinations to distinguish between proliferating and non-proliferating cells. Increases in the Ki-67 index are correlated with increases in the degree of malignancy in astrocytomas and the index is used as a prognostic indicator and to estimate survival probabilities (5,13). In our study, weak positive correlations were found between Trpm4 and Ki-67 (r=0.37; p=0.008) and between Sur1 and Ki-67 (r=0.306; p=0.031).

MRI parameters are the gold standard imaging technique for the diagnosis, surgical planning, and follow-up of glioblastomas (20,43). Advanced MRI sequences, such as diffusion tensor imaging, perfusion, DWI, and magnetic resonance spectroscopy provide additional information about brain tumors beyond the anatomical and functional (17,19,28). Such techniques have been studied for their potential use in the quantitative measurement of vasogenic cerebral edema. This is achieved through their measurements of alterations in the brain's water content, blood flow, and biochemistry (13,17,43). However, there is still no gold standard technique able to produce metric measurements of peritumoral edema volumes (14,27,39).

Many studies have investigated the correlations between histological and molecular markers and pretreatment MR sequences in glial tumors. Such research generally has three main objectives. Firstly, they aim to determine whether particular markers are accurate prognostic indicators. Secondly, they aim to identify any relationships between the markers and the pretreatment MRI findings. Thirdly, they aim to establish the markers' potential as treatment targets. Despite advanced artificial intelligence analyses and the discovery of several new biomarkers, strong, consistent, informative correlations between glial tumors and biomarkers have not yet been established (2,13). The multiform nature of glial tumors is likely to significantly complicate any correlations between the biomarkers and tumor MRI data. In our study, no significant correlations were found between Sur1-Trpm4 ratios and either tumor volume or peritumoral edema volume (Table II).

Cerebral edema increases the risk of neurological morbidity and mortality in both adults and children with brain tumors. Despite substantial research over the last 40 years, glucocorticoids are still the primary therapy used in the treatment of tumor-related cerebral edema. These can have many side effects, including immunosuppression, endocrinopathies, and Cushing's syndrome. Therefore, new treatments for peritumoral edema and related cognitive deficits are needed (9,11,26). The Sur1-Trpm4 complex contributes to many subtypes of cerebral edema. The BBB disintegration and oncotic death of endothelial cells that can result from cytotoxic and vasogenic edema have been demonstrated by several studies (14-16). Inhibitors of these receptors reduce cerebral edema, have neuroprotective effects, and lower mortality rates in ischemic stroke, traumatic brain injury, and subarachnoid hemorrhage (36). In the present study, we identified varying levels of the Sur1-Trpm4 complex among patients with glial tumors. However, we found no significant correlation between peritumoral edema volumes, as measured in FLAIR/T1 images, and Sur1-Trpm4 expression levels.

Study Limitations

The limited number of cases was the greatest limitation of this study. Many more cases are required in future research, and these should include the subgroups of glioblastoma (4). Analysis of glioblastoma subgroups and genetic or mRNA expression may have been more effective and informative than microscopic examination. Another major limitation was our failure to analyze other subgroups of the Sur and Trpm receptor families.

CONCLUSION

In this clinical study, the presence of Sur1-Trpm4 channel receptors in high-grade gliomas was demonstrated for the first time. However, this receptor group was not statistically correlated with the volume of peritumoral edema in preoperative MRI examinations. The Sur1-Trpm4 receptor complex is known to play an active role in subarachnoid

hemorrhage, traumatic brain injury, and stroke. Therefore, there is a need for further preclinical and clinical studies to identify the role and activities of Sur1-Trpm4 receptors in high-grade glial tumor subtypes.

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AUTHORSHIP CONTRIBUTION

Study conception and design: TTD
Data collection: IY
Analysis and interpretation of results: MHS
Draft manuscript preparation: GC
Critical revision of the article: MNO
Other (study supervision, fundings, materials, etc...): AT
All authors (TTD, MHS, GC, IY, AT, MNO) reviewed the results and approved the final version of the manuscript.

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