Research article

Investigation of the pathogenesis, clinical course, and early and late consequences of the zone of perifocal edema of glial brain tumors with its surgical and drug correction

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ABSTRACT

Introduction and Aim: Perifocal edema are the cause of the severity of patients, increasing intracranial pressure and dislocation syndrome. The objective of this study is to plan an adequate approach to the area of perifocal edema in the treatment of patients with glial brain tumors by studying the pathogenesis and consequences.

Methods: 720 patients with glial tumors with varying degrees of malignancy and a zone of perifocal edema were operated and of these, 281 patients with GRADE I-IV astrocytoma, 147 patients with GRADE I-III oligodendroglioma, 115 patients with GRADE I-III ependymoma, and 177 patients with GRADE IV glioblastoma. The zone of perifocal edema was assessed by a point system from 1–5 points.

Results: The glial tumor was significantly more common in the age group of 45-59 years (44.9 ± 2.1 cases per 100 patients). In the zone of perifocal edema at a distance from the tumor up to 1.5-2.0 cm, there was a site of apoptosis, demyelination, and destruction of nerve fibers.

Conclusion: The surgical approach proposed by us with the removal of the apoptosis zone and the zone of perifocal inflammation is the key to the successful recovery of patients, without or with minimal postoperative complications.

Keywords: Perifocal edema; glial tumors; apoptosis; magnetic resonance imaging; intensive care unit.

INTRODUCTION

Peritumorous zone or perifocal edema is a pathological process that occurs with volumetric formations of the brain, in particular with glial tumors of the brain (1-4). Perifocal edema is the cause of the severity of patients, increasing intracranial pressure and dislocation syndrome. Perifocal edema, exceeding the size of the tumor node by 2–3 times, occupies a vast area of the brain (1, 2, 5-7). A pathological chain reaction involving volumetric formation, perifocal edema, intracranial pressure, dislocation syndrome, and violations of cerebral perfusion pressure create a vicious circle leading to death. The interruption of this pathological vicious circle at the pre-, intra- and postoperative stages with the help of medications and surgical interventions is the key to a successful recovery of the patient (3, 4, 8–11).

Perifocal edema is not only a disaster for the brain, but also a protection, rescue of healthy areas of the brain from the toxic effects of the tumor, being a buffer zone between the tumor and healthy brain tissue. In recent years, there have been a number of studies of perifocal edema zones with different results and conclusions, and there is also no single planned approach to the peritumoral zone when removing a brain tumor (3, 4, 7, 12, 13). Therefore, the study and planning of the resolution of perifocal edema of a malignant glial brain tumor are relevant for morphologists and clinicians, especially neurosurgeons. Multiple changes occur in the zone of perifocal edema in order to reduce the protection of healthy brain tissue from the toxic effects of tumor tissue. The objective of this study is to plan an adequate approach to the area of perifocal edema in the treatment of patients with glial brain tumors by studying the pathogenesis and consequences.

MATERIALS AND METHODS

Seven hundred twenty patients with glial tumors with varying degrees of malignancy and a zone of perifocal edema were operated on at the Neurosurgery Department No. 2 of the National Hospital under the Ministry of Health, Kyrgyzstan from 2016–2021. Of

these, 281 patients with GRADE I-IV astrocytoma, 147 patients with GRADE I-III oligodendroglioma, 115 patients with GRADE I-III ependymoma, and 177 patients with GRADE IV glioblastoma. The zone of perifocal edema was assessed by a point system from 1–5 points. The age of patients ranged from 18–75 years, females (n=311 [43.8%]), and males 56.2% (n=409). The average age of patients at the time of surgery was 57.4 years.

General clinical analyses, magnetic resonance imaging (MRI) of the brain by Philips Ingenia 1.5T MRI system (Philips, Amsterdam, Netherlands) with a 15 ml gadolinium-based contrast agent (T1 AX, T2 AX, FLAIR COR, T2 SAG, FLAIR AX, DWI modes), intraoperative examination of tissue structures of the zone of perifocal edema and microcirculation vessels of the cerebral cortex over healthy and affected areas, using transcranial Doppler (TCD) examination, Digi-Lite TM (2 MHz sensor) and intraoperative Doppler with SonoScape S6 pro (SonoScape, Guangdong, China). Histomorphological studies were carried out with a modular microscope (MIKMED, Russia) in the laboratory of the Department of Pathological Anatomy of the I. K. Akhunbaev Kyrgyz State Medical Academy. During tissue biopsy in the area of perifocal edema of the tumor, pronounced changes were easily washed away under the influence of a jet of saline fluid, fixed in 10% neutral and acidic formalin, fixator at a distance of 1.0 cm from the tumor. The sections were prepared with a thickness of 7–8 microns by standard methods and stained with well-known methods. The water content in the tissues was determined by drying to a constant mass and the content of sodium, potassium, lipids, and other trace elements were determined by ozonation in the laboratory of the Department of Pathological Physiology of the I. K. Akhunbaev Kyrgyz State Medical Academy. For the purpose of dynamic control of morphological changes in the zone of perifocal edema in the postoperative period, a control group of 100 patients was isolated. In the control group, patients were selected with a diagnosis of malignant gliomas with different histogenesis and stages and underwent an MRI examination on the third, seventh, and tenth days.

The obtained data are presented as the mean ± standard deviation. Statistical analysis was performed using Excel.XLSTAT v2020.1 (Microsoft, Addinsoft, France). The Mann–Whitney test was used to assess the significance of differences between the groups. Three levels of probability $p > 0.05$; $p < 0.05$; $p < 0.001$ were calculated. Confidentiality was maintained concerning the data collected and this study was approved by the I.K. Akhunbaev Kyrgyz State Medical Academy Bioethics Committee (Protocol No. 3 dated May 25, 2020).

RESULTS

The glial tumor was significantly more common in the age group of 45–59 years (44.9 ± 2.1 cases per 100 patients), 60–75 years (30.9 ± 1.9%), p<0.001, a fairly high incidence of the tumor was also at the age of 18–44 years (24.2 ± 1.8%), p<0.001 (Table 1).

Table 1: Age and gender characteristics of glial tumors per 100 patients (n=720)

Age (years)	Total		Male (n=300)		Female (n=234)	
	n	M±m	n	M±m	n	M±m
18–44	257	24.2 ± 1.8	86	16.1 ± 1.5	43	8.1 ± 1,1***
45–59	331	44.9 ± 2.1	119	22.3 ± 1.8	121	22.6 ± 1.8*
60–75	132	30.9 ± 1.9	94	17.6 ± 1.6	71	13,3±1,4**

M±m = mean ± standard deviation, n = frequency, *p > 0.05; **p < 0.05; ***p < 0.001.

Depending on gender, most cases of glial tumors were in the age group of 45–59 years, while no significant differences were found between male (22.3 ± 1.8%) and female (22.6 ± 1.8%) patients, p>0.05. In 60–75 years, in most cases, the tumor was found in males (17.6 ± 1.6%), then in females (13.3 ± 1.4%) patients, p<0.01. Glial tumor in the age group of 18–44 years was twice as common in males (16.1 ± 1.5%) than in females (8.0 ± 1.1%), p<0.001.

According to the histogenesis of a glial tumor with astrocytoma, there were 38.4 ± 2.1 cases per 100 patients (n=205), oligodendroglioma (24.7 ± 1.8%; n=132), p<0.001, ependymoma (20.4 ± 1.7%), p>0.05, glioblastomas (16.4 ± 1.6%), p>0.05 (Table 2). With astrocytoma (21.3 ± 1.7% and 17.0 ± 1.6%), oligodendroglioma (13.1 ± 1.4% and 11.6 ± 1.3%), ependymoma (10.8 ± 1.3% and 9.1 ± 1.2%), there were no significant differences in the frequency of occurrence between males and females, p>0.05. Glioblastoma was significantly more common in males (10.4 ± 1.3%) than in females (6.0 ± 1.0%), p<0.01.

Table 2: Frequency of glial tumors by gender per 100 patients (n=720)

	Glial tumor	Total (n=720)		Male (n=409)		Female (n=311)	
		n	M±m	n	M±m	n	M±m
1	Astrocytoma	281	38.4 ± 2.1	154	21.3 ± 1.7	127	17.0 ± 1.6*
2	Oligodendroglioma	147	24.7 ± 1.8	86	13.1 ± 1.4	61	11.6 ± 1.3*
3	Ependymoma	115	20.4 ± 1.7	86	10.8 ± 1.3	49	9.1 ± 1.2*
4	Glioblastoma	177	16.4 ± 1.6	110	10.4 ± 1.3	74	6.0 ± 1.0**

M±m = mean ± standard deviation, n = frequency, *p > 0.05; **p < 0.05; ***p < 0.001.

Of the total number of cases of astrocytoma (38.4 ± 2.1%), pilocytic (Grade I) accounted for 9.8 ± 1.2% (n=52), fibrillar (Grade II) – 14.0 ± 1.5% (n=75), p<0.01, anaplastic (Grade III) – 14.6±1.5% (n=78), p>0.05. Patients with oligodendroglioma (24.7 ± 1.8%; n=132), of them with Grade II oligodendroglioma (8.4 ± 0.3%; n=45) of patients, Grade III anaplastic oligodendroglioma (9.4±1.2%; n=50) of patients, p>0.05, and mixed Grade III oligoastrocytoma degrees (6.9 ± 1.0%; n=37), p>0.05 are observed. Patients with ependymoma accounted for 20.4 ± 1.7 cases per 100 patients with glial tumor (n=109), of them with Grade I subependymoma (3.7 ± 0.8%; n=20) patients, Grade I myxopapillary ependymoma – 5.2±0.9% (n=28 patients, p>0.05, mixed Grade ependymoma II (4.9 ± 0.9%; n=26) patients, p>0.05, Grade III anaplastic ependymoma – 6.6±1.0% (n=35), p>0.05, patients. There were (16.5 ± 1.6%; n=88) patients with Grade IV glioblastoma. The zone of perifocal edema in glial brain tumors occupies an extensive area outside the tumor node, especially in malignant glial tumors and the size of the zone of perifocal edema is 2-4 times larger than the tumor node. The zone of perifocal edema does not have clear boundaries and a contour with a tumor and healthy areas of the brain, its transitions are not completely visualized in MRI studies (Fig. 1).

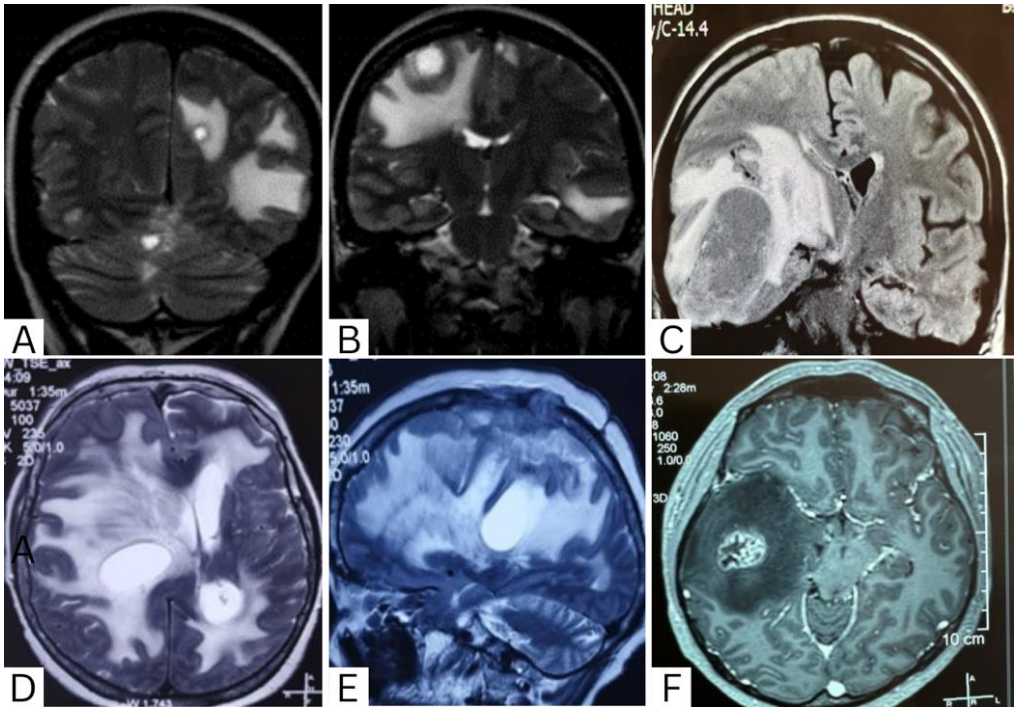

Fig. 1: Perifocal edema in glial brain tumors (A, B, C, D, E, and F).

The zone of perifocal edema in most cases has an identical macroscopic morphological picture with the tumor tissue during intraoperative imaging. With such a morphological picture, the possibility of total removal of the glial tumor and damage to adjacent healthy areas of the brain is excluded. These unclear parameters of the perifocal edema zone are fraught with consequences in the postoperative period. The study of the zone of perifocal edema is necessary to reduce postoperative consequences such as continued growth and severe symptoms of prolapse, which reduce the quality of life. Mainly in the pathogenesis of the zone of perifocal edema in glial brain tumors, there are vasogenic and cytotoxic types of edemas. At the initial stages of tumor development, vasogenic edema occurs, followed by cytotoxic edema. Vasogenic edema begins to prevail over cytotoxic edema as the degree of malignancy of the tumor increases, which on MRI images manifests itself in the form of pronounced demyelination of white matter fibers. Vasogenic edema is observed in anaplastic astrocytoma (Grade III), anaplastic oligodendroglioma (Grade III), mixed oligoastrocytoma (Grade III), ependymoma (Grade III), and glioblastoma (Grade IV). Cytotoxic edema is observed in pilocytic astrocytoma (Grade I), fibrillar astrocytoma (Grade II), oligodendroglioma (Grade II), subependymoma (Grade I), and myxopapillary ependymoma (Grade I).

MRI examination of the brain is the gold standard in neurosurgery, having advantages over other neuroimaging devices, especially 1.5 or 3.0 T devices using contrast agents to verify tumor lesions of the brain and characteristics of the zone of perifocal edema. Tumor and perifocal edema are not discontinuous pathological components that increase intracranial hypertension and create brain dislocation. In such cases, the main pathological factor is a zone of perifocal edema that exceeds the size of the tumor several times. Neuroimaging using MRI brain imaging can reduce the threat to the patient's life. The severity of the zone of perifocal edema in glial brain tumors according to MRI is presented in points (Table 3).

Table 3: Severity of perifocal edema in glial brain tumors by magnetic resonance imaging (in points)

Zone	1 zone Weak hypostasis	2 zone Moderate edema	3 zone Marked edema	4 zone Strong marked edema	5 zone Extensive hypostasis
Points	1.0–1.5	2.0–2.5	3.0–3.5	4.0–4.5	>5.0

Thus, the more malignant the tumor, the higher the severity of edema. A score of 1.2 and 3 points is observed in pilocytic astrocytoma (Grade I), fibrillary astrocytoma (Grade II), oligodendroglioma (Grade II), subependymoma (Grade I), and myxopapillary ependymoma (Grade I). A score of 3.4–5 points is observed in anaplastic astrocytoma (Grade III), anaplastic oligodendroglioma (Grade III), mixed oligoastrocytoma (Grade III), ependymoma (Grade III), and glioblastoma (Grade IV).

The staining results were evaluated using a light microscope (Leica, Germany) with 100-, 200- and 400-fold magnification. For all markers, the localization of staining in the cell was determined to include the nucleus, cytoplasm, and membrane. The number of positive cells was evaluated in the zones containing a maximum number. With growing tumor tissue, a large number of vessels and round-cell infiltrates were observed. Such a picture with infiltration and admixture of a large number of neutrophils was noted not only in the tumor tissue but also in the zone of perifocal edema, which can be a diagnostic criterion in determining the volume of surgery for the removal of high-grade glial brain tumors.

An intraoperative thorough morphological analysis of the tissue of the zone of perifocal edema was performed. The tissue is whitish yellow in places yellowish-greenish in color, the consistency is flabby-mucous, the zone is little vascular – the arteries are narrow, the veins are stasis, with mechanical action, the tissue easily disintegrates, is easily washed under a stream of liquid (Fig. 2).

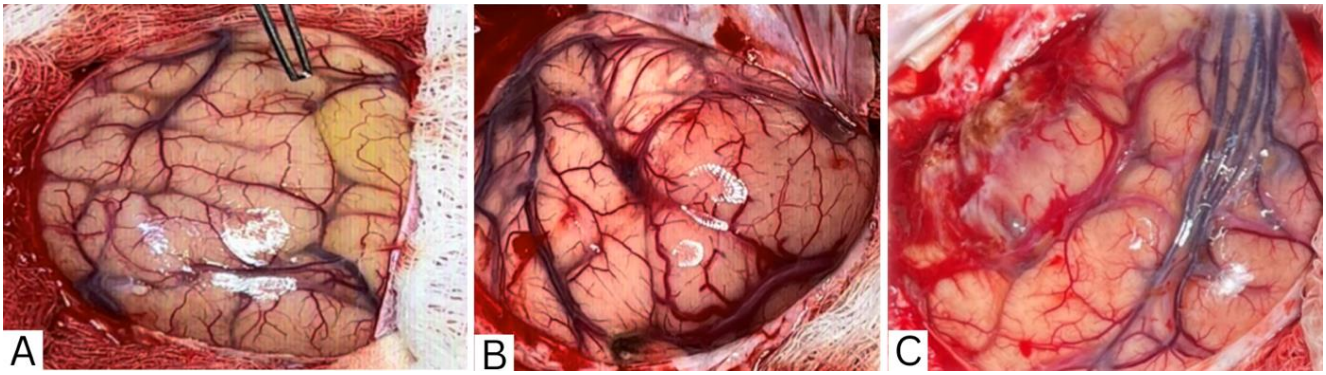

Fig. 2: Intraoperative picture of the zone of perifocal edema (A, B, and C).

Histological examination of the tissue of the zone of perifocal edema showed significant changes in the cortical zone, thinning of the thickness of the cortex, demyelination of fibers, hyperplasia, and desquamation of the vessels of the cerebral cortex. Neurons and neuroglia were not differentiated, especially those adjacent to the zone of perifocal edema of the tumor. There were shaped changes in glial cells, in the form of hyperplasia and hypertrophy of astrocytes, vacuolization of the cytoplasm of oligodendrocytes.

According to morphological, histological, and water-electrolyte changes, the zone of perifocal edema was divided into three zones: the first border zone with the tumor is the zone of apoptosis; the second is the zone of perifocal inflammation; the third is the zone of reactive change (Table 4). Morphometric indicators of the zone of perifocal edema, cellularity is reduced 4–5 times than normal indicators of white matter cellularity, in the zone of perifocal edema – 245–265 ± 10.8 cl/mm2 compared to 900–950 ± 17.8 cl/mm2.

Table 4: Perifocal edema zones according to morphological, histological, and water-electrolyte changes

Perifocal edema area and morphological changes	Apoptosis zone	Area of perifocal inflammation	Reactive Change Zone
Macroscopic changes	Complete destruction, pale yellow, flabby, softened, width up to 0.5 cm	Pale, partial destructive, softening elements, vascular-free, width up to 1 cm	Slightly pale, there are no other changes

Dilution of white matter	The change is expressed in the form of microcysts, voids, spongiosis,	Moderate in the form of mesh rarefactions	Insignificant
Histological changes	Axonopathy, myelopathy, gliocytopenia	Demyelination, gliosis, angiopathy, convolutes, optional changes	Swelling and swelling of axons, moderate demyelination
Water availability	+4.2 ± 0.5%	+3.0 ± 0.4%	+2.1 ± 0.4%
Presence of lipids	Marked decrease in lipids >60%	Marked decrease in lipids >50%	Marked decrease in lipids >30%
MRI picture	Hyperintense signal	Hyperintense signal	Hyper-, iso-, hypointense signal

Multiple small voids were found, located diffusely, forming a porous structure. Around a malignant tumor in the medulla, the zone of perifocal edema extends to 5.0–6.0 cm, in the zone of perifocal edema, sharp changes in water, lipids, sodium and potassium are observed. At a distance from the tumor up to 0.8–1.0 cm, the water content increased by almost +4.2 ± 0.5, and at a distance up to 1.5–2.0 cm, the water content increased by +3.0 ± 0.4 (Figure 5, 6, 7). An increase in the sodium concentration by a distance of 0.8–1.0 cm – 57.0 ± 3.2, by 1.8–2.0 cm – 42.0 ± 2.5 ($p<0.001$). Increases in potassium indicators at a distance of up to 0.8–1.0 cm - 49.0 ± 4.8, and at a distance of 2.0 cm – 45.9 ± 4.1 ($p>0.05$). Reduction of lipids in the white matter at a distance of 1.0 cm from the tumor – up to 0.51 ± 0.07, at a distance of 2.0 cm – 0.77 ± 0.09 ($p<0.01$), normally 1.24 ± 0.14, these indicators indicate the process of demyelination and damage to myelin fibers. This pattern was observed at a distance of 1.0 cm from the tumor in the white matter, and at a distance of 2.0 cm the indicator was 0.78 ± 0.09, gradual normalization of lipid levels was observed at a distance of 3.5–4.0 cm from the distance of the tumor in the white matter of the brain.

In the zone of perifocal edema at a distance from the tumor up to 1.5–2.0 cm, there was a site of apoptosis, demyelination and destruction of nerve fibers (Table 5).

Table 5: Violations of the water-electrolyte composition

Area of perifocal edema	Water, %	Sodium, mmol/kg	Potassium, mmol/kg	Lipids, g
White matter in the focus up to 1 cm	+4.2 ± 0.6	57.0 ± 2.6	49.0 ± 4.5	0.51 ± 0.06
White matter at a distance of up to 1-2 cm	+3.0 ± 0.5	42.0 ± 3.0	45.9 ± 4.6	0.77 ± 0.08

In the zone of perifocal edema, where there were pronounced manifestations of alterations in the form of dystrophic changes and cell necrosis, demyelination, and damage to nerve fibers in the white matter of the brain showed a hyper intense MR signal in the T2 mode. In the morphological picture, edema manifested itself in the form of rarefaction of white matter with the development of spongiform structures and the formation of microcysts and voids; there were hyperplasia and reactive changes in glial cells. The reaction from the local phagocytic system was manifested by an increase in the number of micro gliocytes, their transformation into granular balls and accumulation around the vessels. One of the most important components of the zone of perifocal edema of malignant gliomas is the presence of proliferating vessels. The formed capillary convolutes with endothelial proliferation, in turn, act as a phagocytic filter on the decay and exchange products of the glial tumor. Morphological changes in the water-electrolyte composition of brain cells and intercellular space, vessels and nerve fibers in the zone of perifocal edema are expressed, especially in malignant glial tumors. These pathological changes appear not only due to the mechanical and toxic effects of the tumor, but also to protect healthy areas of the brain from the aggressive effects of a malignant tumor, being a buffer zone, draining toxic decay products of malignant glioma cells.

All patients of the control group before surgery and in the postoperative period on the third and seventh days underwent dynamic neuroimaging using MRI. In almost all patients, malignant glial tumors with an extensive zone of perifocal edema were verified, in which the resolution of edema on MRI images lasted for many up to seven days and in a small group till 10 days. On the third day in the postoperative period, there was a regression of hypertension and focal symptoms, by the 10th day after surgery, there was a complete regression of hypertension and up to 60–70% recovery of symptoms of prolapse. Taking into account the MRI images and neurological status, patients were prescribed dehydration therapy: synthetic glucocorticoid dexamethasone 8 mg (2 times/day for 7 days), 1–2 days before surgery and 5–6 days after surgery, osmotic diuretic mannitol 15% 400 ml (1 time/day, intravenously), 1–2 days before surgery and after the operation 3–4 days, reosorbilact

in a dose of 400 ml (6–7 ml/kg body weight, intravenously) drip solution affecting the electrolyte balance for 3–5 days after the operation.

Considering clinical cases

A 61-year-old patient diagnosed with Anaplastic astrocytoma (grade III), images before surgery and on the third and seventh days after surgery were presented in Fig. 3.

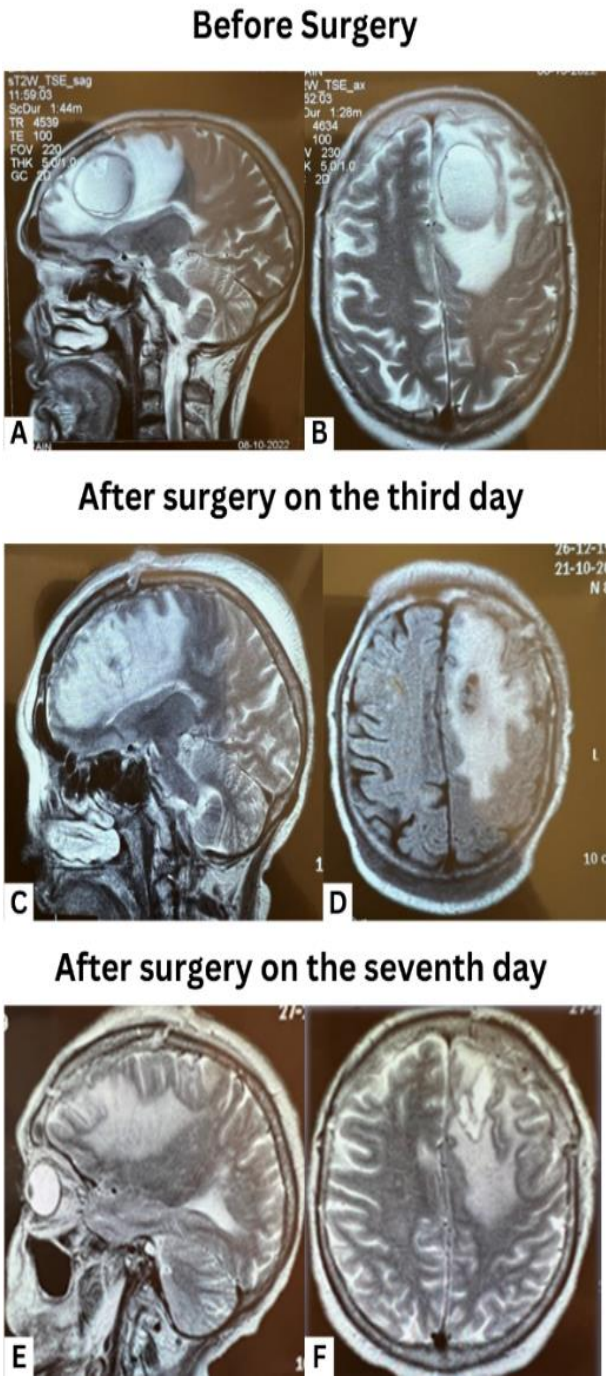

Fig. 3: Anaplastic astrocytoma (grade III), images before surgery and after surgery on the third and seventh day (A, B, C, D, E, and F).

A 64-year-old patient diagnosed with glioblastoma (grade IV), images before surgery and on the third and seventh days after surgery were presented in Fig. 4.

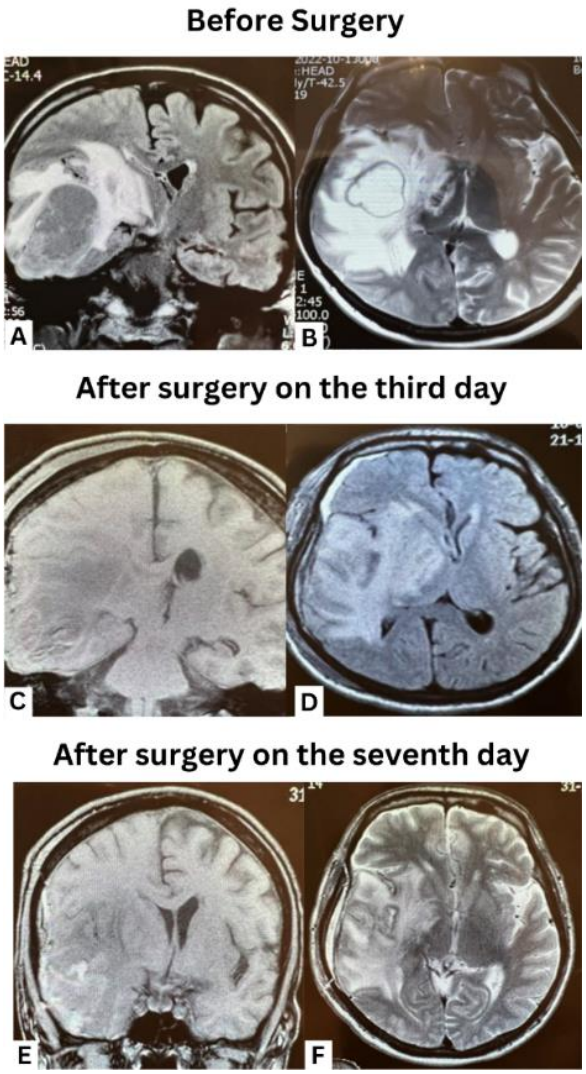

Fig. 4: Glioblastoma (grade IV), images before surgery and after surgery on the third and seventh day (A, B, C, D, E, and F).

DISCUSSION

In many studies, it has been noted that the phenomena of peritumoral angiopathy with structural changes of vessels in the form of hypertrophy and pericalibration of vessels are observed around the glial tumor. In the zone of perifocal edema, the intercellular fluid increases, the blood-brain barrier is broken, increasing the permeability of the capillary endothelium, the extracellular and intracellular ratios of potassium, sodium and calcium electrolytes, the content of lipids and fluid in cells change. As a result of these changes, neurons and glial cells, axons, and dendrites are destroyed in the zone of perifocal edema, and the process of apoptosis is observed (2, 6, 14, 15). At the same time, toxic substances accumulate that adversely affect healthy adjacent areas of the brain, in particular, the products of cell decay of the zone of perifocal edema and tumors.

Histological examination in the zone of perifocal edema of a glial brain tumor shows three layers of tissue change: the invasion layer; the demarcation layer and the proliferation layer of micro- and macro glial cells. And also in this zone, migrations of tumor cells were detected at a distance from the tumor node

(3, 6, 9, 15). All these changes are serious factors for the prognosis of the recurrence of glial tumors of varying degrees of malignancy and the appearance of various early and late complications. A planned approach to the peritumoral zone is necessary for the treatment of a patient with a glial brain tumor.

Malignant glial tumors, having a rapid growth rate, increased metabolic processes, and decay has toxic and mechanical effects on healthy brain tissues. The zone of perifocal edema serves as a buffer between the tumor and brain tissue, eliminating the decay products of the tumor. A pronounced extensive zone of perifocal edema in malignant glial tumors of the brain edema plays a major role in the severity of hypertension-dislocation syndrome, 2–3 times larger than the size of the tumor node.

Morpho histological examination of the perifocal edema zone made it possible to optimize surgical intervention when removing areas of apoptosis and invasion of tumor cells in the perifocal edema zone and minimize postoperative complications in the form of an epileptic seizure and continued tumor growth.

When examining the zone of perifocal edema of malignant glial tumors of the brain, gross changes in the water-electrolyte composition in cells and intercellular space, pronounced hyperhydration, delipidation, with the appearance of multiple cysts and voids, spongiosis, angiopathy and demyelination, changes in the shape of neurons and glial cells, with the presence of an extensive zone of irreversible processes in brain cells-apoptosis and a layer of coarse invasion.

The zone of perifocal edema performs a buffering and cleansing function, eliminating the decay products of the tumor and cells of the zone of perifocal edema with the help of a drainage form of oligodendroglia and vascular capillary convolutes.

Adequate pre- and postoperative dehydration therapy with the inclusion of dexamethasone, mannitol, reosorbilact, and monitoring of the course of perifocal edema allowed rapid recovery of neurological deficits and reduced the time of stay of patients in the hospital.

CONCLUSION

The surgical approach proposed by us with the removal of the apoptosis zone (0.5 cm) and the zone of perifocal inflammation (up to 1 cm) is the key to the successful recovery of patients, without or with minimal postoperative complications, since an irreversible process of apoptosis has been launched in these zones and the migration of tumor cells at a distance from the tumor node has been verified, in connection with which these areas do not recover in the postoperative period and in the future may cause a number of serious complications up to the development of epileptic syndrome and continued tumor growth.

CONFLICTS OF INTEREST

None.

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