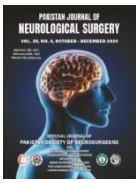

PAKISTAN JOURNAL OF NEUROLOGICAL SURGERY (QUARTERLY) – OFFICIAL JOURNAL OF PAKISTAN SOCIETY OF NEUROSURGEONS

Original Research

Epilepsy Surgery Outcomes in Patients with Drug-Resistant Forms with Low-Grade Tumors

Oleg Levchenko, Igor Trifonov, Mikhail Sinkin, Ayna Shakhmanayeva, Anastasia Skalnaya
Neurosurgical Department, Russian University of Medicine, Moscow, Russia

ABSTRACT

Objective: To evaluate the efficacy of neurosurgical treatment of patients with drug-resistant structural epilepsy caused by low-grade brain tumors.

Materials and Methods: 30 patients with drug-resistant structural epilepsy caused by low-grade tumors. Preoperative evaluation and surgical treatment were performed from 01.01.2016 to 31.12.2023. As a preoperative evaluation, all patients underwent neurological and neuropsychological examination, the semiology of seizures was assessed, and neuroimaging and neurophysiological studies were performed. A histological examination of resected brain areas was performed. Surgical outcome assessed by J. Engel Surgical Treatment Outcome Scale (1993) at 12, 24 months.

Results: 30 patients were treated surgically, 10 (33%) were men and 20 (67%) – women. The mean age of the patients was 29.76 years. Focal motor and non-motor seizures were noted in 12 (40%) patients. 18 (60%) patients had bilateral tonic-clonic seizures with focal onset. All 30 patients underwent resection surgery: 10 patients (33%) underwent anterior mesial temporal lobectomy (AMTLE) , 17 patients (57%) – lesionectomy, 2 – AMTLE plus lesionectomy, and one – lesionectomy plus selective amygdalohippocampectomy (SAH). The results of surgical treatment 12 months after surgery were evaluated in 25 patients. Engel I outcomes after 12 months were in 18 patients (72%), at 24 months in - 73%.

Conclusion: The results of our study demonstrate the efficacy of surgical treatment in patients with drug-resistant structural epilepsy caused by low-grade brain tumors. Significant improvement in seizure control was seen in the Engel I results at 12 and 24 months after surgery (72% and 73%, respectively).

Keywords: Drug-Resistant Epilepsy, LGG, AMTLE (Anterior Mesial Temporal Lobectomy), Seizures.

Corresponding Author: Igor Trifonov
Neurosurgical Department, Russian University of Medicine, Moscow, Russia
Email: dr.trifonov@mail.ru

Date of Submission: 01-10-2024
Date of Revision: 10-12-2024
Date of Acceptance: 11-12-2024
Date of Online Publishing: 15-12-2024

Date of Print: 31-12-2024

DOI: 10.36552/pjns.v28i4.1014

INTRODUCTION

Brain tumors are the most common cause of symptomatic focal epilepsy. Brain tumors are the

cause of first-diagnosed seizures in 5% of cases[1,2] and 13% of MR-positive forms of focal epilepsy.[3] Epileptic seizures are the first clinical finding in 30-50% of patients with brain tumors and develop plater in 10-30%.[4] Epileptic seizures could cause severe neurological impairment (transient hemiparesis, aphasia, sleep disturbances, memory loss, etc.), which adversely affects the quality of life and leads to psychological and social problems (low self-esteem, depression, anxiety, unemployment, social isolation, stigmatization, inability to drive, etc.).[5,6] Persistent seizures in the postoperative period in patients receiving anticonvulsant therapy significantly worsen their neuropsychological status.[7]

The terms "chronic epilepsy" associated with brain tumors, where the duration of seizures exceeds 2 years in the context of a slow oncologic process, are often used to describe "epileptoma" and "long-term epilepsy-associated tumors (LEAT)".[8]

The pathophysiological mechanisms of brain tumor epileptogenesis are not fully understood. J.H. Jackson noted in 1882 that the causes of epilepsy in patients with brain tumors are the presence of a slow-growing tumor in the gray matter of the brain and "sudden sharp pathological discharges of nerve cells" causing epileptic seizures.[10,11] W. Penfield suggested that impaired vascularization of the cortex surrounding the tumor could lead to hypoxic-ischemic neuronal changes.[11,12]

Impaired vascularization of the cortex surrounding the tumor, direct irritation of the brain by the tumor, and denervation hypersensitivity due to partial disconnection of the cerebral cortex have been suggested as the main causes of epileptic seizures.[13]

Pathogenetic factors of tumor epileptogenesis may include tumor histology and localization, disruption of the blood-brain barrier, the gap junctions (nexuses), molecular genetic alterations, morphologic changes in the tissues surrounding the tumor, hypoxia, acidosis, metabolic disorders, ionic changes, glutamate neurotransmission, GABA neurotransmission, immunologic and inflammatory changes.[14] Glioneuronal tumors are tumors of the central nervous system consisting entirely or partially of cells with neuronal differentiation, diagnosed mainly by histological and immunohistochemical studies. The most common glioneuronal tumors are gangliocytomas, gangliogliomas, dysembryoplastic neuroepitheliomas, and extraventricular neurocytomas.

MATERIALS AND METHODS

Study Setting and Duration

Preoperative evaluation and surgical treatment were conducted from 01.01.2016 to 31.12. 2023 at the Neurosurgical Department of Russian Medical University (Russia, Moscow).

Inclusion Criteria

Adult patients ≥18 years with confirmed drug-resistant forms of epilepsy, intracerebral brain tumors identified by brain MRI, and low-grade tumors confirmed by histopathology. As a preoperative evaluation, all patients underwent neurological and neuropsychological examination, the semiology of seizures was assessed, and neuroimaging and neurophysiological studies were performed. A histological examination of resected brain areas was performed. Surgical outcome was assessed using the J. Engel Surgical Treatment Outcome Scale (1993) at 12, and 24 months after surgery.

Exclusion Criteria

Patients with an unconfirmed diagnosis of drug-resistant epilepsy without low-grade brain tumors and without preoperative neurological, neuropsychological, neuroimaging, and pathomorphological studies.

Data Collection Tool

Patient data, i.e. name, age, gender, time of onset and duration of the disease, the clinical picture of epileptic seizures, brain MRI data, scalp, and invasive EEG monitoring data were noted.

RESULTS

Age Distribution

A total of 30 patients with drug-resistant structural epilepsy caused by low-grade tumors were included in the study. At the time of surgery, 63% (3) are under the age of 20, 16 are aged 21-30, 8 are aged 31-40, and 3 are over 41. The mean age of the patients was 29.76 years. The mean age of disease onset was 16.75 years. The mean disease duration was 13.34 years.

Gender Distribution

There were 10 (33%) men and 20 (67%) – women.

EEG Findings

All patients underwent scalp video-EEG monitoring with seizure recording. Based on video-EEG monitoring data, the seizure onset zone was localized in the right hemisphere in 20 (66%) patients, in the left hemisphere in 9 (30%) patients, and in one patient the seizure onset zone could not be lateralized. Deep and cortical electrodes were implanted for invasive video EEG monitoring to determine the "seizure onset zone" and "irritation zone" in seven patients (23%). During EEG monitoring, focal motor and non-motor seizures were recorded in 12 patients (40%), and bilateral tonic-clonic seizures with focal onset were recorded in 18 patients (60%).

Distribution by MRI

Brain MRI revealed epileptogenic lesions in 30 patients (100%), with LGG localization in the temporal lobe in 15 (50%), the parietal lobe in 7 (23%), the hippocampus in 2, the frontal lobe in 1, the occipital lobe in 1, and two or more lobes in 4. In 20 (66%) patients the LGG was localized in the right cerebral hemisphere, in 9 (30%) patients in the left cerebral hemisphere, and in one patient bilateral LGGs were identified.

Distribution by Surgical Resection

All 30 patients underwent resective surgery: 10 patients (33%) underwent anterior mesial temporal lobectomy (AMTLE), 17 patients (57%) – lesionectomy, 2 – anterior mesial temporal lobectomy plus lesionectomy and one – lesionectomy plus selective amygdalohippocampectomy (SAH). Right-sided resection was performed in 19 (63%) patients, left-sided performed in 10 (33%) patients, and in one patient, bilateral LGG resection was done. No postoperative complications were noted during both invasive video-EEG monitoring and surgical resections in our group of patients.

Distribution by Histopathology

Histological examination revealed low-grade tumors (grade 1-2) in 17 patients (56%): diffuse astrocytoma – 4 patients, oligodendroglioma – 5, oligoastrocytoma – 2, fibrillary astrocytoma -1, NOS - 1, DNET -1, ganglioglioma - 2, gangliocytoma – 1 and a combination of focal cortical dysplasia with low-grade tumors – FCD IIIb in 13 patients (44%): DNET – 8 patients, pilocytic astrocytoma - 1, ganglioglioma - 2, oligodendroglioma – 2.

Distribution by Outcomes

The results of surgical treatment 12 months after surgery were evaluated in 25 patients: 18 patients (72%) became seizure-free – Engel I: 16 patients (64%) – Engel Ia, 2 patients – Engel Ib, 3 patients (12%) had – Engel IIIa, one patient – Engel IVa and 3 patients (12%) – Engel IVb.

The results of surgical treatment 24 months

after surgery were evaluated in 23 patients: 17 patients (73%) became seizure-free – Engel I: 15 patients (65%) – Engel Ia, 2 patients – Engel Ib, one patient – Engel IIa, one patient – Engel IIb, one patient – Engel IIIa, 2 patients – Engel IVb and one patient – Engel IVc.

So, Engel I outcomes 12 months after surgery were in 18 patients (72%), at 24 months in – 73%. Based on histopathology, in patients with LGG only, Engel I outcomes at 12 months were 64%, and in patients with LGG plus FCD – 83% (Table 1).

Table 1: Engel scale outcomes in patients with LGG and FCD IIIb 12 months after surgery.

Engel outcomes	Histopathology	
	LGG	FCD IIIb
Engel I	9 (64%)	9 (81%)
Engel III	1 (7%)	2 (19%)
Engel IV	4 (29%)	
Total number of patients	**14**	**11**

DISCUSSION

In our study, the average duration of the disease from its onset to the time the patient was referred to a neurosurgeon was 13.34 years. In epilepsy surgery, the average period from the diagnosis of epilepsy to surgery in adults is about 20 years.[15] The reasons for a long delay in surgery for drug-resistant epilepsy may be a lack of complete information on the efficacy and safety of surgical treatment, lack of sufficient accessible literature on methods of surgical treatment of epilepsy for both patients and specialists, the reluctance of neurologists to refer patients to a neurosurgeon, justifying this by possible severe postoperative neurological disorders, insufficient equipment of centers for surgical treatment, and, which causes some concern, in some cases, the desire of doctors "not to let the patient go" for several reasons, including for conducting sponsored clinical trials of drugs.[16] Such a long delay in brain tumor surgery is unacceptable due to the risk of developing malignancy of brain tumors with the development of irreversible complications.[17,18] A patient with a detected structural lesion on MRI should be referred to a neurosurgeon, according to the classification of brain tumors, verification of the diagnosis can only be carried out after pathomorphological, immunohistochemical, and molecular genetic studies.[19]

The Engel I results in 12 and 24 months after surgery were 72% and 73%, so our epilepsy surgery results in patients with drug-resistant forms with low-grade tumors are comparable with the studies by Meguins et al, Kurzwell et al.[20,21]

In our research, patients with low-grade tumors combined with focal cortical dysplasia had better surgical outcomes than patients with low-grade tumors alone, Engel I outcome after 12 months was 81% and 64% consequently. This may be explained that in patients with FCD IIIb were performed additional resection of surrounding LGG brain tissue, then only lesionectomy in patients with LGG. Excision of the tumor alone and preservation of abnormal dysplastic tissue around the tumor may lead to the persistence of seizures after surgery. In approximately 30% of patients, the seizure onset zone may not correspond to the tumor location, due to the presence of a secondary epileptogenic zone. The increased risk of secondary epileptogenesis is most often associated with the patient's young age, long history of the disease, and tumor localization in the temporal lobe.

Epilepsy surgery in brain tumor patients is not just tumor removal. The type of tumor, its location, pathophysiology, and epileptogenesis determine the treatment of patients with epilepsy. Treatment tactics are determined by the type and location of the tumor and the presence of focal cortical dysplasia.

The importance of a comprehensive preoperative evaluation cannot be overstated. The multidisciplinary team approach, including neurological and neuropsychological examination, semiology of seizures assessment, neuroimaging, and neurophysiological studies, enabled us to

identify the underlying causes of epilepsy and develop an individualized treatment plan for each patient.

Each case should be approached individually by a multidisciplinary team of specialists (neurologists, epileptologists, neurosurgeons, neurophysiologists, neuropsychologists, pathomorphologists, neuroradiologists). After a comprehensive preoperative evaluation of the patient and careful and balanced planning of the surgical intervention, the patient has a high chance of complete seizure control and a significant improvement in quality of life.

CONCLUSION

The results of our study demonstrate the efficacy of surgical treatment in patients with drug-resistant structural epilepsy caused by low-grade brain tumors. Significant improvement in seizure control was seen in the Engel I results at 12 and 24 months after surgery (72% and 73%, respectively).

The main type of histopathology in patients with drug-resistant forms was the combination of FCD IIIb and DNET – 26% and oligodendroglioma – 16%. Patients with a combination of FCD and LGG had better outcomes than those with LGG alone.

RECOMMENDATIONS

Patients with brain tumors and drug-resistant epilepsy should undergo preoperative examination to achieve seizure-free: high-resolution MRI of the brain, the scalp of invasive video EEG monitoring, etc. with seizure recording to verify the epileptogenic zone, the complete resection of which leads to seizure control.

REFERENCES

1. Olafsson E, Ludvigsson P, Hesdorffer D, Kjartansson O, Hauser WA, Gudmundsson G. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. The Lancet Neurology [Internet]. 2005 Oct 1 [cited 2020 Mar 9];4(10):627–34. DOI: 10.1016/s1474-4422(05)70172-1
2. Bromfield EB. Epilepsy in patients with brain tumors and other cancers. Rev Neurol Dis. 2004;1 Suppl 1:S27-33. PMID: 16400292.
3. Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county-A population based study. Epilepsia. 2015;25;56(5):699–706. DOI: 10.1111/epi.12972
4. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. The Lancet Neurology. 2007;6(5):421–30. Doi: 10.1016/S1474-4422(07)70103-5
5. Cowie CJA, Cunningham MO. Peritumoral epilepsy: Relating form and function for surgical success. Epilepsy & Behavior. 2014;38:53–61. DOI: 10.1016/j.yebeh.2014.05.009
6. Zelano J, Klecki J, Christensen J, Tomson T, Malmgren K. The provision of epilepsy care across Europe 2017: A 17-year follow-up survey. Epilepsia Open. 2019;4(1):144–52. Doi: 10.1002/epi4.12306
7. Klein M, Engelberts NHJ, van der Ploeg HM, Kasteleijn-Nolst Trenité DGA, Aaronson NK, Taphoorn MJB, et al. Epilepsy in low-grade gliomas: The impact on cognitive function and quality of life. Annals of Neurology. 2003;54(4):514–20. DOI: 10.1002/ana.10712
8. Luyken C, Blümcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, et al. The Spectrum of Long-term Epilepsy-associated Tumors: Long-term Seizure and Tumor Outcome and Neurosurgical Aspects. Epilepsia. 2003;44(6):822–30. DOI: 10.1046/j.1528-1157.2003.56102.x
9. Wetjen NM, Cascino GD. Resective surgery of neoplasms. 2015 Oct 2;842–57.
10. Hughlings-Jackson J. Localised convulsions from tumour of the brain. Brain. 1882;5(3):364–74. DOI: 10.1093/brain/awr241
11. Ketz E. Brain tumours and epilepsy. In: Vinken PJ, Bruyn GW editor(s). Handbook of Clinical Neurology. Vol. 16, Amsterdam: North-Holland Publishing Company, 1974:254-69.
12. Penfield W. Relation of intracranial tumors and

symptomatic epilepsy. Archives of neurology and psychiatry. 1940;44(2):300.
DOI: 10.1001/archneurpsyc.1940.02280080060002

13. Echlin FA, Peck D, Schmer C, Brown LM. The supersensitivity of chronically "isolated" cerebral cortex as a mechanism in focal epilepsy. Electroencephalography and Clinical Neurophysiology. 1959;11(4):697–722. DOI: 10.1016/0013-4694(59)90110-5.
14. You G, Sha ZY, Yan W, Zhang W, Wang YZ, Li SW, et al. Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. Neuro-Oncology. 2011;14(2):230–41. Doi: 10.1093/NEUONC/NOR205
15. Berg AT. Understanding the delay before epilepsy surgery: who develops intractable focal epilepsy and when?. CNS spectrums. 2004;9(2):136-44. DOI: 10.1017/S109285290000849X
16. Benbadis S, Heriaud L, Tatum W, Vale F. Epilepsy surgery, delays and referral patterns—are all your epilepsy patients controlled? Seizure. 2003;12(3):167-170. DOI: 10.1016/S1059-1311(02)00320-5.
17. Heiland DH, Staszewski O, Hirsch M, Masalha W, Franco P, Grauvogel J, Capper D, Schrimpf D, Urbach H, Weyerbrock A. Malignant Transformation of a Dysembryoplastic Neuroepithelial Tumor (DNET) Characterized by Genome-Wide Methylation Analysis. J Neuropathol Exp Neurol. 2016 Apr;75(4):358-65. DOI: 10.1093/jnen/nlw007. Epub 2016 Feb 27. PMID: 26921879.
18. Nakasu S, Nakasu Y. Malignant Progression of Diffuse Low-grade Gliomas: A Systematic Review and Meta-analysis on Incidence and Related Factors. Neurol Med Chir (Tokyo). 2022;62(4):177-185. DOI: 10.2176/jns-nmc.2021-0313. Epub 2022 Feb 22. PMID: 35197400; PMCID: PMC9093671.
19. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;2;23(8):1231-1251. DOI: 10.1093/neuonc/noab106. PMID: 34185076; PMCID: PMC8328013.
20. Meguins LC, Adry RA, Silva Júnior SC, Pereira CU, Oliveira JG, Morais DF, Araújo Filho GM, Marques LH. Gross-total resection of temporal low grade gliomas is a critically important factor in achieving seizure-freedom. Arq Neuropsiquiatr. 2015 Nov;73(11):924-8. DOI: 10.1590/0004-282X20150141. Epub 2015 Oct 6. PMID: 26517215.
21. Kurzwelly D, Herrlinger U, Simon M. Seizures in patients with low-grade gliomas--incidence, pathogenesis, surgical management, and pharmacotherapy. Adv Tech Stand Neurosurg. 2010;35:81-111. DOI: 10.1007/978-3-211-99481-8_4. PMID: 20102112.

Additional Information

Disclosures: Authors report no conflict of interest.
Ethical Review Board Approval: The study conformed to the ethical review board requirements.
Human Subjects: Waiver of Consent was obtained from the ethical review board.
Conflicts of Interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:
Financial Relationships: All authors declare that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Funding: N/A.
Data Availability: Data will be made available upon an adequate request by the principal author IT (dr.trifonov@mail.ru)
Other Relationships: All authors declare that there are no other relationships or activities that could appear to have influenced the submitted work

AUTHORS CONTRIBUTION

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Oleg Levchenko	1. Editing and quality insurer
2.	Igor Trifonov	2. Study design and methodology, paper writing, data collection and calculations, analysis of data and interpretation of results
3.	Mikhail Sinkin	3. Data collection and calculations
4.	Ayna Shakhmanayeva	4. Analysis of data and interpretation of results
5.	Anastasia Skalnaya	5. Literature review and referencing