Outcomes with acyclovir treatment in herpes simplex encephalitis after surgery for solid CNS tumors: a case report and systematic review of the literature

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Abstract

Background. Herpes simplex encephalitis (HSE) occurring within 30 days after neurosurgery for solid CNS tumors is underrecognized and underreported but remains important because of high morbidity and mortality. We present the case of a 41-year-old woman who had HSE after craniopharyngioma surgery, and delayed recognition and treatment led to a poor outcome. Subsequently, we review reported HSE cases after neurosurgery for solid CNS tumors and describe outcomes after treatment with and without acyclovir.

Methods. A literature search was performed for cases meeting the above criteria. Information was gathered regarding patient demographics, tumor types, symptoms, diagnostic workup, therapy, and outcomes.

Results. Eighteen cases were studied. Encephalopathy, fever, and seizures were the most common symptoms. A majority of patients (78%) received IV acyclovir, with a 79% survival rate with treatment. Mortality rate was 100% in untreated cases. The median time to starting acyclovir was 17 postoperative days (range, 8–53 days). Most patients received steroids, but its use was not associated with a specific outcome.

Conclusions. HSE may develop following neurosurgical resection, and the threshold for suspicion of this condition should be extremely low in a patient who shows compatible symptoms (encephalopathy, fever, or seizures) or does not recover as planned. Moreover, in case of suspicion of HSE, acyclovir should be promptly started until infection can be definitely ruled out. A delay in diagnosis of HSE and failure to treat may result in severe morbidity as well as mortality. This observation may warrant further study.

Keywords

acyclovir | central nervous system tumors | herpes simplex encephalitis | neurosurgery | postoperative

Viral encephalitis is frequently characterized by fever, changes in mentation, seizures and, in many cases, focal neurologic deficits.¹ Between 2000 and 2010, herpes simplex encephalitis (HSE) was the most common cause of encephalitis identified in a survey of hospitalized patients in the United States.² Mortality can be as high as 70% in untreated cases compared with 30% with adequate treatment, and even in treated cases

neurological sequelae are frequent.^{3,4} The use of antiviral medications can improve the outcome and decrease morbidity and mortality.

When there is suspicion of HSE, important workup includes routine serum studies as well as serum cultures and serology to check for coexisting infections (eg, bacterial infections, HIV, Epstein-Barr virus), lumbar puncture with PCR testing for

HSV-1 and 2 DNA (sensitivity >95% and specificity >99%),³ as well as routine cell count, glucose, and protein, MRI brain, and an EEG, which may show a characteristic pattern of lateralized periodic discharges (Supplemental Fig. 2).

HSE has been reported previously after neurosurgery for various conditions, such as epilepsy^{5,6} or trigeminal nerve decompression.⁷ It has also been reported after cranial radiation therapy for brain tumors.⁸ HSE occurring after surgery for CNS tumors has been reported rarely, and is likely more common than previously thought. Recognition of postoperative HSE can be challenging since the symptoms (eg, encephalopathy, fever, and seizures) are nonspecific and can be attributed to other postoperative complications such as aseptic meningitis, or in the case of craniopharyngioma or pituitary surgery, metabolic imbalance from diabetes insipidus. Imaging interpretation can be complicated by the presence of edema and postsurgical changes. Typical MRI findings in HSE include prolongation of T2 signal and reduced diffusion-weighted imaging signal in the temporal lobes and insulas, as well as fluid-attenuated inversion recovery signal change in those sites.⁹

In this work, we first present the case of a 41-year-old woman who had surgery for a craniopharyngioma and was diagnosed with HSE postoperatively, and then review reported postneurosurgical HSE in cases of solid tumors of the CNS, the most common symptoms to look for, and their outcome after treatment with acyclovir. Acyclovir inhibits the HSV-specific DNA polymerase, so is active only in HSV-infected cells. Normal cells lack the HSV-specific thymidine kinase enzyme, making this drug selective to affected cells and nontoxic to healthy cells.¹⁰ The recommended treatment is IV acyclovir 10 mg/kg every 8 hours for 21 days. There have been case reports of acute kidney injury precipitated by acyclovir,^{11,12} though a prospective cohort study of 276 patients showed acyclovir-induced nephrotoxicity in only 5% to 10% of cases, all of which were reversible with IV hydration, dose reduction, or discontinuation of the drug.¹³ The use of antivirals may reduce morbidity and mortality of HSE, whether it occurs by latent reactivation or primary infection³; and given the life-threatening nature of HSE, the benefits of treatment may outweigh the risk of untreated disease or potential nephrotoxicity of acyclovir, which could be avoided by adequate hydration and renally adjusting the dose.

Case

Our patient is a 40-year-old right-handed woman without any known past medical history who presented to an outside hospital following a motor vehicle accident. A non-contrast CT scan of the head revealed a large suprasellar tumor. MRI of the brain suggested the diagnosis of a craniopharyngioma with a maximum dimension of 3.2 cm (Fig. 1A). Approximately 1 month later, repeat imaging showed enlargement of the mass (Fig. 1B), and she underwent an elective open biopsy at an outside hospital. Nondiagnostic tissue was obtained. An elective stereotactic biopsy was performed approximately 2 months later, at which time the tumor showed further enlargement (Fig. 1C). She subsequently developed hydrocephalus along

Fig. 1 MRI Evaluation of Third Ventricular Tumor. A, Sagittal T1-weighted MRI at the time of initial presentation shows an approximately 3-cm contrast-enhancing mass in the third ventricle and suprasellar cistern. B, Follow-up imaging (T1-weighted with gadolinium) approximately 3 months later shows a significant increase in the size of the tumor to approximately 4 cm in maximal dimension. C, Axial T1-weighted MRI with gadolinium enhancement just prior to resection shows further increase in the size of the tumor as well as development of hydrocephalus. D, Immediate postoperative T1-weighted MRI with gadolinium contrast shows gross total resection of the tumor via an interhemispheric transcallosal approach.

with lethargy, confusion, and short-term memory dysfunction. Tissue from this biopsy confirmed the diagnosis of craniopharyngioma. She was transferred to our institution for further management.

After preoperative evaluation, which revealed central hypothyroidism, central hypogonadism, and impaired vision, the patient was brought to the operating room for resection of the tumor via a right-sided interhemispheric, transcallosal approach with frameless stereotactic guidance. Postoperative imaging revealed gross total resection of the tumor (Fig. 1D). The pathology confirmed adamantinomatous craniopharyngioma (Supplemental Fig. 1, A and B). Immediately postoperatively, the patient was lethargic but following commands. Neurologically, she progressed slower than expected following surgery, and she was not able to feed herself or participate in physical therapy. Hydrocephalus was diagnosed and treated with an external ventricular drain, which was converted to a ventriculoperitoneal (VP) shunt. She subsequently developed generalized tonic-clonic seizures with left hemiparesis and was treated with an antiepileptic drug. EEG showed evidence of epileptiform activity and lateralized periodic discharges in the right hemisphere (Supplemental Fig. 2) despite increasing doses of anticonvulsants. Her VP shunt was externalized and eventually revised to a ventriculoatrial shunt. Following placement of the shunt, imaging indicated resolution of hydrocephalus with evidence of bihemispheric injury

Table 1 List of Patient Cases Included in This Work With Present Case at the Bottom

Case Source, First Author, Year	Patient Age	Sex	Prior history of HSV?	Tumor	Location	Symptom Onset (POD)	Fever?	Seizure?	Encephalopathy?	Diagnosis by?	HSV type	Acyclovir?	If yes, started on POD	Steroids?	Outcome
Aldea, 2003 ¹⁴	28	M	Yes	Glioma	Right brain	7	Yes	Yes	Yes	PCR	1	Yes	9	No	Recovery
Berger, 2016 ¹⁵	70	F	Yes	Meningioma	Left brain	12	Yes	No	Yes	PCR	2	Yes	22	No	Recovery
Fearnside, 1972 ¹⁶	11	M	No	Pituitary adenoma	Midline	8	Yes	Yes	Yes	Path	U	No	-	Yes	Death
Fearnside, 1972 ¹⁶	41	M	No	Pituitary adenoma	Midline	4	Yes	Yes	Yes	Path	U	No	-	Yes	Death
Filipo, 2005 ¹⁷	33	M	U	Schwannoma	Right brain	10	No	No	Yes	PCR	1	Yes	11	Yes	Recovery
Ihekwa, 2009 ¹⁸	35	F	U	Syringomyelia	Spinal cord	21	Yes	No	No	PCR	2	Yes	21	Yes	Recovery
Jaques, 2016 ³	24	M	U	Epidermoid cyst	Right brain	8	Yes	No	Yes	PCR	1	Yes	11	Yes	Neurologic sequelae
Jaques, 2016 ³	53	M	U	Craniopharyngioma	Right brain	18	Yes	No	Yes	PCR	2	Yes	19	Yes	Recovery
Jalloh, 2009 ¹⁹	44	M	Yes	Schwannoma	Left brain	1	Yes	Yes	Yes	PCR	1	Yes	11	No	Recovery
Kuhnt, 2012 ²⁰	40	M	U	Pituitary adenoma	Midline	4	No	Yes	Yes	PCR	1	Yes	20	Yes	Death
Kuhnt, 2012 ²⁰	46	F	U	Meningioma	Midline	7	Yes	Yes	Yes	PCR	1	Yes	12	Yes	Death
Kwon, 2008 ²¹	13	F	U	Craniopharyngioma	Midline	15	Yes	No	Yes	PCR	U	Yes	22	Yes	Neurologic sequelae
Ploner, 2005 ²²	47	F	U	Meningioma	Right brain	10	Yes	No	Yes	PCR	U	Yes	13	Yes	Neurologic sequelae
Raper, 2011 ⁹	65	F	U	Ependymoma	Spinal cord	5	Yes	No	Yes	PCR	1	Yes	8	Yes	Neurologic sequelae
Schiff, 1998 ²³	35	F	U	B cell lymphoma	Left brain	30	Yes	Yes	Yes	Path	1	Yes	34	Yes	Death
Sheleg, 2001 ²⁴	28	F	U	Glioma	Right brain	1.5	No	No	Yes	PCR	1	No	-	Yes	Death
Spuler, 1999 ²⁵	78	F	No	Meningioma	Left brain	10	Yes	Yes	Yes	PCR	1	No	-	Yes	Death
Present case	41	F	U	Craniopharyngioma	Midline	1	Yes	Yes	Yes	PCR	2	Yes	53	Yes	Neurologic sequelae

Abbreviations: F, female; M, male; Path, pathology; PCR, polymerase chain reaction; POD, postoperative day; U, unknown.

Table 2. Characteristics of All Patients and Distribution of Outcomes (n = 18)

Characteristic	Survival ^a	Death
No. of patients	11	7
Age ^b in years	41 (28-53)	40 (28-46)
Male, n (%)	5 (45.45)	3 (42.86)
Time to onset ^b in days	10 (5-15)	7 (4-10)
Fever, n (%)	10 (90.91)	5 (71.43)
Seizure, n (%)	3 (27.27)	6 (85.71)
Encephalopathy, n (%)	10 (90.91)	7 (100.00)
Steroids, n (%)	8 (72.73)	7 (100.00)

^aRecovery + neurologic sequelae.^bMedian (interquartile range).

(Supplemental Fig. 3D). However, these interventions did not improve her neurological condition and she became progressively obtunded with bilateral upper and lower extremity weakness. She required mechanical ventilatory support and was transferred to the medical intensive care unit where she had intermittent fever spikes up to 102°F (38.9°C). Cerebrospinal fluid (CSF) was analyzed for bacterial and fungal infection and returned negative. CSF was also sent for HSV polymerase chain reaction (PCR), which was positive for HSV-2 in 2 separate samples and treatment with acyclovir was initiated on postoperative day 53. Repeat MRI brain showed diffuse leptomeningeal enhancement, particularly in the right frontal lobe (Supplemental Fig. 3, A-C). At the time of ventriculoatrial shunt placement, a tissue biopsy from the right occipital lobe was taken, which confirmed the diagnosis of HSV-2 encephalitis (Supplemental Fig. 1, C and D). A 3-week course of acyclovir was completed without any significant neurological improvement. During the course of her hospitalization, she also received hydrocortisone and prednisone. She remained in a minimally conscious state, and at the request of the family she was discharged to a nursing facility and subsequently lost to follow-up.

In the literature (via PubMed, Google Scholar, ScienceDirect, and Ovid, using the keywords above without limitation on date or language), we found 17 other cases of HSE occurring within 30 days after neurosurgery for solid CNS tumors from 1972 to 2016. Encephalopathy, fever, and seizures were the most common symptoms. A majority of patients (78%) received IV acyclovir, with a 79% survival rate with treatment. Mortality rate was 100% in untreated cases. The median time to starting acyclovir was 17 postoperative days (range, 8-53 days). Table 1 lists the sources and details about each case, Table 2 summarizes the clinical characteristics, and Table 3 displays the outcomes with acyclovir. The results are discussed further below.

Discussion

The proposed mechanisms of postoperative HSE have been discussed elsewhere and are thought to be a primary

Table 3. Comparison of Overall Outcomes (All Patients) and Outcomes With Acyclovir

Group	Survival ^a	Recovery	Neurologic Sequelae	Death
All (n = 18)	11 (61%)	6 (33%)	5 (28%)	7 (39%)
Acyclovir (n = 14)	11 (79%)	6 (43%)	5 (36%)	3 (21%)

^aRecovery + neurologic sequelae.

infection or reactivation of latent virus in the body. The stress and trauma of neurosurgery and immunosuppression (for example, due to corticosteroids) have been implicated as possibilities.^{3,9} The number of reported HSE cases after neurosurgery for solid CNS tumors in our literature search was lower than HSE cases reported in other conditions, perhaps since many cases may not be recognized because of the nonspecific symptoms of encephalopathy, fever, and seizures. Adverse outcomes can sometimes be attributed to other causes.

Table 1 shows 18 cases reported in the literature from 1972 to 2016 (including the present case) of patients who developed HSE within 30 days after undergoing neurosurgery for solid tumors in the CNS.^{3,9,14-25} and Table 2 summarizes the demographics, clinical characteristics, and outcomes. As shown in Table 3, the majority (14/18, 78%) of the patients received acyclovir. Survival (the proportion of patients with recovery plus those with neurologic sequelae) in all patients was 61%, compared with 79% in those who received acyclovir (see Table 3). It should be noted that 2 of the cases were reported in 1972, before the drug was available.¹⁶ Nearly half (43%) of patients who received acyclovir achieved a full recovery. As shown by the data, morbidity and mortality in HSE are very high when treatment is delayed or not available.^{16,20,23-25} In case of suspicion of HSE, acyclovir should be promptly started until infection can be definitely ruled out.

In this review, corticosteroids did not seem to have any correlation with patient outcomes. Literature review found that a delay in recognition and treatment may result in severe morbidity: Nephrotoxicity developed in only 5% to 10% of the cases in a prospective cohort of 276 patients.¹³ In conclusion, HSE may develop following neurosurgical resection and the threshold for suspicion of HSE should be extremely low in a patient who shows compatible symptoms (encephalopathy, fever, and seizures) or does not recover as planned. Moreover, in case of suspicion of HSE, acyclovir should be promptly started until infection can be definitely ruled out. A guideline for workup of these patients has been provided in the introduction. Further research with prospective trials and larger number of patients may be warranted.

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Conflict of interest statement. None declared.

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