Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: **James I. Ausman**, MD, PhD University of California, Los Angeles, CA, USA

Case Report

Herpes simplex reactivation or postinfectious inflammatory response after epilepsy surgery: Case report and review of the literature

Anna Lo Presti, Alexander G. Weil, Toba N. Niazi, Sanjiv Bhatia

Division of Pediatric Neurosurgery, Department of Neurosurgery, Miami Children's Hospital, Miami, FL, USA

E-mail: Anna Lo Presti - annaloprestivega@gmail.com; Alexander Gregory Weil - alexandergweil@gmail.com; Toba Nyra Niazi - toba.niazi@mch.com; *Sanjiv Bhatia - sbhatia@med.miami.edu

*Corresponding author

Received: 21 June 14 Accepted: 09 December 14 Published: 25 March 15

This article may be cited as:
Lo Presti A, Weil AG, Niazi TN, Bhatia S. Herpes simplex reactivation or postinfectious inflammatory response after epilepsy surgery: Case report and review of the literature. Surg Neurol Int 2015;6:47.

Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2015/6/1/47/153882

Abstract

Background: Herpes simplex virus encephalitis (HSVE) is the most morbid clinical syndrome associated with the human herpes virus. Despite treatment with appropriate dosages of acyclovir, neurologic relapse of HSV infection have been reported after cranial surgery. Rarely, neurological deterioration due to postinfectious inflammatory response without demonstrable HSV reactivation may recur following cranial surgery.

Case Description: We report a case of a 17-year-old girl who presented with a HSVE relapse on the 6th postoperative day following resective surgery for medically refractory epilepsy and review the literature. Postinfectious inflammatory reaction may be the underlying mechanism in cases with no HSV identified on cerebrospinal fluid (CSF) or brain polymerase chain reaction (PCR), such as in the current case.

Conclusion: HSVE must be suspected in patients with previous history of HSVE and postoperative fever associated with an altered state of consciousness and/or seizures. Considering the high mortality and morbidity rates associated with HSVE, an adequate prophylactic administration of acyclovir should be considered for patients with previous history of HSVE undergoing neurosurgical procedures, especially when surgery involves the site of a previous herpetic lesion.

Key Words: Cranial surgery, herpes simplex virus encephalitis relapse, postinfectious inflammatory reaction, prophylaxis, reactivation

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.153882

Quick Response Code:

INTRODUCTION

Herpes simplex virus encephalitis (HSVE), mostly caused by herpes simplex virus type 1 (HSV-1), is the most morbid clinical syndrome associated with the human herpes virus. Mortality rates of this condition approach 19% in treated patients[1] and rise to 70% in untreated patients.[4,34,35] Despite treatment with appropriate dosages of acyclovir, neurologic relapse of HSVE has been reported frequently, especially in children, in whom relapse rate may approach 26%.[12,26,27] The mechanisms of these relapses remain unclear. Common hypotheses include reactivation of a latent herpes virus[12,36] and postinfectious immuno-inflammatory response.[5,16,18,25,26,28] Rarely, HSVE may occur following cranial surgery. A total of 10 adults[1,7,8,11,13,23-25,30,33] and 6 pediatric cases have

been reported in the literature.[3,7,10,15,19,21] We report a case of a 17-year-old girl who presented with presumed postinfectious immune-inflammatory relapse following resective surgery for medically refractory epilepsy, review the literature and provide recommendations for management.

CASE REPORT

History and examination

A 17-year-old immunocompetent girl presented to our service for pharmacoresistant epilepsy. She had a history of HSVE at the age of 6 when she presented with seizures. She was treated with a complete course of acyclovir. She underwent an uneventful recovery and returned to baseline and did not have seizure recurrence until 6 years later. At the age of 12 years, she developed intractable seizures consisting of staring, confusion, face droop, and flushing. Seizures persisted despite multiple antiepileptic drugs (AEDs) and she was brought in for evaluation. Preoperative magnetic resonance image (MRI) showed an area of encephalomalacia involving the anterior and mesial aspect of the right temporal lobe, right frontal operculum, and right insula [Figure 1], which correlates with concordant hypometabolism on F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET). Video electroencephalogram (VEEG) showed seizure onset originating predominantly from the right frontal lobe. Functional MRI showed left expressive and receptive language activation and bilateral primary visual cortex and supplementary motor area activation.

Operation

A right frontotemporal craniotomy was performed, followed by intraoperative recording using a strip over the temporal lobe, a grid over the frontal lobe, and a depth electrode, which was inserted in the insula under magnification. Intraoperative electrocorticography (ECoG) showed that the temporal lobe was extremely active and the frontal lobe also had frequent epileptic discharges. A tailored right temporal lobectomy, amygdalo-hippocampectomy and right frontal lobe disconnection were performed. No intraoperative steroids were used.

Postoperative course

Postoperative MRI showed expected postoperative changes with no complication [Figure 2]. The patient was discharged home 4 days after surgery, afebrile, with baseline exam and free of seizure on oxcarbamazepine, lamotrigine, and tapering doses of steroids.

On the 6th postoperative day (POD) she presented with two consecutive episodes of generalized tonic-clonic seizures and three episodes of mouth twitching with unresponsiveness, associated with postictal left facial weakness and fever. The computerized tomography (CT) of the brain performed at another medical center did not show significant findings. The following day, she was transferred to the pediatric intensive care unit of our center for further management. Physical examination revealed mild left facial palsy and fever. Rest of the neurological examination was otherwise unremarkable. There were no signs of wound infection. A new brain MRI confirmed no significant changes compared with prior postoperative MRI. There were no extra-axial collections suggestive of empyema. The patient continued with persistent fever and partial seizures involving the face despite AEDs that included her usual medication with the addition of clobazam, levetiracetam, phenytoin, benzodiazepine drip, and corticosteroids. The patient was placed on continuous VEEG and a lumbar puncture was performed. Cerebrospinal fluid (CSF) testing showed 2 white blood cells/ml (differential: 2 lymphocytes, 0 polymorph), 26.9 mg/dl of protein, normal glucose levels and a negative gram stain. CSF, blood, and urine samples were sent for culture (all were eventually negative) and empiric treatment with vancomycin and ceftazidime was started. On the 10th POD, the patient's condition gradually worsened. A repeat CSF study was normal but follow-up MRI showed extensive cytotoxic edema with restricted diffusion in the right fronto-orbital, insular, and posterior frontal cortex [Figure 3a and b]. The cause of the fever and seizures was unclear, but

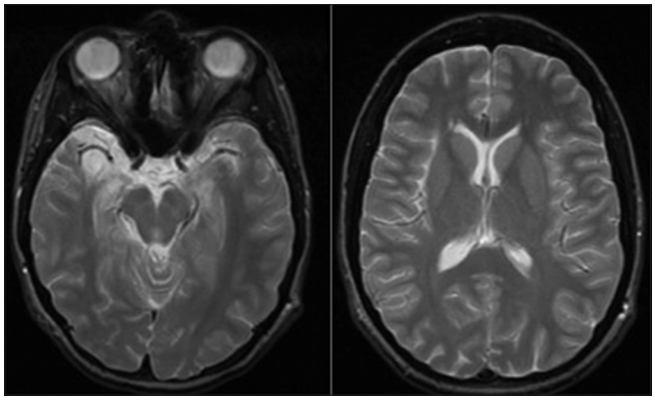

Figure 1: Preoperative axial T2WI MRI showing encephalomalacia involving the anterior and mesial aspect of the right temporal lobe, right frontal operculum, and right insula

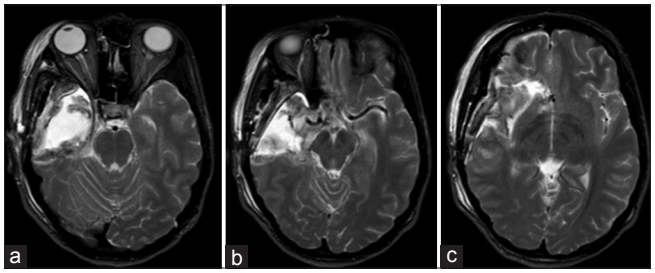

Figure 2: Immediate postoperative axial T2WI MRI revealing right temporal lobectomy, amygdalo-hippocampectomy and right frontal lobe disconnection with no evidence of complications

clinical suspicion of HSVE relapse was considered, especially in the setting of a prior history of HSVE and clinical evolution. On CSF analysis, HSV, CMV, EBV, HV 6-7-8 polymerase chain reaction (PCR) were negative and the viral and fungal CSF culture remained negative as well. Acyclovir treatment was started at 40 mg/kg/day. On the 12th POD, the patient became hemodynamically and respiratory unstable, requiring sedation, intubation, and ventilator support for 6 days. Thereafter, she had with progressive improvement of fever and seizures, but cognitive deterioration and new onset left hemiparesis persisted. Serial MRI showed progression of the signal changes revealing at the end extensive gray and white matter disease with patchy enhancement in both cerebral hemispheres, worse in the right side extending into the right basal ganglia, thalamus and pons [Figure 3c and d]. After antiviral therapy for 21 days the patient recovered enough to follow commands, however, aphasia, dysphagia and left upper weakness remained. MRI performed 1-month following surgery revealed persistent changes of the right hemisphere and left frontal lobe [Figure 4].

The final pathology report from surgical resection revealed encephalomalacia of cortex characterized by cystic degeneration/cavitation, astrocytic gliosis with gemistocytic astrocytes and perivascular lymphocytic monocyte cuffing. There were no viral inclusion bodies and *in situ* hybridization for HSV DNA was negative. These findings were consistent with chronic encephalitis [Figure 5].

At follow-up 1 year after surgery in an outpatient clinic, the patient is seizure-free. However, she has left hemiparesis, severe difficulty in swallowing requiring jejunostomy tube, dysphasia, and flat affect. She also has mild behavioral impairment and emotional lability manifested by fluctuations in level of cooperation from quiet and smiling to marked irritability.

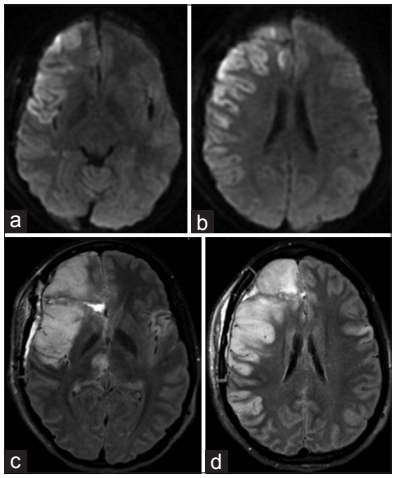

Figure 3: (a-b) Postoperative axial MRI on the 10th POD showing extensive cytotoxic edema with restricted diffusion in the right fronto-orbital, insular, and posterior frontal cortex. (c-d) Serial postoperative axial MRI showed extensive cytotoxic edema involving the right fronto-parietal-temporal and insular cortex, right thalamus, and left fronto-insular cortex

DISCUSSION

Six prior cases of postcraniotomy HSVE in children have been reported in the literature, of which four have occurred following resective surgery for medically refractory epilepsy and two followed tumor resection [Tables 1 and 2]. The diagnosis of HSVE relapse following cranial surgery relies on clinical, CSF, and radiological findings. Usually, a history of HSVE infection can be identified in the history. However, there are some reports that tiny amounts of HSV DNA can be detected in the brain of many adults without neurological disease,[6] which would explain why a relapse has been proposed, even without previous history of HSVE. The four patients who underwent epilepsy surgery presented with a previous history of HSVE, therefore in those cases HSVE was considered to be a relapse. Although the two patients operated for tumor resection did not have previous history of HSVE, a relapse secondary to virus reactivation was likely the cause. In all cases, symptoms appeared within 10 days of surgery. The most common presenting sign was fever, which was present in all of cases, followed by focal or generalized seizures, reported in three cases [Table 1].

CSF analysis reveals variable findings in cases of HSVE. Although CSF in HSVE usually has a raised white cell count with lymphocyte predominance and raised protein, findings can be variable and protein or white cell counts have been reported as normal. This supports the idea that CSF PCR testing should not be restricted to patients with abnormal basic CSF findings (glucose, cell count, protein level).[26] The sensitivity of CSF PCR for detecting HSV DNA is about 96%, and the specificity in experienced

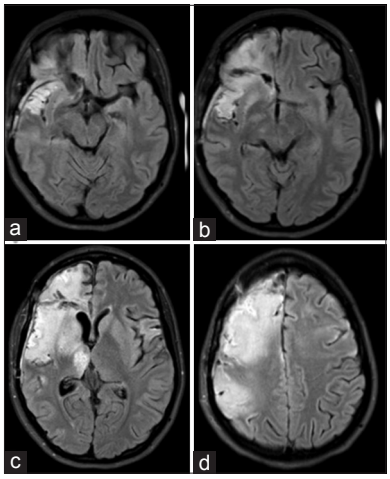

Figure 4: (a-d) Axial MRI performed 4 weeks after surgery revealing extensive gray and white matter disease with patchy enhancement in both cerebral hemispheres, worse in the right side, extending into the right basal ganglia, thalamus and pons

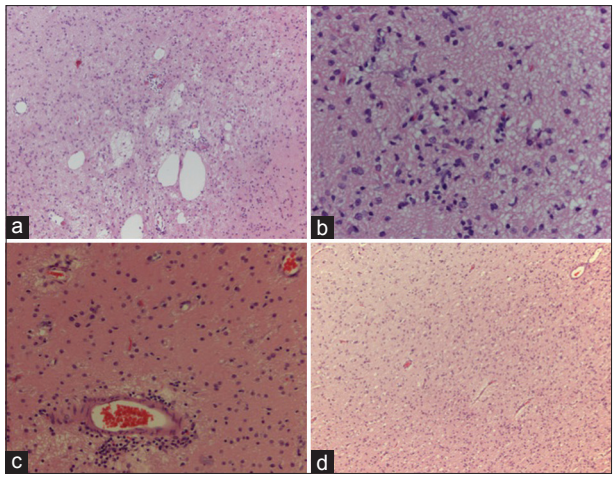

Figure 5: Pathology revealing encephalomalacia of cortex characterized by cystic degeneration/cavitation (a), astrocytic gliosis with microglial nodules (b), perivascular lymphocytic monocyte cuffing (c) and reactive gliosis (d). There are no viral inclusion bodies. There is pyramidal neuronal loss in hippocampus

laboratories is about 99%,[14,31] but in a significant number of relapse cases PCR can remain negative.[2,5,12,26,27,29,36] In our review, CSF PCR was positive for HSV-1 in the five patients where it was reported [Table 2].

Neuroimaging is of great diagnostic importance in cases of suspected HSVE, specially MRI [9]. At the early stages of HSVE, lesions result from damage to the blood–brain barrier with consequent cerebral edema, characterized by low signal changes on T1-weighted and increased signal on T2-weighted imaging. The typical pattern involves one or both temporal lobes and occasionally the insular cortex and the gyrus rectus of the frontal lobes, involvement of the pons has also been described.[20] The lesions evolve toward hemorrhagic and necrotic lesions.[17,32] Of the five reported cases of postcraniotomy HSVE in which MRI findings were reported, only one did not show changes on imaging. In the other four patients, MRI revealed new changes consisting in edema, diffusion restriction, and/or abnormal enhancement in one or both temporal and frontal lobes, the insular cortex, and the angular gyrus [Table 2].

Although the above-mentioned diagnostic tests all highly suggest postcraniotomy HSVE as the underlying process in our patient, other diagnoses must be considered in the setting of new onset neurological deterioration in association with persistent seizures and fever. Postoperative bacterial central nervous system (CNS) infection was considered, but laboratory test and images findings did not support that theory. In addition, the patient's condition worsened despite antibiotic treatment. The diffusion-weighted MRI changes may have been secondary to status epilepticus, however, this would not have explained the fever nor the radiological progression and persistence for months despite improvement of seizures. Although the lesions may theoretically have been caused by arterial ischemia, the presence of fever and the lesion location involving multiple vascular territories (right Middle Cerebral Artery, right Posterior Cerebral Artery, left Middle Cerebral Artery) render this unlikely. Finally, clinical presentation with rapid progression of fever, seizures and functional deterioration, the previous history of HSVE, the improvement following acyclovir therapy all support postcraniotomy HSVE diagnosis. In addition, thalamus involvement had been previously reported in HSVE.[22]

Regarding pathology findings in the brain tissue, microscope appearance of HSVE differs between the acute to chronic phase. In the acute phase, earliest lesions contain scanty parenchymal inflammation but at a more advanced stage lesions usually contain sheet of necrotic cells, foci of hemorrhage and an intense perivascular and interstitial infiltrate of lymphocytes and macrophages. Nuclear inclusions are sparse at this later stage and viral DNA can usually be detected in frozen or paraffin sections by *in situ* hybridization or PCR. In the chronic phase, the normal gray and white matter is replaced by cavitated glial scar tissue and occasional cluster of lymphocytes are still seen in the meninges and brain parenchyma.[6] Pathology reports from surgical epilepsy resection were presented in three of these HSVE relapse cases, and all of them showed characteristic findings consistent with previous viral infection. In one case, a postmortem examination was performed and findings were consistent with acute necrotizing encephalitis due to herpes virus [Table 2].

The pathogenic mechanisms underlying HSVE relapses in general include reactivation of a latent herpes virus and postinfectious immune inflammatory response. Reactivation from a herpes virus that has previously established latent infection within the CNS affected by herpes encephalitis is the most commonly proposed mechanism after surgery and this is supported by the detection of DNA HSV in CSF or in brain tissue, along with the appearance of a new typical herpetic cortical lesion.[5,12,16,26,29] On the other hand, postinfectious immune inflammatory process has been postulated in cases of relapse in which HSV DNA was undetected in the CSF by PCR or in brain tissue and diffuse white matter involvement or diffuse edema are present in MRI.[5,16,18,26] Choreoathetoid movements have also been reported, but its absence does not exclude a postinfectious immune inflammatory process.[4] In 2006, Sköldenberg *et al.*[27] proposed that in the absence of widespread focal damage caused by replication of the HSV, it seems possible that immunological cytotoxicity plays a major role in the pathogenic events occurring during encephalitic relapse. This interpretation was supported by the measurement of elevated CD8 levels

Table 1: Clinical data in children with herpes simplex virus encephalitis after brain surgery

Case no.	Ref no.	Age	Previous history of HSVE	Prophylactic acyclovir therapy after surgery	Type of surgery	Period to relapse after surgery	Clinical presentation
1	7	11 years	No	No	Bifrontal craniotomy and adenoma resection	8th POD	Fever, seizures
2	3	8 years	Yes (16 months)	No	Selective left amygdalo-hippocampectomy for MTS	6th POD	Fever, aphasia and drowsiness
3	19	13 years	No	No	Anterior interhemispheric and subfrontal approach for craniopharyngioma resection	<6th POD	Fever and drowsiness
4	10	23 months	Yes (7 months)	20 mg/kg every 8 hour	Right functional hemispherectomy for medically refractory epilepsy	1st POD	Fever and irritability
5	21	19 years	Yes (3 years)	No	Frontal topectomy for medically refractory epilepsy	10th POD	Fever, headache, seizures
6	15	11 years	Yes (5 years)	No	Left parietal corticectomy	5th PO	Fever, lethargy, seizures
7	Current case	17 years	Yes (6 years)	No	Temporal lobectomy+amygdala-hippocampectomy and right frontal lobe disconnection for medically refractory epilepsy	6th POD	Fever, seizures

POD: Postoperative day, HSVE: Herpes simplex virus encephalitis, MTS: Mesial temporal sclerosis

Table 2: Radiological and biological data in children with herpes simplex virus encephalitis after brain surgery

Case no.	Ref no.	HSV-1 CSF PCR	Pathology report from surgical resection	CSF WBC (% lymph)	CSF protein (mg/dl)	New radiological brain lesion	Suggested pathogenesis
1	7	Not available	Perivascular polymorphonuclear infiltrates and Intranuclear inclusion bodies (postmortem examination)	10 WBC/ml 6 lymph/ml (60%)	45	A carotid angiogram shows displacement of the right ACA to the left, suggesting an intracerebral lesion	Possible reactivation
2	3	Positive	Microglial nodules, and perivascular lymphocyte infiltrates	Pleocytosis 95% lymph	600	MRI: Edema in Left temporal lobe spreading toward the rest hemisphere involving cortical gyri and sulci	Reactivation
3	19	Positive	Not reported	5 WBC/ml 3 lymph/ml (60%)	113,9	MRI: Cerebral infarction on the left frontal lobe and insula	Possible reactivation
4*	10	Positive (8th POD)	Multiple remote infarctions and microglial nodules. Not viral inclusions	0	< 6	MRI: No new lesions	Reactivation
5*	21	Positive (2nd POD)	Not reported	10 WBC/ml 8% lymph	49	MRI: Multilobar infarctions in watershed distribution. In right occipital, temporal lobes, left frontal and bilateral parietal lobes	Reactivation
6	15	Positive	Microglial cell nodules Perivascular lymphocytic infiltrations	105 WBC/ml 99% lymph	90,01	MRI: Swelling and hyperintensity in the left temporoparietal region on T2-weighted images	Reactivation
7	Current case	Negative	Encephalomalacia of cortex (cystic degeneration/cavitation), astrocytic gliosis, perivascular lymphocytic monocyte cuffing. There are no viral inclusion bodies	2 WBC/ml 100% lymph	26,9	MRI: Diffusion restriction in the grey and white matter with patchy enhancement in both cerebral hemispheres, right basal ganglia, thalamus and pons	Postinfectious inflammatory response

Note: 4* By the time the PCR was positive, CSF showed 1050 WBC, 13% lymph, and 638 mg/dl of protein 5* By the time the PCR was positive , CSF showed 83% lymph and 108 mg/dl of protein, POD: Postoperative day, MRI: Magnetic resonance image, WBC: White blood cells, PCR: Polymerase chain reaction, CSF: Cerebrospinal fluid, HSV: Herpes simplex virus, ACA: Anterior cerebral artery

in CSF, which is a marker of activated T-cell mediated cytotoxicity. Increased CSF levels of soluble Fas, a proinflammatory molecule that is involved in regulation of apoptosis induced by Fas ligand, can also be detected in HSVE relapse further supporting this theory. Even though there is no demonstrable HSV-DNA in the CSF of our patient, there may well be local viral replication in the brain tissue in the absence of any leakage of virus into the CSF, responsible for the immunological events associated with the development of relapses. The clinical symptom complex following a recent craniotomy in the setting of a prior HSVE suggests consideration of this diagnosis. The six previous cases of postoperative HSVE, likely occurred from reactivation of a latent virus. Of these, five had documented HSV PCR and one showed acute HSVE on postmortem evaluation. In the current

case, the absence of HSV DNA isolated from the CSF and the extensive gray and white matter disease on MRI suggest a postinfectious immune inflammatory process as the pathogenetic mechanism involved in the relapse instead of actual viral reactivation. Despite the fact, our patient showed improvement of fever and seizures on treatment, she developed left hemiparesis, cognitive impairment, and radiological progression of lesions while on treatment with acyclovir and steroids. Some authors have suggested that the absence of efficacy of antiviral treatment in preventing or improving symptoms in cases of HSVE relapse support this immune mechanism as well.[4] However, there are some series that have reported relapses with negative HSV PCR and good outcome after acyclovir treatment.[5,12,26] Whether or not acyclovir and/or steroids are an effective treatment in this type of relapse remain unclear.

The specific stimuli responsible for triggering a HSVE relapse remain unclear. Associated factors include immunodeficiency states, trauma, bacterial infections, and radiation, but no clear evidence of surgery as trigger factor has been proved. In the current case, relapse could have been triggered by surgical manipulation of brain parenchyma at the previous site of herpes infection, as has been proposed in three of the prior postcraniotomy for epilepsy HSVE relapse cases. However, we have to keep in mind that these patients may have a temporary immunodeficiency as a result of surgical stress and corticosteroid administration, which could act as triggers as well.[28]

HSVE is a highly morbid condition. Of the six reported cases of postcraniotomy HSVE, two died and two remained with significant neurological deficits. The other two patients had good outcome with mild impairments. The patient with the most benign clinical evolution received prophylactic acyclovir therapy of 20 mg/kg/dose every 8 h starting the day of surgery. Based on the morbidity of HSVE reactivation, we have adopted this strategy of covering epilepsy surgery patients with a history of encephalitis with prophylactic perioperative acyclovir starting the day prior to surgery and continuing for 10 days.

CONCLUSION

HSVE in neurosurgical patients is a rare but potentially life-threatening complication that must be particularly suspected in patients with previous history of HSVE and unexplained postoperative fever associated with an altered state of consciousness and/or seizures. Whether or not prophylactic acyclovir therapy can avoid relapses or at least minimize the expression of the disease remains unclear. Based on this review and considering the high mortality and morbidity rates associated with HSVE, an adequate prophylactic administration of acyclovir should be considered for patients with previous history of HSVE undergoing neurosurgical procedures, especially when surgery involves the site of a previous herpetic infection.

REFERENCES

1. Aldea S, Joly LM, Roujeau T, Oswald AM, Devaux B. Postoperative herpes simplex virus encephalitis after neurosurgery: Case report and review of the literature. Clin Infect Dis 2003;36:96-9.
2. Barthez-Carpentier MA, Rozenberg F, Dussaix E, Lebon P, Goudeau A, Billard C, *et al*. Relapse of herpes simplex encephalitis. J Child Neurol 1995;10:363-8.
3. Bourgeois M, Vinikoff L, Lellouch-Tubiana A, Sainte-Rose C. Reactivation of herpes virus after surgery for epilepsy in a pediatric patient with mesial temporal sclerosis: Case report. Neurosurgery 1999;44:633-5.
4. De Tiège X, De Laet C, Mazoin N, Christophe C, Mewasingh LD, Wetzburger C, *et al*. Postinfectious immune-mediated encephalitis after pediatric herpes simplex encephalitis. Brain Dev 2005;27:304-7.
5. De Tiège X, Rozenberg F, Burlot K, Gaudelus J, Ponsot G, Héron B. Herpes simplex encephalitis diagnostic problems and late relapse. Dev Med Child Neurol 2006; 48:60-3.
6. Ellison D, Love S, Chimelli L, Harding B, Lowe J, Vinters H, *et al*. Neuropathology. A Reference Text of CNS Pathology. 3rd ed. Philadelphia: Elsevier – Mosby; 2013. p. 308-12.
7. Fearnside MR, Grant JM. Acute necrotizing encephalitis complicating bifrontal craniotomy and pituitary curettage. Report of two cases. J Neurosurg 1972;36:499-502.
8. Filipo R, Attanasio G, De Seta E, Viccaro M. Post-operative Herpes simplex virus encephalitis after surgical resection of acoustic neuroma:A case report. J Laryngol Otol 2005;119:558-60.
9. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, *et al*. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. Lancet Infect Dis 2010;10:835-44.
10. Gong T, Bingaman W, Danziger-Isakov L, Tuxhorn I, Goldfarb J. Herpes simplex virus reactivation after subtotal hemispherectomy in a pediatric patient. Pediatr Infect Dis J 2010;29:1148-50.
11. Ihekwaba UK, Battersby RD. Type 2 herpes simplex reactivation after craniocervical decompression for hind brain hernia and associated syrinx. Br J Neurosurg 2009;23:326-8.
12. Ito Y, Kimura H, Yabuta Y, Ando Y, Murakami T, Shiomi M, *et al*. Exacerbation of herpes simplex encephalitis after successful treatment with acyclovir. Clin Infect Dis 2000;30:185-7.
13. Jalloh I, Guilfoyle MR, Lloyd SK, Macfarlane R, Smith C. Reactivation and centripetal spread of herpes simplex virus complicating acoustic neuroma resection. Surg Neurol 2009;72:502-4.
14. Kennedy PG, Steiner I. Recent issues in herpes simplex encephalitis. J Neurovirol 2013;19:346-50.
15. Kim SH, Lee SG, Kim SH, Kim DS, Kim HD. Relapsed herpes simplex virus encephalitis after epilepsy surgery. J Epilepsy Res 2013;3:28-31.
16. Kimura H, Aso K, Kuzushima K, Hanada N, Shibata M, Morishima T. Relapse of herpes simplex encephalitis in children. Pediatrics 1992;89:891-4.
17. Koelfen W, Freund M, Gückel F, Rohr H, Schultze C. MRI of encephalitis in children comparison of CT and MRI in the acute stage with long-term follow-up. Neuroradiology 1996;34:490-3.
18. Koenig H, Rabinowitz SG, Day E, Miller V. Post-infectious encephalomyelitis after successful treatment of herpes simplex encephalitis with adenine arabinoside: Ultrastructural observations. N Engl J Med 1979;300:1089-93.
19. Kwon JW, Cho BK, Kim EC, Wang KC, Kim SK. Herpes simplex encephalitis after craniopharyngioma surgery. Case report. J Neurosurg Pediatr 2008;2:355-8.
20. Livorsi D, Anderson E, Qureshi S, Howard M, Wang YF, Franco-Paredes C. Brainstem encephalitis an unusual presentation of herpes simplex virus infection. J Neurol 2010;257:1432-7.
21. Lund M. Herpes simplex virus reactivation and encephalitis after topectomy. J Pediatr Health Care 2011;25:323-7.
22. Navin P, Delanty N, Brennan P, Looby S. Herpes simplex virus encephalitis involving the right thalamus. BMJ Case Rep 2013 [In Press].

23. Perry JD, Girkin CA, Miller NR, Kerr DA. Herpes simplex encephalitis and bilateral acute retinal necrosis syndrome after craniotomy. Am J Ophthalmol 1998;126:456-60.
24. Ploner M, Turowski B, Wöbker G. Herpes encephalitis after meningioma resection. Neurology 2005;65:1674-5.
25. Prim N, Benito N, Montes G, Pomar V, Molet J, Rabella N. Human herpesvirus 1 meningoencephalitis after trigeminal neuralgia surgery. J Infect 2013;67:79-81.
26. Schleede L, Bueter W, Baumgartner-Sigl S, Opladen T, Weigt-Usinger K, Stephan S, *et al*. Pediatric herpes simplex virus encephalitis: A retrospective multicenter experience. J Child Neurol 2013;28:321-31.
27. Sköldenberg B, Aurelius E, Hjalmarsson A, Sabri F, Forsgren M, Andersson B, *et al*. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. J Neurol 2006;253:163-70.
28. Spacca B, Mallucci C, Riordan A, Appleton R, Thorp N, Pizer B. HSV encephalitis in a child with brain stem glioma: A rare complication of therapy Case report and review of the neurosurgical literature. Childs Nerv Syst 2007;23:1347-50.
29. Spiegel R, Miron D, Yodko H, Lumelsky D, Habib A, Horovitz Y. Late relapse of herpes simplex virus encephalitis in a child due to reactivation of latent virus: Clinicopathological report and review. J Child Neurol 2008;23:344-8.
30. Spuler A, Blaszyk H, Parisi JE, Davis DH. Herpes simplex encephalitis after brain surgery: Case report and review of the literature. J Neurol Neurosurg Psychiatry 1999;67:239-42.
31. Steiner I, Schmutzhard E, Sellner J, Chaudhuri A, Kennedy PG, European Federation of Neurological Sciences, European Neurologic Society. EFNS-ENS guidelines for the use of PCR technology for the diagnosis of infections of the nervous system. Eur J Neurol 2012;19:1278-91.
32. Tyler LK. Herpes simplex virus infections of the central nervous system: Encephalitis and meningitis, including Mollaret's. Herpes 2004;11 Suppl 2:57-64A.
33. Uda T, Koide R, Ito H, Hosono A, Sunaga S, Morino M. Relapse of herpes simplex virus encephalitis after surgical treatment for temporal lobe epilepsy: Rare complication of epilepsy surgery. J Neurol 2013;260:318-20.
34. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, *et al*. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med 1986;314:144-9.
35. Whitley RJ. Viral encephalitis. N Engl J Med 1990;323:242-350.
36. Yamada S, Kameyama T, Nagaya S, Hashizume Y, Yoshida M. Relapsing herpes simplex encephalitis: Pathological confirmation of viral reactivation. J Neurol Neurosurg Psychiatry 2003;74:262-4.