SHORT REPORT

Herpes simplex encephalitis after brain surgery: case report and review of the literature

Andreas Spuler, Hagen Blaszyk, Joseph E Parisi, Dudley H Davis

Abstract

Intracranial infection after neurosurgical intervention most often is caused by bacteria. A rare case of fatal herpes simplex encephalitis after removal of a meningioma is described and similar cases reported in the literature are reviewed. Recent diagnostic tools, including detection of herpes viral DNA sequences by polymerase chain reaction, complement clinical suspicion and facilitate mandatory early diagnosis, because herpes encephalitis, without rapid initiation of treatment, may lead to severe disability or death.

(J Neurol Neurosurg Psychiatry 1999;67:239–242)

Keywords: herpes simplex virus; encephalitis; brain surgery

Herpes simplex encephalitis has an estimated annual incidence of 1 to 4 per million population and is the most common viral encephalitis in immunocompetent patients.1–3 It is thought to result from centripetal spread of reactivated virus from cranial nerve ganglia to the brain.4–9 This poorly understood mechanism may be facilitated by certain stress factors, trauma, and immunosuppression.10–13 Herpes simplex encephalitis responds to early, aggressive antiviral therapy, unlike most viral encephalitides, whereas untreated herpes simplex encephalitis is usually fatal.14–15 Rapid reliable diagnostic techniques, such as polymerase chain reaction amplification of herpes simplex virus (HSV) DNA sequences from CSF therefore are mandatory.16–18 In current neurosurgical practice, serious intracranial infection after surgery is rare and almost exclusively caused by iatrogenic bacterial species. We describe the unusual occurrence of herpes encephalitis after uncomplicated removal of a convexity meningioma.

Case report

CLINICAL COURSE

Three months before admission, this previously healthy 78 year old woman developed headaches, moderate cognitive deficits, and a mild right hemiparesis. Brain MRI showed a left parasagittal meningioma in the premotor area. The patient underwent uneventful tumour resection. Postoperatively, all neurological deficits improved markedly. She was discharged after completion of a 4 day course of tapering dexamethasone (4 mg four times on the day of surgery; 3 mg, 2 mg, and 1 mg four times daily on the first, second, and third postoperative day, respectively). Ten days after surgery, she acutely developed difficulties talking and counting while playing cards, followed by several focal motor seizures involving first the right face and later the arm and leg. Postictally, she was aphasic and hemiparetic on the right. She was febrile (38.3°C) and had a neutrophilic leukocytosis (19×10³ cells/l). On arrival at our institution 1 day later, she was somnolent, dysphasic, and hemiparetic. Several right sided motor seizures were seen. Obtundation prompted intubation. Despite high serum concentrations of phenytoin, twitching of the right face and hand continued. Over the next week, she remained febrile (up to 40.2°C) with slow fluctuations in temperature. On admission, brain CT showed slight contrast enhancement at the operative site and unremarkable temporal lobes. Video EEG monitoring recorded continuous 2–3 Hz spike and wave background activity over the left hemisphere, especially in the posterotemporal region. Lumbar puncture disclosed a mild CSF pleocytosis (89 cells/ml, 70% neutrophils, 26% monocytes) with normal glucose and protein. All initial bacteriological and serological CSF studies, including a polymerase chain reaction for HSV DNA, were negative. On the next day, the EEG pattern evolved into left sided periodic lateralised epileptiform discharges (PLEDs) and subsequently bilateral independent PLEDs were recorded. Initial MRI disclosed cortical signal alterations, best seen on the FLAIR sequences, involving the left frontal and insular cortices and hippocampus. Brain MRI on the fourth hospital day showed hyperintense and broadened cortical bands, consistent with a progressively swollen and oedematous cortical mantle throughout the left hemisphere. These findings were most striking in the immediate perioperative zone. Signal abnormalities of intermediate intensity were found in the hippocampus, medial thalamus, and occipital and lateral parietal neocortex, and they were least pronounced in the remainder of the left hemispheric neocortex as well as the cortex in the parasagittal right frontal lobe and anterior cingulate gyrus (figure A). Based on these stud-
ies, the possibility of an infectious cerebritis was raised. Repeat lumbar puncture showed slight pleocytosis (38 cells/ml, 50% monocytes, 35% lymphocytes) with mildly increased protein (94 mg/dl) and now yielded a positive HSV polymerase chain reaction, and the diagnosis of herpes simplex encephalitis was made. DNA sequencing disclosed HSV type 1. After the diagnosis, therapeutic options and likely outcomes were discussed with the family. Because of the patient’s advanced age and the imaging evidence of significant parenchymal injury to the dominant hemisphere, the decision was made not to aggressively treat the patient with antiviral medications. The patient remained on comfort care only, never regained consciousness, and died 9 days after the onset of symptoms.

**NECROPSY STUDIES**

A complete necropsy study was performed. At necropsy, HSV was distributed widely throughout the brain, as demonstrated by typical Cowdry A inclusions (figure B), immunoreactivity to anti-HSV antibodies (figure C), and extensive intranuclear virions on electron microscopy (figure D). Specifically, HSV inclusion bodies were distributed diffusely throughout the right and left cerebral hemispheres, cerebellum, midbrain, brainstem, and cervical spinal cord, although the grossly visible necrotising inflammatory process was most prominent in the left parietofrontal cortical region. There were widespread leptomeningeal and perivascular chronic inflammatory cell infiltrates, extensive cortical grey matter rarefaction, microglial activation, and neuronal necro-

**MRI and histopathological correlates of herpes simplex encephalitis.** MRI FLAIR sequences (A) manifest increased cortical signal in infected areas (arrows) and non-specific postoperative changes (*) 4 days after the first symptoms. Infected neurons show classic intranuclear Cowdry A inclusions (B) on haematoxylin and eosin stain and HSV antigen (C) with polyclonal rabbit anti-HSV 1 and 2 antibody as recommended by the manufacturer (Biogenex, San Ramon, CA, USA). Electronmicroscopy shows virions in the nucleus of a neuron (D).
Herpes simplex encephalitis after brain surgery

A superimposed brain death syndrome with patchy cortical and subcortical dunksiness was seen, coupled with mild generalised cerebral oedema. Herniations were not seen. Both the right and the left trigeminal ganglia were negative for HSV, as assessed by immunohistochemistry and polymerase chain reaction. Performed in retrospect, polymerase chain reaction for HSV DNA on the surgically resected meningioma including a small cortical fragment, was negative.

The remainder of the findings was largely unremarkable, except for ulcerocalculic grade 4 (of 4) aortic atherosclerosis, grade 2–3 (of 4) coronary atherosclerosis (non-critical disease), mild pulmonary oedema, few scattered foci of bronchopneumonia in both lungs, and bilateral serous pleural effusions of 200–250 ml on each side.

Discussion

Herpes simplex encephalitis as a complication of a neurosurgical procedure is very rare. The literature documents only one additional case in which fatal herpes simplex encephalitis followed surgery for a high grade glioma. Although occasional cases are reported in which a cerebral tumour was associated with herpes simplex encephalitis, in each, there had been additional factors inferring compromise of the immune response: infection with the human immunodeficiency virus together with cerebral metastasis, and brain irradiation and long term dexamethasone therapy for cerebral metastases. These findings are consistent with the presented patient, in whom postoperative stress plus steroid therapy may have contributed to HSV reactivation with evolving herpes simplex encephalitis.

The remote possibility of the simultaneous chance occurrence of two events (surgery plus herpes simplex encephalitis), however, cannot be entirely excluded.

The source of the HSV infection in this patient is of interest. Cutaneous infection with the human HSV is common, with HSV type 1 in cold sores and type 2 in genital herpes. The double stranded DNA virus often survives and persists in nerve ganglia corresponding to the dermatomes involved in primary infection. Cutaneous reactivation is thought to be triggered non-specifically by various forms of stress and may evoke to severe systemic disease in patients with compromising diseases, burns, or surgery, or in patients with compromised immunocompetence as after organ transplantation.

Neurosurgical interventions involving peripheral nerve roots or ganglia may provoke reappearance of cutaneous herpetic eruptions. Similarly, surgery of the gasserian ganglion or the preganglionic trigeminal nerve may provoke peripheral HSV disease that follows the pattern of trigeminal sensory innervation. Even after manipulation of the facial nerve during surgery for acoustic neuroma, cutaneous reactivation of HSV has been reported.

Most cases of herpes simplex encephalitis probably result from reactivation of latent virus residing in sensory ganglia. Uninvolvement of the trigeminal ganglia in our patient does not exclude reactivation of latent cerebral virus, perhaps from olfactory pathways. As in most cases of herpes simplex encephalitis of the adult, HSV type 1 was found in our patient.

The postoperative presentation of our patient included many of the clinical features typical of herpes simplex encephalitis. The CSF findings were also typical but non-specific. Periodic PLEDs support the suspected diagnosis, but unfortunately, are non-specific and may be seen in very different cerebral lesions. Brain MRI is the most sensitive imaging modality to detect encephalitis related cortical changes, especially T2-weighted and FLAIR sequences. The distribution of cortical lesions in MRI mirrors the well known affinity of the HSV for the grey matter of the limbic system. The discrepancy between the extent of the disease as assessed by MRI and the extent seen at necropsy reflects differences in sensitivity of both methods as well as a 5 day interval between the last MRI and the patient’s death. Imaging and EEG are neither sensitive nor specific enough to meet current standards in medical practice, particularly in early disease, whereas the sensitive and specific previous “gold standard” brain biopsy is invasive and expensive.

The polymerase chain reaction has revolutionised the diagnosis of herpes simplex encephalitis. It offers a rapid, sensitive and specific, inexpensive, and only minimally invasive tool for initial diagnosis and disease monitoring. Specific antiviral therapy is often (and should be) started in clinically suspect cases, even before a firm diagnosis is established.

The drug of choice for herpes simplex encephalitis is currently acyclovir with other derivatives being tested in clinical studies. Acyclovir specifically targets herpes viruses, significantly improves the clinical outcome, and has a low toxicity. This approach does not necessarily interfere with the diagnostic process, as HSV sequences are typically detectable for up to 5 days after initiation of acyclovir treatment.

This case broadens the range of herpes simplex encephalitis and emphasises the importance of the polymerase chain reaction in arriving at this diagnosis. Herpes simplex encephalitis should be considered in patients with postoperative seizures and fever. Results from the polymerase chain reaction may be initially negative, and the procedure should be repeated in clinically suspect cases as a favorable clinical outcome depends on early specific antiviral therapy which in turn is dependent on excellent clinical judgement supported by polymerase chain reaction analysis of CSF for HSV.

4 Koskinen M, Piiparinen H, Mannonen L, et al. Herpes encephalitis is a disease of middle aged and elderly people: polymerase chain reaction for detection of herpes simplex