Postherpetic Anti-N-methyl-D-aspartate Receptor Encephalitis after Hemispherotomy in a Patient with Intractable Startle Epilepsy

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Abstract

Herpes simplex encephalitis (HSE) has been increasingly reported after neurosurgical procedures, mostly after tumor resections in patients with a prior history of HSE. Early detection and appropriate treatment are essential to prevent high mortality of the disease; however, there are diagnostic difficulties due to nonspecific prodromal symptoms. In addition, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been reported after HSE as an immunological relapse. Here, we report a case of postherpetic anti-NMDAR encephalitis following right hemispherotomy for intractable startle-induced seizures, to emphasize the importance of early diagnosis and appropriate treatment. To our knowledge, this is the first reported case of anti-NMDAR encephalitis after postoperative HSE, and the third reported case of hemispherotomy as a curative treatment for startle epilepsy.

Keywords
- herpes simplex encephalitis
- hemispherotomy
- startle epilepsy
- autoimmune
- pseudoneoplasm
- anti-NMDAR antibody

Introduction

Herpes simplex encephalitis (HSE) is the most common cause of viral encephalitis, and there have been an increasing number of cases reported after surgery; without treatment, the mortality rate associated with HSE is high.[1,2] N-methyl-D-aspartate receptor antibody (NMDAR-Ab) production was reported in 13 of 44 (30%) adults with HSE.[3] Furthermore, several studies suggest that patients with worsening and relapsing symptoms after HSE should be assessed for anti-NMDAR encephalitis.[4,5] This is the first report of NMDAR encephalitis following epilepsy surgery.

On different perspective, epilepsy surgery is increasingly being performed as a treatment for intractable seizures. Hemispherotomy is a type of surgical procedure involving circumferential hemispheric disconnection with minimal removal of brain; it is preferred in patients with intractable seizures due to large hemispheric lesions.[4] Startle epilepsy is rarely reported and characterized by reflex seizures triggered by unexpected acoustic, visual, or somatosensory stimuli.[6] Primary and supplementary sensorimotor, premotor, and perisylvian cortical areas are hyperexcitable due to focal or large hemispheric lesions; these play a role in (mostly drug-resistant) startle-induced, harmful seizures with tonic posturing of the limbs. There are only two published cases of hemispherotomy as a treatment option for startle-induced seizures and large hemispheric lesions.[7,8] Here, we present an original case with postherpetic anti-NMDAR encephalitis after hemispherotomy for intractable startle epilepsy.

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Case Report

A 17-year-old girl with intractable startle-induced seizures and left-sided hemiparesis was admitted to our clinic. She had experienced seizures since 9 months of age following complicated febrile illness. Symptoms included left hemiparesis that included left-hand fine finger movements, although she was able to ambulate. She was not investigated for diagnosis of that febrile illness, and laboratory data are absent. Magnetic resonance imaging (MRI) of the brain showed right-side partial calcification, perirolandic cortical and subcortical encephalomalacia, and volume loss (►**Fig. 1A**; upper part). Focal startle-induced seizures persisted multiple times a day despite treatment with levetiracetam, carbamazepine, clobazam, and lacosamide.

During long-term video electroencephalography (vEEG) monitoring, interictal EEG revealed active spiking in the frontocentrotemporal regions of the right hemisphere. Seizures recorded during vEEG monitoring were characterized by startle-induced tonic posture of the left upper extremity and leftward deviation of the eyes. Onset of ictal EEG changes was lateralized to the right hemisphere.

The patient underwent right hemispherotomy with partial removal of the parietal calcified lesion for pathologic investigation after discussion in our epilepsy conference. There was a round, circumscribed, fibro-osseous lesion, and histopathology revealed this to be a "calcifying pseudoneoplasm" (►**Fig. 2**).

Two days following the operation, cranial computed tomography (CT) showed only expected postoperative changes with no complications. The patient's consciousness fluctuated along with persistent fever during the first postoperative week. The patient's EEG demonstrated generalized slowing, voltage suppression, and periodic lateralized epileptiform discharges (PLEDs) in the right hemisphere. As hemispherotomy is only a disconnection procedure and interictal EEGs do not usually change, continuing to show the active epileptiform anomaly during the postoperative period in seizure-free patients, we assumed that some unexpected frequent seizures might cause fluctuating consciousness and clinical deterioration. MRI of the brain revealed bilateral, asymmetrical, insular, and medial temporal T2 hyperintensity in the orbitofrontal and medial temporal lobes, and insular and gyral contrast enhancement suggested HSE (►**Fig. 1B, D**; upper part). Lumbar puncture was performed on day 15 after surgery and revealed lymphocytic pleocytosis, protein levels of 45.6 mg/dL, normal glucose and chlorine levels, and absence of oligoclonal bands. Subsequently, empiric acyclovir therapy was started at 30 mg/kg/d in three divided doses. Bacterial and fungal cultures were negative, and herpes simplex virus (HSV) type 1 testing by polymerase chain reaction (PCR) obtained from cerebrospinal fluid (CSF) was positive. The patient underwent acyclovir therapy for 21 days. After acyclovir therapy, HSV type 1 immunoglobulin M (IgM) titer was negative. On postoperative day 44, her responsiveness improved, and she was able to communicate with a few words and ambulate with assistance. Her cognitive functions were remarkably improved.

On postoperative day 62, her neurological status deteriorated, and orofacial dyskinesia and hallucinations developed. NMDAR-Abs were found positive in serum and CSF with immunohistochemistry. MRI of the brain revealed bilateral asymmetrical T2 hyperintensity in the orbitofrontal and medial temporal lobes (►**Fig. 1**; lower part). In response to immunotherapy (pulse steroid administered at a dosage of 1,000 mg/d for 7 days followed by 10 cycles of plasmapheresis), dyskinesia, behavioral abnormalities, and hallucinations were significantly reduced. She was discharged at postoperative day 92 with behavioral and memory problems but free from seizures.

One year after her initial presentation, the patient was seizure free on antiepileptic treatment. She had markedly improved social interactions without dyskinesia but with mild residual amnesia. She was able to walk without assistance.

Discussion

This case demonstrated instances of postoperative HSE and subsequent anti-NMDAR encephalitis, which had never been reported following epilepsy surgery before. In addition to these very rare and recently recognized complications, this case is also interesting because it is the third case of a patient who underwent hemispherotomy for startle-induced seizures and became seizure free. An unexpected pathological finding of a small calcified tissue diagnosed as a "calcified pseudoneoplasm," an extremely rare pathological entity is also interesting and its role in these complications is not well understood.

HSE is rarely observed after neurosurgical interventions, and only 13 cases have been reported, few of them underwent surgery for epilepsy.[1,2] Clinical symptoms and EEG changes, which occur in patients with HSE, may cause a misdiagnosis as diagnosing HSE is difficult. Changes of the patients' consciousness and clinical deterioration may be presumed to be a result of seizure recurrence. EEG findings in HSE include nonspecific diffuse or focal slowing, temporal lobe spiking or sharp wave activity, triphasic complexes, and PLEDs; these findings are suggestive of, but not specific to, HSE.[9] PLEDs were recorded in our patient but were not enough to suggest a HSE diagnosis, since her preoperative EEG recordings showed active spiking at the same lateralization. MRI reveals medial temporal and insular T2 hyperintensity and gyral contrast enhancement, bilaterally and usually asymmetrically in patients with HSE; these findings are suggestive of HSE.[10] Laboratory studies may not reveal indicators of the disease in the early phases of HSE: CSF cell counts are normal in 5 to 10% of cases, especially in children; CT results are normal in one-third of patients in the first week of the disease; MRI is normal in up to 10% of cases; and PCR analysis may not show viral DNA replication initially,[11] although the PCR test has a sensitivity and specificity of 96 and 99%.[11] The current recommended treatment regimen is 10 to 15 mg/kg of acyclovir every 8 hours for 14 to 21 days.[6] The rate of mortality is 70% in untreated patients, and only 3% of untreated patients resume normal functions.[11]

The underlying mechanism of postoperative HSE, whether due to primary infection or reactivation, is not well understood. Our patient did not have a prior history of HSE; however, upon further investigation after surgery, HSV type 1 immunoglobulin G was detected in serum and CSF samples, although

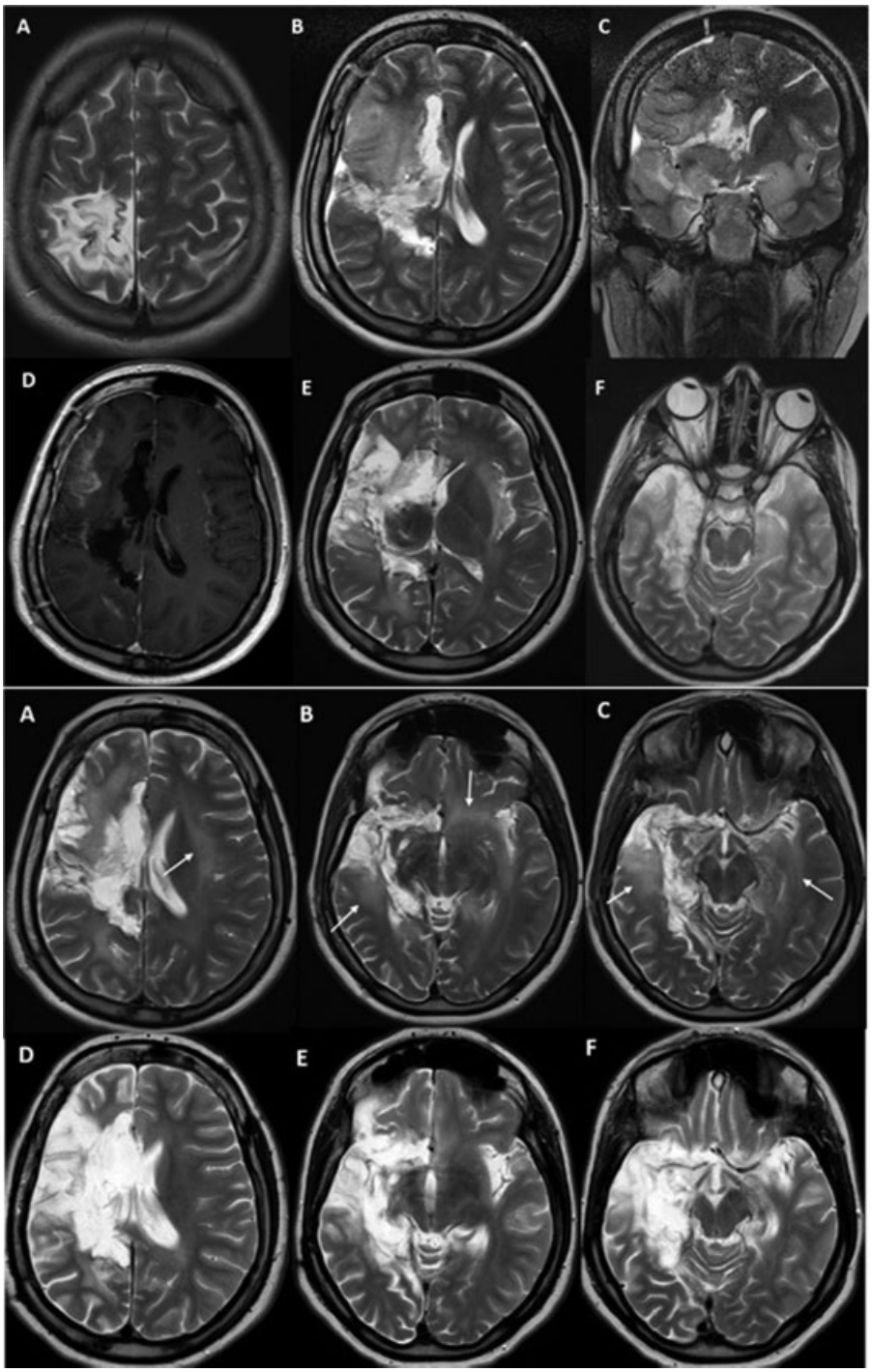

Fig. 1 (**Upper part**) (**A–F**) Preoperative axial T2W image shows right perirolandic cortical and subcortical hyperintense chronic lesion (**A**). Five days after right-side hemispherotomy surgery. Axial (**B**) and coronal (**C**) T2W images show bilateral insular and medial temporal abnormal T2 hyperintensity and swelling. Postcontrast T1W image reveals gyral enhancement of the lesions (**D**). Thirty days after onset of neurological symptoms show decrease in signal intensity in lesions on T2W images (**E**, **F**). (**Lower part**) (**A–F**). At postoperative day 62, axial T2W images show new hyperintense lesions on medial temporal lobes, left inferior frontal region, and centrum semiovale (**A–C**, arrows). At postoperative day 92, axial T2W images demonstrate marked cystic encephalomalacia and volume loss in affected areas (**D–F**). T1W, T1-weighted; T2W, T2-weighted.

HSV type 1 IgM was absent. This finding supported a probable HSV type 1 infection early in life.

Clinical deterioration after HSE treatment with acyclovir is usually due to autoimmune encephalitis related to the anti-NMDAR antibody.[3,5] Symptoms such as chorea, orofacial dyskinesias, dystonia, ballismus, altered mental status, seizures, aggression, agitation, and sleep disturbances can be attributed to clinical manifestations of anti-NMDAR encephalitis.[3,5,12–14] Immunotherapy regimens that have been used in reported cases of postherpetic anti-NMDAR encephalitis are varied; first-line therapies included intravenous immunoglobulin and plasmapheresis. Patients who were

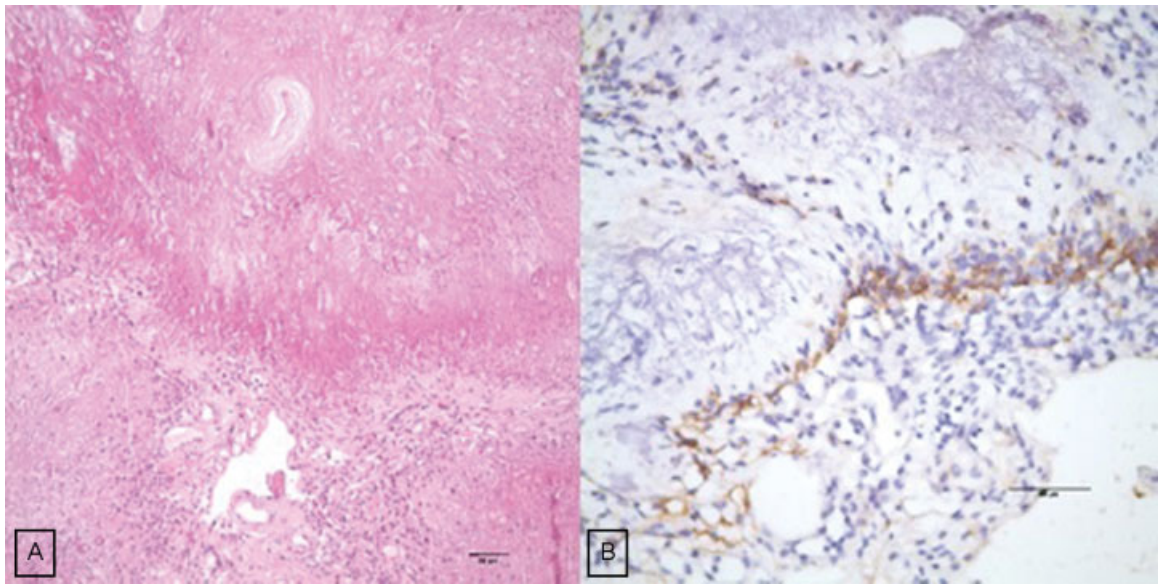

Fig. 2 (**A, B**). Granules and strands of calcified chondromyxoid material is radially oriented (hematoxylin and eosin stain) (**A**) and rimmed by epithelioid cells that express epithelial membrane antigen by immunohistochemistry (**B**).

unresponsive to first-line therapies were treated with immunosuppressants, such as cyclophosphamide, cyclosporine, rituximab, or mycophenolate mofetil.[3,12–14] The patient considered in this study improved after plasmapheresis treatment, which was considered a supportive finding for anti-NMDAR encephalitis.

Since startle epilepsy is rare and characterized by harmful and mostly drug-resistant seizures, surgery may be a treatment option, especially hemispherotomy, which can be offered to patients with large hemispheric lesions and intractable startle-induced seizures. Unfortunately, there is not enough data on this treatment paradigm, and only two cases have been published in the literature.[7,8] Our patient is the third case with intractable startle-induced seizures and a unilateral large hemispheric lesion who was seizure-free 1 year after hemispherotomy despite serious complications.

Calcifying pseudoneoplasms of the central nervous system are derived from nonneoplastic, reactive, proliferative processes that give rise to either extra-axial or intra-axial masses. Underlying causes are trauma, infection, or inflammation. Seizures (28%), headache (28%), and cranial nerve affection (15%) are the most common symptoms of intracranial calcified pseudoneoplasms.[15] We do not know the role for this type of lesion in postoperative HSE.

In conclusion, HSE is a rare but life-threatening complication of neurosurgical procedures. Empiric antiviral therapy must be considered if HSE is suspected postoperatively. Currently, no recommendations have yet been made for prophylactic antiviral treatment. Despite treatment with acyclovir, abrupt deterioration should lead the clinician to a probable diagnosis of postherpetic anti-NMDAR encephalitis, as immunotherapy can further improve these patients' condition.

In selected patients with intractable startle-induced seizures and large unilateral hemispheric lesions, hemispherotomy can be successful to stop seizures. Physicians who perform epilepsy surgery can overcome these rare, postoperative complications and challenges if they are aware of them.

Disclosure
None of the authors has any conflict of interest to disclose.

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