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Short communication

Histopathological evidence that hippocampal atrophy following status epilepticus is a result of neuronal necrosis

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ABSTRACT

Medial temporal lobe epilepsy is commonly associated with hippocampal atrophy on MRI and hippocampal sclerosis on histopathological examination of surgically-resected specimens. Likewise, it is well-established that prolonged seizures and status epilepticus can lead to hippocampal edema as noted on MRI.

In this paper, the authors present an unusual patient with prolonged refractory status epilepticus, due to limbic encephalitis associated with anti-GAD antibody, who underwent palliative epilepsy surgery. Bilateral hippocampal edema was noted on preoperative MRI. Histologic evaluation confirmed presence of acute necrosis and neuronal loss in the left hippocampal formation. Follow-up MRI several months after surgery demonstrated severe atrophy of the contralateral right hippocampus.

This is the first clear histopathological evidence that hippocampal atrophy following status epilepticus is the result of acute neuronal necrosis and cell loss.

1. Introduction

A long-standing controversy remains whether hippocampal sclerosis in patients with temporal lobe epilepsy is a cause or a consequence of recurrent seizures [1]. Some neuronal populations are particularly vulnerable to damage from status epilepticus (SE) or recurrent/prolonged seizures, e.g. cornu ammonis areas 1 and 3 (CA1 and CA3) pyramidal cells and dentate hilar neurons [2–4]. The neurologic sequelae of SE can be severe as described in a number of human neuropathologic studies [4–6], neuroimaging studies [7–9], and animal studies [3].

Several prospective and retrospective studies have demonstrated an important relationship between a history of prolonged febrile seizures in early childhood and mesial temporal sclerosis [10–14]. In contrast, other prospective studies have failed to show a clear link between febrile seizures and mesial temporal sclerosis [15]. Hippocampal sclerosis is more frequently associated with developmental brain abnormalities such as focal cortical dysplasia and heterotopia, which supports the hypothesis, that prolonged febrile seizures are not necessarily the underlying cause of hippocampal sclerosis. There is also evidence that prolonged and frequent seizures do not inevitably cause severe neuronal loss [16], and that good outcome is possible following months of refractory status epilepticus (RSE) [17].

We present a unique case where prolonged SE first led to severe bilateral hippocampal edema as noted on MRI. Surgical removal of the epileptic left hippocampus for treatment of RSE revealed acute necrosis and cell loss on histopathological examination. Follow-up neuroimaging demonstrated severe atrophy of the contralateral hippocampus. This is the first reported neuropathological correlate of persistent seizures causing acute hippocampal edema with necrosis and leading to eventual hippocampal sclerosis and atrophy.

2. Case history

A 30 year-old right-handed woman without significant past medical history developed new-onset headaches. A few days later, she presented with a flu-like illness and was treated with oseltamivir phosphate. Over the next few days, her headaches worsened, she started vomiting, and later had her first generalized tonic–clonic seizure. In the emergency room, she had recurrent generalized seizures despite first and second line intravenous antiepileptic medications. She was intubated and admitted to the intensive care unit. She continued to seize in spite of multiple anti-seizure drugs and was diagnosed with medically-refractory SE. CT scan of the brain and the initial cerebrospinal fluid (CSF) studies on the day of admission were also unremarkable. Polymerase chain reaction for herpes simplex virus types 1 and 2 was negative. She was treated

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with acyclovir and ceftriaxone for possible viral and bacterial central nervous system infection, respectively. She remained in RSE despite multiple anticonvulsants including phenytoin, phenobarbital, levetiracetam, lacosamide, as well as continuous propofol infusion. Her seizure semiology consisted of clonic activity of the right face, arm, and leg with occasional secondary generalization. Repeat lumbar puncture and CSF analysis on two additional occasions were also unremarkable. Scalp electroencephalogram (EEG) revealed bilateral epileptiform abnormalities consisting of periodic lateralized epileptiform abnormalities, which were more frequent over the left cerebral hemisphere and electrographic seizures, which were lateralized to the left cerebral hemisphere (Fig. 1). MRI of the brain 10 days after seizure onset showed bilateral hippocampal enlargement with increased T2 and FLAIR signal intensity consistent with acute hippocampal edema (Fig. 2A).

Since her seizures remained refractory to multiple antiepileptic drugs, she was treated with high-dose pulse steroid therapy for five days followed by a course of intravenous immunoglobulin (IVIG) for presumed autoimmune encephalitis. She did not respond to the immunomodulatory therapy and remained in SE. At this point, the patient was transferred to our comprehensive epilepsy center for further management. At our institute, continuous video-EEG monitoring over several days revealed that all of her seizures arose from the left frontal and temporal regions.

A follow-up MRI of the brain showed distinct areas of T2/FLAIR hyperintensity involving the cingulate cortex and frontal operculum of the left frontal lobe (Fig. 2B). There was also persistent increased signal of the hippocampi bilaterally. A 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG) PET scan showed diffuse hypometabolism with a superimposed focal decreased uptake involving the left frontal and temporal lobes. She remained in RSE for over a month despite multiple anticonvulsants as well as immunomodulatory therapy requiring prolonged ventilatory support and intensive care. Due to lack of progress, all options including two-staged epilepsy surgery, continued medical management, supportive care only and one-stage surgery under ECoG guidance were discussed as a team and with family. The epileptogenic zone appeared to be localized to the left frontal and temporal areas. Based on continuous video-EEG monitoring, FDG-PET, and neuroimaging findings, a decision was made at the multidisciplinary epilepsy case management conference to proceed with a single stage palliative epilepsy surgery to resect the epileptogenic zone.

Intraoperative electrocorticography with arrays of subdural grid electrodes showed frequent epileptiform activity and electrographic seizures arising from the left lateral and inferior frontal lobe as well as the inferior temporal lobe (Fig. 3). In addition, electrographic seizures were captured from the left hippocampus by a 6-contact depth electrode inserted using image-guidance via a lateral approach through the middle temporal gyrus (Fig. 4). Functional cortical mapping of the sensorimotor cortex was performed. The resection margin was determined after taking into consideration location of the eloquent cortex (established on the basis of functional mapping and anatomical landmarks) and epileptogenic zone (detected by extensive intraoperative ECoG) (see Fig. 3). A large prerolandic left frontal (including frontal opercular and anterior cingulate gyrus) and anterior temporal resection was completed including removal of the left mesial temporal structures.

Histopathological examination showed neuronal shrinkage as well as microglial activation with mild astrocytosis in the neocortical sections. No microglial nodules were seen, and only sparse mononuclear inflammation was present, primarily in the subarachnoid space. Sections of the left medial temporal lobe, including hippocampus, showed extensive neuronal loss and acute necrosis with marked astrocytosis in the hippocampus, mainly involving CA1 but with milder neuronal loss in other parts of the hippocampus and subiculum (Fig. 5). Patchy mononuclear inflammation, chiefly lymphocytes forming perivascular cuffs and extending into the surrounding parenchyma, was present in the hippocampal formation, most prominently in the fascia dentate and end plate. The infiltrate consisted mainly of CD3-immunoreactive T cells, with CD8 forms more abundant than CD4-positive cells. CD68-immunoreactive activated microglial cells were numerous throughout the hippocampus, and macrophages were frequent in the necrotic area CA1. No microglial nodules or instances of neuronophagia were noted. No viral inclusions were identified with routine stains, by immunohistochemical staining for Herpes simplex virus 1, cytomegalovirus, or adenovirus, or by *in situ* hybridization for Epstein–Barr virus.

Postoperatively, she remained intubated scalp EEG continued to show electrographic seizures requiring continued aggressive treatment with intravenous drips for partial SE including seizures originating independently from contralateral hemisphere. Meanwhile, the results of the serum and CSF autoantibodies became available. Serum anti-glutamic acid decarboxylase (GAD) antibody titer was elevated at >250 U/ml (normal: <5 U/ml). She remained in RSE despite a second course

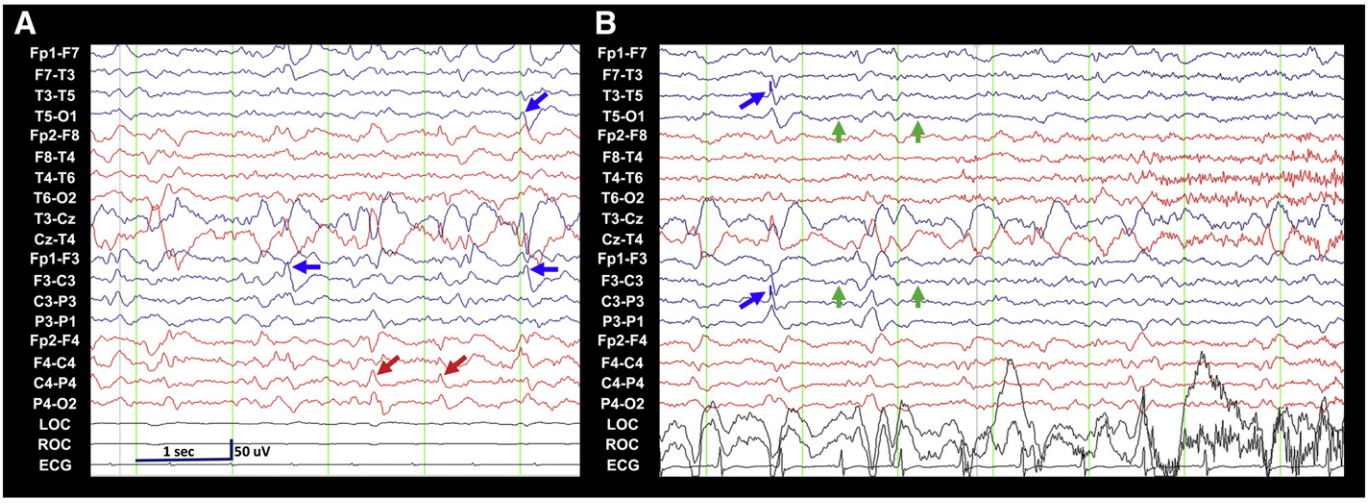

Fig. 1. Scalp EEG. A: A scalp EEG in longitudinal bipolar montage (double banana) with temporal electrode chains on the top of the page and parasagittal chain on the bottom of the page. The blue lines represent left sided scalp electrodes and red lines represent right-sided electrodes. The EEG shows bilateral independent spikes and sharp wave discharges (red arrows in right hemisphere, blue arrows in left hemisphere). B: Another EEG sample depicted in the same montage shows initial sharp wave (blue arrows) followed by a low amplitude fast frequency waves (green arrows) over the left hemisphere indicative of electrographic onset of a seizure. A few seconds later EMG artifact is recorded from the right-sided channels coinciding with the movements of the right side of the body.