Clinical commentary

Epileptic Disord 2011; 13 (4): 446-51

Serial EEG and MRI changes in status epilepticus-induced excitotoxic neuronal necrosis

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Received July 23, 2011; Accepted November 13, 2011

ABSTRACT – Prolonged status epilepticus may directly cause selective neuronal necrosis due to excitotoxic mechanisms, as observed in experimental models and described in case reports. A 36-year-old woman presented with right hemiplegia and aphasia following a generalised tonic-clonic status epilepticus of two hours duration. Accompanying serial MRI with advanced imaging techniques, EEG and histopathology of the cortical tissue of the patient were all compatible with excitotoxic neuronal necrosis. In this histopathologically-proven rare case of status epilepticus-induced excitotoxic neuronal injury, the observation of delayed cortical laminar necrosis on MRI, together with paroxysmal lateralised epileptiform discharges on the EEG, suggests that these changes may be an early sign of impending and ongoing excitotoxic neuronal injury and delayed cell death caused by glutamate release due to excessive neuronal firing in status epilepticus.

Key words: EEG, epilepsy, status epilepticus, MRI, MR spectroscopy

Selective neuronal necrosis is associated with hypoxia, ischaemia, toxic factors, metabolic disturbances and also status epilepticus (SE) (Tsuchida *et al*., 2007). Case reports and experimental studies suggest that prolonged SE may directly cause selective neuronal necrosis due to excitotoxic mechanisms (Donaire *et al*., 2006; Holmes, 2002; Wasterlain *et al*., 1993). In this case report, we aimed to demonstrate the presence and clarify the mechanisms involved in the development of excitotoxic neuronal injury (ENI) in humans using accompanying serial EEG, MRI and advanced imaging techniques including proton spectroscopy, dynamic susceptibility contrast enhanced MRI and MR angiography.

Case report

A 36-year-old woman was admitted to the emergency unit with generalised tonic-clonic seizures of two hours duration. At arrival, generalised tonic-clonic seizures were observed and no focal seizures were described by eyewitnesses. The

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doi:10.1684/epd.2011.0472

patient's history revealed that she was diagnosed with mesial temporal lobe epilepsy in childhood and she had had a right anterior temporal lobectomy eight years ago for her refractory automotor seizures. In spite of epilepsy surgery, she still experienced two to three tonic-clonic seizures a year. Her antiepileptic treatment consisted of lamotrigine (200 mg/d) and clobazam (10 mg/d). She received levothyroxine at 50 mg/d due to hypothyroidism diagnosed five years ago.

Neurological examination revealed an unconscious patient with a Glasgow Coma Scale score of 7 and right hemiplegia. She localised painful stimuli. She was afebrile and there were no meningeal signs. Optic fundi and cranial nerve examinations were normal. Oculocephalic reflexes could be elicited. Deep tendon reflexes were decreased on the right and both plantar responses were indefinite. Her systemic examination was unremarkable. Investigations revealed a normal haemogram and metabolic parameters including glucose, creatinine, urea, electrolytes, calcium, magnesium, phosphorous and near-normal brain MRI at admission (*figure 1A*). Herpes simplex virus PCR was negative. Free T3, free T4 and anti-Tg levels were within normal range. EEG disclosed generalised slowing with left frontal sharp slow waves and reduced voltage on the left (*figure 2B*). The seizures were immediately controlled with anticonvulsant therapy that consisted of *iv* diazepam and phenytoin in the emergency unit, after which the patient was transferred to the intensive care unit where metabolic parameters were stably maintained during follow-up. On the third day, left hemispheric paroxysmal lateralised epileptiform discharges (PLEDs) emerged on EEG (*figure 2C*). Repeated cranial MRI on the fourth day revealed a diffuse signal increase in the left cerebrum on T2 weighted images, vascular enhancement on postcontrast T1 weighted images and prominent cortical diffusion restriction. The volume of the left cerebrum had extensively increased causing shift. There was intracranial vascular

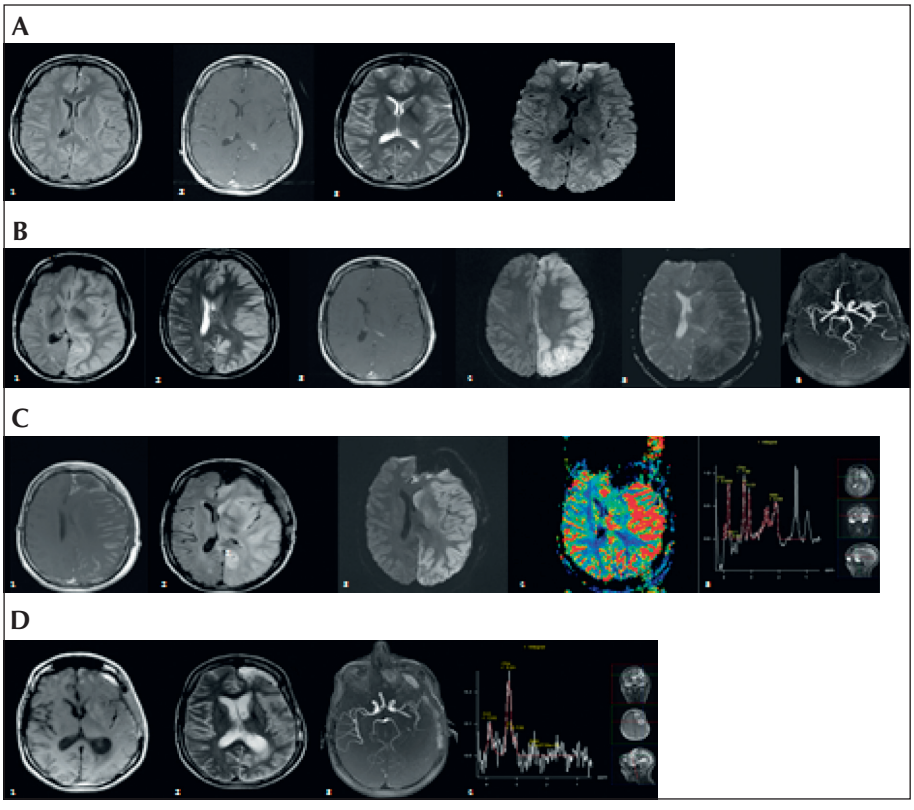

Figure 1. (A) First day: normal findings on postcontrast T1 (2), T2 (3) and diffusion weighted images (4). There is subtle cortical hyperintensity on FLAIR images (1).
(B) Fourth day: diffuse signal increase in FLAIR (1) and T2 weighted image (2) and signal decrease in postcontrast T1 weighted image (3) and diffusion restriction (4) in left cortical areas. Increased left cerebrum volume with shift to the right hemisphere in ADC (5). Left hemispheric vascular signal asymmetry on collapsed 3D TOF image (6).
(C) Thirteenth day: pial enhancement on postcontrast T1 (1), signal changes on FLAIR (2), diffusion weighted images (3), hyperperfusion on left cerebrum in rCBF (4) and decreased NAA, mioinositol, increased choline, glutamine-glutamate, lactate on short TE single voxel proton spectroscopy (5).
(D) Cortical laminar necrosis plus basal ganglia and thalamus necrosis on T1 weighted image (1), prominent cerebral atrophy on T2 weighted image (2), reversed vascular changes on collapsed 3D TOF image (3), and decrease in all metabolite peaks except choline on short TE proton spectroscopy (4).

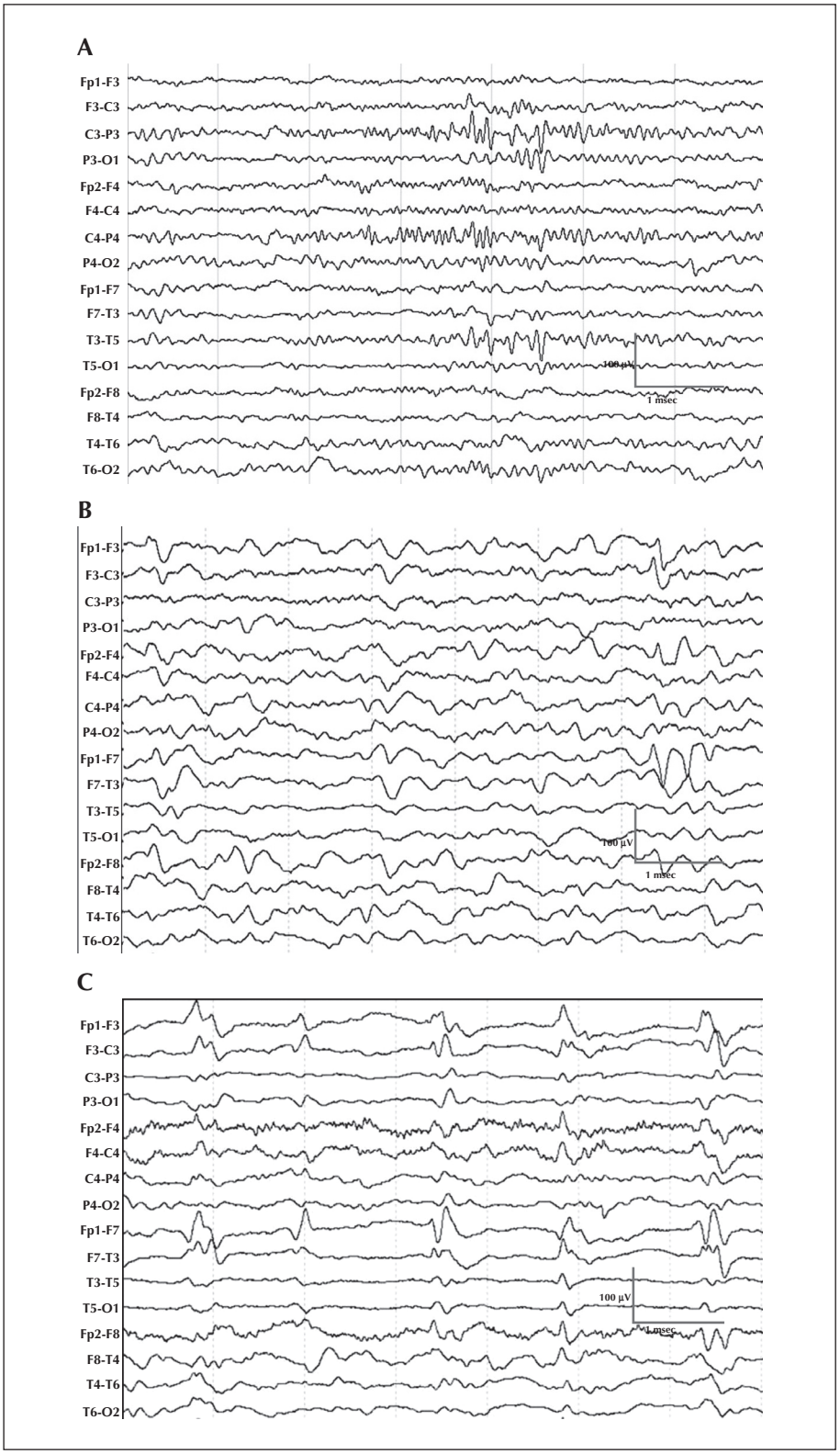

Figure 2. (A) Pre-status epilepticus EEG with rare left prominent centrotemporal spikes. (B) First day EEG: generalised slowing with left frontal sharp waves. (C) Third day: left hemispheric PLEDs.

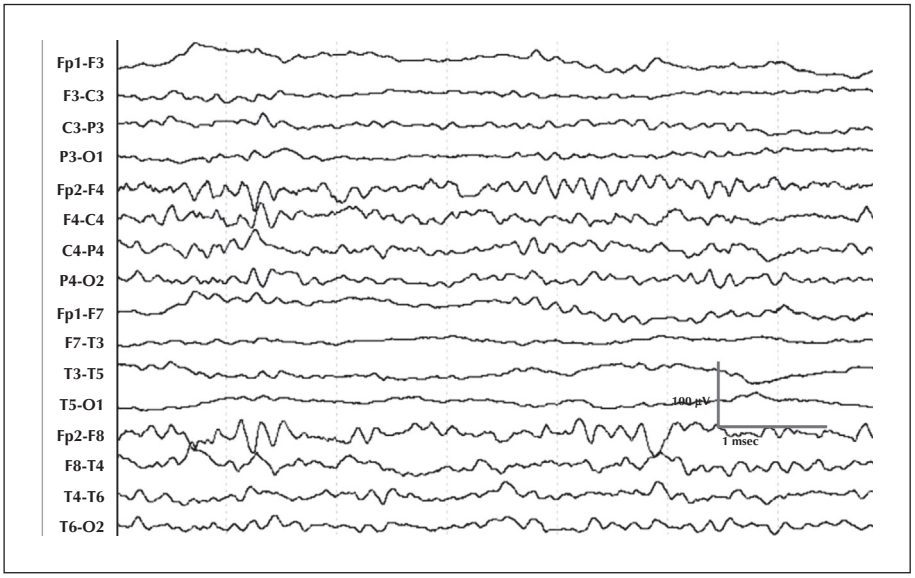

Figure 3. Fourth day EEG: resolution of PLEDs, voltage depression on the left side.

signal asymmetry dominant on the left, on collapsed 3D TOF images (*figure 1B*) with voltage depression on the left hemisphere with resolution of PLEDs on the EEG on the same day (*figure 3*). On the seventh day, brainstem compression signs were observed and the patient underwent urgent decompressive surgery.

On the thirteenth day, MRI showed additional ipsilateral deep grey matter involvement. There was increased signal of the ipsilateral middle cerebral artery on MRI, and leptomeningeal vascular enhancement on postcontrast T1 weighted images (*figure 1C*). 3D TOF MRI angiography and dynamic susceptibility contrast enhanced perfusion MRI revealed prominent hyperperfusion on the ipsilateral hemisphere rather than ischaemia. N-acetyl-L-aspartate (NAA)/creatine and mioinositol/creatine ratios were decreased. Choline/creatine and glutamine-glutamate/creatine ratios were increased and there was a significant double peak at 1.33 ppm, compatible with lactate on short time of echo single voxel proton spectroscopy (*figure 1C*). On the thirty-seventh day, which was the late subacute/early chronic period, MRI and MR spectroscopy displayed significant alterations. There was prominent ipsilateral cerebral atrophy with T1 hyperintensities both in cortical **a**nd deep grey matter. MR Spectroscopy obtained at the same period showed a prominent decrease in NAA/creatine, mioinositol/creatine and glutamate-glutamine/creatine ratios. There was a dominant choline peak (*figure 1D*).

Pathological examination of the extirpated cortical tissue disclosed diffuse changes that were composed of allocortical tissue designated with selective cortical and subcortical neuropil changes and neuronal necrosis. Concurrently, some neurons had well preserved chromogranin particles (*figure 4A*) and intact vascular structure. The pia-arachnoid membrane was composed of regular elements (*figure 4B*). There was no evidence of infection. As the patient became stable, she was discharged from the hospital with right hemiplegia and aphasia.

Discussion

Selective neuronal necrosis develops in the neocortex and hippocampus in experimental SE following prolonged electrographic discharges (Tsuchida *et al*., 2007). In the acute stage, astrocytosis is observed in the histopathology and in the chronic stage there is cell loss and gliosis (Corsellis and Bruton, 1983; DeGiorgio *et al*., 1992; Fujikawa *et al*., 2000; Men *et al*., 2000; Soffer *et al*., 1986). Evaluating the consequences of SE in humans is difficult because most cases of SE in humans are complicated by metabolic perturbations (DeGiorgio *et al*., 1992; Fujikawa *et al*., 2000). In this case report, other metabolic and toxic factors were absent. Different mechanisms have been proposed to lead to neuronal injury in SE. There is significant increase in cerebral metabolic demand for glucose and oxygen in SE that leads to a compensatory increase in CBF. In the case of further metabolic demand, adenosine triphosphate depletion and lactate accumulation occurs and this leads to hypermetabolic neuronal necrosis (Wasterlain *et al*., 1993). There are also excitotoxic mechanisms mediated by both N-methyl-D-aspartate (NMDA) and non-NMDA receptors. In SE, glutamate plays an important role as an excitatory neurotransmitter. The activation of NMDA

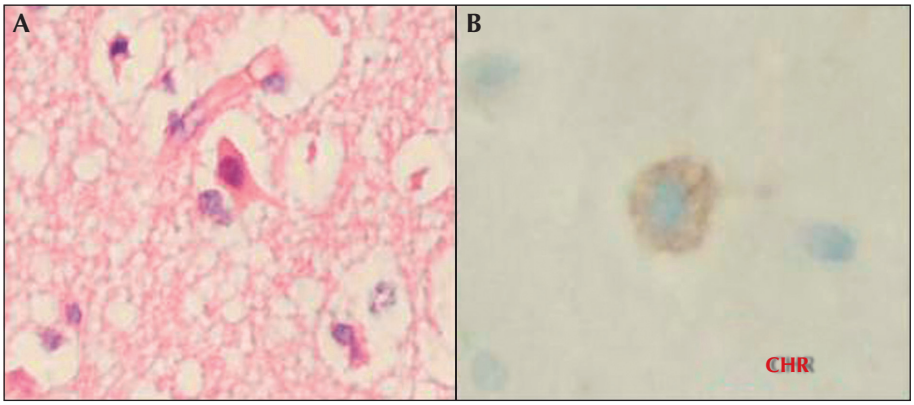

Figure 4. (A) Selective neuronal necrosis, perikaryal vacuoles, perineural satellitosis and cytotoxic/vasogenic oedema, with intact vascular structure (H&E: x200 original magnification). (B) Surviving viable neurons with observable chromogranin reactivity (biotinylated streptavidin complement; chromogranin, x400 original magnification).

receptors mediates excitatory mechanisms and causes calcium entry into the cell and excitotoxic cell death (Holmes, 2002).

With regards to the aetiology of SE, the following should be considered: antiepileptic drug (AED) non-compliance, central nervous system (CNS) infection, cerebrovascular disease, mass lesion, trauma, systemic metabolic disorders, alcohol or drug withdrawal, and substance abuse or other toxin exposure.

During serial MRI of the patient, a different pattern of involvement was observed relative to acute ischaemia. Normal findings immediately following SE and the late appearance of areas of T2 signal changes with diffusion restriction which did not respect vascular territories were contrary to ischaemia and suggested delayed development of neuronal injury. Systemic metabolic disorders including encephalopathy associated with thyroid disorder and mass lesion were excluded by radiological and laboratory examinations. There were no signs of CNS infection such as stiff neck, fever, *etc*. Spinal tap at admission was not performed since the patient had a history of epilepsy which was still active, suggesting that the aetiology of SE was epilepsy *per se*. Later in the course of the disease with development of cerebral oedema and shift, spinal tap was contraindicated. PCR for herpes simplex virus was negative and not suggestive of CNS infection, as was the neuropathological examination which showed no evidence of CNS infection. The patient's history did not reveal trauma, alcohol or drug withdrawal, substance abuse or other toxin exposure. However, since the patient was unconscious, AED non-compliance could not be assessed, *i.e*. it was not possible to determine whether an AED dose was not taken.

Prominent hyperperfusion on dynamic susceptibility contrast enhanced perfusion MRI and ipsilateral gyral atrophy with T1 hyperintensities including basal ganglia and thalamus was compatible with cortical laminar necrosis. 3D TOF MRI angiography and dynamic susceptibility contrast enhanced perfusion MRI revealed prominent hyperperfusion on the ipsilateral hemisphere rather than ischaemia. NAA/creatine and mioinositol/creatine ratio decrease, choline/creatine and glutamine-glutamate/creatine ratio increase and dominant double peak at 1.33 ppm compatible with lactate on short time of echo single voxel proton spectroscopy might be regarded as ongoing dynamic cell turnover. During the late subacute/early chronic period, MRI and MR spectroscopy findings and prominent atrophy with T1 linear hyperintensities on the ipsilateral gyrus were all compatible with cortical laminar necrosis. There were also MRI findings of basal ganglia and thalamus necrosis during the last follow-up MRI visit. MR spectroscopy obtained at the same period supported the necrosis with a prominent decrease in NAA/creatine, mioinositol/creatine and glutamate-glutamine/creatine ratios. The dominant choline peak might be proof of ongoing dynamic cell turnover. Normal MRI just after the episode and a history of infrequent seizures makes it unlikely that the neuropathological changes compatible with ENI were present prior to the episode of SE. This injury may be partly caused by excitatory neurotransmitter release which is a late complication of excessive neuronal firing in SE as shown in experimental models (Holmes, 2002). In experimental models, excitotoxic neuronal necrosis is largely prevented by NMDA receptor antagonists, suggesting that SE-induced neuronal damage is partly mediated by NMDA receptors from excessive endogenous glutamate release (Clifford *et al*., 1990; Fariello *et al*., 1989; Fujikawa, 1995; Holmes, 2002).

The present case and other human cases from the literature support animal models implicating excitotoxic neuronal injury in SE with supporting

histopathological evidence. It may further be hypothesized that this phenomenon is closely related to the proposed mechanisms of postictal paresis (Gallmetzer *et al*., 2004).

The simultaneous appearance of changes in MRI and MR spectroscopy, compatible with excitotoxic neuronal injury and concomitant EEG changes characterised by PLEDs, is significant. These changes may be a clue of evolving and ongoing excitotoxic neuronal injury or even radiological and electroencephalographic correlates of this process. More human observations and experimental studies should be carried out in order to uncover the mechanisms of SE-induced excitotoxic neuronal injury. □

Disclosure.
This work was not supported by any grant and was presented as a poster at the National Epilepsy Congress, Turkey 2009.

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