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Subsequent Bilateral Hippocampal Diffusion Restriction and Atrophy in Repeated Status Epilepticus

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ABSTRACT. ***Background:** Cortical lesions in status epilepticus have been reported but the underlying mechanisms are poorly elucidated. **Case summary:** We report on a female patient (75 years) with a history of alcohol abuse who presented with complex partial status epilepticus and lateralized epileptiform discharges in the left frontal and temporal regions in EEG. While cranial magnetic resonance imaging (MRI) showed left hippocampal T2-hyperintensity and diffusion restriction, cerebrospinal fluid was normal and revealed no limbic encephalitis-related antibodies. Following treatment with levetiracetam, seizures ceased and the patient was dismissed. Nine months later, she was readmitted with generalized status epilepticus. Cranial MRI now showed hippocampal diffusion restriction and T2 hyperintensity, but in the right hemisphere, as well as atrophy and partial gliotic transformation of the initially affected left hippocampus. **Discussion:** Although hippocampal damage due to antibody-negative limbic encephalitis cannot be ruled out, our observation of subsequent bilateral hippocampal diffusion restriction with gliotic transformation may demonstrate permanent seizure-induced structural brain damage and underlines the importance of further research to elucidate the effects of prolonged epileptic discharges on cerebral structural integrity.*

KEY WORDS. *Diffusion restriction, hippocampus, limbic encephalitis, magnetic resonance imaging, status epilepticus.*

INTRODUCTION

Status epilepticus is linked to mortality rates of up to 39% (Betjemann and Lowenstein 2015, Rossetti et al. 2006). This neurological emergency has been linked to structural brain damage but the underlying pathophysiology is not fully elucidated. Although animal studies have identified a variety of possible mechanisms whereby prolonged epileptic seizure activity compromises structural integrity of cortical neurons, including adenosine triphosphate (ATP) deficiency, lactic acidosis, and inflammation, it remains unclear whether, and to what extent, these mechanisms may apply to humans (Wasterlain et al. 1993). Hippocampal and extratemporal changes in magnetic resonance imaging (MRI) following status epilepticus, including diffusion restriction and increased intensity in T2-weighted images, have previously been reported in patients, but diagnosis of status epilepticus-related structural brain damage remains challenging, as similar MRI lesions are also seen in inflammatory brain diseases such as limbic encephalitis (Lansberg et al. 1999, Urbach et al. 2006).

CASE SUMMARY

A 75-year-old female patient with a previous history of alcoholism presented to our facility with repeated, prolonged loss of awareness, oral automatisms, and blank stare.

She was currently not consuming alcohol and had no history of complex partial epilepsy. She also had a history of atrial fibrillation, arterial hypertension, and hypercholesterolemia as well as a previous resection of a nodular basal cell carcinoma anterior to the medial right canthus. She had been treated with lercandipine, acetylsalicylic acid, ezetimibe, and simvastatin. She had not been treated with oral anticoagulation due to treatment noncompliance. The patient had no history of autoimmune dysfunction, stroke, or other neurological diseases. Laboratory assessment revealed elevated serum concentrations of C-reactive protein (17.6 mg/L) and nitrituria. Assessment of cerebrospinal fluid (CSF) was normal and repeated immunohistochemical assessment of both CSF and serum did not detect any limbic encephalitis-related antibodies, including onconeural antibodies (anti-Hu, anti Ma-2, anti-CV2/CRMP5, anti-Ri, and anti-amphiphysin) and surface antibodies (anti-VGKC complex, anti-NMDAR, anti-AMPA, and anti-Gaba b). EEG showed predominant alpha activity and a frontal and temporal slowing in the left hemisphere (theta, 20%, delta 5–10%). The EEG also showed left-sided periodic lateralized epileptiform discharges (PLEDs) (Figure 1). Based on clinical and EEG findings, complex partial status epilepticus was diagnosed. Cranial MRI demonstrated left hippocampal diffusion restriction and T2 hyperintensity (Figure 2, A, B). Treatment with levetiracetam (1000 mg twice daily) and cefuroxime was initiated and the patient was dismissed following cessation of seizures and EEG abnormalities. During hospitalization, she did not show any signs of alcohol withdrawal. Nine months later, she was readmitted to the hospital with generalized tonic-clonic status epilepticus. The diagnosis was based on the characteristic clinical presentation with loss of consciousness and prolonged regular pattern of extension and contraction of the extremities. While CSF analysis was again normal, EEG did not detect any epileptic discharges but showed focal slowing in the right frontal and temporal regions. Routine laboratory assessment was normal except for elevation of creatinine kinase serum concentration (4.11 $\mu\text{mol/s}^*\text{L}$). Cranial MRI now showed hippocampal diffusion restriction and increased T2 signal intensity, similar to the previous scan but in the right hemisphere, as well as atrophy and partial gliotic transformation of the initially affected left hippocampus (Figure 2, C, D). Following acute status epilepticus management at the neurological intensive care unit, including intravenous treatment with clobazame and increase of levetiracetam dosage (increase to 1500 mg twice daily), the patient was successfully stabilized and seizures ceased. After six days she was discharged symptom-free.

DISCUSSION

Even though the reported MRI findings of hippocampal diffusion restriction and consecutive volume loss with partial gliosis are similar to previous reports of progressive atrophy of temporomesial structures in limbic encephalitis, in this case of repeated status epilepticus, repeated immunohistochemical evaluation of serum and CSF did not



FIG. 1. EEG recordings (obtained after the first admission of the patient to our clinic) show periodic lateralized epileptiform discharges. The amplifier was set at $7\mu\text{V}/\text{mm}$. The low-frequency filter was set at 0.3 sec, the high-frequency filter at 70H, respectively.

reveal any signs of either paraneoplastic or nonparaneoplastic encephalitis (Urbach et al. 2006). While an antibody-negative limbic encephalitis form cannot be ruled out, remission of symptoms following antiepileptic treatment without additional application of immune modulating therapy may support the interpretation that the bilateral hippocampal damage observed in our patient is the consequence of prolonged epileptic activity. Although this conclusion remains speculative, as spontaneous remission of seronegative limbic encephalitis without any inflammatory treatment has been previously reported, our patient presented twice with an intermittent symptom-free

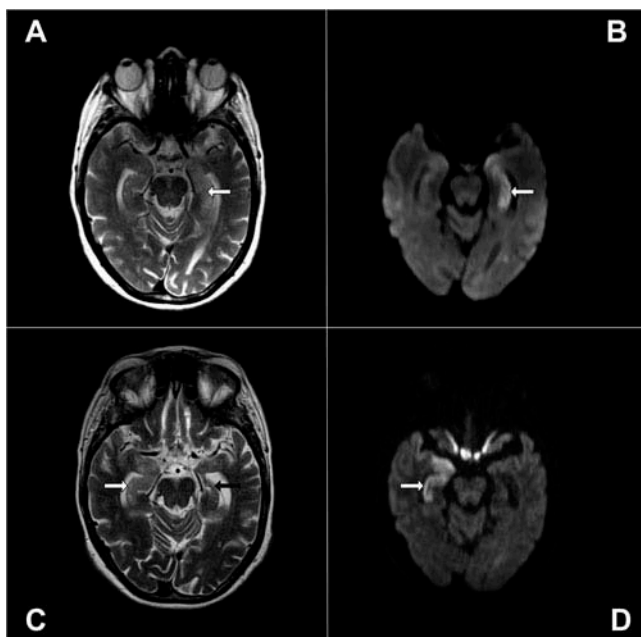


FIG. 2. MRI shows left hippocampal T2-hyperintensity (A) and corresponding diffusion restriction (B) and, following second status epilepticus, contralateral T2 and diffusion lesions (C,D) (white arrows). Figure C also shows gliotic transformation of the initially affected left hippocampus (black arrow). These findings are suggestive of seizure-induced brain damage and are also seen in limbic encephalitis.

episode of nine months and showed no signs of central inflammation in repeated CSF analysis (Najjar et al. 2011).

The acute hippocampal lesions observed in our patient are consistent with a previous retrospective analysis of patients with status epilepticus that identified eight patients with hippocampal increased T2 signal intensity and corresponding diffusion restriction as well as local atrophy in follow-up MRI (Cartagena et al. 2014). However, differently from our patient, six of the reported eight patients also had lesions in extratemporal brain regions such as the frontal cortex and the thalamus, and two additional patients had no abnormalities in the hippocampus but showed T2 hyperintensity in both the cerebellum and the brain stem. Although this retrospective study did not find a specific pattern of configuration and localization of MRI lesions, it emphasized the need for clinical data on status epilepticus-related brain damage.

To the best of our knowledge, this is the first report of subsequent bilateral hippocampal diffusion restriction with consecutive gliotic transformation and atrophy. While these lesions vividly demonstrate permanent structural brain damage, the possible

underlying mechanisms remain speculative. Status epilepticus has been previously linked to compromised ATP metabolism of hippocampal neurons due to increased glucose utilization without sufficient increase of blood flow, and consecutive cytotoxic cell swelling and vasogenic edema leading to hypermetabolic necrosis (Wasterlain 1993, Cartagena 2014). Additionally, excitotoxic mechanisms mediated by both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors opening neuronal calcium channels have been suggested to contribute to cell damage in status epilepticus (Wasterlain 1993, Shorvon and Walker 2005, Arman et al. 2011). Furthermore, the results of in vitro analysis of human brain tissue from pharmacoresistant patients with mesial temporal lobe epilepsy who underwent focal resection surgery lend support to the animal research-based hypothesis of toll-like receptor 4, activating transcription factor-3, and interleukin 8-mediated inflammation in status epilepticus. This study even found a positive correlation of inflammation mediator expression and seizure frequency, supporting its possible clinical relevance (Pernhorst et al. 2013).

Recent research has focused on the pathways of ATP-induced microglial activation in status epilepticus to elucidate the underlying mechanisms and identify potential treatment targets. In rats, activation of microglial cells in response to status epilepticus shows region-specific patterns in the hippocampus. Status epilepticus-induced microglial responses appear to be modulated by P2X7 receptor function as well as NMDA receptor function, but the exact mechanisms of regional-specific microglial activation remain not fully elucidated (Choi et al. 2012, Eyo et al. 2014, Mesuret et al. 2014). Animal studies have demonstrated that prolonged seizures lead to release of ATP from cells with consecutive activation of the P2 class of purinoceptors (Burnstock 2008). P2X receptors are cation-permeable receptors that gate depolarizing entry of calcium and sodium. These ionotropic receptors are expressed by cerebral glia and neurons. Several P2X receptor subtypes are upregulated after status epilepticus (Henshall et al. 2013). Among P2X subtypes the P2X7R receptor seems to play a prominent role in epilepsy-induced brain damage. The P2X7R receptor induces microglial activation and mediates the release of interleukin 1 β , a proepileptogenic inflammatory cytokine. There are also data from animal studies indicating that this receptor directly modulates neurotransmission and gliotransmission and mediates migration of immune cells into brain tissue (Engel et al. 2012, Henshall and Engel 2015). Antagonism of the P2X7R in an animal model of increased P2X7R expression in the neocortex and hippocampus was shown to reduce severity of seizures, activation of microglia, and release of interleukin 1 β , and consequently brain damage (Engel et al. 2012). While these findings indicate that P2X receptors may constitute potential targets for seizure-controlling treatment strategies and antagonism of neuroinflammation post-status epilepticus, the potential translation of the animal research-based findings into humans remains to be explored.

Although the aforementioned animal and ex vivo studies of status epilepticus provide insight into possible pathways whereby seizure activity may lead to brain damage, we can neither determine the specific mechanistic cause of hippocampal atrophy

in our patient nor rule out the possibility of antibody-negative limbic encephalitis-induced brain damage and consecutive symptomatic epilepsy. However, viewed in conjunction with the current literature, our observation of subsequent hippocampal diffusion restriction with consecutive atrophy and gliotic transformation demonstrates the need for further research to elucidate the underlying pathomechanisms of status epilepticus-associated brain damage. Moreover, this report of progressive hippocampal lesions in status epilepticus may contribute to further investigations of longitudinal brain damage pattern analysis in epileptic patients and to a better understanding of structural disease progression.

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REFERENCES

- Arman F, Kaya D, Dincer A, Sav A, Pamir MN. Serial EEG and MRI changes in status epilepticus-induced excitotoxic neuronal necrosis. *Epileptic Disord* 2011;13:446–51.
- Betjemann JP, Lowenstein DH. Status epilepticus in adults. *Lancet Neurol* 2015;14:615–24.
- Burnstock G. Purinergic signalling and disorders of the central nervous system. *Nat Rev Drug Discov* 2008;7:575–90.
- Cartagena AM, Young GB, Lee DH, Mirsattari SM. Reversible and irreversible cranial MRI findings associated with status epilepticus. *Epilepsy Behav* 2014;33:24–30.
- Choi HK, Ryu HJ, Kim JE, Jo SM, Choi HC, Song HK, Kang TC. The roles of P2X7 receptor in regional-specific microglial responses in the rat brain following status epilepticus. *Neurol Sci* 2012;33:515–5.
- Engel T, Gomez-Villafuertes R, Tanaka K, Mesuret G, Sanz-Rodriguez A, Garcia-Huerta P, Miras-Portugal MT, Henshall DC, Diaz-Hernandez M. Seizure suppression and neuroprotection by targeting the purinergic P2X7 receptor during status epilepticus in mice. *FASEB J* 2012;4:1616–28.
- Engel T, Jimenez-Pacheco A, Miras-Portugal MT, Diaz-Hernandez M, Henshall DC. P2X7 receptor in epilepsy; role in pathophysiology and potential targeting for seizure control. *Int J Physiol Pathophysiol Pharmacol* 2012;4:174–87.
- Eyo UB, Peng J, Swiatkowski P, Mukherjee A, Bispo A, Wu LJ. Neuronal hyperactivity recruits microglial processes via neuronal NMDA receptors and microglial P2Y12 receptors after status epilepticus. *J Neurosci*. 2014;34:10528–40.
- Henshall DC, Diaz-Hernandez M, Miras-Portugal MT, Engel T. P2X receptors as targets for the treatment of status epilepticus. *Front Cell Neurosci* 2013;7:237.
- Henshall DC, Engel T. P2X purinoceptors as a link between hyperexcitability and neuroinflammation in status epilepticus. *Epilepsy Behav* 2015;49:8–12.
- Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. *Neurology* 1999;52:1021–7.
- Mesuret G, Engel T, Hessel EV, Sanz-Rodriguez A, Jimenez-Pacheco A, Miras-Portugal MT, Diaz-Hernandez M, Henshall DC. P2X7 receptor inhibition interrupts the progression of seizures in immature rats and reduces hippocampal damage. *CNS Neurosci Ther* 2014;20:556–64.
- Najjar S, Pearlman D, Zazzag D, Devinsky O. Spontaneously resolving seronegative autoimmune limbic encephalitis. *Cogn Behav Neurol* 2011;24:99–105.
- Pernhorst K, Herms S, Hoffmann P, Cichon S, Schulz H, Sander T, Schoch S, Becker AJ, Grote A. TLR4, ATF-3 and IL8 inflammation mediator expression correlates with seizure frequency in human epileptic brain tissue. *Seizure* 2013;22:675–8.

- Rossetti AO, Hurwitz S, Logroscino G, Bromfield EB. Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry* 2006;77:611–5.
- Shorvon S, Walker M. Status epilepticus in idiopathic generalized epilepsy. *Epilepsia* 2005;46(Suppl 9):73–9.
- Urbach H, Soeder BM, Jeub M, Klockgether T, Meyer B, Bien CG. Serial MRI of limbic encephalitis. *Neuroradiology* 2006;48:380–6.
- Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 1993;34(Suppl 1):S37–53.