Clinical commentary

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Transient lesions of the splenium of the corpus callosum following rapid withdrawal of levetiracetam*

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ABSTRACT – Transient lesions of the splenium of the corpus callosum are characterized by MRI findings. The lesions are very rare, but significant from a clinical standpoint as differential diagnoses include serious conditions such as encephalitis, meningitis, and neuroleptic malignant syndrome. In addition, it is reported that some are attributed to the withdrawal of antiepileptic drugs. Here, we present a case of transient lesions of the splenium of the corpus callosum following rapid withdrawal of levetiracetam alone. To the best of our knowledge, this is the first report of such a case. Moreover, it is reported that cases of incidental transient lesions of the splenium of the corpus callosum are detected in Japan more often than in other countries, and as a result are prone to over-triage. Taking this into consideration, in the event of transient lesions of the splenium of the corpus callosum, the utmost attention must be paid to clinical symptoms and history relating to any of the aforementioned serious conditions.

Key words: Transient lesion, splenium of the corpus callosum, MRI, levetiracetam, drug side-effect, anticonvulsant

Transient lesions of the splenium of the corpus callosum (SCC) are characterized by MRI findings. The MRI signal pattern consists of T2 hyperintensity, T1 hypointensity, hyperintense signal on heavily diffusion-weighted imaging (DWI), and hypointensity on apparent diffusion coefficient (ADC) maps (Nelles *et al*., 2006). The focal lesions are found in different clinical conditions, and some are attributed to the withdrawal of antiepileptic drugs (AEDs) (Mirsattari *et al*., 2003).

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The pathophysiological mechanisms of reversible lesions of the SCC remain unclear. The finding is very rare, but significant from a clinical standpoint as differential diagnoses include serious and fatal conditions such as encephalitis, meningitis, and neuroleptic malignant syndrome. It has been reported that withdrawal of carbamazepine (CBZ) accounts for the majority of drug-induced cases of lesions of the SCC. Levetiracetam (LEV) is increasingly used as anticonvulsant therapy due to an apparent low toxicity. Somnolence, asthenia, headache, dizziness, and nervousness are the most frequently reported side effects (Nasrallah and Silver, 2005). LEV is an (S)-enantiomer of the ethyl analogue of piracetam, in the class of nootropic drugs, classified as pharmacologically safe. Although the precise mechanism of action is unknown, in animal models it has been shown to bind to synaptic vesicle protein SV2A. This protein has been related to modulation of synaptic vesicle exocytosis and neurotransmitter release. Animal models have shown that the affinity for SV2A is associated with protection against seizures, making it an important target for new AEDs (Wright *et al*., 2013). Nelles *et al*. (2006) reported two patients in whom a splenial lesion was seen after cessation of LEV, but CBZ was combined with LEV in those cases. Here, we report an SCC lesion following rapid withdrawal of LEV alone. To the best of our knowledge, this is the first report of such a case.

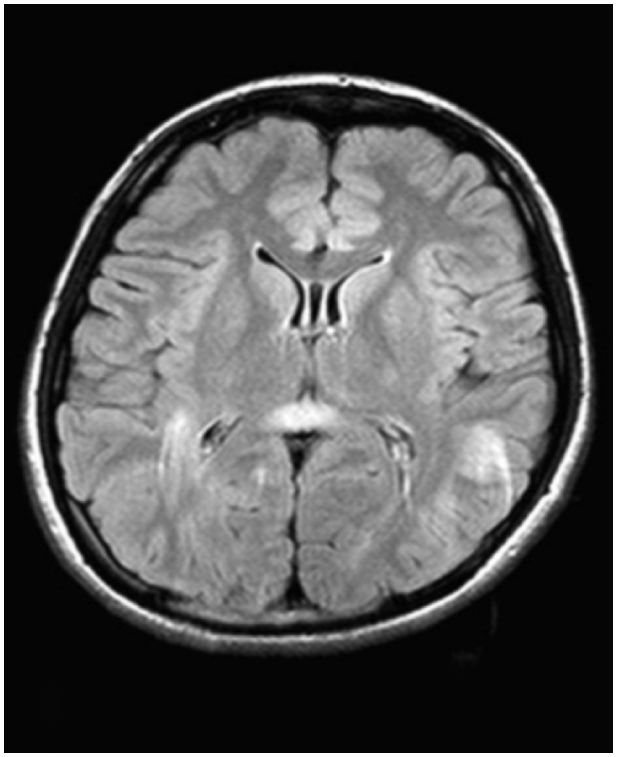

Figure 1. Brain MRI performed on the nineteenth day after admission (19 days after cessation of LEV), revealing an isolated oval-shaped abnormal signal on a mid-portion of the SCC with high intensity on T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR).

Case study

An 18-year-old female presented at our hospital with depressive symptoms over the last month. She had been receiving treatment with AEDs for two years due to the following symptom: while having a conversation with her mother, she suddenly gazed at a point and was unable to talk for several minutes. The symptom reoccurred approximately once a week following the first episode. She had no history of drinking or narcotic usage and her family medical history was unremarkable. She had no past medical history besides dental treatment involving an orthodontic bracket. At the time of her first visit, she was taking 1,000 mg/day LEV for control of the above epileptiform symptom for two months. However, her symptom had shown no signs of improvement and, moreover, she had entered a depressive episode, which was thought to be a drug-induced psychiatric side effect. Also, we found that she had been experiencing auditory hallucinations, insertion of thoughts, and delusions of persecution. EEG findings were normal. This led us to conclude that schizophrenia was a more valid diagnosis than epilepsy. As a result, LEV was immediately stopped and second-generation antipsychotics were administered as a main treatment drug on admission. To rule out intracranial lesion, MRI of the brain was performed on the nineteenth day after admission (19 days after cessation of LEV). MRI revealed an isolated oval-shaped abnormal signal on a mid-portion of the SCC with high intensity on T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) (*figure 1*). However, neither physical nor neurological symptoms were observed on examination. Blood tests and lumber puncture were performed to rule out encephalitis and meningitis. Findings were negative. As a result, we decided to pay close additional attention to her symptoms. Repeat MRI of the brain, 26 days after initial scanning (45 days after withdrawal of LEV) showed no presence of SCC. The final diagnosis was refractory schizophrenia, and her psychotic symptoms improved with clozapine treatment.

Discussion

Brain MRI of our patient, who was finally diagnosed with schizophrenia, showed an isolated ovoid lesion in the SCC after administration of the AED LEV was discontinued. In our case, the lesions of the SCC showed high intensity on T2WI and FLAIR. Unfortunately,

T1-weighted imaging (T1WI), DWI, and ADC mapping could not be correctly assessed due to artefacts caused by the orthodontic bracket. It has been reported that lesions of the SCC generally show low intensity on T1WI, high intensity on DWI, and a decreased ADC map (Nelles *et al*., 2006).

The pathophysiology of transient lesions of the SCC is unknown. Kim and colleagues reported that the cytotoxicity of AEDs themselves may be related to transient lesions of the SCC (Kim *et al*., 1999). Krause and colleagues reported that changes in serum arginine vasopressin concentrations caused by cessation of AEDs may cause focal brain oedema (Krause *et al*., 1983). Honda and colleagues reported that the transiently decreased ADC map may be related to transient lesions of the SCC (Honda *et al*., 2006). Most AEDs, including CBZ, target cation channels and also interact with antidiuretic hormone (ADH), both of which can influence water balance. AEDs can potentiate the antidiuretic effect of ADH, and continuous AED treatment can lead to a reduction in ADH serum levels. Lesions in the SCC in patients on AEDs may indicate transient cerebral oedema mediated by the influence of the rapid change in serum levels of ADH.

Moreover, two cases of syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hyponatraemia induced by LEV are reported (Nasrallah and Silver, 2005; Ari *et al*., 2015). Therefore, LEV may involve the same pathway used by other AEDs to induce SCC by interacting with ADH and affecting water balance. However, as hyponatraemia was not detected in our case, the above speculation may not be valid. An *in vitro* study showed that LEV could effectively reduce brain water content, lessen brain oedema, and protect brain tissue by down-regulating aquaporin 4 (AQP4) mRNA expression (Jin *et al*., 2016). Thus, conversely, cessation of LEV may increase brain water content and lead to brain oedema by up-regulating AQP4 mRNA expression. In our case, this may have been a pathophysiological mechanism for transient lesions of the SCC in response to LEV.

On the other hand, it has been reported that incidental cases of transient lesions of the SCC are more often detected in Japan than in some other countries (Yogi and Murayama, 2010). This is due to a comparatively greater availability of MRI and a greater tendency for Japanese physicians to utilize it. It is often said that patients with transient lesions of the SCC tend to have unnecessary or invasive examinations, such as lumber puncture (Yogi and Murayama, 2010). Moreover, these patients have no neuropsychiatric symptoms and a history of withdrawal of AEDs.

Taking this into consideration, in the event of a lesion of the SCC, additional careful attention must be paid to clinical symptoms and history related to the aforementioned serious and fatal conditions which comprise the differential diagnoses. In our case, a history of cessation of AEDs was apparent, but psychotic symptoms were protracted. Accordingly, we decided to focus on ruling out clinical conditions such as encephalitis and meningitis by performing lumber puncture after consultation with neurologists. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
The authors have no conflict of interest to disclose.

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TEST YOURSELF

(1) What are the characteristic imaging features of transient lesions of the splenium of the corpus callosum?

(2) What should be considered in the differential diagnosis of transient lesions of the splenium of the corpus callosum?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".