Epileptic Disord 2020; 22 (5): 678-82

Efficacy of rituximab on seizure control and cognitive symptoms in leucine-rich, glioma-inactivated 1 (LGI1) limbic encephalitis: a high-density electroencephalography case study

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Received April 30, 2020; Accepted July 27, 2020

ABSTRACT – LGI1 encephalitis is an autoimmune disorder characterized by cognitive symptoms and seizures, which rarely respond to common antiepileptic drugs (AEDs). Rituximab (RTX) is a CD-20-depleting monoclonal antibody which has been used for the treatment of LGI1 encephalitis, however, its efficacy remains controversial. A 54-year-old woman came to our attention due to memory loss and gambling. Brain MRI revealed areas of bilateral hippocampal hyperintensity and LGI1 antibodies were found in both serum and cerebrospinal fluid. Immunotherapy with steroids was started, followed by intravenous immunoglobulins with partial improvement. The patient developed multiple generalized tonic-clonic seizures. She was then administered intravenous rituximab with significant improvement for both cognitive symptoms and seizure control. High-density EEG was recorded before treatment, seven days after the first dose and seven days after the second dose. Topoplot and power spectrum analysis were performed for each recording. Interictal epileptiform discharges, as well as theta power bands, were significantly reduced after each dose, while topoplot analysis showed reduced spreading over posterior and frontal electrodes for interictal epileptiform discharges of temporal origin. Our experience indicates that rituximab is a valid treatment for LGI1 encephalitis, demonstrating efficacy for both cognitive symptoms and seizure

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doi:10.1684/epd.2020.1213

control. High-density EEG could represent a novel, safe and reproducible method to study epileptogenesis in autoimmune limbic encephalitis.

Key words: leucine-rich glioma-inactivated 1, limbic encephalitis, epilepsy, immunotherapy, rituximab

Limbic encephalitis (LE) is an autoimmune disorder characterized by psychiatric disturbances, seizures and working memory deficits. In leucine-rich, glioma-inactivated 1 (LGI1) encephalitis, focal seizures, such as pathognomonic faciobrachial dystonic seizures (FBDS), gelastic seizures, ictal bradycardia, and sensory and autonomic seizures usually occur before cognitive disturbances, while on the other hand, generalized tonic-clonic seizures (GTCS) are rarely observed, and often seen in later stages of the disease. Cognitive and psychiatric disturbances encompass a wide range of symptoms, such as short-term amnesia, behavioural disturbances (hazardous behaviours, irritability), hallucinations or insomnia (Binks *et al*., 2018). Immunotherapy is the most effective treatment for this condition, both for cognitive symptoms and seizure control, but the effectiveness of anti-CD20 therapy, *e.g.* rituximab (RTX), is fairly controversial (Irani *et al*., 2014; Markovic *et al*., 2020).

We report a case of LGI1 encephalitis in a patient treated with RTX, in whom the effect of treatment on epileptic manifestations was evaluated using 256-channel high-density electroencephalography (HD-EEG).

Case report

A 54-year-old Caucasian woman came to our attention with a three-month progressive history of depression, memory loss, and gambling. Her neuropsychological evaluation showed severe anterograde and retrograde amnesia, confabulation and a dysexecutive syndrome. A brain MRI scan showed areas of bilateral hippocampal hyperintensity on T2/FLAIR sequences. A mild increase in protein CSF concentration (50.4 mg/dL; normal range: 15-45 mg/dL) was detected, with normal cell count (5 NE/μL; normal value <5 NE/μL); CSF oligoclonal bands were absent. Onconeural and neuronal surface antibodies were tested in serum and CSF, and both samples were positive for LGI1 antibodies. Whole-body 18-FDG-PET CT showed increased FDG uptake in the left hippocampus, without underlying malignancies. LGI1 LE was diagnosed. The patient underwent a high-dose i.v. steroid treatment (methylprednisolone at 1,000 mg for five days), followed by oral steroid therapy, without substantial improvement with regards to cognitive and behavioural performance. Steroids were withdrawn due to side effects. Subsequently, the patient experienced generalized seizures with no clear evidence of focal origin (generalized seizures of unknown onset). Despite antiepileptic treatment with levetiracetam (1,000 mg x3) and lacosamide (200 mg x2), no adequate seizure control was obtained. Three weeks after high-dose steroid treatment, the patient was treated with i.v. immunoglobulins (0.4 g/kg for five days), with partial improvement of neuropsychiatric symptoms, but poor efficacy on seizures. One month later, treatment with intravenous RTX (1;000 mg x 2, 15 days apart) was started. The patient strikingly improved; indeed, no further seizures occurred, standard EEG was unremarkable, and the neuropsychological evaluation resulted within normal range. Six months after the last dose of RTX, the patient returned to us with a cognitive relapse (worsening of anterograde amnesia, mild confabulation, tendency to reiterate phrases and ideas), with no further seizures. The relapse completely resolved with a single dose of RTX at 1000 mg.

In order to evaluate the possible effect of RTX on epileptic manifestations, in particular interictal epileptiform discharges (IEDs), we performed a 256-channel HD-EEG (Electrical Geodesic, Inc., Eugene, OR, USA) study at baseline before RTX treatment (T0), seven days after the first dose (T1) and seven days after the second dose (T2), each recording with at least a 30-minute duration. EEG signals were collected using the Net Amps 300, a high-input impedance amplifier (Electrical Geodesics Inc., Eugene OR, USA) with a 256-Hz sampling rate. All channels were digitally filtered with the 0.5-35-Hz second-order bandpass filter. Power spectral density (PSD) was calculated using scripts developed in MATLAB (MathWorks Inc., Natick, MA) on 60-second artifact-free epochs for each channel using Welch's periodogram. The relative power in each spectral band (delta: 1-4 Hz; theta: 4-8 Hz; alpha: 8-13 Hz; beta: 13-30 Hz) was calculated for each channel. IEDs were identified in each recording by a neurologist with experience in electroencephalography and analysed on Topoplot in order to evaluate, by visual inspection, their amplitude and diffusion on single electrodes.

At T0, IEDs were detected by all electrodes, but with higher amplitude in temporal lobes. At T1, IEDs showed a similar pattern, with sparing of central electrodes. At T2, IEDs were confined only to temporal lobes and presented reduced amplitude when

compared to T0. Power spectral analysis showed a predominant diffuse theta activity that progressively reduced after each dose of RTX. Topoplots, theta power bands and bipolar EEG findings are summarized in *figure 1*.

The patient gave her informed consent for the publication of the study.

Discussion

In our patient, RTX was strikingly effective in treating LGI1 encephalitis. The efficacy of RTX for LGI1 encephalitis has been debated. In a retrospective cohort of LGI1 patients, evaluating seizure frequency and modified Rankin Scale (mRS), RTX was clearly effective in only two of five patients (Irani *et al.*, 2014). It should be noted that RTX was administered at later stages of the disease. Another retrospective study of a large cohort of patients with autoimmune LE (Lee *et al.*, 2016) provided some evidence in favour of the use of RTX in terms of mRS, but no specific sub analysis according to patients' serostatus was performed.

A major point against the efficacy of RTX in LGI1 encephalitis (Irani *et al.*, 2014) is that LGI1 antibodies are likely to be pathogenic (Irani *et al.*, 2010), and

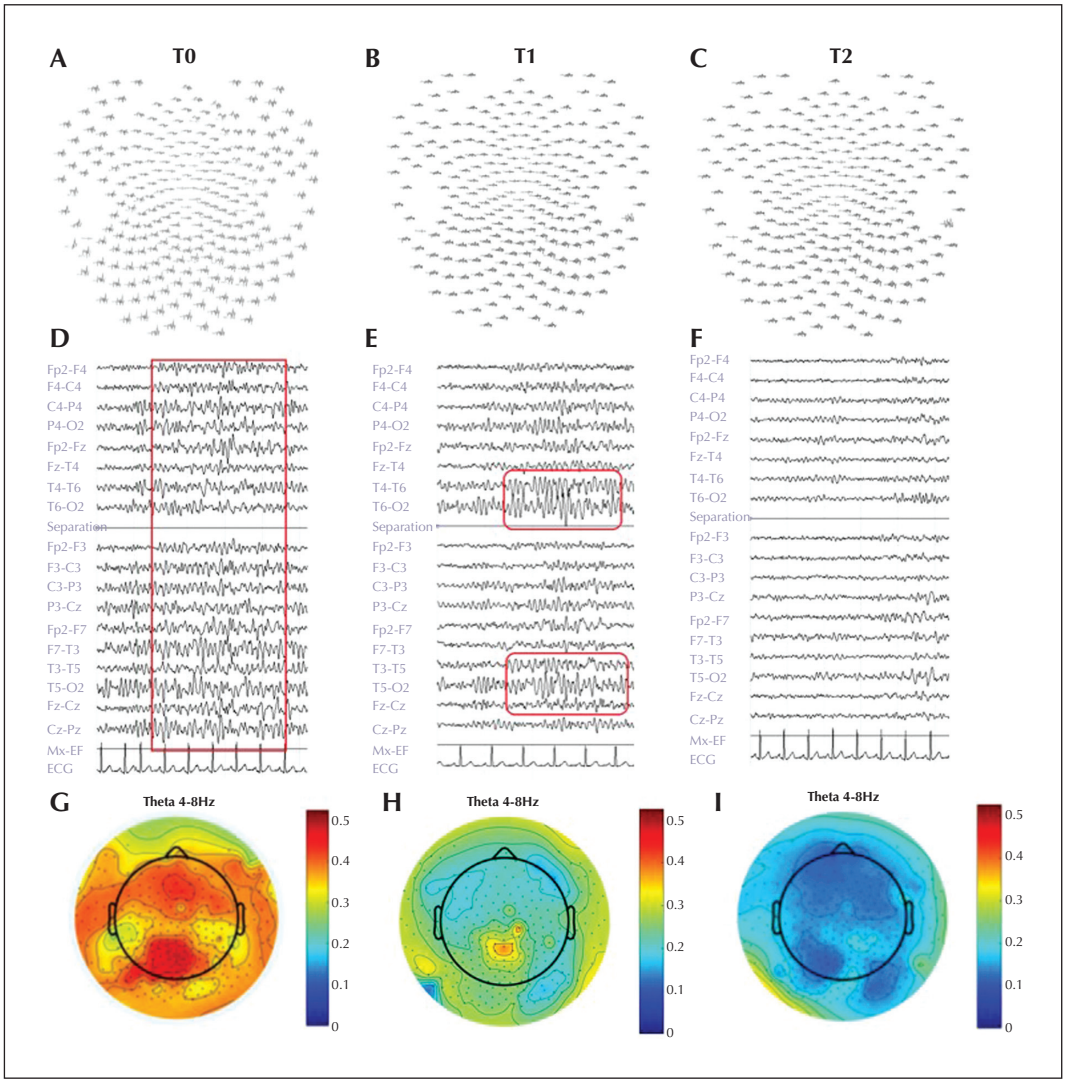

Figure 1. EEG findings before (T0), seven days after the first dose (T1) and seven days after the second dose of RTX (T2). (A-C) Topoplot analysis showing interictal epileptiform discharges (IEDs) originating from temporal lobes with subsequent spreading to the posterior and frontal electrodes at T0 (A). At T1 (B), IEDs are strictly localized to temporal lobes and absent at T2 (C). Bipolar EEG findings at T0, T1 and T2 in (D), (E), and (F), respectively, showing a progressive decrease in IEDs after treatment with rituximab. (G-I) Theta power band activity, which is more prominent at T0 and progressively normalizes after treatment.

anti-CD20 treatment usually does not have a major impact on antibody titres since antibody-secreting cells (ASCs) do not express CD20. Furthermore, it has been recently highlighted that LGI1 autoimmunity is characterized by the presence of an intrathecal monoclonal B-cell response, despite the frequent absence of LGI1 antibodies in CSF and oligoclonal bands (Kornau *et al*., 2020; Lehmann-Horn *et al*., 2020). This unique feature may contradict the use of anti-CD20 therapies that are unable to cross the blood-brain barrier, and therefore favour CNS-penetrating and ASC-targeted drugs.

However, a recent report (Markovic *et al*., 2020) showed the prompt efficacy of anti-CD20 in a patient with aggressive LGI1 LE with a cognitive relapse, two months after disease onset. In this case, steroid monotherapy optimally controlled focal seizures during the acute phase of the disease, while RTX was strikingly effective for cognitive symptoms. In our patient, the improvement of both cognitive symptoms and seizure control was achieved only after treatment with RTX, about five months after the onset of the disease and two months after the diagnosis of LGI1 LE. It could be argued that the improvement was secondary to a cumulative dose of previous first-line immunotherapies, however, one month had passed from the previous intravenous immunoglobulin cycle and the patient was already waned off steroids when RTX was administrated. Moreover, the HD-EEG findings and clinical improvement demonstrated remarkable concurrence. Before RTX, at T0, IEDs were mainly expressed in the temporal lobes, consistent with CA3-CA1 hippocampal epileptogenesis associated with LGI1 antibodies (Romoli *et al*., 2019), and subsequently diffused to the other cortical regions. After two doses of RTX, the spreading of the IEDs was significantly reduced, since IEDs were strictly localized to their temporal foci. Furthermore, a similar remarkable reduction was found based on the analysis of spectral power data; theta power band progressively reduced after each dose of RTX with an improvement in alpha power band. The role of slow activity is particularly intriguingly since it has been hypothesized to represent limbic status epilepticus (Kaplan *et al*., 2012). Taken together, all these findings support the efficacy of RTX in controlling seizures in patients with LGI1 encephalitis.

For LGI1 encephalitis, well-established characterization of ictal and interictal EEG patterns is lacking, and besides a peculiar pattern in FBDS (Vogrig *et al*., 2019), only unspecific abnormalities such as generalized or focal theta/delta slowing and temporal IEDs have been described (Gao *et al*., 2016; Chen *et al*., 2017). A major limitation of the previous studies was the use of standard scalp EEG, which may not detect discharges originating from deep structures (Chen *et al*., 2017). HD-EEG could be a useful tool to characterize these patterns. Indeed, while it was only possible to detect generalized IEDs using standard EEG, HD-EEG allowed us to identify their temporal origin and their subsequent generalized spreading, proving that, in this condition, even generalized seizures may have a focal origin in deeper structures. HD-EEG has been used mainly in the setting of source localization in refractory epileptic patients due to its high temporal and good spatial resolution, as well as its capability of evaluating deep brain regions such as temporal lobes (Del Felice *et al*., 2014; Storti *et al*., 2014). Indeed, electric source imaging (ESI) has the potential to separate the primary focus from propagation areas and is becoming a fundamental tool in multimodal presurgical epilepsy evaluation. Further studies, including more patients with limbic encephalitis and using ESI, may better define spatial and temporal diffusion of IEDs. This hypothesis is particularly interesting since other neuroimaging techniques that are part of presurgical epilepsy evaluation, in association with ESI (Storti *et al*., 2014), such as arterial spin labelling and PET, are more frequently being used in the field of autoimmune neurology.

Conclusion

Treatment with RTX led to a substantial improvement in cognitive symptoms and complete seizure control in a patient with LGI1 encephalitis. The HD-EEG study, which may represent a novel method to study epileptogenesis in LE, confirmed the efficacy of RTX in reducing IEDs spreading from the temporal lobes and reducing the theta power band. Further evidence is needed to confirm RTX efficacy in LGI1 encephalitis using randomized, double-blind, controlled trials. □

Disclosures.
None of the authors have any conflict of interest to declare.

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