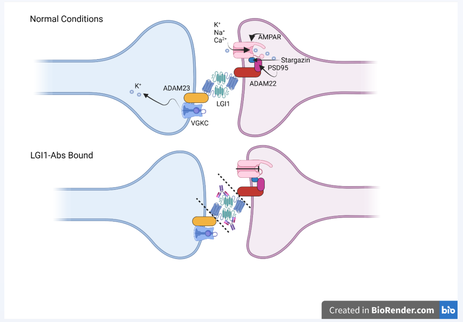
Patient-derived leucine-rich glioma inactivated 1 (LGI1) protein antibody causes seizures in a passive transfer rodent model

Sukhvir Wright,[1] Manoj Upadhya,[1] Jack O'Brien-Cairney,[1] Richard Rosch,[2] Gavin Woodhall,[1] Dietmar Schmitz,[3] Harald Prüss,[3] Hans-Christian Kornau[3]

[1]School of Health and Life Sciences, Aston University, Birmingham, UK [2]Department of Clinical Neurophysiology, King's College Hospital NHS Foundation Trust [3]German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

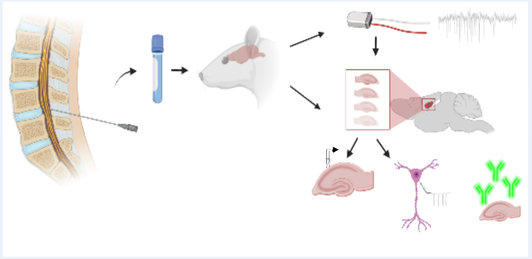
INTRODUCTION and AIMS

Facio-brachial dystonic seizures (FBDS), limbic encephalitis and cognitive impairment are seen in patients with autoantibodies to the leucine-rich glioma inactivated 1 (LGI1) protein.[1,2] Despite successful modelling of the cognitive changes in vivo, seizures have not been seen. Using patient cerebrospinal fluid derived monoclonal LGI1 antibodies (LGI1-mAbs) we developed a passive transfer rodent model to investigate the in vivo and in vitro electrophysiological effects.[3,4]



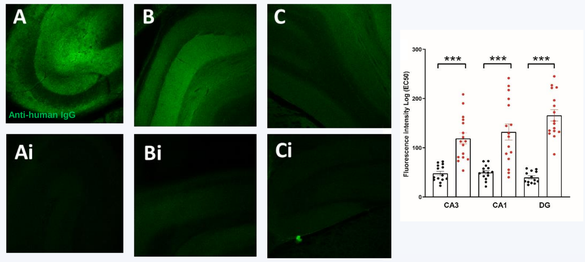
MATERIALS and METHODS

Juvenile male Wistar rats were implanted with osmotic pumps (Alzet,USA) containing control antibodies (n=6) or LGI1 monoclonal antibodies (mAbs) (n=6) for 7-day intracerebroventricular antibody infusion. Wireless EEG transmitters (Opensource Instruments) were used to record EEG from a hippocampal CA3 depth electrode for 21 days. EEG was analysed using automated ictal event detection (Neuroarchiver) and custom code for powerband analysis. Brain slices were used for in vitro electrophysiology and immunostaining.

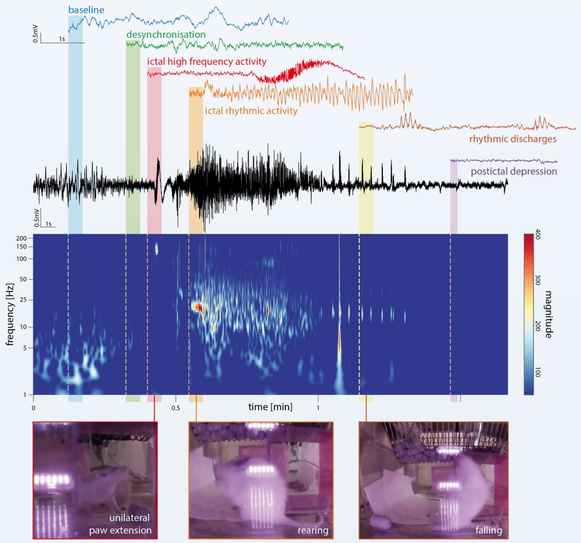


RESULTS

Hippocampal binding of the LGI1-mAbs was confirmed on post-mortem immunohistochemistry.



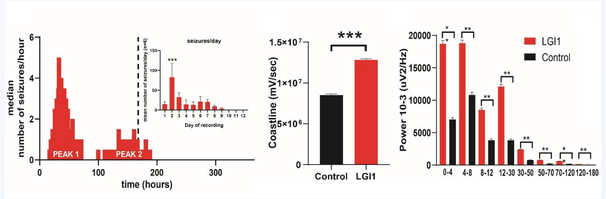
Video-EEG analysis and automated ictal event detection revealed spontaneous epileptic seizures in all 6 LGI-mAb infused rats and none in controls.



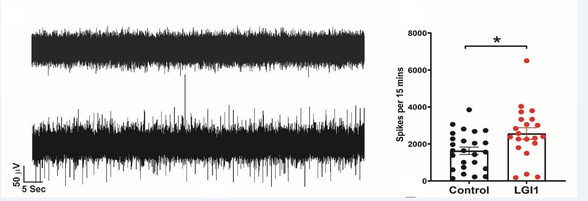
Example EEG trace (black) from LGI1-mAb infused rat recorded from depth electrode placed in hippocampal CA3 with highlighted, colour-coded breakdown of seizure EEG features at different phases of the seizure.

RESULTS

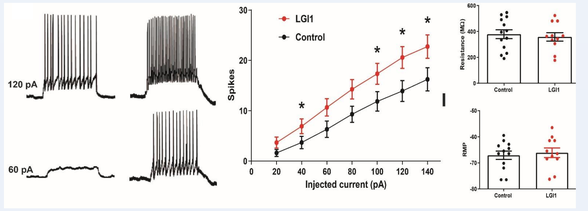
Two discrete peaks of seizure activity were observed within the 7-day infusion period, the highest seizure frequency observed on day 2. EEG coastline length was significantly increased in LGI1-mAb animals compared to controls ($p<0.001$). The power in all EEG frequency bands was significantly higher in the LGI1-Mab infused animals ($p<0.01$).



Local field potential recordings from day two LGI1-mAb injected brain slices (n=21 slices from 8 animals) showed an increase in spontaneous ictal-like spike activity in the CA3 region as compared to control slices (n=25 slices from 9 animals; $p=0.01$).



Hyperexcitability of CA3 pyramidal cells from LGI-mAb infused slices was also seen in whole-cell patch clamp recordings (n=11 cells from 3 animals vs 13 cells from 4 animals; $p<0.05$).



CONCLUSIONS

LGI1-Abs are associated with FBDS, tonic-clonic and temporal lobe seizures in affected patients. In this study we have demonstrated the emergence and evolution of seizures during an intracerebroventricular infusion of patient CSF-derived monoclonal LGI1 autoantibodies in vivo. Continuous wireless depth EEG recordings from the CA3 region of the hippocampus revealed an initial explosive onset of convulsive seizures within 48 hours of antibody infusion showing phenotypic parallels with FBDS. This was followed by a second, smaller peak of ictal activity. This observed EEG change reflects the natural history of LGI1 autoantibody-associated seizures in humans that start with an initial high frequency of acute seizures progressing to an epileptic encephalopathy/limbic encephalitis. It is now well established that immunotherapy can halt the progression to limbic encephalitis if FBDS is identified and treated acutely in patients.[5] This bi-phasic seizure model will greatly facilitate pre-clinical treatment trials providing a window of intervention between the first and second seizure peaks to assess therapeutic effectiveness.

REFERENCES

1. Lai, M., et al., Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol, 2010. 9(8): p. 776-85.
2. Irani, S.R., et al., Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain, 2010. 133(9): p. 2734-48.
3. Wright, S.K., et al., Multimodal electrophysiological analyses reveal that reduced synaptic excitatory neurotransmission underlies seizures in a model of NMDAR antibody-mediated encephalitis. Commun Biol, 2021. 4(1): p. 1106.
4. Kreye, J., et al., Encephalitis patient-derived monoclonal GABAA receptor antibodies cause epileptic seizures. J Exp Med, 2021. 218(11).
5. Irani, S.R., et al., Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain, 2013. 136(Pt 10): p. 3151-62.