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Case Report

Laser interstitial thermal therapy for NPRL3-related epilepsy with multiple seizure foci: A case report

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ABSTRACT

Introduction: NPRL3 gene mutations cause autosomal dominant familial focal epilepsy of variable foci (FFEVF) and is characterized by focal epilepsy arising from different brain regions including temporal, frontal, parietal and occipital lobes. About 50% of patients with NPRL3 related epilepsy are resistant to medical treatment. Method: We present a case of 27 years old man with NPRL3 related focal drug-resistant epilepsy. Stereotactic EEG showed two independent seizure foci, namely, left hippocampus and left orbitofrontal cortices. He underwent laser interstitial thermal therapy for ablating both foci in the same procedure that led to seizure cessation. Conclusion: laser interstitial thermal therapy can be an effective treatment for drug resistant NPRL3 related focal epilepsy with better tolerance and less morbidity as compared to open surgical resection, particularly in those with multiple seizure foci.

Introduction

NPRL3 (nitrogen permease regulator-like 3) variants have been linked to familial focal cortical dysplasia type II, which is pathologically characterized by dysmorphic neurons and balloon cells [1,2]. Mutations in the NPRL3 gene cause an autosomal dominant familial focal epilepsy with variable foci (FFEVF) characterized by focal seizures originating from different cortical regions, including temporal, frontal, parietal, and occipital lobes [3]. Seizures associated with FFEVF can begin at any time from infancy to adulthood. Nearly 50% of patients with NPRL3 related epilepsy are resistant to treatment with anti-seizure medications [3]. Here, we present a case of drug-resistant NPRL3-related epilepsy with a novel heterozygous pathogenic NPRL3 germline mutation. Stereotactic EEG (SEEG) recording revealed two independent seizure foci, one in the left hippocampus and the other in the left orbitofrontal cortex. He underwent laser interstitial thermal therapy (LITT) to ablate both foci in a single procedure resulting in cessation of seizures.

Case report

A 27-year-old right-handed man presented with drug-resistant epilepsy since age 24. His seizures were described as feeling dizzy, staring, heavy breathing, face turning red, body stiffening and shaking with tongue biting and loss of consciousness lasting 1–2 min. His seizures were predominantly nocturnal. His neurological examination was normal. There was no history of traumatic brain injury, CNS infections or childhood febrile seizures. He was initially treated with lamotrigine, levetiracetam and valproate with minimal benefit. At presentation, he had been treated with oxcarbazepine 900 mg twice daily, clobazam 10 mg twice daily and zonisamide 100 mg twice daily. However, he continued to have weekly focal impaired awareness seizure and monthly focal to bilateral tonic-clonic seizures. Family history was notable for epilepsy in several family members. His mother had epilepsy during childhood and seizures stopped spontaneously around her puberty. His 29-year-old brother started having seizures in his early teens and was diagnosed with nocturnal frontal lobe epilepsy (NFLE) that has been well controlled with valproate.

Long-term video-EEG monitoring revealed heterogeneous interictal epileptiform discharges (IEDs) in the left temporal, frontotemporal and orbitofrontal regions (Fig. 1). Left temporal intermittent rhythmic delta activity was also observed. Seizures originated in the left temporal region with early propagation to left orbitofrontal region. Brain MRI and FDG-position emission tomography (PET) were normal. Functional MRI localized language to the left hemisphere. Neuropsychological evaluation showed an average full scale IQ (FSIQ = 100) and impairments in confrontation naming, processing speed, set shifting, and visual constructional planning. Genetic testing (Invitae epilepsy panel, San Francisco, CA) with sequence analysis and deletion/duplication testing of 181 genes

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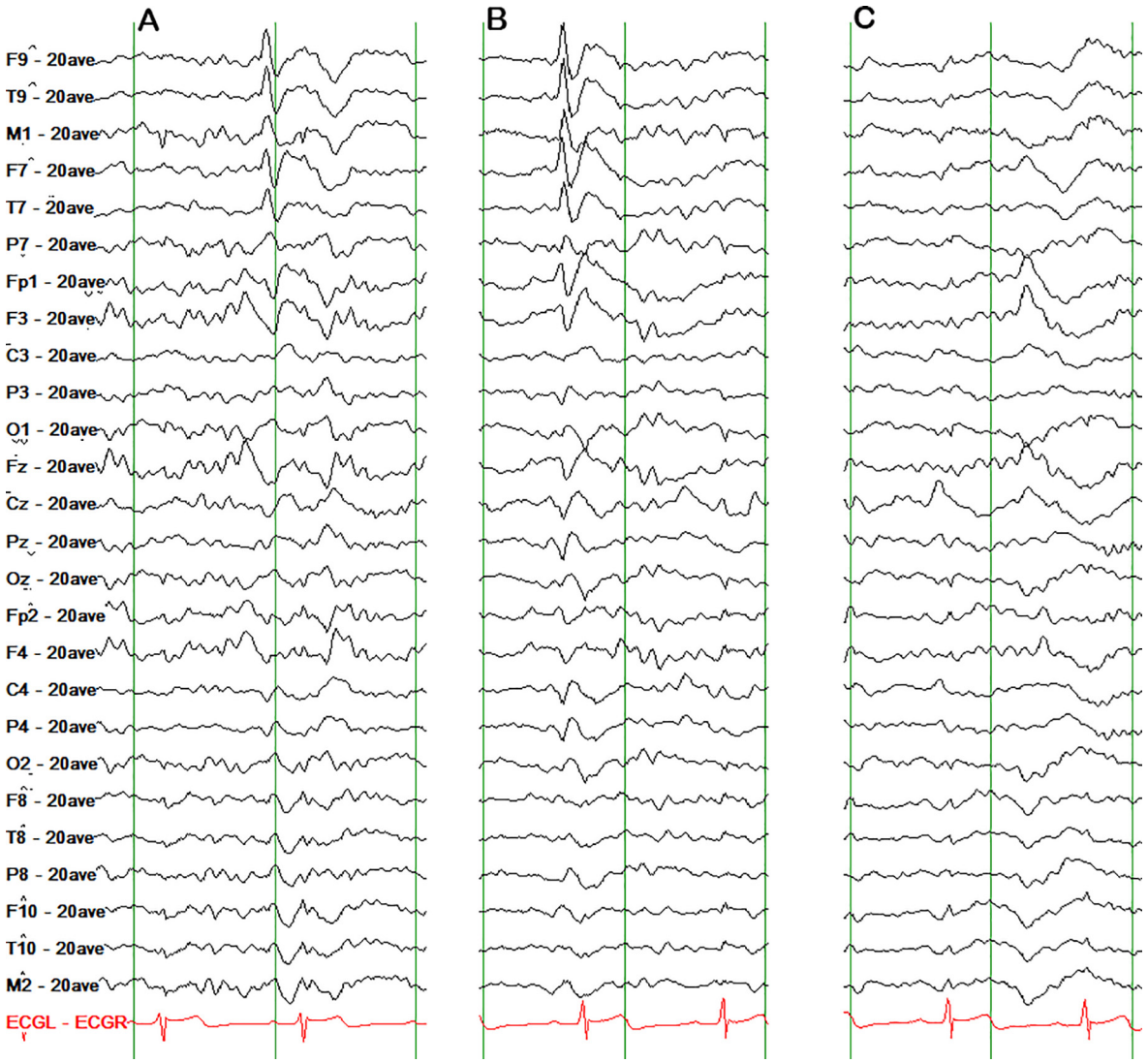

Fig. 1. Heterogeneous interictal epileptiform discharges. **A:** Left temporal sharp wave. **B:** Left frontotemporal sharp wave. **C:** Left orbitofrontal sharp wave. High pass filter: 1 Hz. Low pass filter: 70 Hz. Sensitivity: 10 μV/mm.

revealed a novel pathogenic heterozygous variant c.1270C > T(pArg424*) in exon 12 of NPRL3 gene. The sequence change creates a premature translational stop codon. No mutations were noted in any of the acetylcholine receptors tested.

He underwent SEEG recording with depth electrodes sampling the bilateral amygdalohippocampal complexes, the left anterior, mid and posterior temporal regions, and the left orbitofrontal cortical area. Independent seizure foci were observed in the left hippocampus and the left orbitofrontal cortex (Fig. 2). After discussions with the patient on the benefits and risks of responsive nerve stimulation and LITT as potential treatment options, the latter was chosen for a better chance of seizure freedom that he deemed essential to his employment. The two seizure foci were ablated in a single procedure. The patient has been seizure-free for 12 months after the LITT surgery, and he had no surgical complications except for a transient subjective memory difficult reported by the patient.

Discussion

The mechanistic target of rapamycin (mTOR) signaling pathway is a chief regulator of neural stem cells growth, differentiation, maturation, migration and dendritic development, and is inhibited by GAP activity toward Rag complex 1 (GATOR1) protein complex (DEPDC5, NPRL2, and NPRL3) in response to cellular amino acid level [1,3]. Genetic mutations of GATOR1 complex components have been implicated in the pathogenesis of a wide spectrum of malformations of cortical development (MCD) such as focal cortical dysplasia II, hemimegalencephaly, and megalencephaly. They are associated with familial focal epilepsies such as FFEVF, autosomal dominant nocturnal frontal lobe epilepsy and familial temporal lobe epilepsy [1,3].

The patient in this case had a novel NPRL3 heterozygous germline variant. We speculate that the nonsense mutation resulted in loss of function due to a truncated protein product and haploinsufficiency, which led to the hyperactivation of mTORC1 singling that causes MCD. Given that the brain MRI and PET were normal, the MCD may be related only to altered cortical lamination in this patient, although the tissue was not biopsied so could not be confirmed by histopathology. The clinical manifestations in this case were consistent with those of NPRL3 variants reported in the literature [1,2]. Intellectual function, neurological examination, and neuroimaging were normal. The presenting symptomatology and response to medical treatment varied among the three affected

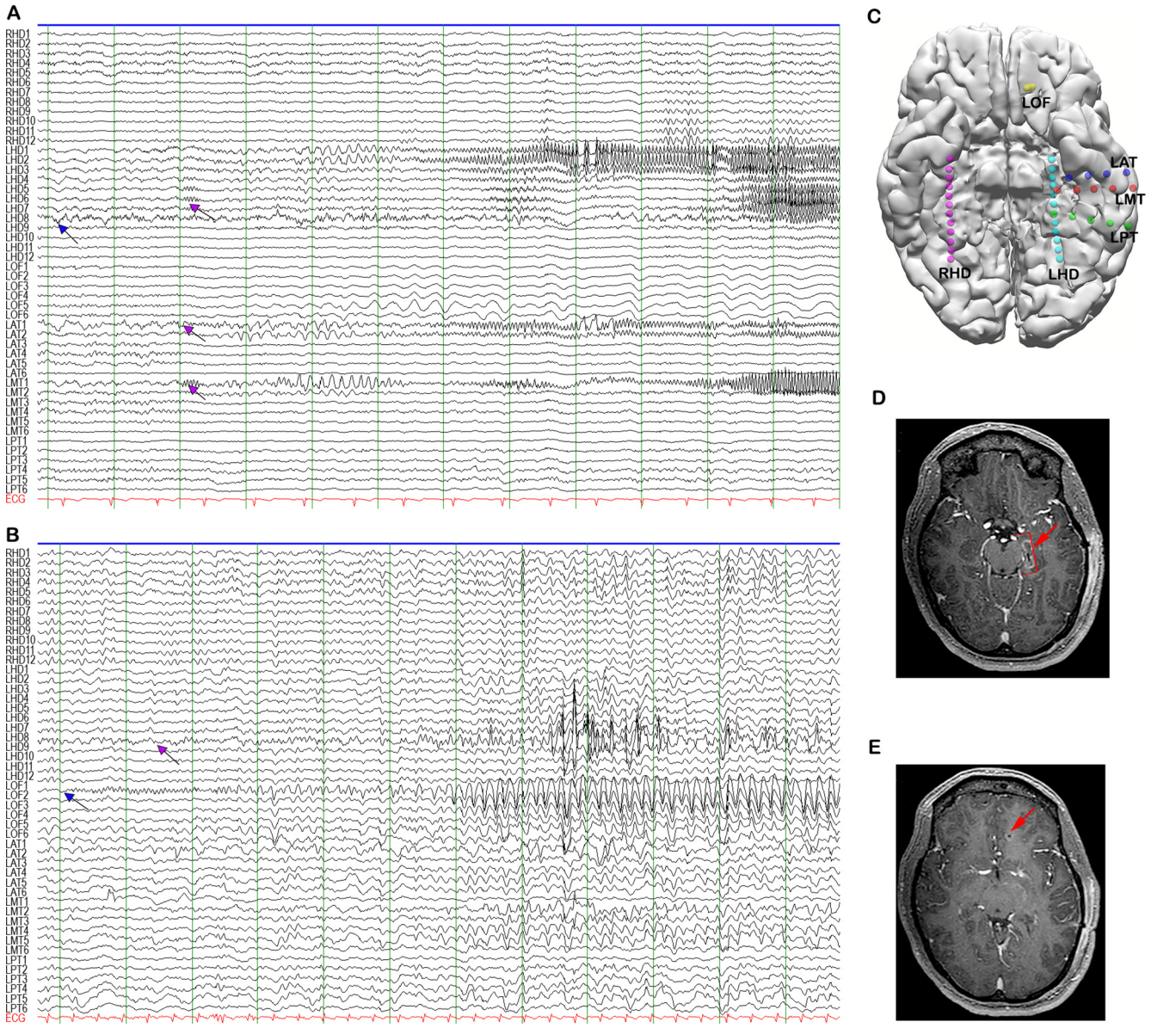

Fig. 2. Illustrations of two independent ictal onsets, depth electrode localization and post-ablation lesions. **A:** left hippocampal ictal onset (LHD7, 8) with propagation to the left anterior temporal (LAT1, 2) and basal temporal (LMT 1, 2) regions. **B:** Left orbitofrontal ictal onset (LOF1) with propagation to the left hippocampus (LHD8). **C:** 3D co-registration (bottom view) of pre-implant brain MRI with post-implant head CT using Curry software version 8 (Compumedics, Charlotte NC. USA). RHD, right hippocampal depth; LHD, left hippocampal depth; LAT, left anterior temporal; LMT, left mid-temporal; LPT, left posterior temporal; LOF, left orbitofrontal. Hippocampal depth electrodes were placed through occipital approach with contact 1 in the furthest anterior orientation. Lateral temporal depth electrodes were placed through the orthogonal approach with contact 1 in the furthest mesiotemporal orientation. Orbitofrontal depth electrode was placed through the oblique approach with contact 1 in the furthest mesiobasal frontal orientation. **E:** Post-contract brain MRI showing the post-ablation lesion in the left amygdalohippocampal complex (red arrow). **F:** Post-contract brain MRI showing the post-ablation lesion in left orbitofrontal region (red arrow). RHD: right hippocampal depth; LHD: left hippocampal depth; LOF: left orbitofrontal; LAT: left anterior temporal; LMT: left mid-temporal; LPT: left posterior temporal. High pass filter: 1 Hz. Low pass filter: 70 Hz. Sensitivity: 100 μV/mm.

family members. His mother, the proband, had a spontaneous seizure remission; his brother has a clinical diagnosis of NFLE and has been well controlled with valproate; and the patient had intractable epilepsy with frontal and temporal foci.

GATOR1-related epilepsy is associated with a markedly increased incidence (~10%) of sudden unexpected death in epilepsy (SDUEP) [1], as compared with the global incidence of 0.22/1000 person years in children and 1.2/1000 person years in adults with epilepsy. The early onset seizures, drug-resistance, and predominantly nocturnal seizures observed in these patients are well-documented risk factors for SUDEP, and therefore, seizure control is paramount for the prevention of SUDEP in this patient population. In a recent case study, target therapy with mTOR inhibitor sirolimus was effective in a neonate with refractory NPRL3-related with epilepsy, but the therapy had to be stopped due to a severe respiratory infection [4]. Early data suggested that resective epilepsy surgery may provide favorable seizure outcomes, and the presence of germline GATOR1 variants does not represent a contraindication for surgery [1,3]. Here, we report that LITT can be an effective treatment for drug-resistant NPRL3-related focal epilepsy with better tolerance and less morbidity compared with open resective surgery, particularly for patients with multiple seizure foci that are commonly not suitable for open resection.

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Ethical standard

This case report was approved by the institutional Review Boards (IRB19-1263) at the University of Chicago.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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