[Research Letter]

Neuroanatomical basis of faciobrachial dystonic seizures in LGI1-antibody encephalitis

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Introduction

Leucine-rich glioma inactivated 1-antibody encephalitis (LGI1-Ab-E), the most common form of autoimmune encephalitis, typically presents with faciobrachial dystonic seizures (FBDS), a hallmark feature characterized by brief dystonic jerks of the face and arm.[1,2] Other semiologies include piloerection, thermal paresthesia, and paroxysmal dizziness.[2] These seizures often lack corresponding electroencephalographic (EEG) changes, meaning they are commonly mistaken for functional attacks.[2] Although putative cellular mechanisms underlying LGI1 antibody-mediated epileptogenesis have been reported,[2] the neuroanatomical basis underlying the distinct clinical manifestations of FBDS remains debated.

Magnetoencephalography (MEG) is a highly sensitive tool for detecting cortical neuronal activity, offering high temporal and spatial resolution. Its technical advantages enable detection of neural signals that are often imperceptible on EEG.[3] Here, we present a neuroanatomical explanation for FBDS and its variants through MEG analysis.

Methods

Simultaneous MEG (306 channels) and EEG recordings were acquired from patients with LGI1-Ab-E presenting with active symptoms and frequent FBDS, at two centers: Seoul National University Hospital and Mayo Clinic, USA. Video monitoring was performed during MEG to confirm FBDS events. Magnetic source localization was performed using single or multiple Equivalent Current Dipole (ECD) models. This study was approved by the institutional review boards of both participating institutions.

Results

Seven patients (5 male, 2 female; mean age 53 ± 13.1 years), all with serum LGI1-IgG

presented with typical clinical features (Table) and underwent MEG. All patients had active seizures at the time of testing, including varying degrees of FBDS or related semiologies. MEG revealed interictal epileptiform discharges (IEDs) that were not observed on prior or concurrent EEGs.

ECD modeling localized dipoles to cortical regions with clear neuroanatomical alignment to patient-reported symptoms (Figure 1A, 1C). Patients with active FBDS exhibited contralateral IEDs that preceded clinical symptoms by 1-2 seconds (ID 1, 7) (Figure 1B, Table), with dipoles localized either to the primary motor cortex, specifically the faciobrachial area of the motor homunculus, or to the medial temporal lobe. The patient with paroxysmal dizziness spells exhibited IEDs in the insular cortex (ID 2). Patients with recurrent thermal sensory attacks had dipoles localized to the somatosensory cortex (ID 3, 4). Typical electrographic seizures were absent in all patients.

Discussion

The electrophysiological basis and localization of FBDS and associated distinctive semiologies in LGI1-Ab-E have remained elusive. Our findings demonstrate involvement of distinct neuroanatomical regions corresponding to the specific semiologies of FBDS and other LGI1-Ab-E associated seizures: the face and arm regions of motor cortex for classical FBDS, the somatosensory cortex for thermal sensory attacks, and the vestibular insular cortex for paroxysmal dizziness spells. These differential localizations to somatotopically relevant cortical areas suggests regionally altered neuronal excitability, likely mediated by LGI1-antibodies.[2] Detailed EEG analyses have also suggested a role for primary motor cortex in FBDS, in conjunction with the striatum.[4] Indeed, LG11-Ab-E is frequently associated with basal ganglia T1 signal changes and hypermetabolism,[5] and this region may yet form a direct or indirect epileptic network with cortical regions.

In addition to localization, these findings confirm FBDS and other short-lived phenomena in patients with LGI1-Ab-E are indeed seizures. LGI1-antibodies can induce neuronal molecular disruptions and hyperexcitability, that may manifest as IEDs.[2] Antibody-mediated ictogenesis and subsequent epileptogenesis can induce acute symptomatic seizure or focal autoimmune-associated epilepsy.[6]

Limitations may include the relatively small number of cases and potential insensitivity of MEG. Nevertheless, our study is the largest MEG series in LGI1-Ab-E to date and overcame a major challenge of recruiting actively unwell, seizing patients. Further studies using network analysis and higher-resolution electrophysiologic techniques with accurate symptom-event correlation may provide more information about the neuroanatomical localization of FBDS semiology.

Author Contributions

Drs Ahn and S-T Lee had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ahn, Irani, S-T Lee.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Ahn, Karaminiya, S-T Lee.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Ahn.

Obtained funding: S-T Lee.

Administrative, technical, or material support: Ahn, Karaminiya, Shin, Ha, Kim, Irani.

Supervision: Irani, S-T Lee.

Conflicts of Interest Disclosures

Dr. S-T. Lee serves on advisory boards for Roche/Genentech, Arialys, argenx, and Advanced Neural Technologies, and Piehealthcare.Dr. Irani has received honoraria/research support from Amgen, Argenx, UCB, Roche, Janssen, IQVIA, Clarivate, Slingshot Insights, Cerebral therapeutics, BioHaven therapeutics, CSL Behring, and ONO Pharma, and receives licensed royalties on patent application WO/2010/046716 entitled 'Neurological Autoimmune Disorders', and has filed two other patents entitled “Diagnostic method and therapy” (WO2019211633 and US app 17/051,930; PCT application WO202189788A1) and “Biomarkers” (WO202189788A1, US App 18/279,624; PCT/GB2022/050614).
The remaining authors have no conflicts of interest.

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The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing statement

Data available: No

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Figure legends

Figure 1. MEG-Based Cortical Source Localization of Epileptiform Discharges in LGI1 Encephalitis

A. Composite coronal sections showing group-level localization of interictal epileptiform discharges (IEDs). IEDs from individual patients are color-coded. Two patients (ID 5, 6) had occipital discharges that are not depicted in this figure. **B.** A representative spike (highlighted in red) localized to the medial temporal region, occurring approximately 2 seconds before the onset of FBDS (gray box). **C.** Schematic illustration of neuroanatomical correspondence between MEG-derived IEDs and recurrent clinical symptoms.

Abbreviations: FBDS=faciobrachial dystonic seizure; LGI1=leucine-rich glioma inactivated 1; MEG=magnetoencephalography; IED=interictal epileptiform discharge.

Table. Patient Clinical Information

ID	Age, sex	Symptoms	FBDS and its variants semiology	MRI FLAIR change	EEG findings	MEG findings
1	42, F	FBDS, memory impairment, psychiatric symptoms.	Brief dystonic jerks in both arms, with stinging pain in right shoulder, occipital area, and leg.	Both medial temporal lobes	NA	Spikes in right mid-posterior-medial-basal temporal regions, including hippocampus.
2	61, M	FBDS, paroxysmal dizziness spells, psychiatric symptoms, memory impairment, focal to bilateral tonic-clonic seizures.	Dystonic jerks in both arms (right > left).	Normal.	Small amount of intermittent generalized theta slow waves.	Spikes and sharp transients in the right mid-parietal region, left mid-parietal and insular regions.
3	56, M	FBDS, thermal paresthesia in left arm and leg, memory impairment.	Brief jerks in right arm and leg. Sharp electric pain in left arm, spreading to occipital area, bilateral arms and legs.	Left medial temporal lobe.	Normal EEG.	Sharp transients in the right temporo-parieto-occipital junction, left postcentral gyrus, and medial occipital region.
4	48, M	FBDS, memory impairment.	Dystonic jerk in right arm and leg, followed by numb pain in right arm, face, and leg.	Normal	Fast activity in the central area.	Sharp transients in the right insular, parietal regions, left mid-temporal, posterior-superior temporal and insular regions.
5	31, F	FBDS, recurrent nausea and piloerection in the right arm, déjà vu, memory impairment, homonymous hemianopia.	Recurrent chills in the right arm and hand, with or without brief dystonic jerks.	Both medial temporal lobes.	Few interictal discharges in the left temporal area.	Spikes and sharp transients in the right occipital lobe.
6	73, M	FBDS, memory impairment, confusion, falls.	Brief dystonic jerks in both arms and face (left > right).	Right medial temporal lobe.	Intermittent generalized theta slowing.	Sharp transient in the right occipital region.
7	63, M	FBDS, paroxysmal dizziness spells, imbalance, short-term memory impairment, hyponatremia.	Brief jerks in left arm, spreading to right arm, face, and leg with preserved awareness.	Right hippocampus (atrophy).	Normal EEG.	Atypical discharges just anterior to the right precentral gyrus within 1 to 2 seconds prior to FBDS onset.

Abbreviations: EEG=electroencephalogram; F=female; FBDS=faciobrachial dystonic seizure; FLAIR=fluid attenuated inversion recovery; ID=index; M=male; MEG=magnetoencephalogram; MRI=magnetic resonance imaging; NA=not available