LGI1 Encephalitis: Autoimmune Epilepsy or Movement Disorder

Sir,

Leucine-rich glioma-inactivated 1 (LGI1) encephalitis is a rare autoimmune encephalitis characterized by memory deterioration, faciobrachial dystonic seizures (FBDS), and hyponatremia. FBDS are still a pathognomonic feature of LGI encephalitis.[1,2] It is a seizure or paroxysmal movement disorder that is not clear as they respond to immunotherapy and not to antiseizure medications (ASM).[1-3] Magnetic resonance imaging (MRI) brain is normal or shows hippocampal swelling, hyperintensity, restricted diffusion initially, and atrophy later.[1,2] FBDS usually precedes cognitive deterioration, and early detection and immunotherapy are thought to prevent cognitive deterioration.[2] Very few patients underwent long-term video electroencephalography (VEEG) monitoring and detailed analysis of seizures or movement disorders. The exact origin of FBDS, it is from the frontal or temporal lobe, is not clear, as well as their electroclinical evolution. The aim of the study was to study clinical characteristics, imaging features, and outcomes of LGI1 encephalitis with special emphasis on analysis of VEEG of FBDS and their ictal correlation to answer important questions about FBDS being a true seizure or movement disorder.

We performed a retrospective review of patients with LGI1 encephalitis during the period of January 2016–December 2020 who underwent long-term VEEG monitoring for characterization of their events, through our electronic database. The neurocognitive evaluation was performed using Addenbrooke's cognitive examination (ACE III) and clinical dementia rating (CDR). Seven patients had LGI1 encephalitis, five females and two males. In all patients, the diagnosis was missed on initial evaluation, and one was diagnosed as a functional disorder. The LGI1 antibodies in the blood and/or cerebrospinal fluid (CSF) were positive in all. Three patients had hyponatremia; the minimum serum sodium level was 126 mEq/L. All patients had FBDS, presenting symptoms in five (71%), two had cognitive decline followed by FBDS. Five patients had alternating FBDS, that is, some events involving the right side and some events involving the left side. [Table 1 and Figure 1] Leg onset faciobrachiocrural dystonic seizures (FBCDS) were present in three patients. The duration of FBDS was <15–20 s, occurring at a frequency of 5–10/h. EEG during FBDS showed only movement artifacts and no ictal pattern. In one patient, temporal ictal rhythm was noted, during focal seizure with impaired awareness. [Figure 2] The background activity was normal, and sleep structures were well formed in all patients. In addition to FBDS, three patients had myoclonus. One patient had falls and sustained injuries due to myoclonus. Five patients had cognitive decline, with two requiring significant support for activities of daily living at the

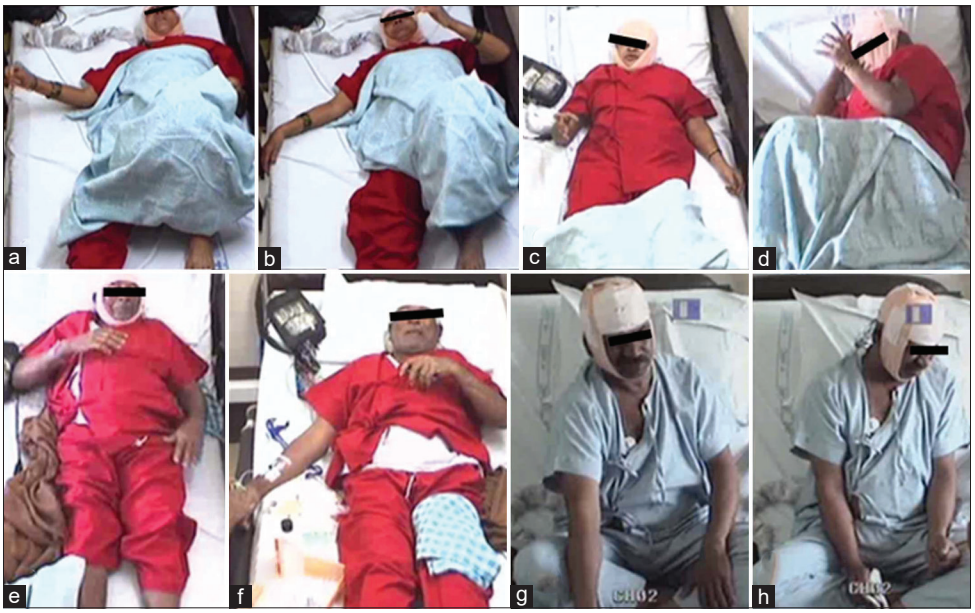

Figure 1: (a-h) Alternating FBDS in four patients

time of evaluation. Cognitive decline was preceded by FBDS from 1 to 6 months. Detailed neurocognitive evaluation was performed on four patients. The caregiver reported marked apathy in activities of daily living (ADL) as compared to premorbid verbal, social activities, and agility. All the patients had moderate to severe verbal memory impairment, especially in recall. Poor verbal fluency and anterograde, as well as retrograde amnesia, were present in all the patients who were performing very well premorbidly. The MRI brain showed bilateral hippocampal hyperintensity in five patients and unilateral in one. [Figure 3] Whole-body positron emission tomography (PET) did not reveal any abnormality, whereas brain PET showed bilateral basal ganglia hypermetabolism in three patients.

All patients received intravenous methylprednisolone and intravenous immunoglobulins. FBDS subsided within 48 h to 7 days of receiving steroids. ASM were stopped within 2 months of receiving immunotherapy. No patient had a recurrence of symptoms, during the follow-up period of 12–36 months (mean 22.7 months). Comparative analysis of pre and post immunotherapy neurocognitive profiles revealed significant improvement in overall cognitive abilities and ADL across subjects.

Irani *et al.*[1] initially described the FBDS in LGI1 encephalitis, occurring very frequently (>100/day). In our study, video EEG showed a frequency of 120–240/day, underestimating its occurrence, which was reported a few times a day. FBDS are very subtle and can be missed easily, as one of our patients was referred to as a non-epileptic event. All patients with suspected FBDS or other movement disorders should undergo short-term Video EEG for characterization of these events. FBDS are usually unilateral but can be alternating; very few cases with alternating FBDS have been reported.[4] In our study, the careful

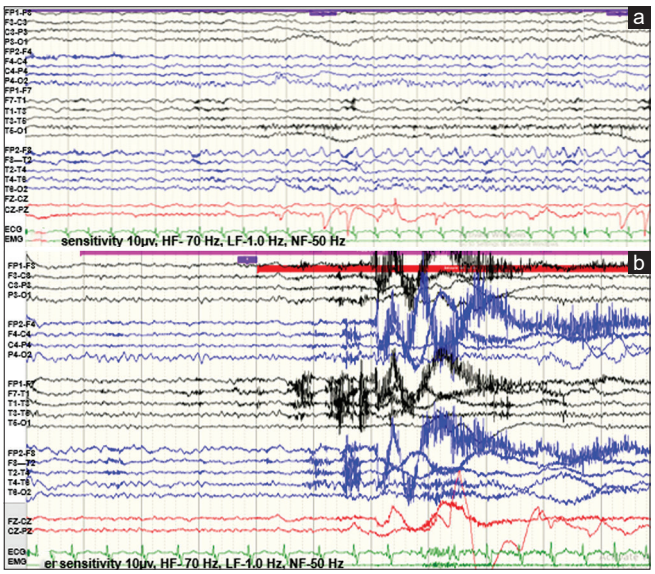

Figure 2: EEG in bipolar montage showing (a) right temporal 3–4 Hz evolving rhythm during a focal seizure with impairment of consciousness; (b) muscle artifact during FBDS without any ictal rhythm

analysis showed five patients with alternating FBDS, although historically, only one type was described. The importance and prognostic role of alternating FBDS on disease courses is not known. The important question about FBDS being a true seizure or movement disorder is still unanswered. None of our patients, during FBDS had any ictal correlate, as EEG showed only movement artifacts. EEG has rarely shown any ictal correlate with FBDS, although correlates have been shown with other types of seizures.[2,5,6] In the literature, mixed clinical phenotypes (tonic-dystonic or myoclonic-dystonic) have been reported for FBDS. Striano *et al.*[6] described three patients with tonic seizures with LGI1 encephalitis, and prolonged

events showed an electrodecremental pattern. Similar EEG finding has not been described in any other study, or in the present study. In view of high frequency, short duration, and facial contraction, the frontal lobe origin of FBDS is thought, but no imaging abnormality in the frontal lobe has been detected.[7] The dystonic posturing of the limb, which is characteristically seen in temporal lobe epilepsy due to the spread to basal ganglia, is seen in FBDS, but the absence of automatism, short duration, and high frequency does not support the origin of FBDS from the temporal lobe.[7] Interictal epileptiform abnormalities have been rarely described again, pointing against epilepsy. Myoclonus has been described with LGI1 encephalitis, but it is rare and can be generalized, focal or multifocal.[8] Myoclonus with cognitive decline in middle age or elderly patients, LGI1 encephalitis, should be considered as differential diagnosis. In the study by Lehong Gao *et al.*[9], on the basis of MEG dipole, FBDS is thought to be insular in origin. Iyer *et al.*[10] suggest fronto-temporo-basalganglia circuit initiating and propagating FBDS rather than attributing its origin to frontal, temporal, or basal ganglia.

FBDS usually do not respond to ASM but immediate response to immunotherapy, further points against epileptic nature. So, in the absence of any focal interictal discharges, ictal correlate, focal imaging abnormality, and good response to

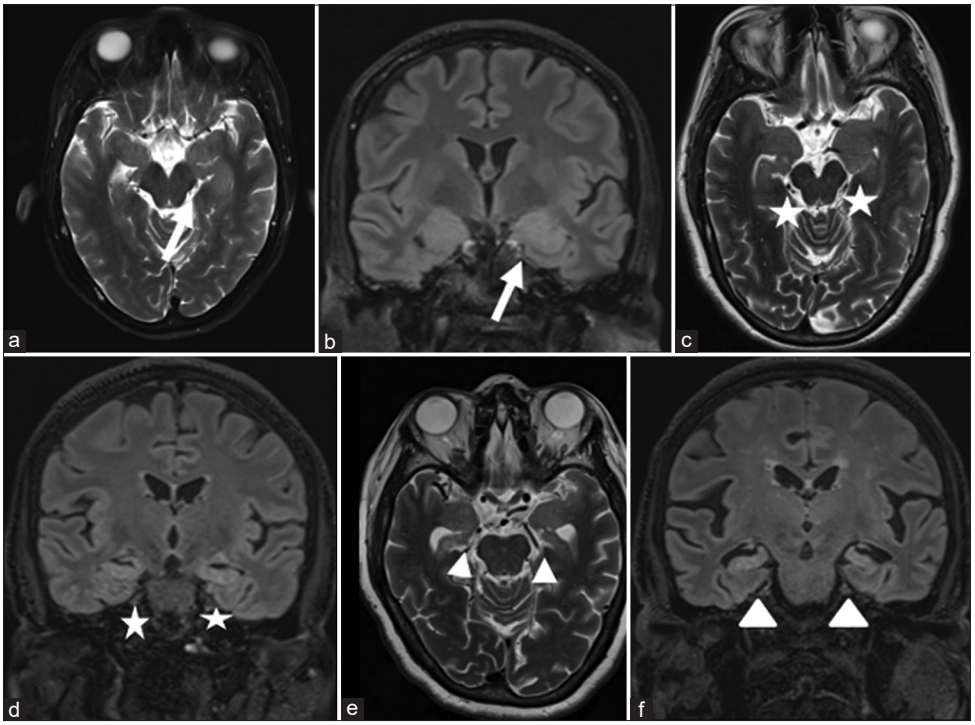

Figure 3: MRI Brain (a) axial T2 and (b) coronal FLAIR image shows mildly bulky left hippocampus and amygdala with hyperintense signal (arrow) (c) axial T2 and (d) coronal FLAIR image shows bilateral hippocampal atrophy with FLAIR hyperintense signal (star) (e and f) bilateral hippocampal atrophy with FLAIR hyperintense signal (arrowhead) *Abbreviations:* EEG = long-term video electroencephalography, FBCDS = faciobrachial dystonic seizures, MRI = magnetic resonance imaging, FLAIR = fluid-attenuated inversion recovery

Table 1: Clinical characteristics, imaging features, and treatment

Case no	Age	Sex	Age of onset	FBDS	Memory impairment	Myoclonus	Onset to treatment months	MRI	Types of immunotherapies	Follow-up duration months
1	53	M	50	Leg onset/ alternating	No	Yes	36	Bilateral hippocampal hyperintensity with cerebellar atrophy	IVIG, IVMP	24
2	51	F	49	Leg onset	No	No	24	Bilateral hippocampal hyperintensity	IVIG, IVMP	36
3	63	M	62	Alternating	Yes	No	12	Bilateral hippocampal hyperintensity	IVIG, IVMP	24
4	63	F	63	Alternating	Yes	No	10	Bilateral hippocampal hyperintensity with cortical atrophy	IVIG, IVMP	24
5	63	F	62	Alternating	Yes	No	6	Bilateral hippocampal hyperintensity	IVIG, IVMP	24
6	58	M	56	Leg onset/ alternating	Yes	Yes	24	Bilateral hippocampal hyperintensity with cerebellar atrophy	IVIG, IVMP	12
7	44	F	43	Yes	yes	Yes	12	Unilateral hippocampal hyperintensity	IVIG, IVMP	15

Abbreviations: IVIG- intravenous immunoglobulin (0.4 g/kg/day for 5 days), IVMP – intravenous methylprednisolone (1 g/kg/day for 5 days)

immunotherapy and no response to ASM, we support the hypothesis of FBDS being a movement disorder rather than epilepsy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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