



Case Report

Faciobrachial dystonic seizures result from fronto–temporo–basalganglial network involvement



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1. Introduction

In 2008, Faciobrachial dystonic seizures (FBDS), characterized by unilateral, short-lived dystonic posturing of the upper limb and face were recognized as an immunotherapy-responsive disorder [1]. They are accompanied by autoantibodies to leucine-rich glioma-inactivated 1 (LGI1), a component of the voltage-gated potassium channel complex (VGKC-complex) [2,3]. Since their initial description, the epileptic origin of FBDS has been extensively debated with no definite conclusions drawn so far [4]. We discuss the clinical, electrophysiological and imaging features of two patients with LGI1 antibody mediated encephalitis who presented with FBDS. We also analyze the existing literature on FBDS and propose the network hypothesis to explain the various features of FBDS described so far.

2. Case vignette 1

A 45-year-old lady presented with a two-month history of intermittent generalized seizures, behavior disturbances and hallucinations along with memory disturbances. On examination she had very frequent events associated with facio-brachial dystonic jerks occurring on either side followed by brief loss of awareness associated with ictal

speech and hand automatisms. The events were of 30–45 seconds in duration. The jerks did not have any electrical correlate. They were associated with movement artifacts followed by 2 seconds of attenuation followed further by right temporal progression of sharp waves coinciding with ictal speech and automatisms (Fig. 1F&G). MRI Brain showed bilateral medial temporal hyperintensities whereas basal ganglia (BG) structures were spared (Fig. 1A&B). Her serum VGKC-antibody (LGI1 antibodies) titer was very high at 3069 pmol/L. 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computerized tomography (FDG PET/CT) showed bilateral BG and amygdalar hypermetabolism (Fig. 1D), and hypometabolism of bilateral frontal and temporal lobes. A thorough work-up for neoplasms was negative. There was no clinical response to antiseizures drugs. She was given a course of intravenous methylprednisolone (IVMP) followed by weekly pulses of IVMP. Two months later on follow-up she showed good clinical improvement in behavior and psychiatric disturbances. FBDS of shorter duration (4–6 seconds) persisted though less in number with occasional loss of balance and fall. Emotional disturbances would trigger the attacks. However loss of awareness and automatisms following the jerks disappeared after treatment. Electrical changes were restricted to movement artifacts without the ensuing temporal lobe changes. This time the serum VGKC-antibody titer was at 560 pmols/L. Repeat MRI showed generalized atrophy and some persistence of the medial temporal hyperintensities (Fig. 1C). A repeat FDG PET/CT showed persistence of the bilateral BG hypermetabolism and disappearance of the amygdalar changes (Fig. 1E). She was started on intravenous immunoglobulins following which her FBDS resolved completely.

3. Case vignette 2

A 53-year-old lady presented with a one-month history of one episode of nocturnal GTCS followed by frequent jerkiness of the left upper limb and occasional falls. The events were of 5–7 seconds in duration. Interestingly her memory and behavior were relatively intact. Clinically she had left-sided FBDS occurring multiple times a day. A few of them were facio-brachio-crural events responsible for her falls. MRI showed T1, T2 and FLAIR hyperintensities involving the bilateral caudate nuclei and putamen (Fig. 1H,I&J) and the substantia nigra on the left side (Fig. 1K). The left hippocampus was edematous. Her interictal EEG showed bilateral temporal slow waves. Her serum LGI1 antibodies assay by immunofluorescence was positive (low VGKC complex IgG

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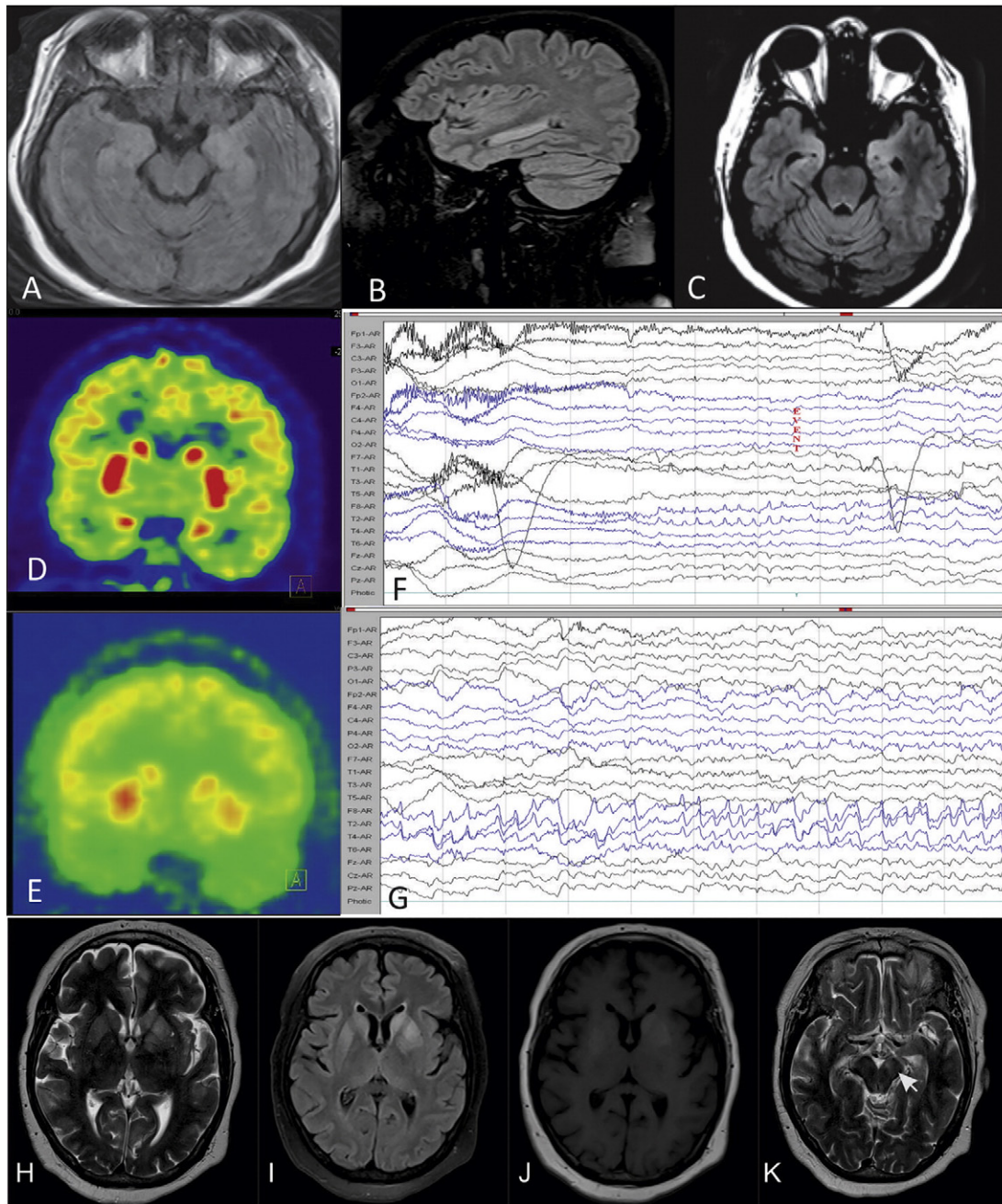


Fig. 1. MRI Brain FLAIR images axial (A) and sagittal (B) of patient 1 showed bilateral medial temporal hyperintensities. MRI FLAIR images axial (C) in two months, follow-up showed diffuse brain atrophy and persistence of medial temporal hyperintensities. PET CT Brain at presentation (D) showed bilateral basal ganglial and amygdalar hypermetabolism. PET CT Brain at two-month follow-up (E) showed bilateral basal ganglial hypermetabolism and disappearance of medial temporal hypermetabolism. Ictal EEG (F,G) showed movement artifacts with the jerk followed by brief attenuation and build-up of right temporal spikes. MRI Brain axial images T2 (H), FLAIR (I) and T1 (J) in patient 2 showed basal ganglia hyperintensities. T2 axial images (K) also showed left sided substantia nigra hyperintensity (white arrow).

values at 0.4 nmol/L) and work-up for neoplasm was negative. Her dystonic events responded nicely to intravenous methyl prednisolone therapy.

4. Discussion

4.1. Existing literature on the pathophysiology of FBDS

Literary contribution to the pathophysiology of FBDS is summarized in Table 1. The nomenclature for these paroxysmal events seen in LGI1 antibody-mediated encephalitis is still debated. The abrupt onset and onset, the paroxysmal nature and the typical semiology suggests epilepsy. However they also resemble dyskinesias or myoclonic jerks. Irani

and colleagues suggested that they most likely represented extratemporal seizures [1]. However, they were cautious and considered nonepileptic generators of these jerk events also and advocated video-EEG telemetry in all patients. Barajas et al. reported one patient with synchronous twitches of arm and face and was unsure whether they represented seizures or a movement disorder [5]. Based on the video-EEG recordings of three patients with FBDS, Andrade et al. concluded that they are tonic seizures and not movement disorders [6]. His arguments were based on the presence of electrodecremental events preceding the onset of facio-brachial dystonic movements of longer duration. He however noted that these changes were absent in similar movements of shorter duration. In a study on 29 patients Irani et al., found that FBDS preceded limbic encephalitis (LE) in the majority

Table 1
Current literature on the pathophysiology of FBDS.

Article	Pt no:	Sz vs MD	EEG	MRI	PET/SPECT	Discussion
Irani et al., 2008 [1]	3	Extratemporal Sz	movement artifact followed by left fronto-temporal theta in pt. 1, normal in pt. 2, temporal lobe sz in pt. 3	BG abn in pt1, normal in pt. 2, b/l HC abn in pt3	–	likely extra temporal seizures. Non-epileptic generators to be considered
Barajas et al., 2010 [5]	1	Sz	temporal lobe seizures	Frontal and HC abn	–	unsure about the pathophysiology of jerks before sz
Irani et al., 2011 [2]	29	FBDS are frontal Sz, temporal sz only after development of LE	Ictal changes in 7(24%)	Normal during FBDS	PET abn in 6 of 8 in temporal, 5 of 8 in BG	Likely sz since, 1. LOC present 2. Stereotyped Ictal dystonia due to BG involvement
Striano et al., 2011 [4] (opinion on Irani et al., 2011)	–	Hemidystonia	–	–	–	Unlikely to be Sz since 1. LOC in minority 2. IEC in minority 3. No clear IOZ 4. Poor response to AED
Andrade et al., 2011 [6]	3	Tonic Sz	Ictal EDP before dystonic events	HC atrophy in 2 normal in 1	–	Ictal EDP suggests remote sz origin from interhemispheric frontal region. Subclinical TNC Sz in all
Boesebeck et al., 2013 [7]	1	Features of both sz and movement disorder	Normal	BG and medial frontal abn	BG hypermetabolism	FBDS originate from cortical and subcortical areas
Flanagan et al., 2015 [8]	26	–	Ictal EEG (23) normal in 20 and 3 had temporal sz	BG and TL changes in 11 of 26 each (42%)	PET in 14 BG changes in 6 and TL changes in 3, diffuse in 3 and bifrontal in 2	BG abn exclusive to pts. with FBDS, c/l to the side of FBDS. BG are the sites of origin of FBDS.

No = number; Sz = seizure; MD = movement disorder; Pt = patient; BG = basal ganglia; b/l = bilateral; c/l = contralateral; abn = abnormalities; HC = hippocampus; LE = limbic encephalitis; LOC = loss of consciousness; IEC = ictal EEG changes; EDP = electro-decremental pattern; TNC = Temporal neocortical; TL = temporal lobe; AED = anti-epileptic drugs.

of patients with LGI1 antibody-mediated encephalitis [2]. He felt that FBDS are frontal seizures and temporal seizures occur on later development of LE. Commenting on this paper Striano et al. pointed out that loss of awareness and ictal EEG changes being present only in a minority, lack of response to AEDs and failure to recognize an ictal onset zone are strong arguments that point against consideration of FBDS as seizures [4]. They postulated hemidystonia instead. Boesebeck et al. noted left medial prefrontal and striatal abnormalities in a patient with right FBDS and suggested that they originated from both cortical and sub-cortical brain areas [7]. Flanagan et al. in a recent study found that BG MRI abnormalities were exclusive to LGI1 antibody-mediated encephalopathy patients with FBDS and were typically contralateral to episodes [8]. He concluded that BG T1 hyperintensity is a clinically useful MRI biomarker of LGI1 antibody-mediated FBDS and suggested BG localization for FBDS.

4.2. Observations from our patients

Let us look into the observations from our two patients. The first patient presented late after two months with full-blown features of limbic encephalitis. The PET scan showed hypermetabolism in the bilateral caudate and putamen and amygdala. Similarly on follow-up, hypermetabolism disappeared from the amygdalae and persisted in the BG. Clinically she had events of longer duration associated with jerks, automatisms and speech along with loss of awareness at presentation. At follow-up, only the brief jerks without loss of consciousness were present. The second patient presented with FBDS prodrome giving us the window of opportunity to prevent full blown LE. The MRI showed BG involvement (including the substantia nigra on the left side which is hitherto undescribed) without much involvement of temporal lobes. These two patients further strengthen the association of FBDS and basal ganglia. Well established movement disorders of basal ganglia origin like chorea [9] and kinesigenic dyskinesia [10] have been described in association with LGI1 antibody mediated encephalitis.

4.3. Basal ganglia and epilepsy

The above data establishes the basal ganglia as primarily responsible for the phenomenon of FBDS. It is appropriate at this juncture to look into evidences linking the BG to epilepsy. The basal ganglia, which include the striatum, pallidum, subthalamic nucleus, and substantia nigra, are involved in a number of parallel, functionally-segregated cortical-subcortical circuits. They receive information from cerebral cortex including hippocampus and amygdala. The substantia nigra pars reticulata is the main output nucleus of the BG. It directly controls the excitability of brainstem premotor networks and through thalamic efferents controls the motor, premotor, prefrontal and limbic areas of the cerebral cortex. Though there is no evidence supporting the involvement of BG in the generation of seizures, they probably provide a gating mechanism modulating their phenotypic expression and seizure control [11,12]. The substantia nigra pars reticulata could be capable of modifying the development, propagation and cessation of seizures. Manipulation of basal ganglia circuits by deep brain stimulation of subthalamic nucleus, substantia nigra and caudate nucleus have shown promising results in control of seizures [13]. Functional imaging studies strongly suggest the involvement of basal ganglia in epileptic seizures [14,15].

4.4. The network hypothesis

The phenomenon of FBDS is best explained by a neural network consisting of cortical and sub cortical regions. Based on our patients and the currently available studies (Table 1), FBDS networks would include bilateral frontal regions, bilateral basal ganglia and bilateral temporal regions mainly the hippocampi and the amygdalae. A schematic representation of the network is shown in Fig. 2. Essentially it is the fronto-temporo-BG circuits initiating and propagating FBDS. LGI1 antibodies initiate pathology in BG followed later by the temporal regions resulting first in FBDS and later limbic encephalitis. Asymmetric

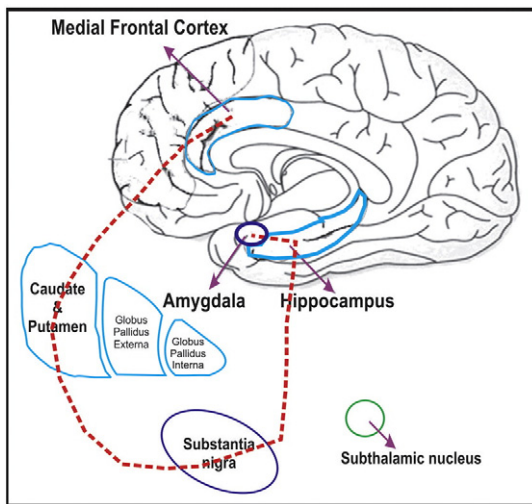


Fig. 2. Schematic diagram showing the fronto-temporo-basal ganglia network (dotted line).

or strictly unilateral involvement is possible resulting in contralateral clinical expression. The network can be entrained from anywhere within the network. Despite multiple sites of entrainment, clinical expression is dependent on the network and remains almost the same explaining the stereotyped episodes of FBDS. Frontal entrainment and subcortical spread to the BG will explain the ictal EEG changes in some patients preceding the movement artifacts of FBDS. The ictal dystonic component correlates with basal ganglia spread. Cortical entrainment accounts for the aura in some and the late temporal lobe involvement explains disturbance of awareness, speech arrest, fear or agitation after the dystonic event in others. Basal ganglia entrainment results in movement artifacts alone in EEG and subsequent cortical spread results in EEG changes or features of temporal lobe seizures. This would explain the absence of EEG changes in FBDS of short duration and ictal changes in those of longer duration. Interruption in any one area of the network will alter the clinical expression. This was seen in our first case where temporal lobe involvement stopped after the initial therapy. This resulted in clinical cessation of loss of consciousness and automatisms. The electrophysiological cessation of spread across the temporal lobe resulted in disappearance of temporal lobe involvement noted the follow-up PET study. The extensive cortical-subcortical circuit involvement will also explain the lack of good response of FBDS to antiseizure drugs.

5. Conclusion

FBDS are at the border zone between movement disorders and epilepsy. As the name implies it constitutes dystonia representing the

movement disorder component signifying involvement of the subcortical structure. Many other features of epilepsy also exist with evidence of cortical involvement. The network hypothesis implicating cortico-subcortical areas of fronto-temporo-basal ganglia regions seems to be the most plausible explanation for the phenomenon of FBDS. The dystonia is due to involvement of the BG part of the network and the remaining features preceding or succeeding it are due to frontal or temporal cortical involvement. However further electrophysiological and functional studies are required to establish this network.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

Statement

The work described above is consistent with the Journal's guidelines for ethical publication.

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