Sporadic Case of LGI1 Autoimmune Encephalitis Feigning as Basal Ganglia Stroke: Exhuming its Pathophysiologic Basis

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Abstract

LGI1 encephalitis is an immune mediated neurological disorder effecting temporal lobe and basal ganglia. The classic clinical syndrome comprises of myoclonic jerks of the ipsilateral upper arms, facial twitching, memory disturbances, behavioral disturbances and hyponatremia. With its overarching symptoms, it does not snug perfectly with either seizure or movement disorder. The main pathological basis is mass production of anti-LGI1 auto-antibodies which strike the LGI1 protein in the neuronal milieu and presynaptic membrane. On grounds of this immune mediated onslaught, LGI1 protein injury transpires and slowing of signal conduction at the synaptic interface never ensues. In patients with aforementioned symptoms, a high degree of clinical suspicion necessitate MRI brain imaging which shows T2 hyperintensity in basal ganglia, temporal lobe and frontal lobe. This can be corroborated with assessing LGI1 antibody levels in the blood and CSF to monitor disease progression as well as treatment response. As soon as diagnosis is confirmed, intravenous corticosteroids, intravenous immunoglobulins or plasma exchange will reverse the epileptic activity and cognitive dysfunction. Long term immunosuppressive therapy is warranted as it is inclined to reduce the onset of temporal lobe epilepsy and hippocampal atrophy. Regular follow up to detect new clinical symptoms and brain lesions is recommended in these patients to reduce morbidity and mortality.

Keywords: *LGI1-encephalitis, autoimmunity, auto-antibodies, epilepsy, myoclonic seizures, cognitive dysfunction, sleep disturbances, steroids.*

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Introduction

Limbic encephalitis is the term coined by English neuropathologists and neurologists in 1960 to denote a disease entity with clinical symptoms < 5 years, antibodies directed at the brain, a predilection to temporal lobe & hippocampus, specific imaging features, and pathological demonstration of chronic lymphocyte-microglial cells in post-mortem brain tissues [1]. LGI1 [Leucine-rich-Glioma inactivated 1] autoimmune encephalitis is an unconventional and atypical form of inflammatory disorder characterized by hall-mark clinical features including faciobrachial dystonic seizures, memory loss, sleep disturbances, behavioral symptoms, and hyponatraemia [2]. The onset and progression of this autoimmune neurological disorder is often insidious and can be variable making the diagnosis challenging. The clinical dilemma that is present even today is that it does not fit clearly into a movement or seizure disorder.With that being said, this disease manifests itself with clinical symptoms that often

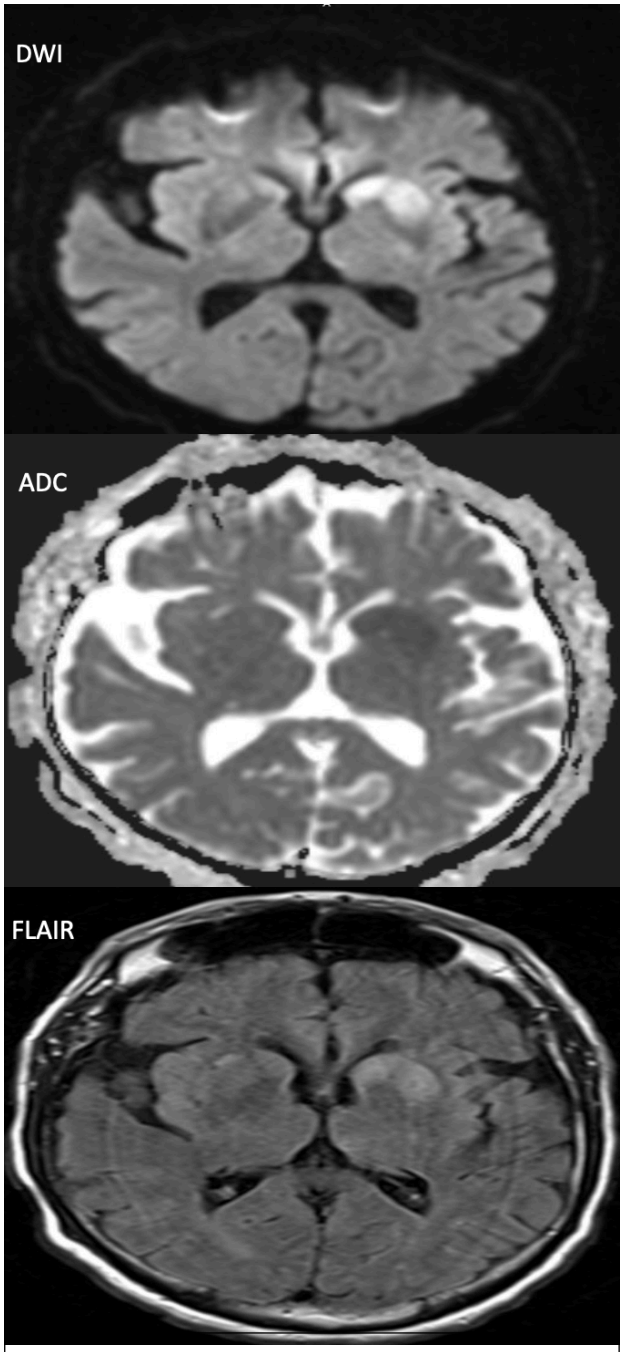

Figure 1: *LGI1 encephalitis.*
Evolution of left basal ganglia findings consistent with prior ischemic stroke or effect of anti-LGI-1 encephalitis. New signal abnormality of the left insular cortex which could signify ongoing/active encephalitis.
Bright on diffusion, dark on ADC = restricted diffusion

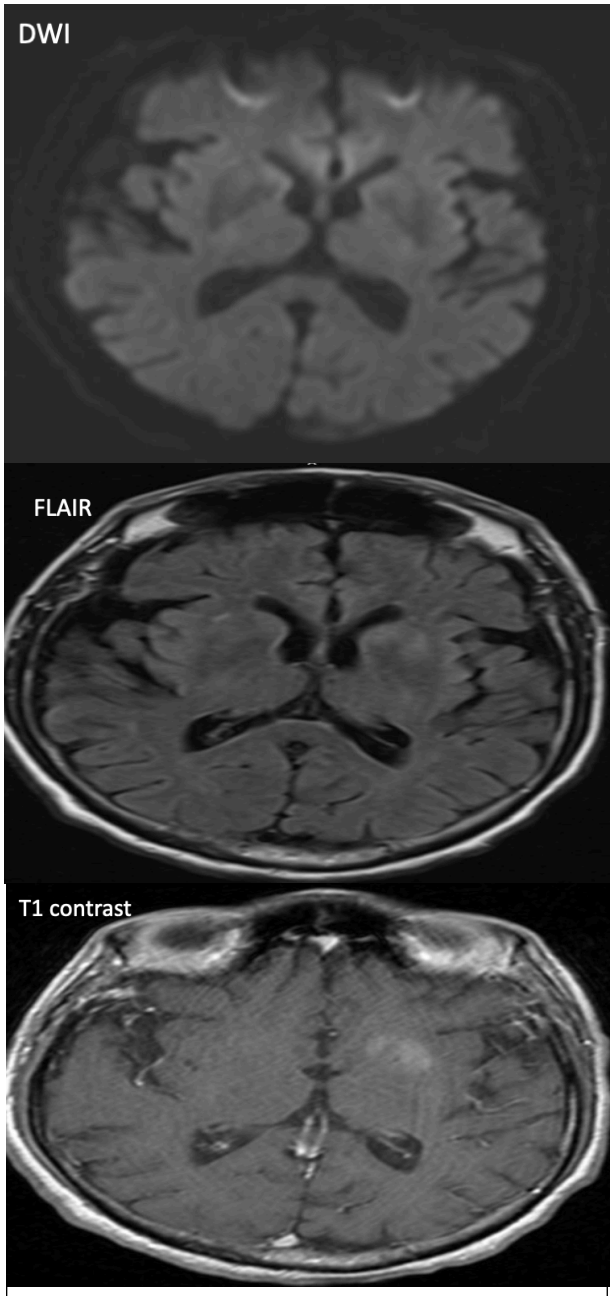

Figure 2 After Treatment: *Resolution of LGI1 encephalitis. Resolution of imaging abnormalities after steroid and IVIG treatment*

mimic other diseases such as epilepsy or dementia or stroke. As a result, the disease is often not considered, and the necessary diagnostic tests are not ordered leading to a delay in diagnosis and accompanying disease progression. We would like to present this unusual case to highlight the awareness of this rare autoimmune neurological disorder. Clinically, in any patient presenting with a combination of symptoms including myoclonic jerks, seizures and dementia, one should have a high degree of clinical suspicion for LGI1 encephalitis. In these patients, antibodies for LGI1 from serum and CSF should be sent early in the work up. This will lead to faster diagnosis, reduce disease progression, and leads to the best outcomes.

Clinical Case

73-year-old male with prior diagnosis of hypothyroidism, and lumbar stenosis presented to the emergency department with agonal breathing and with concern over in-

voluntary arm movements and unwitnessed seizure.

He has past medical history of chronic back pain, thyroid disorder, and hearing loss. His past surgical history includes varicose vein surgery, tonsillectomy and excision of left elbow region. He was transferred from another hospital and there were no transfer records available at this time. History obtained by chart review and his wife who reported that she witnessed right arm contracting and shaking yesterday and was associated with biting of the tongue and bleeding. She mentioned that shaking was continuous and not associated with eye deviation. This is in the setting of 2 weeks' worth of intermittent left arm and face involuntary contractions which are intermittent with retained consciousness. They occurred 3 times per hour, sometimes more but was not accompanied by headaches, and falls. No fever, and chills were associated with these episodes. These episodes were occurring before was started on Medrol dose pack and Gabapentin by his PCP. No previous personal history of stroke, seizure, or family history of seizures. Occasional alcohol use, but no tobacco or drug usage. Gainfully employed in the warehouse for tires. No functional limitations prior to hospitalization.

Neurology consult was made and was seen by the neurologist same day for tremors and jerking of his left arm for 1 week. There was a documented history of previous IV drug abuse. He was documented to have mild coarse tremor in the bilateral upper extremities with normal motor and sensory exam. EKG was normal sinus rhythm. Glucose was 107. Creatinine was 0.9. His sodium was found to be low as 127. CBC was unremarkable. And non-contrast CT of Cervical Spine showed no acute abnormalities excluding fracture or critical canal stenosis. He was given one dose of morphine and Norflex with complete resolution of his tremors and he was discharged with return precautions on baclofen and naproxen.

He was continued on Keppra 1000 BID given his intermittent right-hand clenching and shaking despite fentanyl. His EEG shows wide spread slowing, disorganization, rare intermittent focal slowing in the left temporal region. There are occasional synchronous single jerks of the left arm and left leg. CT scan cervical spine, CT head/neck and CT angiography are unremarkable. MRI brain showed left basal ganglia infarct initially. Follow up MRI brain showed evolution of left basal ganglia findings consistent with ischemic stroke or effect of LGI1autoimmune encephalitis. New signal abnormality of the left insular cortex which could relate to ongoing or active encephalitis. Lumbar puncture and CSF analysis showed WBC 2, RBC 7, Glucose 75, protein 46, IgG index 0.72 (elevated), and IgG synthesis rate 3.4. This is classic case of LGI1 encephalitis manifesting as seizures, brachio-facial dystonic spasms, hyponatremia, and cognitive impairment. He has been treated with high dose steroids, IVIG. These treatments completely resolved the patient symptoms and he was stable. He now is started with long term prednisolone therapy and recommended to follow up with outpatient neuro-immunology for further evaluation and follow up.

Discussion

LGI1 is a glycoprotein released from the presynaptic membrane to interact with presynaptic ADAM domains 22 & 23 for attenuation of signal transduction between synapses and post-synaptic membranes [1]. As LGI1 auto-antibodies were spawned during the disease process, they tether to the LGI1 proteins floating around in the neuronal milieu, henceforth triggering clinical sequelae characteristic of LGI1 encephalitis [1].

Having said that, LGI protein disruption in temporal lobe, hippocampus, amygdala, hypothalamus and kidney will evoke their desecration, thus bring about epilepsy, mood disorders, sleep disturbances and intractable hyponatremia commonly seen in LGI1 encephalitis [1]. According to some researchers, the inception and perpetuation of LGI1 encephalitis can be attributed to the exacerbated and overfatigued firing of the frontal-temporal-basal ganglia circuit [3]. Anatomically, basal ganglia consist of striatum, pallidum, subthalamic nucleus, and substantia nigra. Digging into the neurophysiology, the basal ganglia receives information from the cerebral cortex, processes afferent information and powers the execution of motor efferent pathways in the brain stem and cerebral cortex. It is speculated that LGI1 antibodies have a propensity to cling and demolish the basal ganglia as an opening move [3]. Keeping in mind the close supervision of basal ganglia nuclei with motor networks, they function as upper motor neurons in tempering and fine-tuning of physiological limb movement and coordination. Any disruption in their functioning will herald the unrestricted activation of lower

motor neurons, thus ushering the onset of myoclonic jerks or seizures.

To buttress this hypothesis, clinical research and imaging studies have proclaimed the paramount position of basal ganglia in manipulating the kickoff, perpetuation and stoppage of seizures [4-8]. As the disease progresses, the LGI1 antibodies encircle and dismantle the temporal lobe nuclei, thus triggering the onset of limbic encephalitis [3]. Temporal lobe involvement brings to light symptoms like disturbance of awareness, speech arrest, fear or agitation [3]. Frontal lobe involvement and subcortical spread can sometimes account for EEG changes and aura like symptoms experienced by the patients before seizures [3].
LGI1 encephalitis is diagnosed with presence of clinical symptoms for not more than 5 years, with presence of following any of the following symptoms symptoms including episodic cognitive disturbances, epileptic like myoclonic seizures, emotional instability, dysphrenia [irritability, anxiety, impulsive behavior, mental hallucination, paranoia, stupor and visual hallucination], and hyponatraemia [1, 9-13].
Faciobrachial dystonic seizures (FBDS) are the most important clinical symptoms characteristic of this clinical disorder. Some reports suggest that, patients with LGI1 encephalitis can have as high as 100-240 FBDS per day [2]. Clinically, a faciobrachial dystonic seizure is characterized by a sudden, short, and unilateral spasm of the upper limb and ipsilateral facial twitch [>3 seconds, number of episodes per day], occasionally some exhibit hand dystonia [14]. These are often subtle initially, sudden in onset, and there are typically no postictal effects [3]. In most cases these are unilateral, thus effecting arm and face on one-side, although occasional bilateral cases were reported [15]. Clinical reports indicate that frontal lobe seizures are prone to occur earlier in the disease process whereas temporal lobe seizures are more inclined to manifest in later stages along with LGI1 encephalitis [3, 16].

Moreover, these dystonic spasms occur in earlier stages before the onset of cognitive dysfunction [17]. The most crucial hallmark sign of LGI1 limbic encephalitis is poor response to antiepileptic medications, while have a drastic improvement with usage of corticosteroids [17, 18]. Bilateral and alternating FBDS can sometimes be associated with loss of consciousness and aphasia [15]. Rarely, these spasms can be so fierce and aggressive so that it can spread to trunk and lower limbs, henceforth provoking falls and head injury [14]. There were designated to be extratemporal in origin as they do not fit the criteria for temporal lobe epilepsy or seizure or movement disorder [14, 16]. Some clinical researchers recommended video-EEG monitoring for evaluating them. Although most researchers found no EEG abnormalities except in a report by Andrade et al. [19]. In this report, they revealed that generalized EEG decremental events (pattern for fore-shadow the onset of that longer FBDS (>500 msec), but nevertheless do not forerun be-fore shorter FBDS [19]. In patients presenting with acute encephalopathy, firing up of tonic-clonic seizures along with non-specific EEG changes can pin-down the diagnosis towards LGI1 encephalitis [19].

The tell-tale signs of paroxysmal dystonic disorder affiliated with LGI1 encephalitis include short duration of limb spasms, facial involvement, unresponsiveness to anti-epileptic medications, and diffusion restriction in basal ganglia in PET scans [14]. MRI of brain might reveal prefrontal, striatal and basal ganglia abnormalities on the contralateral the side of FBDS, thus conforming the diagnosis of LG1 encephalitis [3, 20, 21]. High T2 signal and FLAIR [Fluid attenuation inversion recovery] in the bilateral temporal lobe and basal ganglia is most important diagnostic sign for LGI1 encephalitis [22]. Nevertheless in the previous case reports embroilment of hippocampus, temporal lobe, basal ganglia, insular lobe and cerebellar tonsil was demonstrated with LGI1 pathology with MRI imaging [1]. Occasionally, temporal lobe epilepsy is superimposed on paroxysmal dystonic disorder of LGI1 encephalitis, which can be spotted by ECG showing infra-slow activity in the contralateral mid-frontal cortex transpiring 1 minute ahead than the onset of FBDS [23]. These findings are suggestive of widespread wreckage of cortical-subcortical network of basal ganglia, frontal and temporal cortex secondary to deposition of anti-LGI1 auto-antibodies [3, 14]. The spectrum of EEG changes that can be seen in LGI1 encephalitis can be range from slow waves, spike waves, slow & spike waves and absence of abnormalities [1]. To further corroborate the diagnosis, LGI1 antibody can be detected in blood and CSF, although blood levels are more sensitive in gauging disease progression and antibody titre [1]. The odds of finding voltage-gated-potassium

channel antibodies in patients with LG1 encephalitis is very minimal [24]. Pathological examination of postmortem brain tissues usually exhibits neuronal death and lymphocyte infiltration adjoining vasculature in the hippocampus and amygdala [18].

As LGI1 encephalitis closely disguises other neurological disorders, it always prudent to have a high clinical suspicion to differentiate it from them. Accordingly, possible differential diagnosis for these FBDS include startle disorders, paroxysmal non-kinesogenic dyskenesias, and negative myoclonus [16]. Furthermore, these FBGS can be rarely arising from the autoantibodies damaging the voltage gated potassium channels in patients with drug resistant acute onset seizure disorder [25]. Any delay in diagnosis and treatment can be fatal as it triggers hippocampal atrophy and permanent memory loss [1, 12, 16]. In these patients, there is always less responsiveness to anti-epileptics as the immune mediated LGI1 destruction is the main pathology, thus medications that lessen this phenomenon might be a pertinent strategy. On the grounds of this, intravenous corticosteroids, IVIG and blood exchange might offer comprehensive neuroprotection as they might dampen immune system activation, thence attenuating autoimmune mediated LGI1 destruction [26, 27]. Resultantly, numerous case reports demonstrate reversal of epileptic activity as well as backpedaling of cognitive dysfunction [1, 17, 18].

It is quite astounding that; epileptic activity completely disappears whereas cognitive dysfunction is little slow to rebound back to normal [9]. In practical terms, cognitive dysfunction will be permanent in those cohorts who do not receive prompt immunosuppressive therapy [16]. It is always a better strategy to monitor the response to therapy with measuring LGI1 autoantibody in the blood. Long-term and large doses of intravenous corticosteroids in combination with blood exchange are effective in avoiding permanent damage to the temporal lobe, reducing the onset of temporal lobe epilepsy and long-term complications including hippocampal damage [10, 27]. The recurrence rate of LGI1 encephalitis after initial immunotherapy session is approximately 10-20%, with disease resurging as early as 7 years. On account of this, regular follow up recommended to identify new symptoms and signs and these patients also need periodic brain imaging studies to discern new lesions [1, 13, 16, 28].

Conclusion

LGI1 encephalitis is an immune mediated neurological disorder effecting temporal lobe and basal ganglia. The classic clinical syndrome comprises of myoclonic jerks of the ipsilateral upper arms, facial twitching, memory disturbances, behavioral disturbances and hyponatremia. With its overarching symptoms, it does not snug perfectly with either seizure or movement disorder. The main pathological basis is mass production of anti-LGI1 auto-antibodies which strike the LGI1 protein in the neuronal milieu and presynaptic membrane.

On grounds of this immune mediated onslaught, LGI1 protein injury transpires and slowing of signal conduction at the synaptic interface never ensues.

In patients with aforementioned symptoms, a high degree of clinical suspicion necessitate MRI brain imaging which shows T2 hyperintensity in basal ganglia, temporal lobe and frontal lobe. This can be corroborated with assessing LGI1 antibody levels in the blood and CSF to monitor disease progression as well as treatment response.

As soon as diagnosis is confirmed, intravenous corticosteroids, intravenous immunoglobulins or plasma exchange will reverse the epileptic activity and cognitive dysfunction. Long term immunosuppressive therapy is warranted as it is inclined to reduce the onset of temporal lobe epilepsy and hippocampal atrophy.

Regular follow up to detect new clinical symptoms and brain lesions is recommended in these patients to reduce morbidity and mortality.

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Declarations

Consent for publication: The authors clarify that written informed consent was obtained and the anonymity of the patient was ensured. This study submitted to Swiss J. Rad. Nucl. Med. has been conducted in accordance with the Declaration of Helsinki and according to requirements of all applicable local and international standards.

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