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Deep brain stimulation of the centro-medial thalamus for successful management of late-onset intractable Lennox-Gastaut syndrome: A comprehensive case report.

Awadh M. Alahmari[1,5*], Ebia Samkari[2], Ahmad Khani[3], Ashraf Alharthi[4]

[1]Neurology Resident, Department of Neurology, King Saud Bin Abdulaziz University for Health Science (KSAU-HS), Riyadh, Saudi Arabia, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia

[2]Neurophysiology Fellow at King Abdulaziz Medical City, Riyadh, KSA

[3]Professor of Neurosurgery and Head of Neurosurgery Division at KingAbdulaziz Medical City, Riyadh, KSA

[4]Neurology and Epilepsy Consultant & Head of Electrophysiology Division at KingAbdulaziz Medical City, Riyadh, KSA

[5]King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard, Riyadh, Saudi Arabia

Abstract

Introduction: The presented case highlights the challenges in managing refractory LGS and the limited efficacy of current treatments. DBS targeting the centro-medial thalamus shows potential in reducing seizure frequency and improving electrographic activity in LGS patients.

Case presentation: This case report presents the use of Deep Brain Stimulation (DBS) targeting the centro-medial thalamus as potential therapeutic approach for a patient with refractory Lennox-Gastaut Syndrome (LGS), who did not achieve seizure reduction on multiple anti-seizure medications and vagus nerve stimulation.

Results: The findings from this case suggest that targeting the centro-medial thalamus with Deep Brain Stimulation (DBS) a potential intervention for managing refractory Lennox-Gastaut Syndrome (LGS) and achieving seizure freedom.

Conclusion: Future research should focus on conducting randomized controlled trials to establish DBS as a standard treatment for LGS. Careful consideration of the benefits, risks, and long-term outcomes of DBS, along with adherence to patient selection criteria, will be important. Collaboration and evidence accumulation through additional cases and centres can further enhance the understanding of DBS as a viable therapeutic option for this severe and debilitating epileptic condition.

Keywords: Lennox-Gastaut syndrome, Deep brain stimulation, Centro-medial thalamic nucleus

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Introduction

Lennox-Gastaut Syndrome (LGS), a severe and rare form of epilepsy that primarily affects children and persists into adulthood [1]. LGS is potentially catastrophic epileptic syndrome, racing 10% of childhood epilepsies [1,2]. The clinical course of late-onset LGS has not been fully understood with no description previously. The diagnostic and clinical features of LGS may evolve over time and may not all manifest at seizure onset [3]. In the current patient series, the diagnosis of LGS occurred at an average age of 16.5 years, which is older than the typical presentation of epileptic syndrome [3]. LGS is characterized by numerous types, including tonic, atypical absence, and atonic seizures. While 75% of patients have an identified underlying cause, such as malformations of cortical development or hypoxic-ischemic injuries, the etiology remains cryptogenic in the rest [4-6]. Current management strategies for LGS include a combination of Antiepileptic Drugs (AEDs), ketogenic diet, and epilepsy surgery [5,6]. Nonetheless, a subgroup of patients with intractable LGS remains unresponsive to conventional therapies, prompting the exploration of alternative treatment options such as

Deep Brain Stimulation (DBS). There is a prospective trial that was performed in Australia, which shows a reduction in seizure frequency reaching 50% in some patients.

In our case, we present very potential results in a patient with Lennox-Gastaut Syndrome (LGS) who has reached seizure freedom over a quantitative EEG follow-up period of 3 months.

Case Presentation

We present the case of a 40-year-old patient with a late-onset diagnosis of intractable Lennox-Gastaut Syndrome (LGS). He has experienced multiple seizure semiologies, including

First semiology

Started by hearing high-pitched sounds, followed by drop attack, with no postictal.

Second semiology

The patient experiencing the focal behaviour arrest seizure continues for four minutes followed by postictal headache.

Third semiology

Generalized tonic-clonic seizure, then postictal confusion, and fatigue.

The patient has no family history or seizure risk factors. On clinical examination, he exhibits mild cognitive impairment, while findings related to cranial nerve, motor, sensory, and cerebellar function are grossly unremarkable. Throughout his follow-up during six years, he has been prescribed multiple Anti-Seizure Medications (ASMs) and escalated throughout, including levetiracetam (1500 mg bid), zonisamide (300 mg bid), lamotrigine (125 mg bid), valproic acid (500 mg bid), rufinamide (1600 mg bid), and clobazam (2 mg od). Despite the medication regimen, the patient continues to experience multiple seizures, significantly impairing daily functioning. Various medications have been added and escalated over time, but no significant improvement in seizure frequency or duration has been observed. The persistent seizures have severely affected the patient's quality of life.

Vagus-nerve-stimulation

To improve seizure control, the patient underwent vagus nerve stimulation. However, this intervention did not result in significant changes in the frequency and duration of seizures during a two year follow up, highlighting the refractory nature of the patient's Lennox-Gastaut syndrome.

Preoperative-evaluation

Due to the ongoing intractable seizures, preoperative Electroencephalogram (EEG) recordings were performed to evaluate baseline seizure activity and assess the suitability for Deep Brain Stimulation (DBS). Additionally, brain imaging (MRI/CT) was conducted to assess the anatomical suitability for the surgical intervention (Figure 1 and Figure 2).

Surgical procedure

Considering the patient's history of treatment resistance and the lack of response to vagus nerve stimulation, the decision was made to proceed with Deep Brain Stimulation (DBS). The surgical procedure involved precise electrode placement in bilateral CM thalamic nucleus implicated in LGS pathophysiology. Intraoperative monitoring was performed to ensure accurate placement and optimal stimulation parameters (Figure 3).

Clinical outcome and pre/postoperative EEG

Following the DBS procedure, the patient experienced a remarkable improvement in seizure control, achieving seizure freedom for one month. The monitoring has been continued for another two months in which he has no seizures at all. This marked reduction in seizure frequency to none significantly impacted the patient's quality of life, allowing them to regain a sense of normalcy and function more independently (Figure 4 (preoperative) and Figure 5 (postoperative) EEG).

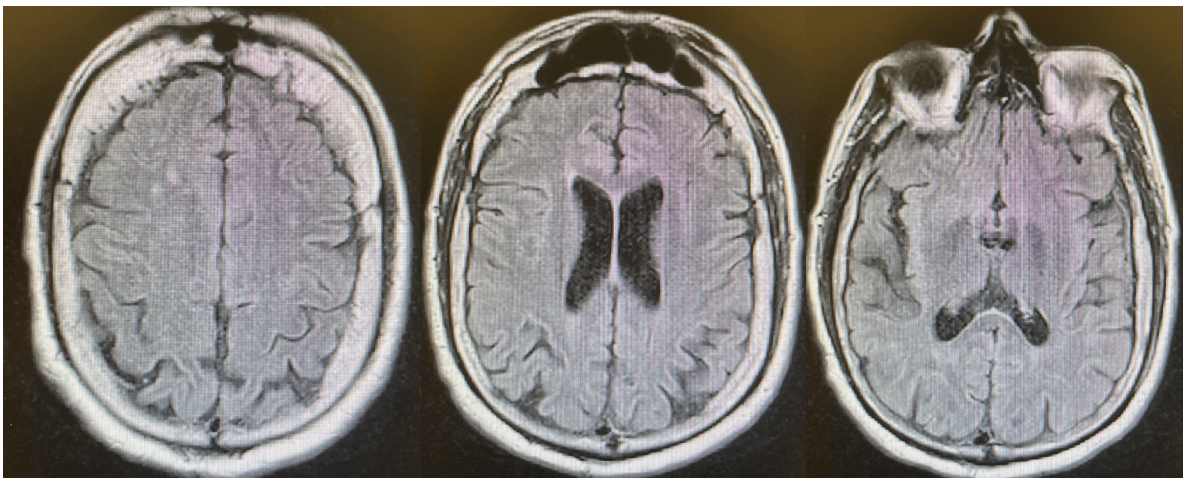

Figure 1. *Brain MRI, multiple horizontal sections demonstrate normal brain tissue and brain MRI showing multiple horizontal sections with normal brain tissue.*

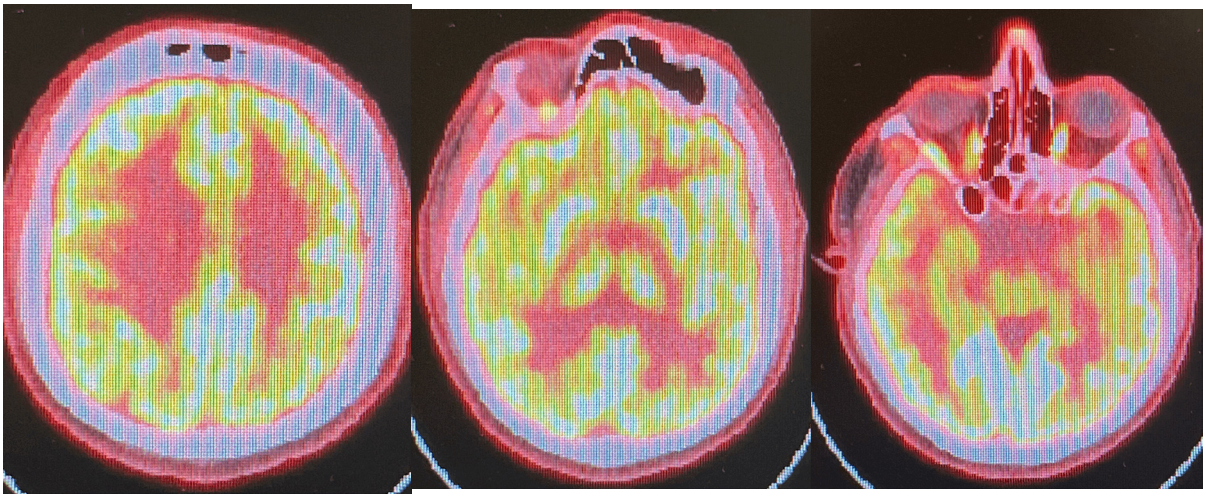

Figure 2. *PET brain scan done prior to the DBS shows symmetrical brain tissue uptake and PET brain scan conducted prior to DBS, showing symmetrical brain tissue uptake.*

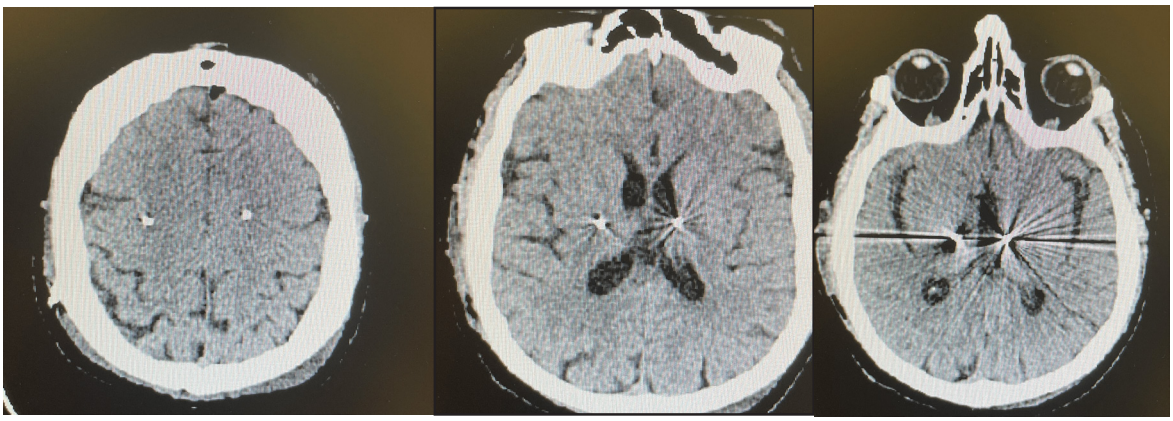

Figure 3. *Brain CT without contrast conducted post-DBS.*

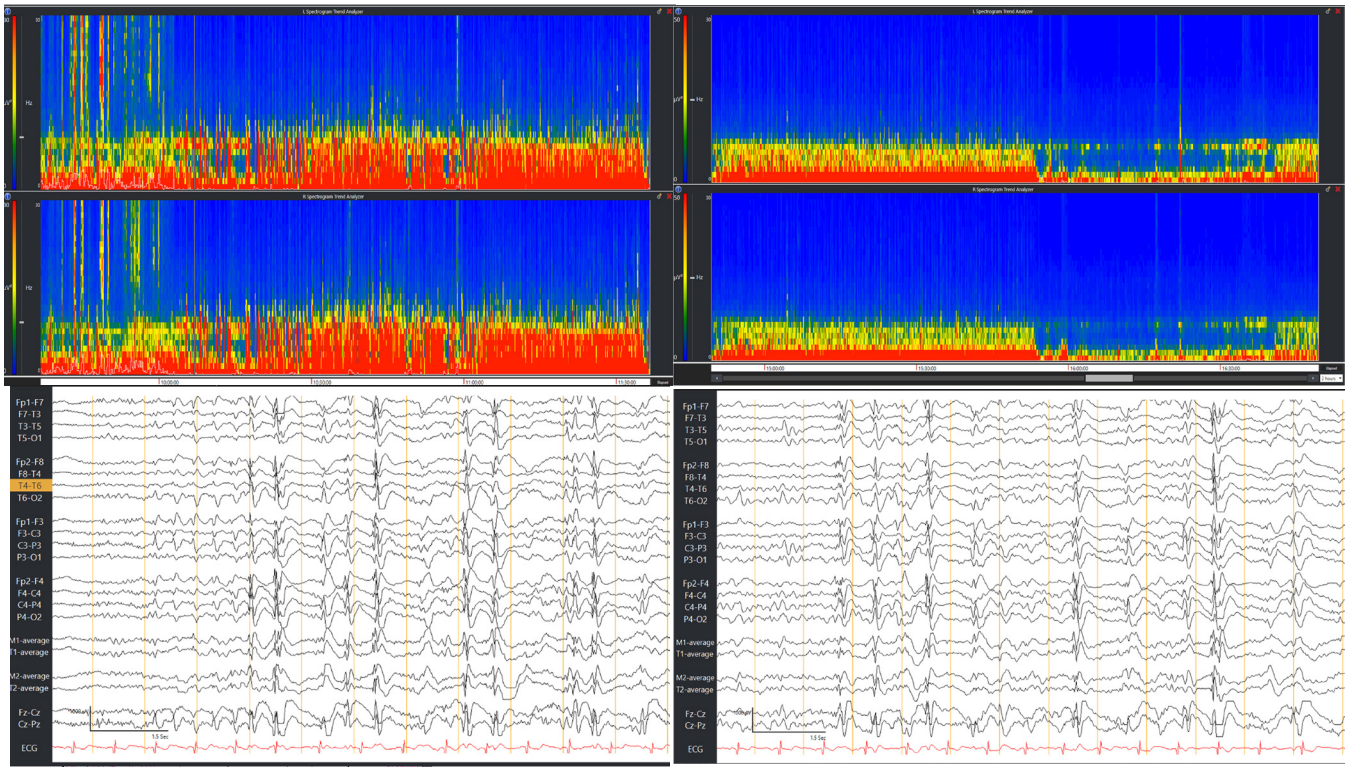

Figure 4. *Quantitative EEG was used to count a random 1-hour segment during NREM sleep, and it was found that the number of discharge complexes was approximately 1050 before DBS.*

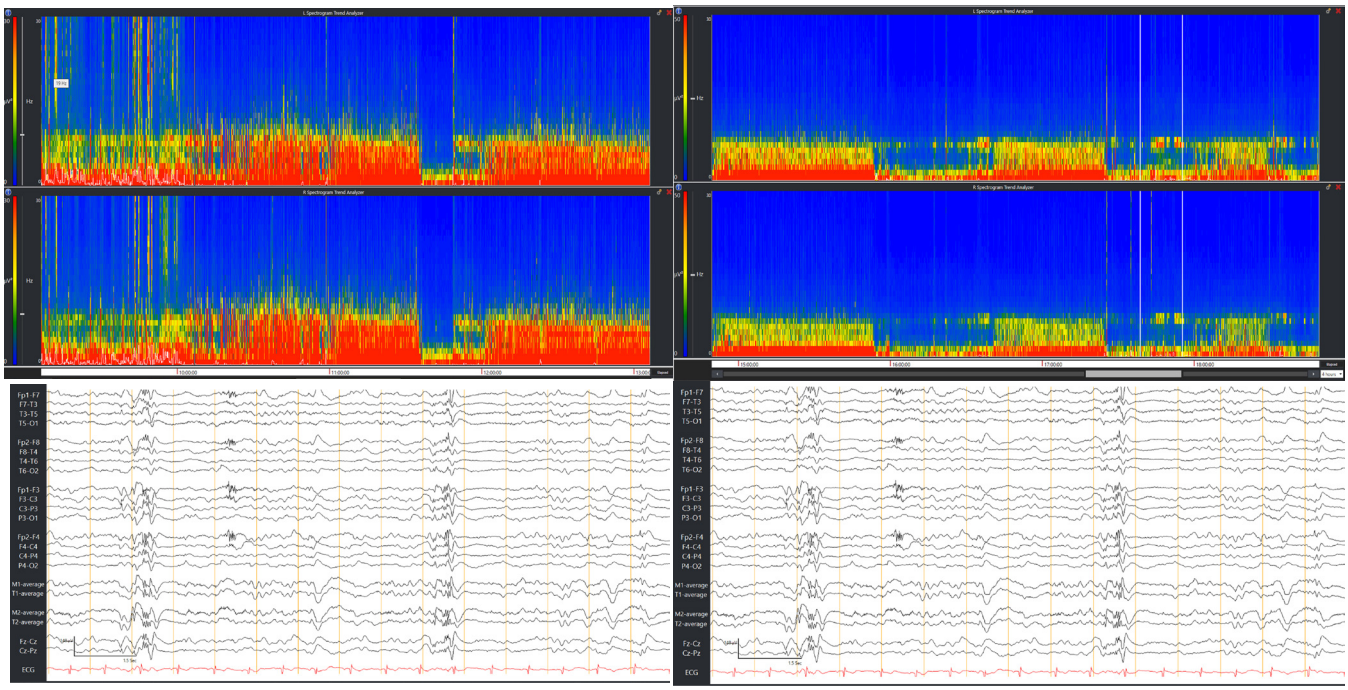

Figure 5. *Quantitative EEG showed a significant improvement, as detected by comparing a randomly selected 1-hour segment during NREM sleep before deep brain stimulation (DBS) to the post-DBS period. The number of discharge complexes improved from approximately 1050 to 490 discharge complexes.*

Results and Discussion

Lennox-Gastaut Syndrome (LGS) is a severe and refractory form of epileptic encephalopathy that poses unique challenges in diagnosis and management [1]. It typically presents in early childhood, with the highest incidence occurring between 3 and 5 years of age. The condition is characterized by progressive cognitive and behavioural impairment [2,3]. Diagnosis of late-onset LGS in adults can be particularly challenging due to diverse and atypical presentations [7]. The diagnostic and clinical features of LGS may evolve over time and may not all be present at the onset of seizures. The natural course of LGS is marked by various types of cognitive impairment and a distinct Electroencephalogram (EEG) pattern of slow spike-wave complexes. Developmental regression and cognitive decline are common, further complicating the management of this condition.

Current treatment options for LGS encompass Antiepileptic Drugs (AEDs), the ketogenic diet, and epilepsy surgery. However, a significant proportion of individuals with LGS do not achieve satisfactory seizure control with these approaches. In fact, the response rates to AEDs in LGS are generally low, ranging from 10% to 20% [1,2]. The ketogenic diet has demonstrated some efficacy, with reported response rates between 30% and 50% [7-10]. Epilepsy surgery, including corpus callosotomy and focal resection, can be considered in select cases but is associated with risks and may not be suitable for all patients. The previous experience with DBS has shown potential results, with up to 50% of cases achieving seizure freedom. However, there are currently no reported cases of complete seizure freedom, and further designed trials are necessary to thoroughly test the efficacy of this approach [11].

In this case, the patient had been on multiple AEDs, including levetiracetam, Zonisamide, lamotrigine, valproic acid, rufinamide, and clobazam, without significant improvement in seizure control. Vagus nerve stimulation was also attempted but did not yield satisfactory results. The lack of response to these conventional therapies highlights the refractory nature of the patient's LGS. Deep Brain Stimulation (DBS) has emerged as a potential alternative for patients with refractory LGS. In this case, DBS was performed targeting the centro-medial thalamus. The rationale behind this specific target stems from the role of the thalamus in modulating epileptic activity and its involvement in the generation and propagation of seizures. DBS in the centro-medial thalamus aims to disrupt abnormal neuronal synchronization and restore normal network activity. The clinical and electrographic responses observed in this case following DBS were highly encouraging. The patient experienced a significant reduction in the spike-wave index and epileptiform discharges on post-operative EEG analysis. Additionally, the patient's mild cognitive impairment may have been positively impacted by the DBS intervention, although further assessment is warranted to confirm this observation. While the specific mechanisms of action underlying DBS in LGS are not yet fully understood, it is believed to modulate aberrant neural activity and restore a more balanced network function. The success of DBS in LGS may be attributed to its ability to directly influence the thalamic circuitry involved in the generation and propagation of seizures.

It is important to note that DBS is not without potential complications. Surgical risks, such as infection, bleeding, and electrode misplacement, should be carefully considered, and appropriate patient selection criteria should be applied. Long-term follow-up and continued monitoring of the patient's clinical response and adverse events are important to evaluate the durability and safety of DBS in LGS.

Conclusion

The presented case highlights the challenges in managing refractory LGS and the limited efficacy of current treatments. DBS targeting the Centro-medial thalamus shows potential in reducing seizure frequency and improving electrographic activity in LGS patients. However, this is the first case of reaching seizure freedom. Future research should focus on conducting randomized controlled trials to establish DBS as a standard treatment for LGS. Careful consideration of the benefits, risks, and long-term outcomes of DBS, along with adherence to patient selection criteria, is crucial. Collaboration and evidence accumulation through additional cases and canters can further enhance the understanding of DBS as a viable therapeutic option for LGS.

Acknowledgment

The authors sincerely thank the patient and their family for their cooperation and consent to share this case for educational purposes. They would also like to express their gratitude to the healthcare team involved in the patient's care for their valuable contributions to the management, diagnostic workup, and surgical intervention.

Declarations

The authors declare no conflicts of interest concerning this case report.

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***Correspondence to:**

Awadh M. Alahmari

Neurology Resident

Department of Neurology

King Saud Bin Abdulaziz University for Health Science (KSAU-HS)

Riyadh, Saudi Arabia

Ministry of National Guard-Health Affairs

Riyadh, Saudi Arabia

King Abdullah International Medical Research Center (KAIMRC)

Ministry of National Guard

Riyadh, Saudi Arabia