Clinical Case Reports

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Vagal Nerve Stimulation for Refractory Epileptic Encephalopathy in Patient with Lissencephaly: Case Report from Indonesia

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Introduction: Lissencephaly is a rare brain malformation that causes severe developmental delays and intractable seizures. Traditional anti-epileptic drugs (AEDs) often fail to control seizures in these patients. Vagal nerve stimulation (VNS) has shown promise as an adjunctive treatment for refractory epilepsy.

Case Presentation: A 19-year-old male with lissencephaly and epileptic encephalopathy was referred for VNS implantation after experiencing poorly controlled seizures despite maximum doses of Levetiracetam and Valproic Acid. The patient had daily seizures and frequent episodes of convulsive status epilepticus. EEG revealed multifocal spikes, primarily in the frontal regions. VNS implantation was performed, initially set at 0.2 mA and gradually increased to 1.5 mA over two months. Follow-up results showed a progressive reduction in seizure frequency. By two months, the patient experienced 5-7 seizure-free days each month, with further improvements noted at six months. At ten months, the seizures were brief and infrequent, and the patient no longer required rescue medication.

Conclusion: VNS therapy significantly improved seizure control and the patient's quality of life. Regular follow-up and tailored adjustments to the VNS settings were essential for optimizing seizure management. This case highlights VNS as a valuable option for managing refractory epilepsy in patients with severe neurological conditions.

Keywords: lissencephaly, refractory epilepsy, vagal nerve stimulation

INTRODUCTION

Lissencephaly, a rare congenital brain malformation, is associated with severe neurodevelopmental delays and profound epilepsy, often presenting as refractory epileptic encephalopathy [1]. Patients with lissencephaly frequently experience a range of seizure types, including infantile spasms, focal, and generalized tonic seizures, which are generally resistant to conventional anti-epileptic drugs (AEDs) [2,3]. Vagal Nerve Stimulation (VNS) has emerged as a promising adjunctive therapy for refractory epilepsy, offering seizure reduction in cases that do not respond to medications alone. VNS involves implanting a device intermittently stimulating the vagus nerve, potentially modulating brain activity to reduce seizure frequency and severity. Previous meta-analyses showed that VNS can significantly improve the seizure frequency, mood and quality of life, especially in patients with drug-resistant epilepsy [4,5]. However, to our knowledge, there are no previous reports on VNS implantation in patients with lissencephaly.

Here, we report the case of a 19-year-old male from Indonesia with lissencephaly and drug-resistant epileptic encephalopathy who underwent VNS implantation following unsuccessful AED regimens. This case highlights the clinical course, VNS optimization strategy, and patient outcome over a 10-month follow-up period, demonstrating the role of VNS as a beneficial adjunctive treatment for epilepsy management in severe neurological conditions like lissencephaly.

CASE REPORT

The patient is a 19-year-old male diagnosed with lissencephaly who has suffered from refractory symptomatic epilepsy since infancy. Seizure onset was at the age of 8 months old, initially presenting as epileptic spasms. At the age of 4 years old, his seizure semiology progressed into both focal and generalized tonic seizures, which continued to date. His seizure burden comprises of 2-3 daily episodes of brief seizure, with 2-3 episodes of convulsive status epilepticus every month. His seizures have been severely

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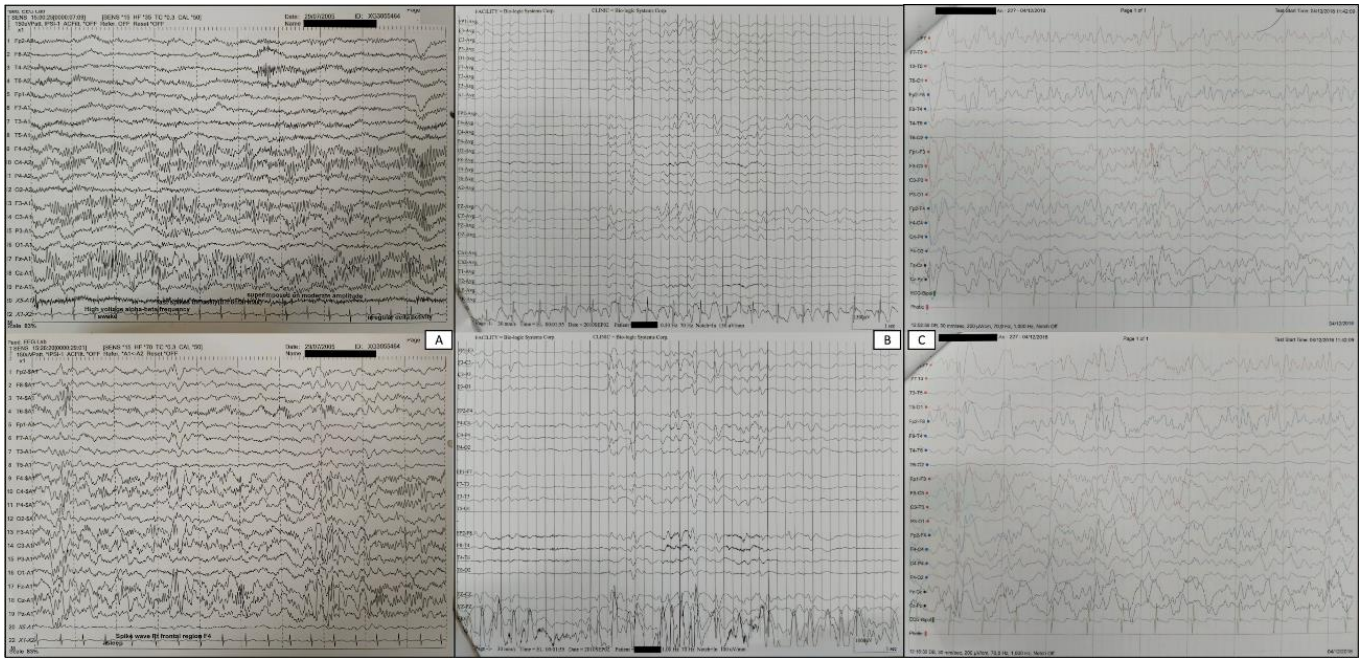

Figure 1 - Serial EEG recordings from the patient at ages 1, 6, and 14 years. Notes: (A) Absence of PDR, slow predominant EEG background, spikes over bi-frontal regions (age 1). (B) Sleep EEG with poorly modulated sleep architectures, with abundant spikes over the frontal regions (age 6), (C) High-amplitude polymorphic pike-and-wave activities over frontal regions, with low voltage EEG background (age 14)

compromising his quality of life as well as his daily functioning.

Serial electroencephalogram recordings were recorded from the patient at the ages of 1, 6, and 14 years old (Figure 1). At 1 year old, EEG showed frequent generalized and multifocal rhythmic slow-wave activity. Subsequent EEG at the age of 6 years old showed less continuous EEG background with ongoing generalized and multifocal slow spike wave discharges compared to the previous results. The third EEG which was performed at the age of 14 years old, the EEG still showed lack of physiological component of EEG background, with abundant generalized and multifocal polymorphic epileptiform discharges. Brain MRI with multiple sequences (T1 and T2-weighted images), with sagittal, coronal, and axial views (Figure 2), showed reduced or absent of gyral pattern, thickened cortex, ventriculomegaly, and abnormal white matter, consistent with lissencephaly. The patient also underwent genetic testing outside our hospital (in Singapore), which revealed a 10% deletion in the ARX gene, a 40% mutation in the LIS1 gene, and alterations in the DCX gene.

Despite being on maximum tolerable doses of Levetiracetam (LEV, 58 mg/kg/day) and Valproic Acid (VPA, 40 mg/kg/day), the patient showed no significant improvement in seizure control. He had also previously failed to respond to Clobazam (CLB) and Phenobarbital (PHB). Given his lack of clinical response to multiple anti-epileptic drugs, as well as the diffuse abnormalities of the intracranial structure, Vagal Nerve Stimulation (VNS) was proposed as an adjunctive therapy to manage his refractory epilepsy.

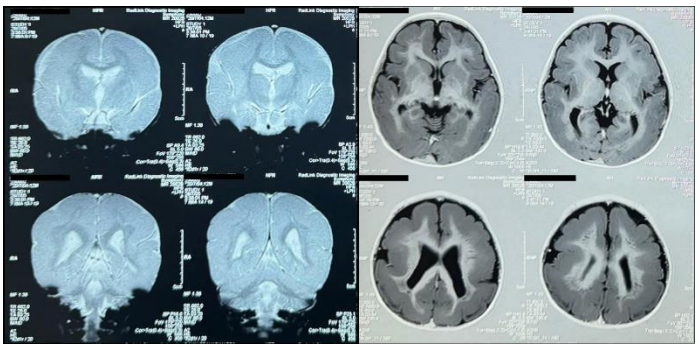

Figure 2 - Multiple MRI sequences (T1 and T2-weighted images). Coronal MRI demonstrates a diffuse smooth cortical surface with absent gyral-sulcal differentiation and a thickened cortex (Left). Axial MRI reveals a diffusely smooth cortex with shallow Sylvian fissures, cortical thickening, and enlarged ventricles (Right).

Surgical Procedure

VNS implantation was performed by one of the authors, a neurosurgeon specializing in epilepsy surgery (AS). The surgery lasted approximately two hours, and was conducted under general anesthesia with an ASA score of 2. Preoperative prophylaxis with 2 g of intravenous Cefazolin was administered 30 minutes before the procedure. During the operation, a subcutaneous pocket was created for the implantable pulse generator (IPG) just below the clavicle. A 7 cm incision was made at the level of C5-C6, following Langer's lines for optimal healing on the left side. The vagus nerve was carefully exposed and isolated over a 4 cm length, around which the electrodes were looped and secured. The lead was then tunneled to the IPG pocket and connected to the generator. An impedance test confirmed satisfactory

electrode placement with readings below 3000 ohms, and the incisions were closed in layers. Post-operative radiological imaging finding is visualized in Figure 3.

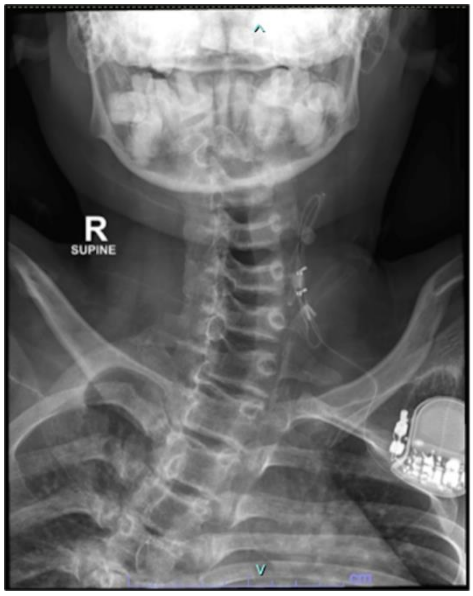

Figure 3 - Post-operative radiological imaging findings

Postoperative Management and VNS Setting

The VNS device was not programmed straight after the implantation. At 1st clinical visit 2 weeks after, the surgical wound was healing nicely without any complication and the VNS was set with initial output current of 0.2 mA and a duty cycle of 10%, as shown in Table 1. Over time, these settings were progressively adjusted to optimize seizure control. By the second month, the output current had been increased to 1.5 mA, while the duty cycle remained at 10%. By the sixth month, the duty cycle increased to 20%, with the output current at 1.5 mA. The magnet current was also adjusted 0.2 mA above the output current. The signal frequency remained constant throughout therapy at 30 Hz, with a pulse width of 500 µs. The signal-on time was initially set at 30 seconds and increased to 60 seconds at six months, while the signal-off time remained fixed at 300 seconds.

Table 1. VNS parameter adjustments

Parameter	Initial	Week 8	Month 24
Output current	0.2 mA	1.5 mA	1.5 mA
Magnet current	0.4 mA	1.7 mA	1.7 mA
Signal Frequency	30Hz	30Hz	30Hz
Pulse width	500µs	500µs	500µs
Signal On Time	30 sec	30 sec	60 sec
Signal Off Time	300 sec	300 sec	300 sec
Duty Cycle	9%	9%	18%

As seen in Figure 4, these adjustments in VNS parameters led to significant improvements in seizure control. At three months, the patient experienced five seizure-free days per month, with 1-2 brief generalized tonic seizures occurring daily. By the sixth month, the seizure-free days increased to 10 per month, with only 0-1 brief seizure per day. At nine months, the patient achieved 14 seizure-free days per month, and the frequency of brief seizures remained consistent. Additionally, there was a notable decrease in the use of magnet swipes and seizure rescue medications, reflecting improved overall seizure management..

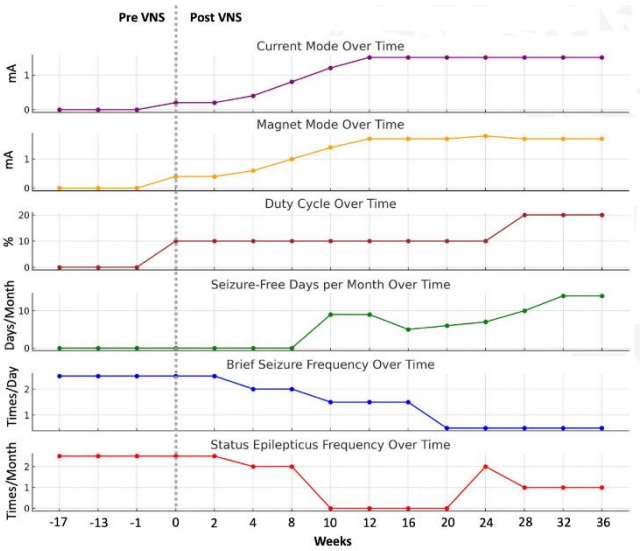

Figure 4 - Outcome during the whole study period

DISCUSSION

In this case, VNS significantly improved seizure control and quality of life for a patient with refractory epileptic encephalopathy secondary to lissencephaly. This case exemplifies the potential of VNS as an adjunctive therapy for individuals with severe, drug-resistant epilepsy, particularly in cases involving structural brain malformations such as lissencephaly, where traditional AEDs alone may be insufficient. Previous studies showed that approximately 54% of patients experience a ≥50% reduction in seizure frequency following VNS therapy, especially among those with Lennox-Gastaut syndrome (LGS), where the responder rate can be as high as 78% [6]. In another study in developmental epileptic encephalopathies (DEE) involving 116 patients with DEE, a seizure control of more than 50% was reported in 73% of cases. Improvements were also noted in alertness, behavior, and neurodevelopment [7].

Previous studies suggest that VNS exerts antiepileptic effects by activating afferent vagal fibers that target key brain regions involved in seizure modulation, such as the locus coeruleus and nucleus of the solitary tract [8,9]. This

stimulation also enhances the release of neurotransmitters like norepinephrine and serotonin, which are crucial for regulating neuronal excitability and dampening seizure activity in areas like the amygdala and hippocampus [9,10]. VNS also may appear to modify brain connectivity patterns, particularly disrupting abnormal synchrony during sleep, a period when seizures often intensify [8,9]. Subsequently, emerging evidence further suggests that VNS may exert anti-inflammatory effects, potentially reducing neuroinflammation that could otherwise heighten seizure susceptibility [9,10]. In this case, progressive titration of VNS parameters, including output current and duty cycle, was essential for optimizing seizure control. By gradually increasing stimulation intensity, the patient achieved meaningful improvements in seizure frequency and duration, highlighting the importance of a personalized, titrated approach to VNS therapy.

In the earlier controlled, multicenter study, 67 patients over 12 years old with refractory partial epilepsy underwent VNS implantation and were randomized to either high-frequency (20 to 50 Hz) or low-frequency (1 to 2 Hz) stimulation. After 14 weeks, the high-frequency group experienced a mean seizure reduction of 30.9%, compared to an 11.3% reduction in the low-frequency group, with only the high-frequency group's improvement reaching statistical significance when compared to pre-operative levels. Additionally, the high-frequency group showed a responder rate (defined as a greater than 50% reduction in seizures) of 38% [11]. A subsequent study involving 114 patients aged over 12 years, which included the 67 patients from the previous study and followed the same protocol, produced similar findings [12]. Of these 114 patients, 100 were observed in an open-label, high-frequency VNS study. Seizure frequency decreased by 20% within the first three months, further decreasing by 32% in months 10 to 12, with responder rates of 28% and 31%, respectively [13].

In a separate double-blind, multicenter study, 196 patients with partial refractory epilepsy (all over 12 years of age) were randomized to high- or low-frequency VNS. After three months, the high-frequency group showed a 27.9% reduction in seizures versus 15.2% in the low-frequency group. This group also demonstrated significantly better scores in global well-being evaluations, though no significant difference in responder rates was observed between groups [14]. This study case reinforces findings from prior studies demonstrating VNS's efficacy in reducing seizure frequency and severity in refractory epilepsy, including a growing body of literature supporting VNS in the pediatric population and cases with developmental anomalies. Notably, the patient maintained stable control over ten months of follow-up, suggesting that VNS, when carefully adjusted, can offer sustainable benefits for seizure management in complex cases.

Despite the promising outcome, several limitations to VNS therapy should be considered. First, achieving optimal VNS settings often requires extensive follow-up and parameter adjustments, which may not be feasible in all clinical settings, especially in low-resource environments. In this case, access to a specialized epilepsy center and multidisciplinary care, including neurology and neurosurgery expertise, was instrumental in achieving the desired outcome. Second, while VNS has shown benefits in seizure reduction, it is not a definitive cure for epilepsy, particularly in patients with underlying brain malformations such as lissencephaly. This patient continued to experience brief seizures even after VNS optimization, though with significantly reduced frequency and severity.

Additionally, VNS therapy can also carry some risks. Previous studies showed that while generally, VNS therapy is safe, it presents risks, with surgical complications such as hematoma (1.9%), infection (2.6%), and vocal cord palsy (1.4%) occurring in 8.6% of implantations overall, and hardware issues in 3.7% of cases, including lead malfunction in 3% [15]. Additionally, common adverse effects include voice alteration in 45.5% of patients, dysphagia in 39.5%, cough in 15%, and dyspnea in 14.3% [16,17]. However, in this case, the patient experienced no surgical complications, but long-term vigilance is necessary as delayed side effects may emerge with chronic VNS use.

Limitations of Study

The primary limitation of this study is the single-case design, which restricts generalizability. While the findings contribute valuable insights, more extensive studies are needed to establish more robust conclusions about VNS efficacy in patients with refractory epilepsy and lissencephaly. Furthermore, as the report follows the patient over ten months, the long-term sustainability of VNS efficacy and potential for further AED reduction remains unknown. Future studies with extended follow-up would help to assess the enduring benefits and possible late complications associated with VNS in this patient population.

CONCLUSION

VNS therapy provided significant improvements in seizure control and quality of life for this patient with lissencephaly and epileptic encephalopathy. Regular follow-up and individualized adjustments of VNS settings were crucial for success, demonstrating that VNS is a valuable adjunctive treatment for refractory epilepsy in patients with severe neurological conditions. Further research is warranted to explore the long-term efficacy and safety of VNS in similar cases, which could inform standardized protocols for VNS use in patients with lissencephaly and other structural brain malformations.

DISCLOSURES

Ethical approval

This study has been reviewed and ethically approved by the Health Research Ethics Committee of the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono Jakarta, Indonesia, with number of DP.04.03/D.XXIII.9/242/2024 (Date: October 22, 2024).

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

The patient gave consent to use his information and images for publication.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Artificial intelligence

ChatGPT-4.0 (OpenAI) was used to create Figure 4 based on data collected and analyzed by the authors. The figure was reviewed and verified by the authors for accuracy prior to inclusion in the manuscript

CONTRIBUTIONS

-**Arie Khairani**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing
-**Adi Sulistyanto**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing
-**Muhana Fawwazy Ilyas**: Conceptualization, Data curation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing

REFERENCES

1. Kattuoa M l., Das JM. Lissencephaly. 2024.
2. Mohamed K, Bakry M, Elmalik EE, et al. Lissencephaly causes refractory neonatal seizures in a term neonate. BMJ Case Rep. 2022;15:e249245. doi: 10.1136/bcr-2022-249245
3. Koenig M, Dobyns WB, Di Donato N. Lissencephaly: Update on diagnostics and clinical management. European Journal of Paediatric Neurology. 2021;35:147–52. doi: 10.1016/j.ejpn.2021.09.013
4. Hajtovic S, LoPresti MA, Zhang L, et al. The role of vagus nerve stimulation in genetic etiologies of drug-resistant epilepsy: a meta-analysis. J Neurosurg Pediatr. 2022;29:667–80. doi: 10.3171/2022.1.PEDS222
5. Kong Y, Zhao K, Zeng D, et al. Effects of vagus nerve stimulation on cognitive function in patients with epilepsy: a systematic review and meta-analysis. Front Neurol. 2024;15:1332882. doi: 10.3389/fneur.2024.1332882
6. Shahwan A, Bailey C, Maxiner W, et al. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. Epilepsia. 2009;50:1220–8. doi: 10.1111/j.1528-1167.2008.01940.x
7. Córdoba NM, Rivera IL, Ortiz De la Rosa JS. Vagal Nerve Stimulation in Developmental Encephalopathies and Epilepsy: A Narrative Revie. J Neurol Disord Stroke. 2023;10:1–8. doi: 10.47739/2334-2307.neurologicaldisorders.1211
8. Pigarev IN, Pigareva ML, Levichkina E V. Probable Mechanism of Antiepileptic Effect of the Vagus Nerve Stimulation in the Context of the Recent Results in Sleep Research. Front Neurosci. 2020;14. doi: 10.3389/fnins.2020.00160
9. Vonck K, Boon P. The Mechanism of Action of Vagus Nerve Stimulation Therapy. Eur Neurol Rev. 2008;3:97. doi: 10.17925/ENR.2008.03.02.97
10. Krahl S, Clark K. Vagus nerve stimulation for epilepsy: A review of central mechanisms. Surg Neurol Int. 2012;3:255. doi: 10.4103/2152-7806.103015
11. Ben-Menachem E, Mañon-Espaillat R, Ristanovic R, et al. Vagus Nerve Stimulation for Treatment of Partial Seizures: 1. A Controlled Study of Effect on Seizures. Epilepsia. 1994;35:616–26. doi: 10.1111/j.1528-1157.1994.tb02482.x
12. The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology. 1995;45:224–30. doi: 10.1212/WNL.45.2.224
13. Salinsky MC. Vagus Nerve Stimulation for the Treatment of Medically Intractable Seizures. Arch Neurol. 1996;53:1176. doi: 10.1001/archneur.1996.00550110128021
14. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures. Neurology. 1998;51:48–55. doi: 10.1212/WNL.51.1.48
15. Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve

stimulation: 25 years of experience at a single center. J Neurosurg Pediatr. 2016;18:97–104. doi: 10.3171/2016.1.PEDS15534

16. Kalagara R, Chennareddy S, Reford E, et al. Complications of Implanted Vagus Nerve Stimulation: A Systematic Review and Meta-Analysis. Cerebrovascular Diseases. 2024;1–9. doi: 10.1159/000536362
17. Alshehri KA, Abuhulayqah SH, Asiry MA, et al. Vagus nerve stimulation in medically refractory epilepsy: Adverse effects and clinical correlates. Neurosciences (Riyadh). 2024;29:10–7. doi: 10.17712/nsj.2024.1.20230006