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PHARMACORESISTANT TEMPORAL LOBE EPILEPSY CONTROLLED BY BILATERAL ANTERIOR THALAMIC NUCLEI THALAMOTOMY

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ABSTRACT

Introduction: Several potential targets have been suggested for the treatment of pharmacoresistant epilepsy, including the medial parts of temporal lobes, caudate nucleus, cerebellum, centromedian nucleus of the thalamus, subthalamic nucleus and anterior thalamic nucleus (ATN). The effectiveness of bilateral ATN thalamotomy as a treatment option for pharmacoresistant temporal lobe epilepsy is a considerable approach in this recent advances. Method: Case report. Result: A 24-year old male patient presented with unknown onset of generalized tonic clonic seizures and serials of drop attacks since 4 years of age. He was also diagnosed with Attention Defcit Hyperactivity Disorder (ADHD) and a history of febrile seizures. Brain MRI was normal. He has been treated with so many combination of antiepileptic drugs (AEDs) with last combination were Valproic acid 500 mg twice daily, Clonazepam 2 mg thrice daily and Zonisamide 100 mg twice daily. Despite all polytherapy AEDs given, he was still having recurrent seizures. Vagal Nerve Stimulation (VNS) was then conducted and seizures were slightly better. After maximal VNS voltage given, seizures became more frequent. ATN bilateral thalamotomy was done five years after, where seizure was better controlled. Levetiracetam 500mg twice daily and phenobarbital 15 mg once was given in concordance to the surgery, and the patient is doing well until now. Conclusion: In pharmacoresistant temporal lobe epilepsy where AEDs and VNS showed no signifcant improvement, ATN bilateral thalamotomy is considered to be a compelling treatment option. As we know, this is a first case report for ATN thalamotomy for epilepsy in south east asia region.

KEYWORDS *Pharmacorsistant epilepsy; temporal lobe epilepsy, ATN thalamotomy*

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INTRODUCTION

Epilepsy is a neurological disorder with around 65 million total cases. The psychological and emotional impact of the disease is a burden for the patients and their caregivers (Ngugi et al., 2010). The term epilepsy is defined as the condition of recurrent, unprovoked seizures (Shorvon et al., 2011). Many etiologies can generate seizures. However, for any reason, in individuals who develop seizures, there is an increase in glutamate activity on the particular receptor of postsynaptic neuron. This mechanism will aggravate the excitatory pathway. Along with it, GABA activity from the inhibitory pathway will diminish. This imbalance between the excitation and inhibition pathway will initiate abnormal electrical activity, and a seizure occurs (Tamber & Mountz, 2012).

Based on ILAE 2017, the seizure is classified into focal onset, generalized onset, and unknown onset. Focal onset defines as seizure that is generating limited from one hemisphere. It can stay localized or distribute to generalized. Patients who have a seizure and can verify awareness of themselves and their environment during the entire seizure period are classified as focal aware seizures. The presence of impaired consciousness during any portion of the seizure will be categorized as a focal seizure with impaired awareness. It will be different in generalized seizures, which generate from the bilateral hemisphere. Almost all the cases of this type have impaired consciousness, so the level of consciousness does not affect classification. Unknown onset is a convenient placeholder for insufficient data that can be reclassified as focal or generalized onsets later.

It is essential to find brain sites that generate abnormal electrical activity or epileptogenic zone (EZ) for surgical treatment, so the removal of EZ can be precise, and the best outcome will be achieved (Fisher et al., 2017). The most common epileptogenic zone (EZ) in the human brain is the temporal brain lobe (TLE), around 40% prevalence rate. Study shows surgical intervention for TLE gives better result compared to antiepileptic medication (Huff & Fountain, 2011; Tatum IV, 2012). Patients with TLE report a lower risk of neurological deficit after undergoing surgical treatment like excision of functional cortex compared to extratemporal lobe epilepsy (ETLE) patients. The ability to control seizures and minimal risk after surgical treatment make TLE cases are preferred for referral to a neurosurgeon (Téllez-Zenteno & Hernández-Ronquillo, 2012). One of the surgical options is stereotactic radiosurgery. Several promising targets include anterior thalamic nuclei (ANT). In addition to ATN, stereotactic radiosuergery can use different targets for drug-resistant epilepsy, such as: medial parts of temporal lobes, cerebellum centromedian nucleus of the thalamus, caudate nucleus and subthalamic nucleus (Morgan et al., 2015; Sillanpää & Shinnar, 2010; Sweeney-Reed et al., 2016). Radiofrequency therapy by making lesions on the thalamus is called thalamotomy. ANT is promising because it is involved in the extensive projection to various cortical and subcortical structures and its role in producing and spreading pathological electrical on epilepsy mechanism (Sitnikov et al., 2018; Van Gompel et al., 2015). The stereotactic lesions on ANT are rarely reported. The article summarizes results of pharmacoresistant temporal lobe epilepsy controlled by bilateral anterior thalamic nuclei thalamotomy.

RESEARCH METHOD

Case Report

A 24-year old male patient presented with unknown onset of generalized tonic-clonic seizures and serials of drop attacks since 20 years ago. He was also diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). He has a history of febrile seizures but negative family history for epilepsy. There were no abnormal findings in the history of the antenatal care and delivery process. The EEG is performed with a result of epileptiform focal in both anterior temporal regions. The patient was then diagnosed with Temporal lobe Epilepsy (TLE) combined with mental retardation. He has been treated with so many combinations of antiepileptic drugs (AEDs); the last combination was Valproic acid 500 mg twice daily, Clonazepam 2 mg thrice daily and Zonisamide 100 mg twice daily. Despite all polytherapy, he was still having recurrent seizures. Vagal Nerve Stimulation (VNS) was then conducted in May 2012, and seizures were slightly better. After maximal VNS voltage was given, seizures became more frequent. After the fail sign Of VNS emerged, the patient was planned for an MRI, but no abnormalities were found. At the same time, VNS stimulation parameters such as voltage, duration, and frequency were increased to reach a level that could control seizures. Eventually, the stimulation reaches a maximal level with the result of an uncontrolled seizure. The patient was then scheduled for a radiofrequency thalamotomy in November 2018.

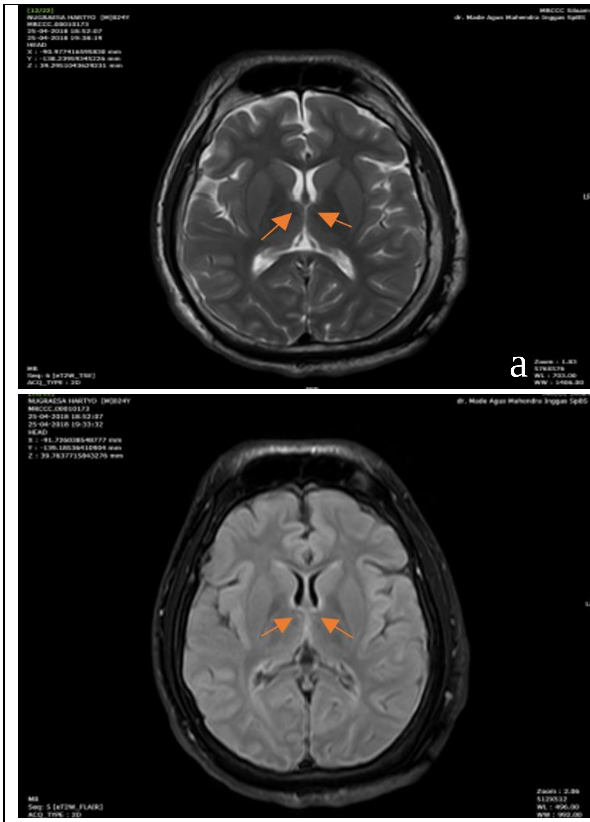
Tabel 1. EEG Examination Timeline

Year	Result Of EEG
2007	Mutifocal on frontal R and frontotemporal S
2011	Multifocal on frontal R, S and temporal S
2015	Multifocal on frontal area

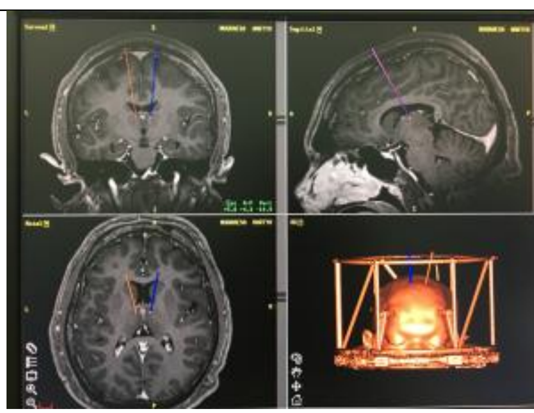
2016	Multifocal mainly in temporal
2018	Slow background wave both hemisfer

Before surgery, target radiofrequency thalamotomy was determined through magnetic resonance imaging (MRI) with contrast and electroencephalography (EEG). MRI with contrast intends to visualize the target during stereotactic destruction. In addition, acquired epileptogenic lesions will also appear. Based on preoperative assessment results, the anterior thalamic nucleus (ATN) was carried out as a stereotactic target.

On the day of surgery, a CRW stereotactic ring was placed on the patient's head under local anesthesia, and Intraoperative Contrast-enhanced CT scans were performed into account the anatomical characteristics of the patient's cerebral blood vessels and ventricular system. The results are combined with preoperative assessments to obtain the electrode port, the entry and placement trajectory. Intraoperative registration of neuronal activity and determination of neurophysiological boundaries of ANT were performed using microelectrode recording(MER) by Medtronic device, which used ATN Stereotactic lesioning in mid commissural point. Destruction was performed with a frequency of 480 kHz at 70 °C for 70 sec. The destruction was conducted in 2 cycles with the same parameters. During the second cycle, the electrode was moved 0.5cm above the first area using a microdrive.



Picture 1a. Magnetic resonance tomography scans of the patient after radiofrequency anterior thalamotomy on the axial view T2; Picture 1b. T1 Flair. Destruction zones are visualized within ANT pointed by arrow.



Picture 3a. Electrode trajectory to ATN in coronal view; Picture 3b. Sagittal view; Picture 3c axial view; Picture 3d. 3D view of CRW stereotactic frame.

Monitoring of the patient was performed postoperatively. One month postoperatively, his condition was weak, and the seizures were still high, then the clinical condition gradually improved, and the seizures decreased. Evaluation of the results of surgical treatment was conducted according to the Engel Surgical Outcome Scale, the results showed an improvement, where the preoperative assessment after the VNS procedure was engel class 3 changed to engel class 2 after radiofrequency thalamotomy. The current condition has been improve by only three seizure episodes a week with no more drop and blackout symptoms. Drug administration is also reduced with the current dose: Levetiracetam 500mg twice daily and phenobarbital 15 mg once was given concordance to the surgery. The patient has been doing well until now.

RESULT AND DISCUSSION

Discussion

Based on the ILEA category, seizure onset is divided into focal, generalized and unknown onset. Cases that don't have enough information or the seizure patterns are not suitable for focal or generalized seizure will be classified as the unknown onset. The symptoms can be motor type, including tonic-clonic, nonmotor, or unclassified. The patient experienced tonic clonic seizure since 20 years ago without any family history of epilepsy. He was diagnosed as temporal lobe epilepsy. TLE is the most common type of seizure in the world with 40 % prevalence rate.

Approximately 1/3 of epilepsy cases are pharmaco-resistant. Patients in this state have a higher long-term mortality rate of 1.59% per year. The most common cause was an unexpected death in epilepsy (SUDEP) (Sillanpää & Shinnar, 2010; Sitnikov et al., 2018). Pharmacoresistant epilepsy is when the patient can't achieve free seizure after using 2 AED with adequate dose and frequency. In this kind of case, surgical treatment is the next step for seizure management. This patient had been using multidrug therapy, but the seizure was not controlled. VNS procedure has also been performed, but the effect was only temporary.

One study shows the case of 7 patients with tremors who undergo thalamotomy after unsuccessful DBS therapy. Six patients report an improvement of symptoms, and 3 of them have improved performing ADL (activity daily living). Although early results revealed that DBS showed better functional outcomes when compared to thalamotomy, there are several advantages of thalamotomy that can be a consideration factor, such as affordable procedure, no need for enormous follow-up, and low-risk infection (Bahgat et al., 2013). In the treatment of epilepsy, bilateral stimulation of ANT with the Medtronic DBS system has been approved by FDA as a second-line treatment to control seizures in refractory epilepsy. The age limit for this procedure is $\geq$18 years old. In 1967, a study of ANT targets for unilateral lesions was conducted in 9 patients. Six patients reported improved seizure frequency where 1 of them was seizure-free.

Sitnikov AR et al. conducted a study comparing the results between ANT DBS with ANT radiofrequency. They included 31 patients with pharmacoresistant epilepsy (age 16–48 years). Twelve patients underwent ANT DBS, and they reported seizure frequency was reduced by 80.3% one year after procedure, with three patients becoming seizure-free. The remaining 19 patients underwent bilateral stereotactic radiofrequency ANT lesions, and As a result, seizure frequency was reduced by 91.2%, five of which were seizure-free (Sitnikov et al., 2018). This data confirms the significant role of ANT in the propagation of epileptic activity and the helpful ANT as a targeted treatment originated from temporal/frontal lobes.

A study published in 2016 reported 13 patients with long-term refractory epilepsy who underwent bilateral stereotactic radiofrequency thermocoagulation of ATN. Early postoperative observations show a 50-90% reduction in seizures frequency in all patients. Drugs received were also reduced, with four patients switching to monotherapy and nine patients switching to a combination of the two drugs at the average therapeutic dose. Studies in patients with pilocarpine-induced seizures and epileptic status have shown that the anticonvulsant effect of ANT radiofrequency destruction occurs only when performed bilaterally or with high-frequency stimulation. Radiofrequency destruction will increase resistance to generalized seizures. The animal study provided showed an amplitude-dependent increase activation within temporal, prefrontal, and sensorimotor cortex at 60 Hz and 145 Hz stimulation, but not with 2 Hz stimulation (Gibson et al., 2016). These studies support the hypothesis that the antiseizure effect of radiofrequency action is amplitude and frequency-dependent. In our report, the Destruction was performed twice with a frequency of 480 kHz at 70 °C for 70 sec. The results of surgical treatment were assessed with Engel scales. Class 1: free of disabling seizures which exclude the first few weeks post-operative seizure, class 2: rare disabling seizure or almost seizure-free, class 3: worthwhile improvement, and class 4: no worthwhile improvement. In this case, the results showed an improvement, where the preoperative assessment after the VNS procedure was Engel class 3 changed to Engel class 2 after radiofrequency thalamotomy.

CONCLUSION

In pharmacoresistant temporal lobe epilepsy, where AEDs and VNS showed no significant improvement, ATN bilateral thalamotomy is considered a compelling treatment option. To increase the efficacy and safety, it is necessary to assess the target radiofrequency thalamotomy before and during surgery. The purpose is to adapt to the anatomical features of the patient. The consideration of surgical treatment such as DBS or radiofrequency thalamotomy in pharmacoresistant epilepsy is based on the characteristics of the patient's disease and the benefits that the patient will get.

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