C A S E R E P O R T

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Satisfying outcome of vagus nerve stimulation applied in the treatment of a patient with drug-resistant epilepsy caused by periventricular nodular heterotopia

Zadovoljavajući ishod primene stimulacije vagusnog nerva u lečenju bolesnika sa epilepsijom rezistentnom na lekove nastalom usled periventrikularne nodularne heterotopije

Stefan Todorović*, Boban Biševac*†, Stevo Lukić*†, Jovan Ilić‡, Dejan Aleksić§

University Clinical Center Niš, *Department of Neurology, ‡Department of Neurosurgery, Niš, Serbia; †University of Niš, Faculty of Medicine, Niš, Serbia; §University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

Abstract

Introduction. Periventricular nodular heterotopia (PNH) is a developmental malformation of the cerebral cortex characterized by abnormal migration of neurons into the cortical plate and is often associated with drug-resistant focal epilepsy. **Case report.** A 33-year-old female patient suffered from drug-resistant epilepsy, which was predominantly characterized by focal seizures, with occasional seizures that had a focal onset and progressed into bilateral tonic-clonic seizures. Magnetic resonance imaging showed bilateral heterotopic nodules in the occipital horns of the lateral brain ventricles. 18-Fluoro-deoxyglucose positron emission tomography – FDG-PET scan demonstrated a zone of reduced glucose metabolism on the right temporal region. Electroencephalogram suggested focal electrocortical activity on the temporo-parieto-occipital regions, predominantly on the right temporal side. The woman was treated with polytherapy (valproic acid, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, clobazam, and lacosamide), but it did not affect the seizure frequency. Due to the bilateral localization of the heterotopic nodules, surgical treatment was not recommended. After a multidisciplinary assessment, we decided on vagus nerve stimulation (VNS) and achieved satisfying seizure control. **Conclusion.** Patients with PNH require multidisciplinary assessment and treatment, while in this report we have a case of a pa-tient in whom satisfying control of drug-resistant epilepsy was achieved after the implantation of the VNS device.

Key words:
brain; congenital abnormalities; drug-resistant epilepsy; epilepsies, partial; magnetic resonance imaging; positron-emission tomography; vagus nerve stimulation.

Apstrakt

Uvod. Periventrikularna nodularna heterotopija (PNH) predstavlja malformaciju u razvoju kore velikog mozga koja se karakteriše abnormalnom migracijom neurona u kortikalnu ploču i često je povezana sa fokalnom epilepsijom rezistentnom na lekove. **Prikaz bolesnika.** Bolesnica stara 33 godine patila je od farmakorezistentne epilepsije, koju su pretežno karakterisali fokalni napadi, sa povremenim napadima koji su imali fokalni početak i širili se u bilateralne toničko-kloničke napade. Nalazima magnetne rezonance pokazano je da bilateralno postoje heterotopični čvorovi duž okcipitalnih rogova bočnih komora mozga. Nalaz *18-Fluoro-deoxyglucose positron emission tomography* – FDG-PET skenera je pokazao postojanje zone smanjenog metabolizma glukoze u desnom temporalnom regionu. Elektroencefalogram je ukazao na fokalnu elektrokortikalnu aktivnost u temporo-parijeto-okcipitalnim regionima, pretežno temporalno desno. Bolesnica je lečena politerapijom (valproična kiselina, lamotrigin, levetiracetam, okskarbazepin, pregabalin, klobazam, lakozamid) koja nije uticala na učestalost epileptičkih napada. Zbog bilateralne lokalizacije heterotopičnih čvorova, hirurški način lečenja nije bio preporučljiv. Nakon multidisciplinarnog sagledavanja, odlučili smo se za stimulaciju vagusnog nerva (SVN) i postigli zadovoljavajuću kontrolu epileptičkih napada. **Zaključak.** Bolesnici sa PNH zahtevaju multidisciplinarno sagledavanje i lečenje, dok u ovom slučaju imamo primer bolesnice kod koje je postignuta zadovoljavajuća kontrola farmakorezistentne epilepsije nakon implantacije uređaja za SVN.

Ključne reči:
mozak; anomalije; epilepsija, farmakorezistentna; epilepsija, parcijalna; magnetska rezonanca, snimanje; tomografija, pozitron-emisiona; n. vagus, stimulacija.

Correspondence to: Jovan Ilić, University Clinical Center Niš, Department of Neurosurgery, Vizantijski bulevar 112/12, 18 000 Niš, Serbia. E-mail: jovanilicneuro@gmail.com

Introduction

Neural migration, together with neural proliferation and cortical organization, represents the fundamental processes of neocortex formation, whose end result is the establishment of a functional cerebral cortex. Inadequate migration and organization of the laminarly structured cortex causes congenital malformations of cortical development [1]. Periventricular nodular heterotopia (PNH) is a rare malformation of cortical development characterized by abnormal migration of neurons to the cortical plate. It is characterized by nodular masses, which protrude into the ventricular lumen. The most common localization is along the occipital horns of the lateral ventricles. PNH is frequently characterized by drug-resistant epilepsy (DRE) and different forms of mental retardation. PNH can be presented as bilateral and symmetrical, bilateral single-noduled, bilateral and asymmetrical, and unilateral with extension to neocortex and unilateral. In more than 75% of cases, the nodules are localized bilaterally [2].

Magnetic resonance imaging (MRI) and 18-fluorodeoxyglucose positron emission tomography - FDG-PET scans play an important role in the recognition and diagnosis of PNH [3, 4]. Vagus nerve stimulation (VNS) should be considered for the treatment of severe DRE, especially if the patients are not candidates for surgical intervention [5]. Hereinafter, we report a case of a patient with satisfying seizure control after the VNS device implantation.

Case report

A 33-year-old woman with a history of DRE was admitted to the hospital for clinical and therapeutic assessment. The patient was born from a normal, full-term pregnancy *via* vaginal delivery and without any perinatal complications. The mild mental retardation was diagnosed in childhood. There was no family history of seizures. The seizures occurred when she was 14 years old, with the frequency of four to five times a day, lasting less than 2 min. She had an epilepsy characterized by focal seizures, occasionally bilateral tonic-clonic seizures. The mother usually noticed that the patient had speech difficulties, could not pronounce words clearly, could not establish contact with her (did not answer calls, and acted as "lost"). This would usually be followed by convulsions in the left arm and leg. Occasionally, the patient reported the feeling of epigastric heat that would radiate cranially. At a later stage of the disease, the seizures took on a new pattern. Moreover, the patient became aggressive during the seizures, even running off on a couple of occasions. Polycystic ovary syndrome (PCOS), diabetes mellitus (DM) type 1, hypothyroidism, and thrombophilia were diagnosed in our patient. Her comorbidities have significantly limited our therapeutic options. Valproic acid (1,000 mg/day) partially controlled the seizures until she was 16 years old when, due to the irregularity of the menstrual cycle, the PCOS was diagnosed. Henceforth, she did not take hormone therapy for PCOS regularly. For those reasons, valproic acid was replaced by lamotrigine (100 mg/day). In addition, the convulsions continued to be frequent, so levetiracetam (1,000 mg/day) was added to the therapy, but without any improvement in the patient's condition. Furthermore, lamotrigine had to be excluded from the therapy due to interaction with hormone therapy. On the other hand, carbamazepine has not been added to therapy due to thrombophilia and the use of warfarin. The seizures became more frequent and complex. Several scars from burns sustained after the seizures were registered on her left hand, and as a result of one convulsion, the patient also suffered serial rib fractures. Her illness caused a severe functional disability.

During the initial hospital examination, the results of the clinical examination were normal. Electroencephalogram (EEG) findings indicated focal electrocortical activity predominantly on the right temporal region (Figure 1). MRI demonstrated bilateral nodular and confluent changes in the occipital horns of the lateral ventricles, which corresponded to ectopic gray matter and indicated congenital cortical malformation, micronodular periventricular gray matter heterotopia (Figure 2). Such a finding was confirmed by the FDG-PET scan (Figure 3), where a zone of reduced glucose metabolism was registered in the right temporal region (polar, mesial, and lateral).

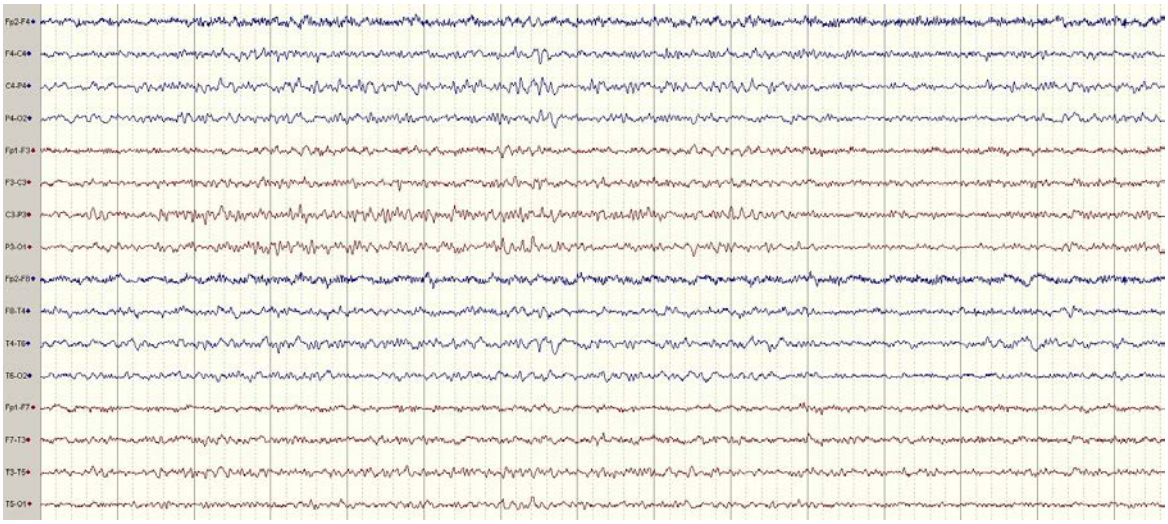

Fig. 1 – Electroencephalogram showing focal electrocortical activity on the temporo-parieto-occipital regions, predominantly on the temporal right.

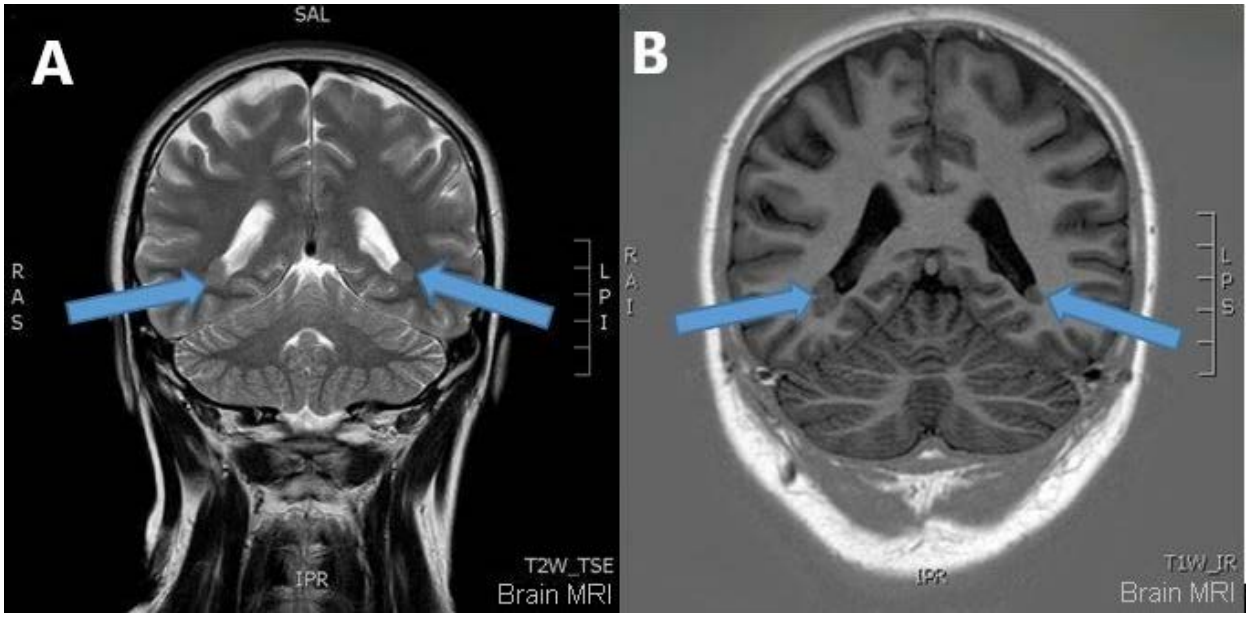

Fig. 2 – Magnetic resonance imaging: A) T2 weighted turbo-spin-echo (T2W TSE); B) T1 weighted inversion-recovery (T1W IR); para-coronal tomograms (A, B) orthogonally oriented to the hippocampus showing bilateral heterotopic nodules of grey matter in the occipital horns of the lateral ventricles (arrows). RAS – right-anterior-superior; LPI – left-posterior-inferior; SAL – superior-anterior-lateral; IPR – inferior-posterior-right; RAI – right-anterior-inferior; LPS – left-posterior-superior.

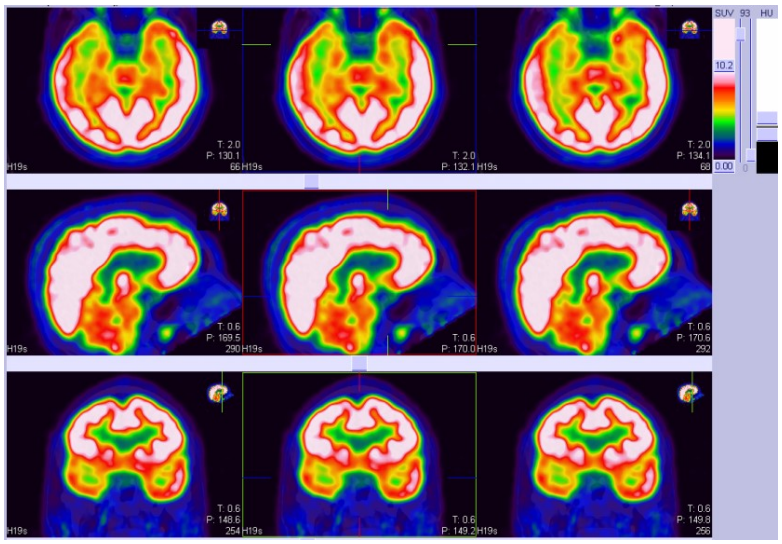

Fig. 3 – 18-Fluoro-deoxyglucose positron emission tomography – FDG-PET, shows a zone of reduced glucose metabolism in the temporal region. The scan indicates high (red) to low (blue) tracer uptake or binding. Images in the upper row represent axial, in the middle row sagittal, and in the lower row coronal plane sections.

Neuropsychological testing (NPT) was also performed. The analysis of the results of the NPT recorded a lower primary intellectual level and educational limitations, as well as a subdepressive effect, with the registration of a drop in visual memory, dysexecutive syndrome on visual material, as well as reduced processing speed. NPT indicated dysfunction of the non-dominant hemisphere.

The seizures continued to occur frequently (several seizures a day), and the patient was hospitalized on several occasions. At her follow-up examinations, the dose of medication was increased (levetiracetam 4,000 mg/day), and other antiepileptic drugs (oxcarbazepine 2,400 mg/day, pregabalin 600 mg/day, clobazam 30 mg/day, lacosamide 300 mg/day) were introduced into the therapy. Even with such polytherapy, the seizures were still frequent. Surgical treatment was controversial due to the bilateral localization of heterotopic nodules around the occipital horns of the lateral ventricles, as well as due to the high risk of visual impairment. Therefore,

the VNS device was implanted (Figure 4). The follow-up examinations were performed three and six months later, as well as one year after the intervention, and there was a significant reduction in the frequency of seizures during that period. A notable decline was observed in the occurrence rate of epileptic seizures, approximately two to three times a week. In the case of our patient, VNS proved to be an appropriate therapeutic modality, given that we achieved satisfying seizure control.

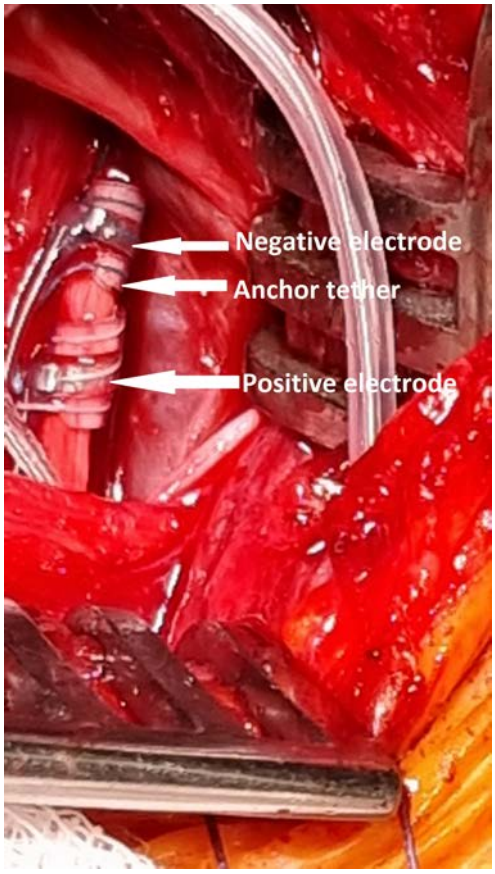

Fig. 4 – Surgical implantation of the vagus nerve stimulation device.

Discussion

We present a patient with DRE due to PNH with numerous severe comorbidities such as DM type 1, PCOS, thrombophilia, and hypothyroidism in whom successful control of epileptic seizures was achieved after the implantation of the VNS device.

The classic form of PNH is often manifested as epilepsy. In addition to epilepsy, some patients may have dysmorphic facial features and intellectual disabilities, which are predominantly of a milder degree. The severity of epileptic seizures and especially mental retardation depends on the degree of cortical abnormality [6]. Raymond et al. [7] reported 13 patients with periventricular heterotopia and epilepsy. The time of onset of the seizures was between 18 months and 20 years of age. Eight patients had bilateral PNH, while five had the unilateral form. Several patients from the bilateral group were similar to ours (from a clinical point of view, EEG and neuroimaging). Similarly, Dubeau et al. [8] reported a study of 33 patients with PNH. Fourteen patients had bilateral lesions. Some of them had normal intellectual and motor functions (64.3%), but some had mild mental retardation (35.7%). Recurrent seizures occurred in 82% of cases. In most of the patients, those were focal seizures with aura. Several of those patients were similar to ours if we consider radiological and clinical expression of malformation.

D'Orsi et al. [9] compared the outcomes of the two groups of patients with malformations of cortical development. Their report included 120 patients, among which 16 of them had PNH. One group included patients with simple PNH without other cortical or cerebral malformation (eight patients). Another group included patients with other cortical or cerebral malformations (eight patients), such as subcortical heterotopia, polymicrogyria, focal dysplasia, schizencephaly, cortical infolding, agenesis of the *corpus callosum*, *mega cisterna magna*, and cerebellar atrophy (PNH plus). The group without associated malformations was usually characterized by normal intelligence and seizures, usually focal, that began during the second decade of life. Seizures were usually rare. The EEG showed focal abnormalities. In the group of patients with associated malformations, seizures were very frequent in most cases, while these patients had mental retardation. The EEG in this group showed focal and bisynchronous abnormalities. This report indicated that the presence of other types of cortical or cerebral malformations, in addition to PNH, determines a poor prognosis. In our case, we had patients without other proven malformations, but seizures were very frequent and associated with mild mental retardation. Gray matter heterotopias are difficult to differentiate from hamartomas of tuberous sclerosis, and MRI is usually required to clarify the diagnosis [10]. On the other hand, the FDG-PET scan illustrates a disorder of glucose metabolism in heterotopic gray matter. This diagnostic method precisely identifies epileptogenic foci, which is crucial for surgical planning and good postoperative seizure control [11]. A pilot study on 19 patients with PNH showed that heterotopic nodules were hypometabolic in 33.33% of patients and that 83.33% of patients with PNH had concordant FDG-PET/MRI findings with the clinical epileptic zone [11]. In our case, clinical and EEG characteristics of the seizures indicated involvement of the temporal lobe. Furthermore, MRI imaging and FDG-PET scans helped us significantly in making the final diagnosis. The complexity of our case was also reflected in the therapeutic limitation. Namely, our patient had a number of therapeutic limitations due to comorbidities. PCOS, thrombophilia, as well as the use of hormone therapy significantly limited our therapeutic options. For these reasons, we had additional difficulties in controlling the seizures. Regarding the data on long-term effects of VNS, the results of a Norwegian population-based study indicated a gradual increase in the beneficial effects of VNS over time, expressed as a cumulative probability of more than 50% reduction in seizure frequency, which was found in almost

60% of patients. Particularly significant results were achieved in a subgroup of patients without intellectual disabilities, with a pronounced probability of achieving a ≥ 75% reduction in seizure frequency. Within specific epileptic conditions, the most pronounced beneficial effects were observed in patients with poststroke epilepsy (75.0%) and post-traumatic epilepsy (70.6%) [12]. Ghaemi et al. [13] reported a study with 144 patients with some of the following features: multifocal interictal epileptiform discharge, unilateral interictal epileptiform discharge, cortical dysgenesis, and psychomotor seizure. Results of their study showed that ten patients remained seizure-free for more than one year after VNS device implantation (6.9%). Seizure frequency improved in 61.8% of patients, but no changes were observed in 31.3% of patients. Moreover, some studies indicated that VNS is a suitable treatment for DRE and can reduce polypharmacy during pregnancy [14].

The opinion of the Council for Functional Neurosurgery was that the operative treatment in our patient was not an appropriate treatment modality due to the bilateral localization of heterotopic nodules around the occipital horns of the lateral ventricles, as well as due to the high risk of visual impairment. Some authors believe surgery should be performed in cases where heterotopic nodules are located outside the eloquent areas and unilaterally [15]. On the other hand, some authors suggest the importance of stereotaxic ablative procedures in the treatment of PNH; however, we did not opt for them due to the high degree of potential occurrence of neurological deficits after these procedures, as well as insufficient data from the scientific literature [16].

Conclusion

In conclusion, significant advances in neuroimaging techniques have improved our knowledge of malformations in cortical development. Evaluation of clinical features and long-term follow-up of these patients is essential but is often neglected. Our case presents PNH as a common cause of DRE. Furthermore, this case emphasizes the difficulties of treating patients with PNH, as well as the role of MRI imaging in recognizing this anomaly. VNS plays an important role in achieving successful control of epileptic seizures. Early recognition of heterotopia is essential for planning the proper treatment.

Conflict of interest

The authors report no conflict of interest and no sources of support that require acknowledgment.

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