Acta Clin Croat (Suppl. 3) 2021; 60:45-49
doi: 10.20471/acc.2021.60.s3.06

Case Report

DELAYED EFFECT OF VNS ON INTERICTAL EPILEPTIFORM DISCHARGES AND PHARMACORESISTANCE IN A PATIENT WITH REFRACTORY PERINATAL POSTISCHEMIC EPILEPSY

Davor Sporiš[1,3,4], Silvio Bašić[1], Darko Chudy[2], Ivana Šušak Sporiš[1,3,4] and Ivana Marković[1,3,4]

[1]Department of Neurology, Dubrava University Hospital, Zagreb, Croatia;
[2]Department of Neurosurgery, Dubrava University Hospital, Zagreb, Croatia;
[3]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;
[4]University of Applied Health Science in Zagreb, Zagreb, Croatia

SUMMARY – A 20-year-old female with refractory perinatal postischemic catastrophic epilepsy and frequent daily generalized atonic, tonic, tonic-clonic and focal seizures was hospitalized in the progressive phase of illness. The diagnosis was confirmed by semiology, interictal electroencephalogram (EEG), long-term video EEG monitoring, and brain magnetic resonance imaging. Repeated interictal EEG findings showed generalized spike and slow wave complexes with a 2-3 Hz frequency. Interictal EEG showed evidence of electroclinical epileptic status on several occasions. She was treated with various antiepileptic drugs without improvement. After verification of her incompetence for normal autonomous living, which resulted in very low quality of life, this patient with refractory epilepsy underwent implantation of vagus nerve stimulator (VNS). In this case report, we present delayed effect of VNS on interictal epileptiform discharges and pharmacoresistance.

Key words: *Epilepsy; Pharmacoresistance; Interictal epileptiform discharges; Vagus nerve stimulation*

Introduction

Epilepsy is one of the most common neurological disorders, characterized by recurrent spontaneous seizures and ictal epileptiform discharges[1]. Among the non-pharmacological treatment options for refractory epilepsy, vagus nerve stimulation (VNS) occupies a unique position as an adjunctive method for patients who are unsuitable candidates for resection neurosurgery.

Long-term VNS studies show response rates between 40% and 50% and long-term seizure freedom in 5% to 10% of patients[2,3]. Research of the VNS activity showed that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers. Crucial brainstem and intracranial structures include the locus coeruleus, the nucleus of the solitary tract, the thalamus, and limbic structures[4]. A major role in the impulse transmission is played by the neurotransmitters GABA, serotonin and adrenergic systems[5]. Desynchronization of abnormal synchronous epileptic activity is one of the hypotheses of the mode of action for an anti-seizure effect[6,7]. Several studies were investigating the effect of VNS on electroencephalogram (EEG) suppressing interictal spikes and seizures during stimulation[8,9].

We report a case of a young woman with refractory catastrophic perinatal postischemic epilepsy who underwent VNS as treatment for her seizure disorder, with improvement of the seizure frequency and delayed effect of VNS on interictal epileptiform discharges.

Correspondence to: *Davor Sporiš, MD PhD*, Dubrava University Hospital, Department of Neurology, Av. Gojka Šuška 6, HR-10000 Zagreb, Croatia
E-mail: davor.sporis@kbd.hr

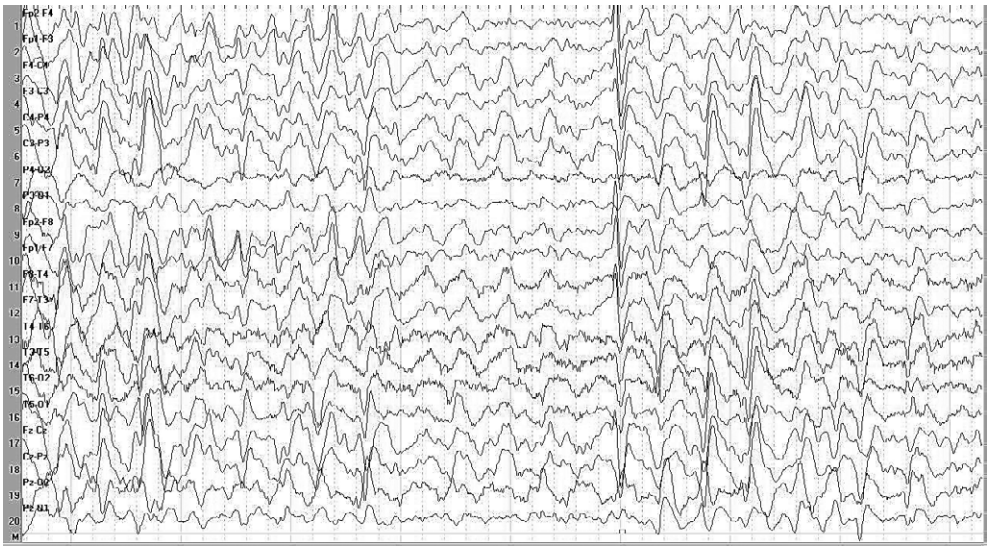

Fig. 1. EEG before implantation of VNS: EEG findings showed interictal generalized spike and slow wave complexes with a frequency 2-3 Hz.

Case Report

A female patient was born in 1999 by spontaneous vaginal delivery after complicated and prolonged labor, Apgar scores 6/4. Immediately after birth, cardiopulmonary resuscitation was performed because of apnea episodes. Initial examination revealed rhinolalia, dysphagia, motor weakness, and hypersalivation. She was treated in the incubator for the first ten days. Shortly after birth, perinatal convulsions were recorded, and she was treated by pediatrician with phenytoin for seven years, without further epileptic manifestations. During that treatment, her childhood was uneventful. At the age of 7 years, the diagnosis of startle epilepsy in response to touch, visual and sound stimuli was established. Semiology was predominated by generalized tonic, tonic-clonic and atonic seizures. On several occasions, she was hospitalized at pediatric department because of uncontrolled seizures. At the age of 8 years, she suffered further exacerbation of the same semiology of epilepsy without sensory induced seizures. At the age of 14 years, frequent seizures originating from the supplementary motor area (SMA) were reported. During growth, she developed mild mental retardation. Brain magnetic resonance imaging (MRI) showed postischemic and gliotic brain changes (perinatal) within the frontoparietal white matter bilaterally, more pronounced on the right side, and a cortico-subcortical porencephalic cyst. Repeated interictal EEG findings showed generalized spike and slow wave complexes with a 2-3 Hz frequency, and occasional findings of electroclinical epileptic status (Fig. 1).

The diagnosis of structural generalized and focal epilepsy (SMA) was established. Due to various semiology of seizures, the patient was treated unsuccessfully with numerous antiepileptic polytherapy, e.g., valproate, carbamazepine, ethosuximide, barbiturate, clonazepam, phenytoin, lamotrigine, topiramate.

At the age of 17 years, her condition deteriorated with frequent daily atonic, tonic and tonic-clonic seizures. According to family history, she had 20 to 40 seizures *per* day. The patient was not competent for autonomous living and she needed 24-h care. Her mental condition was changed and she was depressive and dissatisfied with the very low quality of life.

She presented to our Center for Epilepsy at the age of 20 years. According to her clinical presentation and neuroradiology findings, VNS implantation was indicated. Scalp video EEG telemetry was performed and daily atonic, tonic and focal seizures with bilateral tonic-clonic seizures during sleep were registered. A vagal nerve stimulator (Cyberonics Inc., Huston, TX, USA) was implanted in May 2018 with stimulating electrode attached to the left vagus nerve. Initially, she was followed-up every two weeks, then monthly according to the protocol, and finally after six months she was on 2.25 mA output current/mA, on/off time 30 s/3 min, frequency 30 Hz, pulse with 500 μs. A side

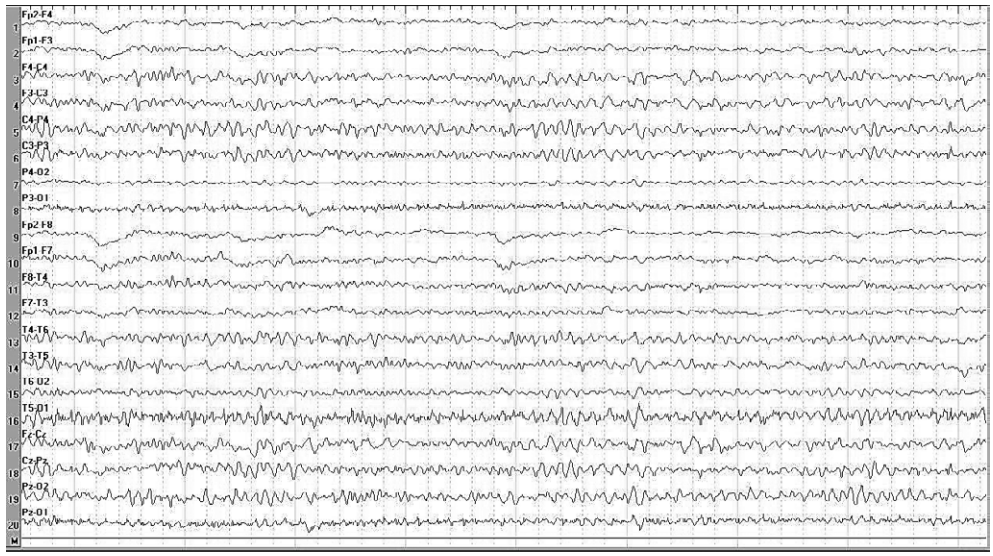

Fig. 2. EEG two years after VNS implantation: EEG findings showing alpha and beta background activity without generalized interictal epileptiform discharges.

effect after VNS implantation was transient voice alteration without any complication furthermore.

Improvement of seizure frequency was first reported one month after VNS implantation and after six months, the improvement was more than 90 percent. She occasionally had a few atonic and focal seizures, and rarely, during sleep, a few tonic-clonic seizures *per* month. At that time, she had 10-20 seizures *per* month on average, mostly during sleep, with 15-day periods without seizures.

After 18 months, she had no atonic, tonic and focal seizures, while generalized tonic-clonic seizures occurred once a week, especially during sleep. She noted periods of a few months without any seizure. At the final stage before VNS implantation, the patient was receiving 3000 mg of levetiracetam, 1500 mg of valproic acid and 2 mg of clonazepam. She had regular EEG monitoring every two months and EEGs after 6 months were less paroxysmal than before VNS. Several EEG findings after 18 months with prolonged hyperventilation and photo stimulation showed alpha and beta background activity without generalized interictal epileptiform discharges and such findings were maintained throughout the next year (Fig. 2).

Discussion

Our patient with refractory perinatal postischemic epilepsy experienced significant improvement (>90%) in seizure control and loss of generalized interictal epileptiform discharges two years after VNS implantation. Improvement of seizure frequency was first reported one month after VNS, and after six months the improvement was more than 90 percent. After 18 months, the patient was free from atonic and focal seizures, while generalized clonic-tonic and tonic seizures occurred once a week. Seizure rates and generalized interictal epileptiform discharges declined with the duration of VNS therapy and stimulation over time.

The results of studies in pediatric epilepsy syndromes show efficacy of VNS in Lennox Gastaut syndrome and other structural epilepsies with predominant tonic, atonic, clonic-tonic and focal seizures[10,11], as it was the case in our patient. Rossignol[10] analyzed a cohort of 28 children and adolescents, classified by epileptic syndromes and treated with VNS using a 6-week rapid ramping protocol. The study showed favorable outcome within 6 months and it remained unchanged for 24 months, with 68% of patients showing ≥50% reduction in seizure frequency including 14% who became seizure free. The type of seizures that were most responsive to VNS therapy included atonic (86%-50% reduction), tonic (100%-50%) and myoclonic (75%-50%) seizures.

Many studies have reported long-term efficacy of VNS in adults. Ardesch[12] demonstrated about 50% overall effect of VNS on seizure frequency after 5 years. De Giorgio[13] reports that 20% of subjects had

75% seizure reduction 1 year after VNS implantation. Furthermore, a Belgian multicenter study[14] reviewed 138 patients with a follow-up of at least 12 months. Overall reduction in the mean monthly seizure frequency was 51%, with 59% responder rate. In this study, ≥50% seizure reduction was achieved in 75% of all patients at 36 months of VNS initiation.

Our patient had regular interictal EEG monthly monitoring and EEG finding after 6 months showed progressive decrease in the duration and frequency of spikes/spike and wave activity compared with pre-VNS and first months after VNS. Several EEG findings obtained after 18 months with prolonged hyperventilation and photostimulation were without paroxysmal epileptiform discharges (spike or spike/wave complex) (Figs. 1 and 2).

VNS activates neuronal networks in the thalamus and other limbic structures. Desynchronization of abnormal synchronous epileptic activity is one of the hypotheses of the mode of action for the anti-seizure effect. We demonstrated the effect of VNS on interictal paroxysmal EEG discharges in our patient and its prolonged and delayed effect over time. Our report is consistent with the studies by Wang *et al.*[8] and Koo[9]. Koo[9] studied long-term effect of VNS on EEG. In this study, five patients were found to have progressive increase in the duration of spike-free intervals and decrease in the duration and frequency of spikes and spike-wave activity with time. Sixteen patients showed progressive decrease in the number of spikes on EEG over time. However, Kuba *et al.*[6,15] studied interictal epileptiform discharges on EEG and showed a clear effect of acute VNS on reducing interictal epileptiform discharges in humans during the stimulation period as compared to the baseline. They also demonstrated the acute effect of VNS on suppression of the interictal and ictal epileptic EEG finding.

In the study by Wang *et al.*[8], interictal EEG activity was influenced by VNS, and interictal epileptiform discharges progressively decreased with time on the EEGs of all patients, and seizures were terminated by the VNS extra stimulation with a handheld magnet. Correspondingly, video-EEG data showed that ictal synchronized paroxysmal epileptic discharges were also terminated by VNS. Several studies have reported adverse side effects in VNS patients including voice alterations, neck pain, severe dysphagia, and infections at the site of implants[2,16]. Most of these side effects, however, were transient and controlled by adjusting current output and using specified antibiotic therapy[17]. Our patient had transient voice alteration and neck pain.

In conclusion, we report on a patient with refractory perinatal postischemic epilepsy with good response to VNS. VNS is an efficient, well-tolerated and add-on therapy for drug-resistant epilepsies, with mild stimulation-related side effects. It can strongly affect epileptiform activity over time, inducing electrophysiological changes in the brain that may also decrease interictal epileptiform discharges (spike and spike/wave complex). This case report shows VNS efficacy in patients with generalized tonic-clonic, tonic, atonic, and focal seizures. For long-term treatment and favorable outcome, it was necessary to adjust current output in terms of correcting the level of stimulation and on-off periods.

References

1. Sander JW, Shorvon, SD. Epidemiology of the epilepsies. J Neurol Neurosurg Psychiatry. 1996;61:433-43.
2. Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology. 1999;53:1731-5.
3. Boon P. Electrical stimulation for the treatment of epilepsy. Neurotherapeutics. 2009;6:218-27.
4. Follesa P, Biggio F, Gorini G, Caria S, Talani G, Dazzi L. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. Brain Res. 2007;1179:28-34.
5. Vonck K, De Herdt V, Boon P. Vagal nerve stimulation – a 15-year survey of an established treatment modality in epilepsy surgery. Adv Tech Stand Neurosurg. 2009;34:111-46.
6. Kuba R, Guzaninova M, Brazdil M, Novak Z, Chrastina J, Rektor I. Effect of vagal nerve stimulation on interictal epileptiform discharges: a scalp EEG study. Epilepsia. 2002;43: 1181-8.
7. Bartolomei F, Bonini F, Vidal E, Trébuchon A, Lagarde S, Lambert I, McGonigal A, Scavarda D, Carron R, Benar CG. How does vagal nerve stimulation (VNS) change EEG brain functional connectivity? Epilepsy Res. 2016;29:141-6.
8. Wang H, Chen X, Lin Z, Shao Z, Sun B, Shen H, Liu L. Long-term effect of vagus nerve stimulation on interictal epileptiform discharges in refractory epilepsy. Neurol Sci. 2009; 284:96-102.
9. Koo B. EEG changes with vagus nerve stimulation. J Clin Neurophysiol. 2001;18:434-41.

10. Rossignol E. Vagus nerve stimulation in pediatric epileptic syndromes. Seizure. 2009;18:34-7.
11. Orosz I, McCormick D, Zamponi N, Varadkar S, Feucht M, Parain D, Griens R, Vallée L, Boon P, Rittey C, Jayewardene AK, Bunker M, Arzimanoglou A, Lagae L. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia. 2014;55(10): 1576-84.
12. Ardesch JJ. Vagus nerve stimulation for medically refractory epilepsy: a long-term follow-up study. Seizure. 2007;16: 579-85.
13. DeGiorgio CM. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 2000;41:1195-200.
14. De Herdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. Eur J Paediatr Neurol. 2007;11: 261-9.
15. Kuba R, Nesvadba D, Brazdil M, Oslejskova H, Ryzi M, Rektor I. Effect of chronic vagal nerve stimulation on interictal epileptiform discharges. Seizure. 2010;19(6):352-5.
16. Ortler M. Deep wound infection after vagus nerve stimulator implantation: treatment without removal of the device. Epilepsia. 2001;42:133-5.
17. Lee HO. Effect of vagus nerve stimulation in post-traumatic epilepsy and failed epilepsy surgery: preliminary report. J Korean Neurosurg Soc. 2008;44:196-208.

Sažetak

ODGOĐENI UČINAK VNS-a NA INTERIKTALNA EPILEPTIFORMNA IZBIJANJA I FARMAKOREZISTENTNOST U BOLESNICE S REFRAKTORNOM PERINATALNOM POSTISHEMIJSKOM EPILEPSIJOM

D. Sporiš, S. Bašić, D. Chudy, I. Šušak Sporiš i *I. Marković*

Mlada žena u dobi od 20 godina s farmakorezistentnom perinatalnom postishemijskom epilepsijom i svakodnevnim učestalim generaliziranim atoničkim, toničkim, toničko-kloničkim te žarišnim napadima hospitalizirana je u pogoršanoj fazi bolesti. Dijagnoza je potvrđena kliničkom slikom, interiktalnim elektroencefalogramom (EEG), video EEG monitoriranjem te magnetskom rezonancom (MR) mozga. Ponavljani interiktalni nalazi EEG-a pokazali su generalizirana izbijanja šiljak-val kompleksa frekvencije 2-3 Hz. U više navrata u interiktalnom EEG-u je evidentiran i elektroklinički epileptički status. Bolesnica je liječena različitim antiepilepticima, ali bez poboljšanja stanja. Zbog učestalih napada bolesnica nije bila sposobna za samostalan život, što je rezultiralo vrlo niskom kvalitetom života te je bolesnica podvrgnuta ugradnji vagusnog stimulatora (VNS). U ovom prikazu slučaja opisujemo odgođeni učinak VNS-a na interiktalna epileptiformna izbijanja i farmakorezistentnost.

Ključne riječi: *Epilepsija; Farmakorezistentnost; Interiktalna epileptiformna izbijanja; Stimulator vagus živca*