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VAGUS NERVE STIMULATION IMPLANTATION IN A PREGNANT PATIENT WITH DRUG-RESISTANT EPILEPSY: A CASE REPORT AND REVIEW OF THE LITERATURE

Abstract.
Introduction. Drug-resistant epilepsy (DRE) affects approximately 30% of patients and poses significant challenges during pregnancy due to seizure-related risks and antiepileptic drug teratogenicity.
Objective. To report the first case in the Russian Federation of successful vagus nerve stimulator implantation during pregnancy in a patient with DRE.
Materials and Methods. A clinical case of a 28-year-old woman with an 11-year history of DRE who underwent VNS implantation at 18 weeks of gestation is presented.
Results. Gradual activation of the stimulator resulted in complete seizure remission and transition to levetiracetam monotherapy. Pregnancy and delivery were uneventful, resulting in the birth of a healthy child.
Conclusion. VNS therapy represents a safe and effective adjunctive treatment option for DRE during pregnancy when resective surgery is not feasible.
Key words: drug-resistant epilepsy; pregnancy; vagus nerve stimulation; neuromodulation; antiepileptic drugs.

ИМПЛАНТАЦИЯ СТИМУЛЯТОРА БЛУЖДАЮЩЕГО НЕРВА У БЕРЕМЕННОЙ ПАЦИЕНТКИ С ФАРМАКОРЕЗИСТЕНТНОЙ ЭПИЛЕПСИЕЙ: КЛИНИЧЕСКИЙ СЛУЧАЙ И ОБЗОР ЛИТЕРАТУРЫ

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Аннотация.
Введение. Лекарственно-резистентная эпилепсия (ЛРЭ) сохраняется примерно у 30% пациентов и представляет особую клиническую проблему во время беременности в связи с риском тератогенности противоэпилептических препаратов и неблагоприятного влияния приступов на мать и плод.
Цель. Представить первый в Российской Федерации клинический случай успешной имплантации стимулятора блуждающего нерва (VNS) во время беременности у пациентки с ЛРЭ.
Материалы и методы. Представлено клиническое наблюдение пациентки 28 лет с 11-летним анамнезом ЛРЭ, у которой на сроке 18 недель беременности была выполнена имплантация VNS-системы.
Результаты. После постепенной активации стимулятора достигнута полная ремиссия эпилептических приступов, произведён переход на монотерапию леветирацетамом. Беременность и родоразрешение протекали без осложнений, ребёнок родился здоровым.
Заключение. VNS-терапия может рассматриваться как безопасный и эффективный метод адъювантного лечения ЛРЭ у беременных пациенток при невозможности резективного хирургического вмешательства.
Ключевые слова: лекарственно-резистентная эпилепсия; беременность; стимуляция блуждающего нерва; нейромодуляция; противоэпилептические препараты.

FARMAKOREZISTENT EPILEPSIYA BILAN OG‘RIGAN HOMILADOR BEMORDA VAGUS NERVI STIMULYATORINI IMPLANTATSIYA QILISH: KLINIK HOLAT VA ADABIYOTLAR SHARHI

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Annotatsiya.
Kirish. Dori-rezistent epilepsiya (DRE) bemorlarning taxminan 30% ida uchraydi va homiladorlik davrida tutqanoqlar hamda antiepileptik dorilarning teratogen ta’siri sababli jiddiy muammolarni keltirib chiqaradi.
Maqsad. Rossiya Federatsiyasida ilk bor homiladorlik vaqtida DRE bilan og‘rigan bemorda adashgan nerv stimulyatorini implantatsiya qilish bo‘yicha klinik holatni taqdim etish.
Material va usullar. 18 haftalik homiladorlikda VNS implantatsiyasi bajarilgan 28 yoshli bemorning klinik kuzatuvi keltirilgan.
Natijalar. Stimulyator bosqichma-bosqich faollashtirilgach, tutqanoqlar to‘liq to‘xtadi va bemor levetirasetam monoterapiyasiga o‘tkazildi. Homiladorlik va tug‘ruq asoratsiz kechdi, sog‘lom bola tug‘ildi.
Xulosa. VNS terapiyasi homilador ayollarda dori-rezistent epilepsiyani davolashda xavfsiz va samarali qo‘shimcha usul bo‘lishi mumkin.
Kalit so’zlar: dori-rezistent epilepsiya; homiladorlik; adashgan nerv stimulyatsiyasi; neyromodulyatsiya; antiepileptik dorilar.

Introduction. According to the definition of the International League Against Epilepsy (ILAE), drug-resistant epilepsy is diagnosed when treatment with two appropriately selected medications (either monotherapy or in combination) fails and is administered for an adequate period of time [1,2]. Approximately one-third of patients with epilepsy remain resistant to drug therapy [3,4].

One of the treatment methods for drug-resistant epilepsy is the implantation of a vagus nerve stimulator (vagus nerve stimulation, or VNS therapy). The VNS therapy system is intended for use as an adjunctive therapy to reduce the frequency of seizures in patients suffering from epileptic disorders with focal seizures (with or without secondary generalization) or generalized seizures for whom resective surgical treatment cannot be performed [5]. For example, in multifocal and brainstem forms of epilepsy, genetically determined epilepsy. This method belongs to the group of neuromodulation techniques and to minimally invasive surgical intervention, which involves controlled therapy with electrical impulses from a generator installed subcutaneously through two electrodes connected to the left vagus nerve in the area of the vascular-nerve bundle in the neck [6]. Stimulation parameters are selected individually after wound healing. Epilepsy in pregnant women remains a pressing issue. Persistent seizures during pregnancy increase the risk of premature birth and miscarriage, placental abruption, and abdominal hematomas [7]. Furthermore, treating epilepsy in pregnant women with antiepileptic drugs (AEDs) is associated with a number of challenges. Specifically, it is necessary to consider changes in AED pharmacokinetics and seizure frequency, major congenital malformations, the impact of AEDs on neuropsychological development, and the possibility of breastfeeding [8]. Pregnancy is not a contraindication for VNS therapy; however, this issue remains poorly understood.

Target. To familiarize neurologists, epileptologists, and neurosurgeons with the first case in the Russian Federation of successful implantation of a vagus nerve stimulator during pregnancy in a patient with drug-resistant epilepsy.

Materials and methods The clinical observation was conducted in the Department of Neurosurgery of the V.M. Bekhterev National Medical Research Center of Psychiatry and Neurology of the Russian Ministry of Health. A 28-year-old female patient presented to the clinic with an 11-year history of drug-resistant epilepsy with a tendency toward recurrent episodes. At 12 weeks of pregnancy, a series of generalized seizures developed while receiving antiepileptic therapy. The examination (EEG, brain MRI according to the epidemiological protocol, transcranial Doppler ultrasound) revealed no focal brain lesions that could serve as a substrate for resective surgery. Laboratory examination (blood and urine tests, coagulation profile) and consultations with specialists (general practitioner, gynecologist, anesthesiologist) revealed no absolute contraindications to anesthesia or surgery. Patient D. was admitted to the neurosurgery department with a diagnosis of drug-resistant epilepsy with secondary generalized seizures, with a tendency to serial progression.

AnamnesisThe child is from the first pregnancy, which was associated with nephropathy and pyelonephritis. The labor was full-term and prolonged, with a 10-hour anhydrous period. Asphyxia and crying were observed after resuscitation. The child was followed by a neurologist with a diagnosis of perinatal encephalopathy. The condition developed with age. At the age of 17, due to increased physical and emotional stress (final exams, intensive sports training), she experienced her first generalized tonic-clonic seizure (loss of consciousness, convulsions, tongue biting, and profuse salivation). She refused hospitalization. According to the patient's mother, from that time on, she began to notice periodic "freezing" episodes in her daughter. A generalized tonic-clonic seizure recurred a year later, occurring during physical exertion. The next seizure occurred in October 2010. She presented to the city epileptology center. At the time of presentation, she was taking carbamazepine 200 mg per day (as prescribed by a local neurologist). Lamotrigine 100 mg per day was prescribed; the seizures persisted, with a frequency of one seizure per month. It was recommended to increase the lamotrigine dose to 200 mg per day. Subsequently, various combinations of antiepileptic drugs were tried (valproic acid in extended-release tablets, benzobarbital, topiramate). During therapy, the seizure frequency decreased to one seizure every 6 months. In September 2012, during pregnancy (12 weeks), remission was disrupted: serial generalized seizures occurred, during which she suffered a concussion and a fracture of the right zygomatic bone. The seizures were not controlled by Relanium, and she was hospitalized in the intensive care unit of the Alexandrovskaya Hospital. She was subsequently referred to the St. Petersburg City Epileptology Center for treatment adjustments. Levetiracetam, 500 mg twice daily (1000 mg/day), was added to the treatment regimen. However, serial generalized seizures persisted, occurring twice a month. Given the potentially high risk of teratogenic effects, it was decided to refrain from adding other antiepileptic drugs. The patient was referred to the Bekhterev National Medical Research Center of Pedagogical Sciences of the Russian Ministry of Health to determine indications for possible additional surgical treatments.

Condition upon hospitalization The patient was admitted at 18 weeks of pregnancy with complaints of generalized seizures, occurring with a head turn to the left, with a frequency of up to two times a month, and a serial course.

Heredity for psychoneurological diseases is not burdened. Higher education. MRI of the brain, cerebral vessels from 19.02.2009: MR picture of subcortical foci in the left frontal lobe, most likely of vascular genesis. MR signs of pathological changes in the main arteries of the brain were not revealed. MRI of the brain from 20.04.2012: MRI data correspond to changes in both cerebral hemispheres, most likely of vascular genesis. EEG from 27.09.2012: the main rhythm is deformed, its individual waves are paroxysmal. The background recording reveals paroxysmal polymorphic activity in the frontal-parietal-temporal regions, mainly of the right hemisphere. The midline structures of the brain are involved in the process. Somatic status. The body type is correct, nutrition is moderate (height 176 cm, weight 72 kg). The skin and visible mucous membranes are clean, of normal color. Heart rate is 82 beats per minute, blood pressure is 105/60. Heart sounds are clear. Breathing is vesicular. No

wheezing. The abdomen is soft, painless. The edge of the liver is at the costal arch. The spleen is not palpable. Mental status. Consciousness is clear. Cooperative. Oriented correctly. No psychoproductive symptoms. Without suicidal tendencies. Neurological status. Consciousness is clear, cooperative, oriented correctly. Pupils - D = S = 2 mm. Full range of eye movements, fine-swinging horizontal nystagmus in the extreme abduction of the eyeballs. Nasolabial folds are symmetrical. Tongue is along the midline. Deep reflexes in the arms are equal and brisk, muscle strength is equal, muscle tone is unchanged; leg reflexes in the knees are brisk and equal. No sensory disturbances were detected. No paresis or paralysis. No meningeal symptoms were present. The upper Rossolimo reflex is bilateral. Babinski syndrome is bilateral. The patient was consulted with a neurosurgeon, and implantation of a system for continuous stimulation of the left vagus nerve was proposed as an additional treatment. All risks associated with surgery and anesthesia were explained.

Ethical aspects The patient provided written informed consent for the surgical intervention.

ResultsIn preparation for surgery, the patient was examined by a therapist, gynecologist, and anesthesiologist. No contraindications to surgical treatment were identified. Additionally, in order to adjust therapy and minimize the negative impact of drug therapy on the course of pregnancy, the patient was consulted by a clinical pharmacologist and epileptologist. On October 31, 2012, the patient underwent implantation of a system for continuous stimulation of the left vagus nerve. The patient was given general anesthesia (sodium thiopental, fentanyl), the total duration of the patient's anesthesia was 2 hours 30 minutes. Extubation was unremarkable. A diagnostic test of the implantable vagus nerve generator (manufacturer - formerly Cyberonics, currently LivaNova, USA) was performed. In the supine position, after preparing and isolating the surgical field, a linear horizontal incision was made through the skin and subcutaneous tissue midway between the mastoid process and the left jugular notch. The platysma muscle was dissected. The left sternocleidomastoid muscle and jugular vein were displaced laterally. The internal carotid artery was bluntly and sharply isolated, and the vagus nerve was isolated over a length of 3 cm and ligated. Hemostasis. An incision was made in the skin and subcutaneous tissue in the left anterior axillary region. A pocket was created for generator implantation. Hemostasis. A wire was tunneled from the surgical wound of the neck to the formed pocket. Two electrodes and an anchor were sequentially placed on the left vagus nerve. A 3-cm loop of the wire was formed and fixed with two clips to the internal fascia of the neck. A 5-cm loop was created on the surface of the sternocleidomastoid muscle and secured with a single clip. The connector was connected to the generator. Diagnostic stimulation was administered, and a decrease in heart rate of 2 beats per minute was noted. The generator was sutured to the fascia in the created pocket. During the surgery, the surgical wounds were repeatedly irrigated with chlorhexidine solution. Layer-by-layer wound closure and intradermal sutures were applied. The wound was cleaned with alcohol, and aseptic dressings were applied. A final postoperative check of the generator and electrode resistance was performed – normal.

The postoperative period was uneventful, postoperative wound healing was by primary intention. Antiepileptic therapy: lamotrigine was gradually discontinued, the daily dosage of levetiracetam was increased to 750 mg twice a day (1500 mg/day). After suture removal, stimulation parameters were gradually increased and adjusted until the therapeutic effect was achieved: 11/14/2012: the stimulator was turned on (current strength - 0.25 mA, pulse time - 30 sec, pause - 5 min, signal frequency parameters - 30 Hz, pulse width - 500 μs, magnet current - 0.5 mA); 20.11.2012: current - 0.5 mA, pulse time - 30 sec., pause - 5 min., signal frequency parameters - 30 Hz, pulse width - 500 μs, magnet current - 0.75 mA; 27.11.2012: current - 0.75 mA, pulse time - 30 sec., pause - 5 min., signal frequency parameters - 30 Hz, pulse width - 500 μs, magnet current - 1.0 mA; 03.12.2012: current 1.0 mA, pulse time - 30 sec., pause - 5 min., signal frequency parameters - 30 Hz, pulse width - 500 μs, magnet current - 1.25 mA; 12/11/2012: current 1.25 mA, pulse time - 30 sec., pause - 3 min., signal frequency parameters - 30 Hz, pulse width - 500 μs, magnet current - 1.5 mA; 12/17/2012:

current - 1.5 mA, pulse time - 30 sec., pause - 3 min., signal frequency parameters - 30 Hz, pulse width - 500 μs, magnet current - 1.75 mA.

Follow-up. The patient was discharged in satisfactory condition, the pregnancy was uneventful. During the early stages of selecting the stimulator parameters, a single (up to several seconds) secondary generalized seizure was observed. Subsequently, no seizures recurred. During a routine EEG performed 6 months after implantation, epileptiform changes were recorded in the right frontotemporal region; 24 months after implantation of the VNS system, no epileptiform changes were recorded. For labor, the VNS parameters were changed: current strength - 1.25 mA, pulse duration - 30 sec, pause - 5 min, signal frequency parameters - 20 Hz, pulse width - 500 μs, magnet current - 1.5 mA. The patient delivered a healthy son by term via Caesarean section. The child was examined by a neurologist, and no pathology was detected. After delivery, the previous parameters were restored. No seizures were observed during the lower parameters. During subsequent observation, the patient had no further epileptic seizures. Due to the stimulator's battery depletion, a planned reimplantation was performed on April 19, 2019.

Discussion. Approximately 0.3-0.5% of all pregnancies occur in women with epilepsy [9]. Of these, approximately one-third suffer from a drug-resistant form of the disease. Persistent seizures during pregnancy can have severe neurological consequences for the fetus and also increase the risk of injury to the mother. Thus, prolonged maternal apnea can lead to fetal hypoxia, which, in turn, leads to acidosis and fetal death [10], as well as to maternal death [11]. Almost all AEDs have a potential teratogenic effect, and this effect is enhanced in the case of polytherapy, which is usually received by patients with FER [12]. Vagus nerve stimulation has been used in Europe as an adjunctive treatment for drug-resistant epilepsy since 1994 and in the United States since 1997. It was registered in Russia in 2009. This method rarely leads to complete remission, but helps alleviate the severity and reduce the number of seizures [13]. There are not many reported cases of using vagus nerve stimulation during pregnancy worldwide: from 1998 to 2017, nine cases of pregnancies and births were described in patients in whom the VNS system was implanted at various stages before pregnancy (including one case of drug-resistant depression) [14-16]. In 2017, an article describing four more cases was published [17]. By 2019, 35 cases of women whose pregnancy proceeded while receiving vagus nerve stimulation had already been described. In the article by AS Marti et al. (2019) [18], seven more pregnancies were described in four women who had previously been implanted with a VNS stimulator. In the world literature, only one case of VNS system implantation during pregnancy is described [20]: a 21-year-old woman with secondary generalized seizures with a frequency of 4-7 per week, despite taking four AEDs (gabapentin, lacosamide, oxcarbazepine, zonisamide), in the 3rd trimester with immediate activation of the stimulator after implantation. Subsequently, a significant improvement in the course of the patient's disease was noted, the absence of any complications and, as a result, the birth of a healthy child. In our case, the implantation of the VNS system is described at 18 weeks of pregnancy. After reaching therapeutic current values, the epileptic seizures completely stopped, the patient was gradually transferred from duotherapy to monotherapy with levetiracetam, and the pregnancy was resolved with the birth of a healthy child. Subsequently, 7 years after implantation, due to the end of the stimulator battery charge, reimplantation of the vagus nerve stimulator was performed.

Conclusion.VNS therapy is a safe and effective adjunctive treatment for drug-resistant epilepsy. Patients with a vagus nerve stimulator can continue therapy after pregnancy. Successful cases of vagus nerve stimulator placement in pregnant women open new treatment options for drug-resistant epilepsy in this special group of patients and provide a basis for further research.

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