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VNS Implantation Effectivness in Drug-Resistant Epilepsy

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Annotation: Despite significant advances in epileptology, treatment-resistant epilepsy accounts for approximately 30% of all forms of this disease. Even taking into account the wide range of modern drug and non-drug treatment methods, there remains a significant proportion of patients with treatment-resistant epilepsy, in whom antiepileptic drugs are ineffective and surgical treatment is impossible. In this group of patients, pharmacotherapy remains relevant with the search for new effective antiepileptic drugs, as well as the search for alternative methods, one of which is vagus nerve stimulation. The authors present a literature review devoted to the indications for use, efficacy, and tolerability of the vagus nerve stimulation method in epilepsy, and a description of an observed case of the effectiveness of this method in a patient with a resistant form of epilepsy.

Keywords: epilepsy, drug-resistant epilepsy, focal epilepsy, focal epileptic seizures, vagus nerve stimulation, efficacy, tolerability.

Despite significant advances in epileptology , resistant epilepsies account for approximately 30% of all forms of epilepsy, especially in patients with focal seizures. According to RS Fisher et al . (2005), at least 30% of patients fail to achieve complete cessation of seizures with antiepileptic therapy. The frequency of drug-resistant cases is approximately the same in adults and children; it is in this group (among patients with resistant forms of the disease) that high rates of epilepsy complications and mortality are observed, as well as a significant decrease in the quality of life of patients [1]. In these cases, there is still hope for the success of neurosurgical treatment and the synthesis of new antiepileptic drugs (AEDs) [2, 3], as well as the search for alternative methods, one of which is vagus nerve stimulation (VNS) [4], approved as an alternative, additional method of treating resistant forms of epilepsy by the US Food and Drug Administration (Food and Drug

Administration (FDA) in 1997 [5]. Vagus nerve stimulation was first studied in 1938 [6]. The first human implantation of a VNS device for the treatment of drug-resistant epilepsy was in 1988 [7, 8]. The method was recommended for use in patients for whom surgical treatment of epilepsy (resection operations) is impossible or has proven ineffective. Thus, this method is primarily indicated for patients with drug-resistant epilepsy who are not candidates for resection of the epileptogenic focus, or for those patients who continue to have seizures after surgical treatment of epilepsy; in these cases, VNS in combination with antiepileptic therapy is an effective alternative method for controlling epileptic seizures and improving quality of life [9, 10]. The RLS method was approved in 1997 for use in patients aged 12 years and older [11, 12], but the currently used RLS systems (Cyberonics , Inc. , USA) were approved by the FDA in 2017 for use in patients aged 4 years and older with focal seizures resistant to drug therapy (FDA, 2017) [13]. Currently, age restrictions for the use of RLS have been lifted in Europe and the Russian Federation, and the method can be used in patients of any age with focal seizures (with or without secondary generalization) or generalized seizures [14]. While in adult patients the method is used primarily for focal epilepsy, in children it is most often used for symptomatic generalized epilepsy [15, 16, 17]. The mechanism of action of RLS is currently poorly understood. The pathophysiological basis of the effect of intermittent vagal stimulation is stimulation of the autonomic nerve pathways. There are several hypotheses for the implementation of the antiepileptic effect of RLS: the neurotransmitter hypothesis (changes in the level of various mediators in certain areas of the brain against the background of RLS), changes in cerebral blood flow and the effect on the bioelectrical activity of the brain. The results of animal studies have shown that RLS leads to an increase in the concentration of norepinephrine in the hippocampus and at the level of the cortex (RW Roosevelt et al ., 2006) [18]. When studying the cerebrospinal fluid of patients against the background of RLS, a significant increase in the level of gamma-aminobutyric acid was revealed; less significant were a decrease in the levels of aspartate , glutamate and an increase in the level of 5-hydroxyindoleacetic acid (E. Ben-Menachem et al ., 1995) [19]. When positron emission tomography was performed to evaluate the effect of RLS on cerebral blood flow in 10 patients (the study was conducted within 20 hours after the start of therapy and after 3 months to evaluate the immediate and delayed effects of RLS), the delayed effects were an RLS-induced increase in blood flow bilaterally in the thalamus, hypothalamus, inferior cerebellar hemispheres, and right postcentral gyrus. The immediate effects of RLS were a decrease in blood flow bilaterally in the hippocampus , amygdala, and cingulate gyrus and an increase in blood flow bilaterally in the insula. No significant changes in blood flow in these areas were detected during the delayed studies. Control of seizures improved with a reduction in some immediate RLS-associated blood flow changes (primarily at the cortical level) and preservation of other RLS-induced blood flow changes (primarily at the subcortical level). The authors suggest that the change in synaptic activity in areas where RLS-induced blood flow changes are preserved may reflect the anticonvulsant effect of RLS (TR Henry et al ., 2004) [20]. In addition to chronic intermittent stimulation, acute stimulation "on demand" can be performed by the patient or an accompanying person using a magnet that is part of the RLS system. Surgical implantation involves placing an electrode on the vagus nerve in the neck between the common carotid artery and the internal jugular vein. The left vagus nerve is used; This is due to anatomical differences in the route of the right and left vagus nerves in the neck (the right vagus nerve passes into the pharynx in front of the subclavian artery, the left vagus nerve goes down between the left carotid artery and the left subclavian artery) and the peculiarities of the innervation of the heart (the right vagus nerve supplies the sinoatrial node, while the left innervates the atrioventricular node) [21]. Stimulation is performed using an electrode that is implanted in the area of the left vagus nerve in the neck. The vagus nerve contains about 20% of the efferent fibers that innervate the muscles of the larynx and provide parasympathetic innervation of the internal organs (heart, lungs, and gastrointestinal tract). About 80% of the vagus nerve fibers are afferent visceral and somatic fibers. Afferent fibers of the vagus nerve project to various parts of the central nervous system, most of which may be the epileptogenesis zone [22].

Efficacy of RLS In general, according to the literature, approximately 40–65% of patients showed improvement with a decrease in attack frequency by at least 50% [23, 24]. Data from a Cochrane review. M. Panebianco et al . (2015) presented data from a Cochrane review that included 5 studies involving 439 patients (the review included only randomized, double-blind, controlled studies that compared different types of RLS). The basic therapy phase varied in 5 studies from 4 to 12 weeks , and the double-blind therapy phase from 12 to 20 weeks . The difficulty of objectively assessing the double-blind phase of therapy in RLS studies is due to the frequent side effects caused by RLS, such as voice changes. Four studies compared high- and low-frequency pulse stimulation (these studies were included in the meta-analysis). The overall odds ratio (95% confidence interval (CI)) for a 50% or greater reduction in seizure frequency across all studies was 1.73 (1.13 to 2.64); high-frequency stimulation was shown to be 1.5 times more effective than low-frequency stimulation. Analysis of discontinuation rates showed that RLS is well tolerated and discontinuation of the treatment is rare. There were no significant differences in discontinuation rates between the high- and low-frequency stimulation groups, but these results cannot exclude the possibility of differences [56]. Data from meta-analyses assessing the efficacy of RLS. DJ Englot et al . (2011) [25] published the first meta-analysis devoted to the efficacy of RLS in epilepsy. The meta-analysis included 74 clinical trials involving 3321 patients with treatment-resistant epilepsy: 3 blinded randomized controlled trials (Class I), 2 unblinded randomized controlled trials (Class II), 10 prospective studies (Class III), and numerous retrospective studies. After RLS implantation, seizure frequency was reduced by an average of 45%; seizure frequency was reduced by 36% within 3–12 months after surgery and by 51% more than 1 year after the start of treatment. At the time of the last follow-up, seizure frequency was reduced by 50% or more in approximately 50% of patients. According to the meta-analysis , significant improvement was also achieved in children and patients with generalized epilepsy. Such etiologic factors of epilepsy as posttraumatic epilepsy and tuberous sclerosis turned out to be favorable prognostic factors. Thus, the analysis of literature data showed that RLS is an effective and fairly well-tolerated method of additional therapy in patients with resistant epilepsy in the absence of indications for resection surgery. However, the authors note that complete freedom from seizures with RLS is rarely achieved, and in about 1/4 of cases the effect cannot be achieved [26]. HJ Wang et al . (2019) studied the predictors of RLS effectiveness in patients with resistant epilepsy according to literature data based on a meta-analysis of 1281 articles. Statistically significant differences between patients with a good response to RLS and ineffectiveness of the method were obtained in terms of the duration of epilepsy ($p = 0.038$). In this study, the following factors were statistically insignificant: age of RLS system implantation ($p = 0.305$), age of seizure onset ($p = 0.530$), seizure type ($p = 0.11$), etiology ($p = 0.187$), and history of previous epilepsy surgery ($p = 0.075$). Thus, the study showed that patients with a shorter duration of resistant epilepsy are better candidates for RLS than younger patients (the effect of the method depends on the shorter duration of epilepsy, not on the younger age) [27]. Most authors indicate an increase in the effect, an increase in the effectiveness of RLS over time, with continued treatment [28]. The effect of RLS may not occur immediately, but this does not allow us to conclude that the method is ineffective; over time, gradual improvement is possible throughout the entire treatment period. During the first 24 months from the onset of RLS, seizure control improves and stabilizes over the subsequent years [29, 30]. In one of the earliest open-label long-term studies of the effectiveness of RLS (GL Morris and WM Mueller , 1999), of 454 patients with an RLS system implanted, 440 received treatment for more than 1 year. A reduction in seizure frequency of more than 50% was noted in 36.8% of patients after 1 year of treatment, in 43.2% after 2 years, and in 42.7% after 3 years. The average seizure reduction from baseline was 35% after 1 year, 44.3% after 2 years, and 44.1% after 3 years. The retention rate in therapy in this study was 96.7% after 1 year, 84.7% after 2 years, and 72.1% after 3 years [31].

VS Wasade et al . (2015) assessed the efficacy of long-term therapy with RLS (over 15 years) in terms of seizure frequency and psychosocial outcomes in patients with treatment-resistant epilepsy. The authors assessed the effect on seizures using the modified Engel classification : class I – remission or rare simple focal seizures, class II – reduction in seizure frequency by more than

90%, class III – reduction in seizure frequency by 50–90%; class IV – reduction in seizure frequency by less than 50%; classes I–III (reduction in seizure frequency by more than 50%) were regarded as a favorable outcome of therapy. Of the 152 patients with drug-resistant epilepsy participating in the study, complete data on seizure frequency reduction were obtained in 80 cases. Of the 80 patients, 16 (20%) were classified as Engel class I, 14 (18%) as class II, 24 (30%) as class III, and 26 (33%) as class IV. Thus, the study demonstrated a reduction in attack frequency by more than 50% in 68% of patients and attack remission in 20% of patients. The majority of patients (80%) reported that long-term therapy with RLS was acceptable [32]. A 2019 meta-analysis of 1281 contemporary literature sources (HJ Wang et al ., 2019) showed that at 6 months , 1, 2, 3, 4, 6, and 12 years after installation of the RLS system, a reduction in attack frequency by more than 50% was recorded in 33.99; 43.42; 46.50; 63.31; 52.71; 54.64; 70.37 and 82.90% of patients, respectively [33]. Results of open and retrospective studies. In the study by authors from St. Petersburg (L.V. Lipatova et al ., 2014), the RLS system was implanted in 9 patients with drug-resistant epilepsy aged 14 to 38 years; the duration of follow-up was 8–12 months. According to the results of this study, in the first 2–3 months after the stimulator installation, half of the cases showed a reduction in the frequency of epileptic seizures by more than 50%, while in the remaining patients the same positive effect was achieved after 8–12 months by correcting the RLS parameters. All patients showed a decrease in the frequency, duration and severity of seizures, and a shortening of the post-ictal period. Side effects in the form of dysphonia and sore throat were observed in 12.5% of patients. These adverse events regressed with changes in magnetic stimulation parameters. Positive dynamics according to electroencephalography data in the form of a decrease in paroxysmal epileptiform disorders was noted in 62.5% of cases. The authors concluded that RLS is a safe and effective additional method of treating drug-resistant epilepsy, which allows reducing the frequency and severity of epileptic seizures [4]. The study by a group of authors from Krasnoyarsk (I.G. Areshkina et al ., 2019) included 13 patients suffering from drug-resistant epilepsy, aged 5 to 38 years. In 1/4 of cases, patients noted a decrease in the number of epileptic seizures already in the 1st month after the initial setup of the RLS system. The effectiveness of treatment increased with long-term use of RLS. Despite the significant duration of drug-resistant epilepsy, a decrease in the severity of epileptic seizures and a decrease in the duration of post-ictal disorientation were revealed. Side effects of RLS were registered in 38.5% of patients; to relieve side effects, the parameters of the stimulator were adjusted. This allowed to continue effective RLS and correct the side effects that had developed . According to the authors, RLS reduces the frequency of epileptic seizures by more than 50% in 20–50% of patients, has long-term effectiveness in patients of any age, and is well tolerated [2]. Despite the fact that only a few patients achieve complete remission after installing the RLS system, a significant number of patients experience an improvement in their quality of life. This is due to a number of positive effects of RLS [34, 35].

Although the main efficacy parameter used in the studies is a reduction in seizure frequency, it is also necessary to take into account a number of additional positive effects of the RLS method, including a reduction in the severity and duration of seizures, post-seizure disorders, a significant reduction in the frequency or cessation of daytime attacks of falls with injury , a significant reduction in the frequency or cessation of episodes of status epilepticus in patients with a tendency to status epilepticus and, accordingly, a reduction in the duration of inpatient treatment.

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