Transauricular Vagus Nerve Stimulation (t-VNS) as a valid predictor of invasive VNS efficacy in drug resistant epilepsy: a case-report

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Abstract

Vagus Nerve Stimulation (VNS) is a palliative therapy for patients with drug-resistant epilepsy. Nonetheless, no predictive factors for efficacy have been identified. Recently, a non-invasive transcutaneous VNS (t-VNS) has been developed. It stimulates an auricular branch of the vagus nerve directed to the same nuclei of VNS. Here we report the case of a young female patient with drug-resistant epilepsy, caused by a right frontal cortical dysplasia. She had the onset of seizures at the age of 4 months, and she presented with a West syndrome in the first year of life; in the following years, she had various types of focal seizures, with rare secondary generalization and frequent falls. She had uncountable seizures every day and a severe psychomotor delay. At the age of eight, she underwent surgery, however without benefit. At 13 years, she tested t-VNS with significant seizure reduction. Stable VNS was then implanted. Quality of life, alertness and performances of the patient improved. Even if it needs demonstration in larger case series, t-VNS could be used to predict the effectiveness of VNS, in order to select the best candidates for a stable implant.

KEY WORDS: VNS, tVNS, drug resistant epilepsy, seizures with falls.

Introduction

Epilepsy is a neurological disorder affecting approximately 1% of the world’s population (1). About 30% of patients with epilepsy continue to seize despite tailored medical therapy. Resection of an epileptic focus can be curative in carefully chosen patients (2). The appropriate selection of surgical candidates requires meticulous preoperative evaluation with high-resolution neuroimaging and electrophysiological recordings. It often includes invasive intracranial recordings. In both adults and children predictors of positive surgical response have been identified: these include temporal focus, gross total lesion resection in case of lesion presence, early surgery, localized and concordant electroclinical and imaging findings, and lack of secondarily generalized seizures (3). Many patients are poor surgical candidates because of multifocal seizure onset or epileptic foci set in proximity of eloquent cortex areas. Moreover, resection fails in some patients (2). For these individuals, palliative surgical options may be considered, like Vagus Nerve Stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS), as well as disconnection procedures such as multiple subpial transections (MST) and corpus callosotomy (CC), or minimally invasive surgical options like stereotactic radiosurgery (SRS) (4).

Left-sided VNS was approved by the US FDA in 1997 as an adjunctive treatment for medically refractory epileptic patients. It is utilized for localization-related epilepsy with multiple or nonresectable foci, after unsuccessful intracranial epilepsy operations, and in some generalized epilepsy syndromes (4). VNS mechanism of action remains poorly understood: stimuli conveyed by the left vagus nerve fibres activate the neurons of the nucleus of the solitary tract (NST) and the neural network of the prefrontal cortex, thalamus, hypothalamus, cingulate, hippocampus desynchronizing cortical activity and decreasing abnormal spiking patterns (5-7). After 3-64 months, 21 to 55% of patients experience more than 50% of seizure frequency reduction; efficacy improves with time.
Anyway, one half of patients received no measured clinical benefit (2, 8). Until now no clear predictors of response to VNS have been identified (2, 4). More recently a transcutaneous VNS (t-VNS) has been developed for patients who are not candidate or simply do not want to undergo VNS implantation (9-13). t-VNS modulates cortical excitability in the same way of VNS, thus modifying Nucleus of the Solitary Tract (NST) excitability through the auricular branch of the Vagus Nerve (ABVN) (14). Intensity of t-VNS is individually selected by the patient according to tolerance; pulses are biphasic, stimulus frequency is 25 per s, pulse width is 250 usec, applied voltage is 25 V on average, and stimulated area is approximately 2 cm2. Stimulation is performed for 4 hours a day, subdivided into 2-3 periods lasting at least one hour each. Here we report the case of a 16-year-old girl with previous unsuccessful resective surgery of a right frontal cortical dysplasia who subsequently underwent t-VNS treatment and VNS implantation with satisfactory control of seizure.

Case report

The patient, aging 16 years at the time of writing, is of Ecuadorian origin; one sister was affected by severe mental disability and lack of language: at the age of 21 she died from a Stevens Johnson syndrome. Our patient had two more healthy sister and brother. Onset of seizures dates back to the age of 4 months with low frequency episodes of forward head flexion and tonic elevation of the upper limbs, occurring several times in a day at the age of six months. When the child was 10 months old, clusters of spasms appeared at waking up and/or falling asleep. The first EEG, at the age of one year, showed right-hemispherical multifocal abnormalities and hypsarrhythmia with a right hemispheric dominant focus. MRI performed at that time was normal. Anti-epileptic drugs (AEDs) were set on: valproic acid, ACTH and vigabatrin, that were ineffective. At the age of 13 months, MRI was repeated showing a right frontal cortical dysplasia (imaging not available). At the age of 2 years seizures were characterized by head fall followed by version of head and eyes (side not known), and rare generalization, despite therapy with clobazam, valproic acid and lamotrigine. She was admitted at the department of Child Neurology, Fondazione IRCCS Istituto Neurologico “Carlo Besta” at the age of 4. General examination revealed weight at 3-10th percentile, height at 10-25th percentile, head circumference at 10th percentile. Neurological examination revealed no focal neurological deficits. Through Griffiths scale a severe psychomotor delay with almost absent language was detected (GQ: 42; mental age: 21 months, chronological age: 4y 4m). Karyotype and telomere rearrangements resulted normal. EEG showed a good background organization and diffuse epileptiform discharges with prevalence in right frontal-cortical dysplasia (Fig. 1).

From the age of 6, a new kind of seizures appeared: grimacing, clinging to mom, head flexion, asymmetric tonic elevation of upper limbs. A long-lasting video EEG was performed showing three types of seizures: in wakefulness the above-mentioned type with right fronto-central ictal onset; less frequent seizures (staring) with a left fronto-central discharge and several tonic seizures during sleep associated with widespread rapid discharge. Resective surgery was thus excluded at that time. In the following two years, the patient developed behavioral disorders with psychomotor instability and a drug resistant epilepsy with very frequent and disabling seizures with falls. Brain MRI confirmed the right frontal focal cortical dysplasia (Fig. 2 A)
After a multidisciplinary discussion between expert neurosurgeons and neurophysiologists anterior right frontal lobectomy was performed when she was 7 (Fig. 2 B). The reasons of surgery were drug resistant epilepsy with poor quality of life and ictal discharges starting always from the right frontal region during seizures causing falls, and prevalence of interictal epileptiform discharges on the right hemisphere. No indication to any further pre-operative more invasive monitoring was given. After right frontal lobectomy, a transient clinical benefit was observed. Histological analysis revealed a IA type focal cortical dysplasia (Fig. 3). She had behavioral and language improvement without additional neurological deficits. One year later, however, daily seizures reappeared.

At age of 13 years, t-VNS was implanted, with reduction of seizures in wakefulness and most disabling drop attacks. When the device was suspended for two months, a worsening of all types of seizures was noted. Subsequently, VNS implantation was performed. Patient’s seizures in wakefulness and tonic sleep seizures decreased markedly; generalization and falls never recurred. Clobazam (among three AEDs, including mesuximide and oxcarbazepine) could be withdrawn. Moreover, an improvement in her quality of life, in alertness and performances was observed. No side effects were reported. According to McHugh outcome classification after tVNS (T1) and VNS implant (T2) she was respectively IIIA and IIA (15). According to Orosz et al. at T2 she would be in the best outcome group (reduction of more than 50% in the predominant seizures) (16).

Immediately after implantation there were no modifications of the EEG pattern, compared to previous ones. However, three years after VNS initiation, we noted a significant improvement of the background activity with a reduction of epileptiform discharges (Fig. 4).

Discussion and conclusion

t-VNS is a new neurostimulator, produced by Cerbomed, to stimulate electrically the auricular branch of the vagus nerve, running in the posterior wall of the external auditory canal, at the left ear (9-13). From this point, the stimulus conveys on the vagal nerve through the vagus nerve stimulation (VNS). In preclinical studies, efferents from the auricular branch of the vagus nerve (ABVN) to the nucleus of the solitary tract (NTS) have been demonstrated, with following projections to the same targets of VNS (14). fMRI, studied in healthy volunteers and patients either with t-VNS or implanted VNS, showed the same pattern of activation (17).

Transcutaneous stimulation has shown the same efficacy as VNS in clinical trials, that is reducing in about 25% of patients >50% seizure frequency, with some patients becoming seizure free; as VNS, t-VNS positive effect improves with time. It does not require surgery and, if unsuccessful, stimulation can be rapidly interrupted. Few side effects have been reported: among them headache, mild skin ulceration, stimulation dependent dizziness and drowsiness (9-13). In our unpublished series of patients, t-VNS showed modest efficacy in very heterogeneous adult and paediatric patients, but it reduced the most disabling seizures with falls confirming previous analogous results obtained with invasive vagal stimulation (18). Side effects during the use of VNS are common,
including cough, hoarseness, voice alteration, with some patients also suffering from nocturnal dyspnoea (19). Implantation is an invasive surgery performed under general anaesthesia with related risks. Postoperative infections occur in approximately 3% of patients.

Until now, no clear predictors of response to VNS have been identified: among best responders are patients with post-traumatic epilepsy, tuberous sclerosis, Lennox Gastaut syndrome, generalized seizures and age at epilepsy onset older than 12, while previous epilepsy surgery has been associated with a poorer outcome (2, 4). These data are not significant, and cannot suggest a precise indication to VNS implantation. The patient here reported represents a typical case in which seizure reduction could not be expected as she was previously operated on without results. Only the good results obtained with t-VNS induced to perform the implant of VNS, that confirmed the effectiveness of the device.

Concerning EEG findings, previous clinical studies showed reduction of pathologic activity in responders if performed at least three months after implantation: in a pilot single arm study Hallböök et al. showed that epileptiform activity reduced after 9 months of VNS in 15 children (13 focal epilepsy, 2 generalized) (20). Bodin et al. reported changes in synchronization between ON and OFF phases and between responder and non-responder patients after 9 months of stimulation (21), while Rizzo et al. showed an improvement in sleep EEG organization 13 months after implantation (22). Confirming these previous data, no acute changes were detected but after three years an improvement of background activity and a reduction of epileptic activity were observed. VNS is effective in almost 50% of very heterogeneous drug resistant patients, leading to a reduction of their seizure frequency, improving with time (19). However, epileptologists have no means to know which candidate subjects could benefit most. So clinicians do not often propose this option as a valid treatment. Furthermore, incidence of side effects has been shown to be as low as the number of candidates to the procedure. Identifying predictive factors could increase its utilisa-
tion, making it worth its high economic burden. The patient here described shows, after VNS implantation, the same trend of seizure reduction observed with t-VNS, in particular for disabling seizures with falls. t-VNS could so be used as a screening procedure to VNS implant. One limitation to this consideration is that sometimes the device is not tolerated, so in patients not using it according to the scheduled stimulation it is not possible to predict VNS efficacy unless trying it. Nonetheless in patients able to go through a preliminary t-VNS trial, like the described one, it could give the physician precious information and confidence on when and how to proceed to invasive VNS. Further studies are requested to confirm these data.

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References


