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Vagal Nerve Stimulation (VNS): A practical option to discontinue rTMS in treatment-resistant depression?

1. Introduction

Vagus Nerve Stimulation (VNS) is emerging as one of the neurostimulation techniques in the armamentarium of psychiatrists to treat treatment-resistant depression (TRD) (Aaronson et al., 2017; Cristancho, Cristancho, Baltuch, Thase, & O'Reardon, 2011; Müller et al., 2018). VNS has been approved in Europe for drug resistant epilepsy since 1994 and was approved in 2005 for adjunctive treatment of chronic or recurrent depression in patients who are in a treatment-resistant or treatment-intolerant major depressive episode. The FDA approval for this indication followed two years later (APA, 2010). Recently, a long-term naturalistic registry study provided fundamental level 2 evidence that adjunctive treatment with VNS is associated with superior patient outcomes compared with patients receiving treatment as usual (Aaronson et al., 2017). Taken together the body of evidence suggests that VNS can be considered for patients with chronic or recurrent depression, particularly in situations where treatment adherence and long-term management have been problematic (Milev et al., 2016).

Herein, we report a case of dramatic improvement of TRD following VNS in a patient on weekly maintenance repetitive transcranial magnetic stimulation (rTMS).

2. Case history

A 43-year-old female presented with a major depressive disorder (MDD) dating back to her postpartum period fifteen years ago, when she was first evaluated in our department of Mood Disorders. At the time of first diagnose she had neither psychiatric nor addiction history. Family history showed MDD in one first degree and two second degree relatives. She is married and lives on a permanent sickness allowance. As she presented severe depressive symptoms with poor response to several trials of different antidepressant medications (BDI-13 score: 29/39; Maudsley staging score: 11 / 15) we first performed a course of 30 rTMS sessions with good antidepressant efficacy (BDI-13 score: 10/39). Magnetic stimulation was performed using a MagVenture MagPro X100 stimulator and a figure eight-shaped water-cooled coil (MagVenture Inc., Georgia, USA). We used a "standard procedure" targeting the left dorsolateral prefrontal cortex and positioned the coil 6 cm anteriorly and in a parasagittal plane from the location of the motor hot spot. Each session consisted of five-second trains with a 25-second inter-train interval at a frequency of 10 Hz at 120% of right motor threshold (total of 2.000 pulses during a 20 min-session). Pharmacotherapy was used as maintenance treatment: sertraline 100 mg/d and hydroxyzine 25 mg /d and was unchanged during follow-up. After acute rTMS, a gradual taper of maintenance rTMS was attempted but the frequency of rTMS could not be cut down below 1 session per week without causing a relapse. Before considering VNS, she had been receiving rTMS maintenance for 7 years. As she showed a response to noninvasive neurostimulation, our multidisciplinary team hypothesized that she may be a good candidate for deep brain stimulation (DBS). Indeed, DBS was at that time regarded by many as a promising surgical option for TRD (Kennedy et al., 2011; Mayberg et al., 2005). However, the patient was extremely reluctant to undertake what she regarded as a very invasive procedure and declined that therapy. She was then offered the alternative option of VNS, which she readily accepted. The patient gave written consent for vagal nerve stimulation.

Medical history showed obesity treated with bariatric surgery (sleeve) at 42 years of age. Since a transient ischemic attack at 43 years of age, she was treated with aspirin 75 mg/d, perindopril 5 mg/day and atorvastatin 10 mg/day. The surgical procedure to implant the VNS Therapy system was uneventful and the patient did not present any dysphonia in the postoperative course. Postoperatively, the frequency was set to 30 Hz, pulse width to 250 μsec, with the following duty cycle (time on = 30 s and time off = 5 min). The output current was set to 0.25 mA, and then increased by 0.25 mA increments every two weeks until reaching to 1.5 mA.

Initially, VNS was used in combination with weekly rTMS maintenance. During TMS sessions, the TMS coil was turned off when placed over the left dorsolateral cortex and then switched on when properly positioned. No specific action was undertaken with regards to the VNS device during rTMS treatment.

Two months after surgery, the frequency of rTMS sessions was switched to every two weeks for a period of two months and then cut down to once a month for the next two months. Six months after surgery, rTMS maintenance was completely stopped without relapse. After nine months, we stopped all antidepressant medication. For the past one and a half years, she remains in full remission (Fig. 1).

3. Discussion

To our knowledge, the interest of this case report is three-fold. First, as previously described, it confirms the safety of the combination of rTMS and VNS in patients with TRD (Philip, Carpenter, & Carpenter, 2014). Although not a controlled study, this case report describes the dramatic impact VNS can have in TRD patients in clinical practice. VNS should be included in the discussion of managing patients who relapse without rTMS maintenance and potentially also ECT as suggested by (Müller et al., 2018). Especially of interest in this patient is that VNS was not only able to abolish the need for rTMS but it also allowed the discontinuance of antidepressant pharmacotherapy which is unusual. Obviously, it cannot be demonstrated that this improvement derives

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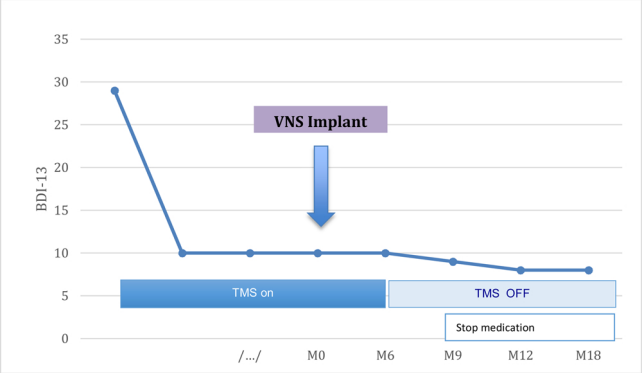

Fig. 1. Graph showing the BDI-13 score score as a function of time.

only from VNS but in the context of this specific patient with very long lasting depression, it is very unlikely that VNS did not play a key role. In the management of chronic and recurrent depression, treatments with long-term efficacy are lacking e.g. one third of patients relapse within 6 months of ECT treatment (Kellner et al., 2006). In this regard, the sustained efficacy of VNS shown in clinical trials and mirrored in this patient is of importance (Nahas et al., 2005; Martin & Martín-Sánchez, 2012).

To date, VNS has yet to obtain wide-spread use in routine management of TRD outside of few highly specialized centers. However recent data does suggest that adjunctive VNS is more effective than treatment as usual (Aaronson et al., 2017). Deep brain stimulation applied to different targets such as CG 25, ventral striatum/ventral capsule, inferior thalamic peduncle or superolateral branch of medial forebrain bundle tends to be currently regarded as the main surgical option for TRD but it remains experimental and further accumulation of data is still warranted (Morishita, Fayad, Higuchi, Nestor, & Foote, 2014). It should be kept in mind that two recent randomized controlled trials (Dougherty et al., 2015; Holtzheimer et al., 2017) failed to provide level A evidence of efficacy of DBS in TRD, therapy which has only an open label evidence base. On top of that, this case illustrates that regardless of its efficiency, DBS is not easily accepted by patients. Patients and their relatives often become very concerned about committing to invasive intracranial procedures. VNS is often considered as a minor surgical procedure leading to greater acceptance by patients. It is also less expensive and can be cost-effective as compared with rTMS (Warnell & Elahi, 2007).

It may also be part of a gradual strategy of increasing invasiveness of surgical options similar to [non resectable] drug-resistant epilepsy in which patients are often considered for VNS before DBS in the anterior thalamus. In case of failure to improve following VNS, the patient may then be more inclined to consider more invasive approaches (Mayberg et al., 2005). In experienced hands, VNS is associated with a very low rate of complications (such as infection, lead breakage or transient dysphonia) (Kahlow & Olivecrona, 2013). Permanent complications related to VNS remain exceedingly rare and should be weighed against the risks of not managing TRD aggressively (e.g. quality of life, suicide) and the potential benefits associated with response.

4. Conclusion

This case report illustrates that VNS can provide an effective minimally invasive chronic neurostimulation treatment for difficult-to-treat depression that can be considered before resorting to more invasive options. VNS may be regarded as an adjunctive treatment for maintenance rTMS responders with the potential goal of prolonging the intervals between rTMS treatments without relapse.

Conflict of interest

All authors declare that they have no conflicts of interest.

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