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Vagus nerve stimulation for depression: a case of a broken lead, depression relapse, revision surgery, and restoration of patient response

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To the Editor

Electrical stimulation of the left cervical vagus nerve delivered through an implanted device (vagus nerve stimulation [VNS]) is a Food and Drug Administration-approved therapy for chronic or recurrent, treatment-resistant major depressive episodes (TRD). Because VNS is a novel antidepressant therapy, literature is limited regarding VNS-related adverse events. We present the case of a patient who experienced a break in the electrical lead connecting the pulse generator (implanted in the chest) to the vagus nerve, his clinical course throughout the process, and his recovery after revision surgery to replace the lead.

The patient, a man aged 47 years with a history of severe, recurrent major depressive disorder, participated in the pivotal clinical trial of VNS for TRD.^{1,2} His pretrial depressive episode lasted 24 months, during which four courses of antidepressant treatment did not provide benefit. His baseline 24-item Hamilton Rating Scale for Depression (HAM-D) score was 33, indicating severe depression. At the completion of the 12-week, double-blind trial phase, during which he received active stimulation, his HAM-D score was 31. During the open-label extension VNS trial phase, his HAM-D score was 28 after 6 months and dropped to 11 after 9 months. At 1-year postbaseline, his HAM-D score was 8 (76% decrease from baseline), indicative of remission (defined as a 24-item HAM-D score ≤ 9). With assessments at 3-month intervals, remission was maintained through month 42 (except at month 24 when his HAM-D score was 15). This pattern of late response to VNS with subsequent durability of benefit is not uncommon.³

At month 42 the patient was seen for a routine visit for device monitoring. VNS settings were as follows: output current, 1.25 mA; signal frequency, 20 Hz; pulse width, 500 μ sec; and signal time, 7 seconds on/33 seconds off. However, the results for the standard lead test indicated that the VNS system was not functioning, including an output current designation of “limit” (for example, the test output current of 1 mA could not be delivered) and a “high lead impedance” (opposition to current flow) associated with a DC-DC converter code of 7 (equivalent to >20 k Ω of impedance). This combination was consistent with a lead break, disconnection between lead and device, or pulse generator battery end of service. The pulse

generator battery end of service was ruled out (the VNS device is designed to report the battery status using an “elective replacement indicator” [ERI], which signals when the voltage of the battery is low and should be replaced). In this case, the patient’s device ERI did *not* indicate low battery or need for replacement. Further, the VNS device behaved as if it was adequately battery powered: it was able to communicate and perform diagnostic tests. After this latter possibility was ruled out, plain chest and neck radiographs failed to show unequivocal evidence of a lead break or disconnection. Data on file with the VNS system’s manufacturer indicated lead survivability for this patient’s VNS model at >98% at 24 months and >95% at 60 months.

The patient expressed anxiety over returning to the “black hole of depression,” and requested that the VNS system be made functional through revision surgery. Over the ensuing 3 months, while logistic issues were addressed regarding surgery, the patient consistently stated that he was not depressed, and rated his mood as a 9 on a 0–10 scale (on which 10 equals no depression). During the first week of month 45, his HAM-D score was 2. Shortly thereafter, however, the patient’s mood began to deteriorate. Although HAM-D assessments were not performed during months 46 and 47, the patient reported severe symptoms of depression that included loss of energy and appetite, sleeplessness, guilt, hopelessness, sadness, concentration problems, anhedonia, anxiety, and social withdrawal.

At the end of month 47, revision surgery was performed to correct the broken lead. During surgery, a lead coil break was found approximately 3 cm past the electrode bifurcation in the direction of the anchor tether. Once the lead was replaced, VNS was reinitiated, after which the patient’s self-reported mood improved rapidly. By his own report, he was “back to normal” within 2 weeks as reflected in a 48-month HAM-D score of 5. The patient continued to report resolution of significant depressive symptoms at all subsequent visits.

This case illustrates several interesting aspects of VNS. The antidepressant efficacy of VNS was maintained for 3 months after discovery of the lead break, a pattern similar to that obtained with electroconvulsive therapy, in which sustained antidepressant efficacy can persist beyond the immediate treatment period. Beginning in the fourth month after detection of device failure, the patient’s deterioration was rapid, progressive, and severe. After surgical revision, the patient reported equally rapid and significant recovery. The speed of recovery suggests that physiologic, biochemical, and/or structural brain alterations associated with a 32-month period of remission may have “primed” the brain for response when VNS was reinitiated. This rapid recovery to an essentially depression-free state stands in contrast to the patient’s initial, delayed VNS response.

This case may be contrasted with that of a woman, aged 41 years, whose depression also began to worsen after 42 months of VNS.⁴ This patient’s symptoms, however, did not reach severe levels (by HAM-D score) until about 60 months after VNS initiation, when lead testing indicated end of service for the pulse generator battery. By that time, she required hospitalization for depression and replacement of the VNS pulse generator. Over the next 9 months, the patient’s HAM-D scores returned to the previous pattern of fluctuation between remission and moderate depression. The primary difference between the two cases is the

relative rapidity with which the first patient's symptoms became severe (about 4 months). Both cases demonstrated relatively rapid recovery patterns after revision surgery.

One final noteworthy point: despite being broken, plain X-rays failed to demonstrate any lead break. Experience in VNS for epilepsy has indicated that this is the typical case, namely, lead breaks in VNS are often not detectable with the use of X-ray (CC communication with technical support, Cyberonics, Inc., Houston, TX). Hence, in such circumstances, one must surmise from the device readings (in this case, an output current designation of "limit" [test output current not deliverable] and a "high lead impedance" [opposition to current flow] associated with a DC-DC converter code of 7) that a lead break had occurred.

Conclusions drawn from this case must be tempered by several limiting factors. Most importantly, the patient's expectancies, regarding both his deterioration and recovery, may have influenced his clinical course. This limitation, however, does not account for his delayed mood deterioration, occurring more than 3 months after the lead break was detected. The lack of HAM-D assessments during his deterioration phase is another limitation, although clinical interviews during this time confirmed the presence of multiple and severe symptoms consistent with a recurrent major depressive episode. Despite these limitations, the case is clearly noteworthy for the significant relapse in depressive symptoms after loss of VNS, followed by a rapid and equally significant recovery once VNS was reestablished. Future research on mechanisms that might mediate such a pattern is needed.

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