Psychotic Exacerbation in a Patient with Seizure Disorder Treated With Vagus Nerve Stimulation

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Vagus nerve stimulation therapy is a relatively new neurophysiological treatment for patients with medically and surgically refractory epilepsy. A device placed under the skin of the left clavicle delivers electrical impulses to the vagus nerve, and from there to the brain [1]. Since its approval by the U.S. Food and Drug Administration in 1997, more than 40,000 patients have been treated with VNS therapy in the United States. According to Sigma Health Care, provider of the VNS device in Israel, there are about 70 VNS patients in Israel, most of them undergoing the procedure in the past 2 years (personal communication, 31 October 2007). It is estimated that 7–10% of patients with seizure disorders suffer from psychotic symptoms as well [2]. The psychotic symptoms commonly reported are hallucinations, delusions and prolonged euphoric states. It was observed that some of these symptoms tend to occur after marked reduction in seizure frequency and normalization of the electroencephalograph [3].

Landolt introduced the concept of "forced normalization" in 1953. He described the appearance of psychotic episodes with total or partial normalization of the EEG in epileptic patients. This phenomenon can be observed after control of seizures by medical or surgical means. It has been suggested that psychotic symptoms can occur by means of the mechanism of forced normalization after seizure control by VNS therapy as well [4]. A search of the literature indicated only a few cases of psychosis concomitant with the treatment of epilepsy by VNS, as reviewed by de Herdt et al. [3]. We present here a patient with seizure disorder who developed psychosis after the implantation of a VNS device.

VNS = vagal nerve stimulation
EEG = electroencephalograph

Patient Description

A 35 year old man was admitted to our psychiatric department in an acute psychotic state after trying to cut his throat, believing he was the devil.

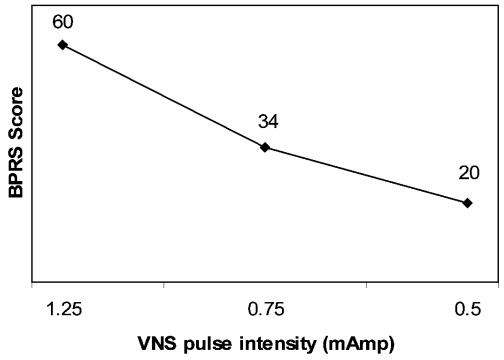
The patient had a history of right frontotemporal epilepsy since the age of 11. This consists of complex partial seizures with and without secondary generalization. His last general seizure was at age 16. With antiepileptic combination therapy of clobazam 40 mg, lamotrigine 250 mg and phenobarbital 50 mg, the frequency of the complex partial seizure decreased to once a week. Video EEG showed three seizure sources: right temporal, left temporal and right frontal. Magnetic resonance imaging was normal.

He had his first psychotic episode at the age of 26 and was admitted to a psychiatric hospital. Since then he had several psychotic events that were managed with antipsychotic treatment. Between psychotic episodes he lived in a hostel for formerly hospitalized psychiatric patients and was functioning well. During that time he was maintained on haloperidol 2.5 mg/day.

Two years before the present admission he started experiencing seizures every day. His condition could not be controlled successfully with anti-epileptic medications, and after a year of no improvement a VNS device was implanted. At the time of implantation daily anti-epileptic treatment consisted of sulthiamine 800 mg, phenobarbital 50 mg, clobazam 40 mg, and oxcarbazepine 1200 mg. The parameters of the VNS device were: pulse rate 30 Hz, 5 minutes off and 30 seconds on, 500 ms pulse width. The intensity of the pulse was gradually increased to 1.25 mA within a few weeks.

About 3 months after the procedure, the seizure frequency had noticeably decreased but his mental state began to deteriorate. He became agitated and acted strangely. On the day of his admission he tried to take his own life by cutting his throat with a knife. He was brought for psychiatric evaluation by order of the district psychiatrist. On examination he was fully oriented but claimed that the soul of his late grandfather had entered his body and that he was the devil. Auditory hallucinations in the form of the voice of God were telling him to kill himself. He remained in a psychotic state for more than 5 months with no response to antipsychotic treatment. Haloperidol 20 mg/day was supplemented with promethazine 150 mg and diazepam 20 mg daily. We hesitated using other antipsychotics for fear of reducing the seizure threshold. Furthermore, the patient had previously responded best to haloperidol. His state deteriorated further. He was no longer oriented and acted violently and impulsively in a way that was never seen during his previous hospitalizations. He was physically aggressive to other patients, broke a television screen and wounded an orderly. At this time his score on the Brief Psychiatric Rating Scale [5] was 60.

In light of the possible link between VNS and psychosis, we requested that the patient's neurologist decrease the electrical stimulation of the VNS. The pulse intensity was decreased from 1.25 to 0.75 mAmp. After only a few days the violence stopped completely. Mentally, he started to gradually improve. He became fully oriented again, with no apparent



Improvement in psychosis with reduction of VNS pulse intensity

delusional thoughts. But still he was very sleepy during the day, talked slowly and had difficulty finding words. He admitted continued intermittent auditory hallucinations. BPRS score had declined to 34. Six weeks later, a further decrease in pulse intensity from 0.75 to 0.5 mAmp was instituted. Again a dramatic improvement was seen. The patient was fully awake all day long, the rate and content of his speech improved and he no longer had auditory hallucinations. BPRS score was 20 [Figure]. No complex partial seizures occurred. In this state he was granted daily leave from the department without escort. We initiated arraignments for discharge to sheltered housing in the community.

Comment

We have described a patient who developed intractable psychosis after the use of a VNS device for treatment of his refractory epilepsy. Although he had a prior history of psychotic illness, the episode reported here was significantly more severe in terms of the content of the delusions, the tenacity with which they were maintained, the explosive violence, and the refractoriness to antipsychotic medication. The improvement in his condition following each reduction in VNS pulse intensity was swift and dramatic.

Eleven cases of VNS inducing or aggravating psychosis have been reviewed in the literature [4]. In all those cases, antipsychotic pharmacotherapy was introduced or adjusted. In our patient the psychosis was refractory to the antipsychotic treatment that had helped him in the past. Only adjusting the VNS pulse intensity brought relief. Our case is unusual for the violence that the psychotic ideation engendered and which posed a serious threat to his environment, caretakers and patients alike. Finally, the degree of tired and reduced alertness that was noted in our patient is also unusual for VNS treatment, which is known to reduce sedation and increase alertness [4]. These symptoms also improved with the reduced pulse intensity.

BPRS = Brief Psychiatric Rating Scale

This is the first reported case of psychosis following VNS therapy in Israel. As this form of therapy, which can provide relief in cases of refractory epilepsy, becomes more widespread, clinicians need to be aware of the paradoxical possibility that normalization of EEG and reduction of seizure activity may be followed by the appearance or exacerbation of psychosis. In such instances, a possible course of action might be a partial reduction in VNS pulse intensity in the hope of navigating a careful course between the Scylla of epilepsy and the Charybdis of psychosis.

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Capsule

The Ashwell receptor mitigates the lethal coagulopathy of sepsis

The Ashwell receptor, the major lectin of hepatocytes, rapidly clears from blood circulation glycoproteins bearing glycan ligands that include galactose and N-acetylgalactosamine. This asialoglycoprotein receptor activity remains a key factor in the development and administration of glycoprotein pharmaceuticals, yet a biological purpose of the Ashwell receptor has remained elusive. Grewal et al. have identified endogenous ligands of the Ashwell receptor as glycoproteins and regulatory components in blood coagulation and thrombosis that include von Willebrand factor (vWF) and platelets. The Ashwell receptor normally modulates vWF homeostasis and is responsible for thrombocytopenia during systemic *Streptococcus pneumoniae* infection by eliminating platelets desialylated by the bacterium's neuraminidase. Hemostatic adaptation by the Ashwell receptor moderates the onset and severity of disseminated intravascular coagulation during sepsis and improves the probability of host survival.

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