

Are psychotic symptoms related to vagus nerve stimulation in epilepsy patients ?

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Abstract

Four patients with refractory epilepsy presented with psychotic symptoms following treatment with vagus nerve stimulation (VNS) to control seizures. Besides its anti-epileptic effect VNS has been shown to have an effect on various cognitive and behavioural functions. VNS is known to increase alertness and reduce sedation, which is independent from seizure control. VNS has also been shown to positively affect cognition and to exert strong antidepressant effects. Co-morbidity in epilepsy often comprises psychiatric illnesses. Increased psychiatric symptoms have mainly been described in association with successful outcome following epilepsy surgery as a result of 'forced normalisation'. Different hypotheses on the underlying aetiology of VNS-induced psychotic symptoms other than the previously described 'forced normalisation' are discussed.

Key words : Refractory epilepsy ; vagus nerve stimulation, psychosis, epilepsy surgery, forced normalisation.

Introduction

Kraepelin and Bleuler already recognized that epilepsy may be associated with psychiatric comorbidity (Bleuler, 1949 ; Kraepelin, 1923). The most frequently reported complaints and symptoms include irritability, depression, anxiety, euphoria, pains and insomnia (Blumer, 2001). These psychiatric symptoms may occur as interictal, pre-ictal, ictal and postictal phenomena. Psychotic symptoms commonly reported are hallucinations, delusions and prolonged euphoric states. These symptoms tend to occur particularly after markedly improved seizure control and normalization of the EEG is achieved and they are consequently thought to result from a predominance of chronic inhibitory mechanisms. These symptoms can be successfully treated with psychotropic drugs. Epilepsy is most commonly treated with antiepileptic drugs. However, 30% of patients do not respond to adequate pharmacological treatment and are considered refractory (Kwan, Brodie, 2000). Vagus nerve stimulation (VNS) is a neurophysiological treat-

ment for refractory patients who are unsuitable candidates for resective surgery (Boon *et al.*, 2001). VNS consists of intermittent electrical stimulation of the left vagus nerve by means of a stimulation-electrode and a programmable pulse generator that is implanted in the subclavicular area. VNS leads to a significant decrease in seizure frequency in 30% of patients. So far only a few single case-reports have described acute psychotic symptoms during treatment with VNS in patients with excellent seizure control (Blumer *et al.*, 2001 ; Gatzonis *et al.*, 2000 ; Murphy *et al.*, 1998). The purpose of this study is to report on 4 patients in a series of 70 patients who underwent VNS for refractory epilepsy in the Reference Center for Refractory Epilepsy at Ghent University Hospital.

Case 1

This 46 year-old male presented at Ghent University Hospital in 1976. At the age of 6 months he had a generalized clonic (GTC) seizure secondary to encephalitis of unknown aetiology. At the age of 14 years he presented with spontaneous gastric bleeding caused by chronic overdose of salicylic acid. When he was 17 years old he had a few episodes of loss of consciousness, which were treated with primidone and later with a combination of phenytoin and phenobarbital. At the age of 19, habitual seizures first occurred and were associated with behavioural disorders such as aggressive spells. The family history was negative for neurological or psychiatric diseases. Seizures started with a feeling of pressure all over the body, followed by loss of contact, extension of both arms and drooling. Afterwards there was a short period of unintelligible speech. A whole episode lasted no longer than 15 seconds. He had at least two habitual seizures per month. Provoking factors were stress and fatigue. Until 1989, only complex partial seizures (CPS) occurred, which were treated with a combination of phenytoin, phenobarbital and carbamazepine. In 1989, the patient began to pre-

sent secondary generalised (SG) tonic clonic seizures with urine loss and tongue biting. On a medication regimen of phenobarbital and carbamazepine he became free of SG convulsions during 4 years. In 1993, he had a period of increasing seizures in combination with behavioural problems and 'out-of-body sensations'. This occurred after cessation of phenobarbital. In 1995, a routine EEG showed a background activity of 10 Hz with low voltage but without epileptiform discharges. During long-term video-EEG-monitoring in 1998, 5 habitual CPS with SG were recorded. The ictal EEG showed diffuse slowing at the onset of the clinical seizure ; there were no clear signs of ictal EEG lateralisation. It was thought that seizure semiology was suggestive for early frontal lobe or insular involvement with spread to the temporal lobe. Optimum magnetic resonance imaging (MRI) showed right-sided hippocampal atrophy. An interictal FDG-PET was normal. The neuropsychological assessment showed normal intelligence and was suggestive for a left-sided temporal dysfunction and bilateral frontal dysfunction. A Wada-test demonstrated a left-sided hemispheric language dominance and a bilateral memory deficit. On the basis of these pre-surgical evaluations, the patient was considered an unsuitable candidate for resective surgery. Subsequently various combinations of carbamazepine, phenobarbital, clonazepam, lamotrigine and topiramate were prescribed, without significant improvement in the frequency of the habitual seizures. In 2001, the patient was admitted in a psychiatric department during a 2-month period due to a severe depression. The patient made a suicide attempt. He was treated with tricyclic antidepressants for 4 months. The same year he divorced and lost his job. A second video-EEG-monitoring and optimum MRI was performed in 2001 to re-evaluate the seizures. This did not add any further information with regard to the localization of the seizure onset. At this time the patient experienced up to 15 CPS per month. Secondary convulsions occurred in up to 50% of the seizures. Ultimately, the patient was treated with VNS in February 2002. Ongoing AED treatment existed of carbamazepine 1200 mg/d, topiramate 250 mg/d and phenobarbital 100 mg/d. Following the implantation procedure and during the ramping-up period, the patient reported a reduction in seizure frequency of 50% and also an improved emotional stability. He found the magnet feature that allows patients to administer an additional VNS pulse train in case of an aura to be helpful to abort an upcoming seizure. On his own initiative and motivated by the fact that he felt much better, the patient tapered the dose of phenobarbital to 10 mg/d, of carbamazepine to 600 mg/d and of topiramate to 150 mg/d which resulted into a temporary increase in seizure frequency. In the following weeks, the VNS output current was gradually increased to 1.5 mA and the stimulation fre-

quency lowered to 25 Hz because of intermittent stimulation-related hoarseness. In March 2003, he experienced 6 to 10 CPS per month. The habitual seizures were reported to be much shorter and SG convulsions had stopped. At this time however, the patient presented with psychotic symptoms such as tactile hallucinations and complex delusions such as the conviction that a perceived injury to his left arm "was growing from the inside towards the outside". A structured psychiatric interview confirmed the psychotic nature of the reported hallucinations and delusions ; subsequently the patient was treated with haloperidol 2 mg/d. In the following months the stimulation output current was further increased to 2 mA and the stimulation frequency changed to 20 Hz due to the recurrence of stimulation-related side effects with higher output currents. The psychotic symptoms became more subtle but continued treatment with haloperidol was felt necessary. At the time of the most recent follow-up consultation, 3 months later, the patient reported no more hallucinations and a significant decrease in the number of seizures to one per month. A follow-up psychiatric interview did not reveal overt psychotic symptoms. His treatment regimen remains unchanged.

Case 2

This 50 year-old man with a previous diagnosis of Lennox-Gastaut syndrome had a normal psychomotor development until the age of 2 years. At that age, he experienced his first seizure consisting of a suddenly occurring loss of contact and unstable gait. The following years he presented a progressive delay in developmental milestones and several types of seizures : atonic seizures, GTC seizures, CPS, myoclonic and tonic seizures. The interictal EEG showed slow spike wave activity during the awake state. The diagnosis of Lennox-Gastaut syndrome was made. The family history revealed one member with tuberous sclerosis. The patient presented at Ghent University Hospital in 1992 with severe mental retardation. At that time, he had daily CPS and less frequent atonic seizures. His anti-epileptic treatment consisted of a combination of valproate, vigabatrin, carbamazepine, phenytoin and clonazepam. Neurological examination showed weak tendon reflexes in all extremities, a frontal gait pattern and positive primitive reflexes. Chromosome analysis revealed no abnormalities. There was no evidence for tuberous sclerosis. A routine EEG recording demonstrated a low voltage background activity with isolated spikes, polyspikes and slow spike and wave activity with right hemispheric preponderance. Optimum MRI showed no structural abnormalities. The maximum seizure-free interval the patient had ever experienced was only a few days. When vigabatrin was added to his AEDs, the atonic seizures became less

frequent. In 2000, he was admitted to the Reference Center for Refractory Epilepsy at Ghent University Hospital for presurgical evaluation. During long-term video EEG-monitoring frequent but short lasting atonic seizures were recorded. The ictal EEG showed a diffuse electrodecrement. The interictal EEG showed frequent and diffuse slow spike and wave discharges. Some polyspike activity was noted during nighttime recordings. Interictal FDG-PET demonstrated a mild frontal hypoperfusion. Based on the clinical semiology and the interictal and ictal EEG patterns the diagnosis of Lennox-Gastaut syndrome was confirmed. The patient was offered treatment with VNS and he subsequently underwent the surgical implantation procedure in July 2000. At that time his AED regimen consisted of a combination of vigabatrin 1500 mg/d, carbamazepine 1200 mg/d, valproate 3500 mg/d and phenytoin 300 mg/d.

VNS was activated at 0.25 mA two weeks following the implantation procedure. Two weeks later the patient's mother reported an episode of aggressive behaviour, confusion, and visual and auditory hallucinations that seemed to be very frightening to the patient. Because of his mental retardation a structured psychiatric interview could not be performed. The symptoms subsided after two weeks, without specific neuroleptic treatment being given. However, there was a reduction in seizure frequency, particularly of the atonic seizures. The stimulation output current was increased to 0.5 mA. Again, one month later, a psychotic episode with striking aggressive behaviour, hallucinations and anxiety was reported. This time, the patient was admitted in a psychiatric facility for a period of 10 days and given an intramuscular treatment with zuclopentixol 200mg/month for a period of 2 months. This resolved the psychiatric symptoms and the antipsychotic treatment could be tapered. Following ongoing treatment with VNS, the patient became more alert and there was a further decrease in seizure frequency. The stimulation output was further increased with 0.25 mA increments every 2-3 weeks. During the ramping up period, there was an episode of axial myoclonic jerks in April 2001, for which clonazepam was added to the treatment. In August 2001, the patient underwent a small surgical intervention with repair of a skin defect, due to local infection of a stitch on the level of the neck incision. There was a full recovery. Two years and eight months following implantation an output current of 2 mA was reached. The patient was considerably less sedated than before treatment with VNS and a 50% seizure reduction was achieved. The psychotic symptoms did not recur. In March 2003 the patient experienced an increased seizure frequency due to the tapering of vigabatrin. Levetiracetam was added to the AED regimen. In April 2003, the generator and the electrodes were explanted because of a chronic inflammatory reac-

tion at the neck incision site. In view of the increasing seizure frequency that was not controlled by increasing the dose of levetiracetam up to 2000 mg/d, the patient will be evaluated for re-implantation with a second generator.

Case 3

This right-handed 38 year-old female with a history of mild mental retardation developed severe refractory epilepsy with complex partial seizures and secondary generalisation at the age of 2 years. Until then there was a normal psychomotor development. The first seizures were not well documented. There was an extended family history of epilepsy, 2 siblings died as a baby because of seizures, one brother died at the age of 42 because of SUDEP. Two other brothers, who reportedly had no epilepsy died in a traffic accident. The patient went to a professional school until the age of 16. From 1985 until 1999, she was treated with various combinations of valproate, carbamazepine, primidone and clonazepam. Routine EEG showed a slow background activity and bilateral, non-synchronous, diffuse epileptiform discharges. When lamotrigine was added to the AED treatment in 1998, seizure frequency decreased dramatically. The patient was admitted in the hospital the same year because of an episode of ataxia and nystagmus, likely related to a pharmacodynamic interaction between carbamazepine and lamotrigine ; after the dose of carbamazepine was tapered, the toxic symptoms disappeared. An optimum MRI performed in 1999 showed mild posterior left-sided mesial temporal atrophy. Video EEG-monitoring was performed ; five seizures were recorded. Ictal EEG showed recruiting epileptiform activity both in the left and right temporal lobe, with difference in preponderance among different seizures. In addition, interictal EEG showed bitemporal independent spikes and spike and waves. Ictal SPECT during a seizure with a preponderant left temporal EEG-onset showed left temporal hyperperfusion. Because of the bilateral temporal lobe involvement, the patient was considered an unsuitable candidate for resective surgery. Subsequently, the patient presented at the Reference Center for Refractory Epilepsy at Ghent University in 2000. She had mild mental retardation and was at that time treated with valproate 2000 mg/d, topiramate 150 mg/d and lamotrigine 300 mg/d. She had at least 2 CPS per month with SG convulsions at least once per month. An habitual seizure was often preceded by an epigastric aura. This was followed by a loss of contact and semi-purposeful behaviour more pronounced on the left side of her body. During seizures, the patient often fell and experienced prolonged postictal sedation and confusion. In 2001 AED treatment was changed into a combination of lamotrigine, primidone and topiramate. In July

2001 she was treated with VNS. The AED regimen remained unchanged. During the ramping-up period, mild hoarseness was reported. The output current was gradually increased until 1.75 mA, without a significant change in seizure frequency. The patient was able to abort a seizure using the magnet. A routine EEG investigation showed diffuse slowing and bilateral asynchronous epileptiform discharges. In June 2002, the patient was admitted to the neurological department because of a reported increased seizure frequency. Long-term video EEG-monitoring did not allow to record habitual seizures. However, during the hospital admission, the patient presented extremely hostile behaviour towards medical staff and she was extremely suspicious of any medical intervention. She was diagnosed with psychosis and acute delusions for which she was transferred to the psychiatric department. There she was treated with haloperidol 2 mg/d which resolved the psychotic symptoms swiftly. The output current of the VNS was set to 2 mA. One month later, the patient suffered from a depression, for which she received an additional treatment with venlafaxine 75 mg/d. During further follow-up 3 months later, the patient reported a marked decrease of CPS during daytime ; she still reported convulsions occurring during nighttime. Psychotic and depressive symptoms were fully controlled. She still complained of a mild intermittent stimulation-related hoarseness. The stimulation parameters were set on an output current of 2.5 mA and a stimulation frequency of 20 Hz. Two months later the patient reportedly died from SUDEP.

Case 4

This 42 year-old right-handed female with a history of a complicated birth with cyanosis and perinatal trauma on day 8 after birth had a normal psychomotor development until the age of 2,5 years. She then suffered from an episode of generalized status epilepticus in afebrile conditions followed by right hemiparesis with full recovery after 24 hours. At the age of 6, she developed CPS with occasional SG convulsions and also atonic seizures. The CPS began with rolling of the eyes, swallowing, mastication and loss of contact. Atonic seizures occurred mostly during the perimenstrual period ; CPS occurred daily. She was treated with all available AEDs. She presented at the Ghent University Hospital in 1994. Clinical neurological examination demonstrated mild mental retardation and a paresis of the right oculomotor nerve. A routine EEG investigation showed focal spikes in the left temporal region. During video EEG-monitoring, 5 CPS were recorded. Ictal EEG showed a left posterior temporo-parietal seizure onset, the interictal EEG recordings showed independent epileptiform activity bilaterally in the frontotemporal area, but also in the left posterior temporal and right fronto-

central region. Optimum MRI showed white matter lesions bilaterally in the parieto-occipital region and in the right temporal lobe, suggestive of sequellae of perinatal asphyxia. Because of the multifocal nature of the seizures, the multidisciplinary team decided that the patient was not a candidate for resective surgery ; a treatment with VNS was proposed. At that time she was treated with carbamazepine 1200 mg and clonazepam 4 mg. The implantation was performed in December 2002. Ramping-up of the output current started 3 weeks later. The AED regimen remained unchanged. The output current was gradually increased with increments of 0.25 mA. The patient complained of hoarseness when an output current of 0.5 mA was reached. Three months after implantation and when an output current of 0.5 mA was reached, psychotic symptoms with paranoid delusions occurred. The caregivers of the patient reported hostile behaviour and at the consultation the patient was extremely suspicious and accused accompanying caregivers of lying about seizure control in the past weeks. A treatment with haloperidol 2 mg/d was started. The psychotic symptoms did not improve and the patient harassed neighbours and failed to trust any caregiver. Non-compliance with oral haloperidol treatment was suspected upon which intramuscular treatment with zuclopentixol 200 mg/month was started. Seizure control had not significantly improved until the output current was increased to 1 mA. This resulted in a reduction of seizure frequency to 1 CPS with SG convulsions/month. Psychotic symptoms have improved but intramuscular neuroleptic treatment with antipsychotic drugs is being continued.

Discussion

This study describes 4 patients, who all had refractory epilepsy and did not become seizure-free despite treatment with various combinations of practically all available antiepileptic drugs. All 4 patients were found to be unsuitable candidates for resective surgery and were subsequently treated with VNS. During the ramping-up procedure of the output current, these 4 patients presented with psychotic symptoms. One patient had a history of psychotic symptoms and other psychiatric co-morbidity such as a depressive episode and behavioural problems before treatment with VNS. The other three patients had mental retardation but had never been diagnosed with a psychiatric condition. One patient had severe mental retardation as part of Lennox-Gastaut syndrome. The two remaining patients had mild mental retardation. Recent reviews on the association between psychosis and epilepsy have not specifically addressed VNS (Sachdev, 1998 ; McLachlan, 2003). So far, only seven cases of psychotic reactions occurring during VNS for epilepsy have been reported in the litera-

ture. One report described a 16-year-old male with daily convulsions and a history of previous psychosis who became acutely psychotic 'after an incredible 2-week seizure-free period' (Murphy *et al.*, 1998). Another case report described a 35-year old male with no history of psychiatric disturbances who became psychotic when seizure frequency was dramatically decreased and scalp EEG abnormalities had been normalised (Gatzonis *et al.*, 2000). Blumer *et al.* reported 5 patients with psychotic symptoms after seizure frequency was reduced by at least 75% (Blumer *et al.*, 2001). Affective disorders and psychosis are often seen in a setting in which previously intractable epilepsy patients suddenly become seizure-free. This can occur with most of the new AEDs, after resective surgery or VNS (Blumer *et al.*, 2001 ; Gatzonis *et al.*, 2000 ; Murphy *et al.*, 1998 ; Trimble, 1996 ; Pakalnis *et al.*, 1987). At the time psychotic symptoms occurred in our patients seizures were far from being controlled. Consequently the observed symptoms cannot be attributed to this so-called concept of 'forced normalisation'. Regarding the potential role of drug treatment as an underlying aetiology for psychosis, all established and newer AEDs such as valproate have the potential to precipitate psychiatric symptoms. At the time of the psychotic episode, two patients were treated with topiramate, a drug that has been implicated in the occurrence of psychotic symptoms (Crawford, 1998). However, one patient had a history of psychiatric disorders before treatment with topiramate and the other patient had already been taking topiramate for more than two years before psychotic symptoms occurred. Therefore it seems unlikely that the psychotic symptoms in our patients were caused by changes in AED treatment. One patient with a 50% reduction in seizure frequency did report to be very satisfied with the treatment upon which he dramatically tapered phenobarbital, topiramate and carbamazepine, which resulted in a temporary increase in seizure frequency. Psychotic symptoms only occurred weeks later, which makes the hypothesis of an ictal or postictal psychosis unlikely. Upon specific interrogation of the patient with regard to his motivation for tapering his AEDs he answered that he felt so well controlled and alert that he did not need these AEDs anymore. In the other patients, the caregivers noted a specific characteristic that was new to them and was also observed during interaction with the patients at the epilepsy clinic. These patients presented with a very suspicious attitude towards close and trusted people.

Many studies have reported the increased alertness in patients treated with VNS independent from seizure control. Often the increased alertness is evaluated in an early stage during the ramping-up procedure at a time when seizures have not been clearly affected. Seizure control with VNS often takes weeks to months to be established during

which the output current is gradually increased. However, there are strong arguments from recent findings that VNS-induced effects on e.g. cognition may occur following a single VNS pulse train (Clark *et al.*, 1999). In a study by Clark *et al.* VNS-induced memory-enhancing effects were observed at output currents that are far lower compared to the output currents that effect seizures. A similar phenomenon has been shown after multiple subpial transections where cognitive improvement may be immediate while seizures persist. Also, recent studies of mood in epilepsy patients treated with VNS reported a positive mood effect with possible decrease of depressive symptoms (Hoppe *et al.*, 2001 ; Harden *et al.*, 2000). Armitage *et al.* demonstrated in a preliminary report that VNS improved the clinical symptoms of depression and sleep architecture (Armitage *et al.*, 2003). Recent controlled studies in patients with refractory depression show promising results with VNS that will be further investigated as a potential antidepressant therapy (Kosel *et al.*, 2003 ; George *et al.*, 2000). Koutroumanidis *et al.* observed psychotropic effects of VNS in two patients with post-ictal psychosis, in two others with depression and in a child with a severe behavioural disorder (Koutroumanidis *et al.*, 2003). Also in children with epilepsy and autistic behaviour, significant improvement in aggressive and antisocial behaviour has been reported (Murphy *et al.*, 2000). Acutely increased alertness and decreased sedation may in some patients manifest itself as a psychosis-like state with hallucinations. This may have the underlying mechanism of action in some of the patients reported in this study. Patients with mild or severe mental retardation may be specifically sensitive for the development of these symptoms. The four cases we reported were not likely to fit into the concept of 'forced normalisation', like suggested by Gatzonis *et al.* as a possible explanation. Forced normalization is thought to be based on the effect of inhibitory mechanisms that overtake when effective antiepileptic treatments are administered. This seems to be in contrast with the finding in our patients who appeared to experience VNS-induced excitatory effects on the central nervous system. Most likely, the psychotic condition observed following seizure control can be induced by any kind of treatment including VNS. The finding of psychotic reactions in our patients is suggestive of an independent VNS-induced effect on central nervous system structures. This effect induces increased alertness but may also result into psychotic symptoms. Antipsychotic treatment appears to be a successful treatment and could be tapered in two of our patients without recurrence of symptoms despite ongoing treatment with VNS and further increase of the output current.

Further investigation and observation will be needed 1. to establish the true nature of the psy-

chotic symptoms ; 2. to differentiate them from purely behavioural symptoms ; 3. to differentiate the underlying mechanisms of these psychotic symptoms during VNS and 4. to investigate which patients may be specifically sensitive for the development of such conditions.

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