

## BRIEF COMMUNICATION

# Parkinsonism induced by VNS in a child with double-cortex syndrome

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### SUMMARY

We describe a child with epilepsy associated with double-cortex syndrome in whom vagus nerve stimulation (VNS) generated parkinsonian symptoms. A 13-year-old girl presented with refractory secondary generalized epilepsy from the age of 6 years and mental retardation. Her electroencephalography (EEG) showed diffuse polyspike and wave discharges. Magnetic resonance imaging (MRI) showed double-cortex syndrome. She was submitted to extended callosal section at the age of 10 years, which yielded 50% seizure frequency

reduction. She was submitted to VNS by the age of 12 years. As stimulation intensity was increased, there was appearance of extrapyramidal symptoms: She developed bilateral tremor and rigidity, and gait and postural disturbance. All symptoms disappeared 7–10 days after VNS was turned off. Several attempts to reactivate VNS led to the same results. During the periods when VNS was on she presented with marked seizure frequency reduction. This is the first report of a clinically evident direct effect of VNS on the basal ganglia.

**KEY WORDS:** Outcome, Callosotomy, Generalized epilepsy.

Vagus nerve stimulation (VNS) has been used increasingly in the treatment of refractory epilepsy. It has been shown to be an effective palliative procedure in focal and generalized epileptic syndromes, in both adults and children (Benifla et al., 2006; Ardesch et al., 2007; Amar et al., 2008).

Although its effectiveness has been confirmed by various studies, the exact pathway through which the antiepileptic effect of VNS is obtained is not yet clear. The nucleus of the tractus solitarius is considered an early relay, but the progression of the up-going information in the cortical direction is not known. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have been employed to study patients undergoing VNS but have so far yielded inconsistent results (Chae et al., 2003). The effect of VNS on basal ganglia physiology is extremely poorly studied. Handforth et al. (2003) published a pilot study, including nine patients, on the effects of VNS on essential tremor, and

showed a small improvement in some patients, but no worsening in any patient. More recently, Marrosu et al. (2007) published a very small series (three patients) reporting on the effects of VNS on cerebellar tremor and dysphagia in patients with multiple sclerosis, showing some degree of improvement, but no worsening of the symptoms. Although thousands of patients have already been submitted to VNS as a treatment for refractory epilepsy, these last two studies remain the only ones to discuss the effects of VNS on basal ganglia and movement disorders. No previous report has pointed out any clinically significant effect of VNS on basal ganglia in persons with epilepsy.

We describe a child with refractory generalized epilepsy (Lennox-like pattern) associated with double-cortex syndrome as seen on MRI in whom VNS generated severe, stimulation-related, parkinsonian syndrome.

### CASE REPORT

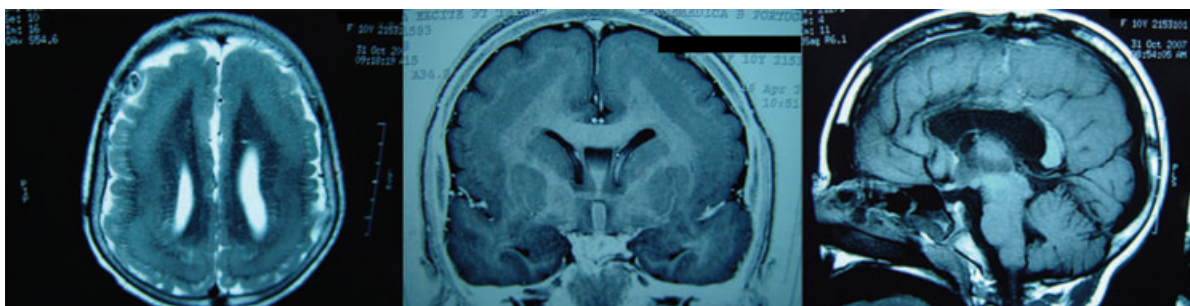
A 13-year-old girl presented with epilepsy from the age of 6 years. She had developmental delay: She walked by the age of 2 years, started talking by the age of 4, and was unable to read or write. She was not able to undergo standard neuropsychological testing. Seizures increased progressively in frequency, and by the time of presentation

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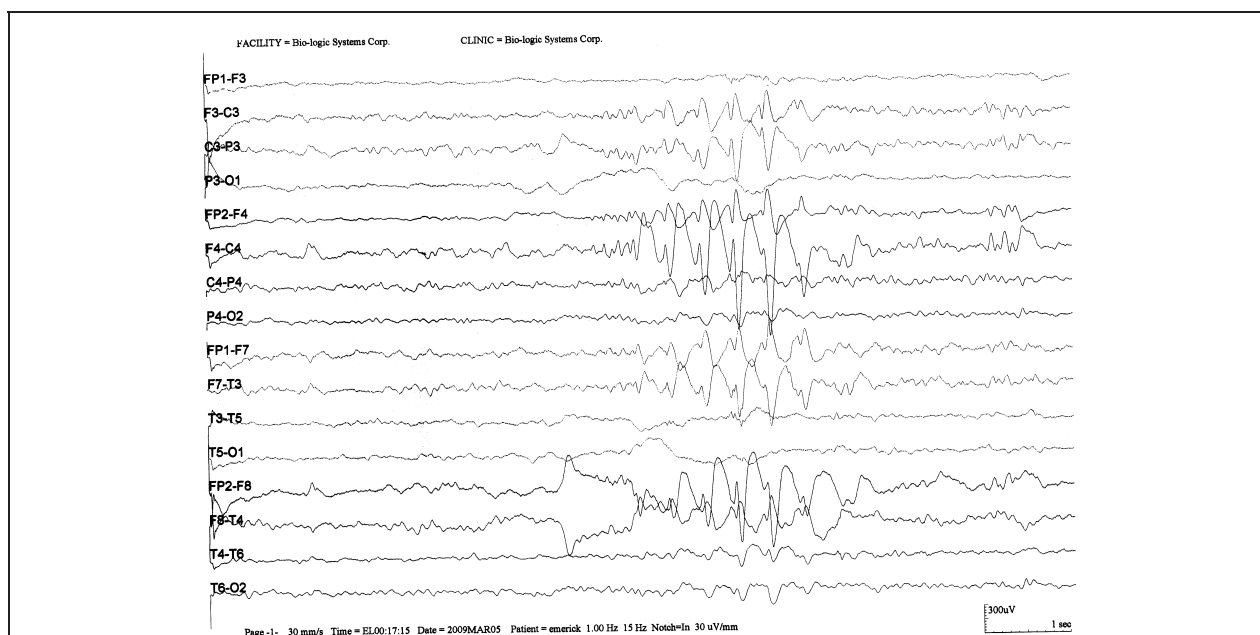
**Figure 1.**

Left and middle: Axial T<sub>2</sub> and coronal T<sub>1</sub> slices showing double-cortex and the basal ganglia. Right: Sagittal T<sub>1</sub> slice showing the extent of callosal section performed before vagus nerve stimulation (VNS).

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she had frequent multiple daily episodes. Seizure types included atonic, tonic, atypical absences, myoclonic, and tonic-clonic ictal events. She was initially treated with high-dose valproate, lamotrigine, and phenobarbital, but seizures remained refractory. Her EEG showed very frequent bilateral and synchronous polyspike and wave discharges. MRI showed diffuse double-cortex syndrome, with visually normal basal ganglia. She was submitted to extended (90%) callosal section by the age of 10 years (Fig. 1). The extent of callosal section was confirmed by postoperative MRI. There was a 50% seizure frequency reduction. Three months after callosal section she developed aggressiveness and hyperactive behavior.

High-dose valproate, lamotrigine, phenobarbital, oxcarbazepine, and topiramate therapy were tried in mono- and polytherapy, but seizures remained refractory and disabling. By the time of VNS implantation she was taking valproate 1,500 mg/day. Drug regimen was kept unchanged during VNS therapy. Her EEG showed post-callosotomy rhythm, including hemispheric independent bilateral spiking and residual secondary bilateral synchrony (Fig. 2). She was then submitted to VNS by the age of 12 years. Stimulus duration and frequency were 500  $\mu$ s and 30 Hz, respectively. Stimulus intensity was increased 0.25 mA every 2 weeks, until 2.0 mA was reached (30 s “on,” 5 min “off”). She presented with insipient move-



**Figure 2.**

Pre-VNS (vagus nerve stimulation) implantation electroencephalography (EEG) sample showing residual secondary bilateral synchrony. Interictal activity always prevailed over the right hemisphere.

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ment disorder when she reached 1.0 mA of intensity. This was characterized by light left-side tremor and rigidity. As stimulation intensity was increased, there was worsening of the extrapyramidal symptoms: She developed bilateral tremor and rigidity (although prevailing on the left side), and gait and postural disturbance. These symptoms ameliorated, but did not disappear, with dopamine agonists and levodopa. All symptoms disappeared 7–10 days after VNS was turned off. A new attempt to turn VNS on at a final stimulus intensity of 2.0 mA was carried out 2 months later, and yielded the same results. Stimulation was discontinued and symptoms remitted again. A third attempt to turn VNS on, this time with a maximum of 1.0 mA, also triggered extrapyramidal symptoms, and the system was definitively shut down. Lower stimulation frequency (20 Hz) and longer off periods (60–90 min) were also tried with similar side effects. During the periods when VNS was on (even with lower intensity: 1.0 mA), she presented with marked seizure frequency reduction (70%), which came back to baseline 2–3 weeks after VNS was discontinued.

## DISCUSSION

This is the first report of a parkinsonian syndrome induced by VNS in a person with epilepsy. Clinical symptoms partially remitted after classic antiparkinsonian treatment. This child had double-cortex syndrome, and her basal ganglia appeared normal in preoperative MRI scans. It is possible that the grossly abnormal connectivity present in patients with double-cortex might explain such an exquisite adverse effect, but this should be confirmed in other similar patients; should this be the case, VNS would not be indicated in this selected group of patients. On the other hand, this was also the first time that a possible direct effect of VNS on basal ganglia relays was clinically proven in humans.

This child became aggressive and hyperactive after callosal section, which is also an uncommon event, since most of the children submitted to callosal section usually become less hyperactive and more focused (Cukiert et al., 2006). We could not rule out that callosal section played a part in the pathogenesis of this adverse event, but extrapyramidal symptoms were seen only after VNS activation, and not after callosotomy.

Many authors have reported an inverse relationship between epilepsy and parkinsonism, and in many patients seizures might disappear after the development of parkinsonian symptoms (Yakovlev, 1928; Vercueil, 2000). Our patient did show an inverse relationship between her

epileptic and parkinsonian symptoms, with marked decrease in seizure frequency when VNS was on and parkinsonian symptoms were present. This seems to suggest that both syndromes share some brain pathophysiologic relays in their modulation, such as the superior colliculi, substantia nigra, and basal ganglia, which might act in different ways in each pathology. Although tremor (resembling essential tremor) might frequently be seen in patients receiving antiepileptic drugs such as valproate, parkinsonism is very rarely seen as a side effect of treatment with antiepileptic drugs or postoperatively.

This was a very unfortunate situation from a clinical perspective, since outcome regarding seizure frequency was very good after VNS was initiated in this child. Deep brain thalamic stimulation would be a therapeutic option for this child, but we could not rule out that abnormal connectivity would also be present in the thalamus.

## ACKNOWLEDGMENTS

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure: None of the authors has any conflict of interest to disclose.

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