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Malignant autosomal dominant frontal lobe epilepsy with repeated episodes of status epilepticus: successful treatment with vagal nerve stimulation

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ABSTRACT – Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a familial partial epilepsy syndrome characterized by seizures suggesting a frontal lobe origin occurring predominantly during sleep. Up to a third of patients may have refractory seizures, with repeated episodes of status epilepticus, intellectual disability of variable degree and psychiatric disturbances. We report a patient with ADNFLE, refractory seizures and repeated episodes of life-threatening convulsive status epilepticus who underwent prolonged video-EEG monitoring and was implanted with a vagal nerve stimulator. At 3.5 years of follow-up, a decrease of more than 80% in seizure frequency was achieved, episodes of status were completely controlled and he displayed improved mood and alertness. Vagal nerve stimulation may be considered as therapy for patients with refractory epilepsies of genetic cause, as well as repeated status epilepticus.

Key words: epilepsy, nocturnal frontal lobe epilepsy, ADNFLE, vagal nerve stimulator, familial, VNS

Nocturnal frontal lobe epilepsy (NFLE) is characterized by seizures occurring predominantly during sleep and a seizure semiology which is suggestive of a frontal lobe origin (Ryvlin *et al.*, 2006). NFLE includes both sporadic and familial forms. Inheritance may be autosomal dominant and such cases are referred to as ADNFLE (8% to 43% of cases). Three ADNFLE loci, including two mutant genes encoding for the α4 and β2 subunits of the nicotinic acetylcholine receptor have been identified (De Fusco *et al.*, 2000; Phillips *et al.*, 1995; Phillips *et al.*, 1998). These mutations are identified only in a minority of patients with ADNFLE.

In both sporadic and familial forms, seizures are usually responsive to antiepileptic drugs. However, in one third of cases, seizures are refractory to medical treatment (Ryvlin *et al.*, 2006), and may evolve into status epilepticus

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(Derry *et al.*, 2008). These patients may display, in addition, cognitive and behavioural disturbances, which seem to occur with worsening of seizures or episodes of status (Derry *et al.*, 2008). The relevance of vagal nerve stimulation (VNS) to treat seizures in this particular syndrome has not been reported so far.

In this case study, we report a 29-year-old patient with refractory ADNFLE and repeated episodes of convulsive status epilepticus who underwent VNS therapy.

Case study

Our patient has a strong family history of epilepsy. His mother had nocturnal motor seizures which were easily controlled with carbamazepine. His maternal grandmother had sporadic generalized motor seizures starting at the age of 21 years. One of his mother's cousins had nocturnal motor seizures which started during her pregnancy and were refractory to medical treatment. A maternal uncle had nocturnal seizures since the age of 15 years, and his son (the patient's cousin) had nocturnal hemimotor simple partial seizures. None of the family members, except our patient, underwent prolonged video-EEG monitoring or genetic testing.

Pregnancy and delivery were uneventful. At the age of three months the patient had generalised convulsive SE, without fever. Lumbar puncture was unrevealing. After the status he started to have clusters of infantile spasms (10-15 a day) and later, afebrile generalized tonic clonic seizures. From the age of six years he only had nocturnal seizures. The family reported motor seizures with sudden extension of both arms, occurring in clusters during the first half of the night (two or three clusters every night, up to a total of 30-40 seizures) and also seizures with generalized shaking, sometimes preceded by stiffening of the trunk (1-2 every night). Approximately once every six months he had prolonged convulsive seizures lasting more than 30 minutes which required hospital admission and treatment with intravenous benzodiazepines and even pentobarbital coma. Neurological examination was normal except for marked psychomotor slowing. Genetic testing for known mutations of ADNFLE was negative, however, a clinical diagnosis of ADNFLE was made based on nocturnal seizures, a seizure semiology suggestive of frontal lobe origin and family history.

The patient was treated with multiple antiepileptic drugs, both as mono and polytherapy, including phenobarbital, carbamazepine, phenytoin, valproic acid, clobazam, lamotrigine, vigabatrin, gabapentin, ethosuximide, clonazepam, topiramate and levetiracetam, without effectiveness. Nicotine patches were used, which seemed to temporarily decrease seizure frequency. When admitted to our Unit he was being treated with phenytoin, topiramate and clonazepam. Blood level of phenytoin was around 35 µg/mL. Lower levels systematically resulted in increased seizure frequency and convulsive status epilepticus. Higher levels produced somnolence and severe ataxia.

Prolonged video-EEG monitoring showed bilateral asymmetric tonic seizures with sudden extension of both arms (right more than left), axial tonic seizures with generalized stiffening and hypermotor seizures that sometimes evolved into clonic jerking of the right limbs. All seizures arose from sleep. Interictal EEG showed polyspikes, spikes

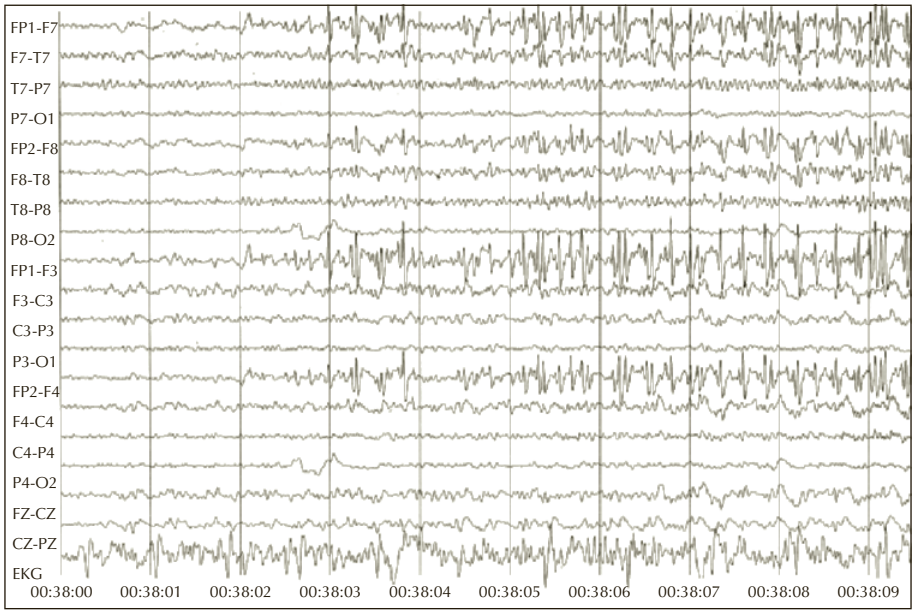

Figure 1. Repetitive spiking over the midline and both frontocentral regions preceding an axial tonic seizure during sleep.

and sharp waves over the vertex and fronto-central regions, bilaterally. Ictal EEG showed repetitive spiking over the midline and both frontal regions, maximum over the left *(figure 1)* or a diffuse electrodecremental pattern followed by a rhythmic theta pattern over the left frontocentral region (Fz > Cz > F3 > C3). Neuropsychological assessment showed intelligence in the lower end of normal range, with impaired attention, operative memory and verbal fluency. Subtle asymmetry in hippocampal size was identified by 3T brain MRI, with no evident lesions in the frontal region.

The patient was not considered a surgical candidate. Given the refractoriness to medical therapy and the repeated episodes of convulsive status epilepticus, a vagal nerve stimulator (VNS) was implanted.

Following implantation, the intensity of stimulation was increased, in steps of 0.25 mA every two weeks. After three months at an intensity of 1.5 mA, a significant reduction (50%) in seizure frequency was noticed by the family. After one year at an intensity of 2 mA, seizure frequency decreased by 80%, as confirmed by repeated video-EEG monitoring; response to stimulation was maintained after 3.5 years of follow-up. Generalized tonic clonic seizures became rare (once every 2-3 months, approximately) and he did not have any more episodes of status epilepticus since implantation. The patient continues to have brief nocturnal bilateral tonic seizures which do not interfere significantly with sleep. An attempt to decrease the dose of phenytoin resulted in increased seizure frequency, thus medication remained unchanged.

The patient now works in a restaurant and shares a supervised apartment. The family reports increased alertness, improved psychomotor speed and mood, without adverse effects from stimulation. Follow-up neuropsychological assessment has shown improved visual memory relative to previous tests.

Discussion

Vagal nerve stimulation is considered an effective and generally safe therapy for patients with intractable epilepsy who are not candidates for epilepsy surgery. Controlled and long-term studies (Montavont *et al.*, 2007; Fisher and Handforth, 1999) have shown that more than 50% seizure reduction occurs in about half of patients. VNS has also been successfully used to abort refractory status epilepticus (De Herdt *et al.*, 2009). A clear response to stimulation was observed early after implantation and at medium intensities which was increased and maintained with time (Montavont *et al.*, 2007), as well as increased alertness and improved psychomotor speed (Hallbook *et al.*, 2005). In our case study, the complete control of repeated episodes of life-threatening convulsive status epilepticus is particularly impressive and resulted in a radical change in quality of life for the patient and his family.

To our knowledge, this is the first report in the literature concerning the effectiveness of VNS in patients with ADNFLE and drug refractory seizures. Animal models have shown that mutated nicotine receptors of acetylcholine (nAChRs) display increased sensitivity to Ach (Klaassen *et al.*, 2006). PET studies in humans have shown significant changes in brain nAChR density, with a high concentration of receptors in the thalamus, pointing towards an over-activated cholinergic pathway ascending from the brainstem (Picard *et al.*, 2006). Other neurotransmitter systems, such as the GABAergic system, may also be enhanced in ADNFLE (Klaassen *et al.*, 2006). Although the exact mechanism of action of VNS remains to be elucidated, it has been postulated that afferent vagal synapses attenuate seizure activity through neurotransmitter modulation (Zagon and Kemeny, 2000). Crucial brainstem and intracranial structures which may be influenced by chronic stimulation include the locus coeruleus, nucleus of the solitary tract, thalamus and limbic structures (Cunningham *et al.*, 2008). This is accompanied by changes in cerebral blood flow and cerebral metabolism. Positive clinical efficacy has been correlated with chronic thalamic hypoperfusion in SPECT studies (Vonck *et al.*, 2008). This downregulation of enhanced cholinergic thalamocortical pathways may be related to the anti-seizure effect in patients with ADNFLE.

In summary, vagal nerve stimulation may be an effective therapy for malignant cases of epilepsy of presumed genetic origin as well as repeated status epilepticus. □

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

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