Pearls & Oysters:

A case of refractory nocturnal seizures

Putting out fires without smoke

Pantelis P. Pavlakis, MD,
PhD
Laurie M. Douglass, MD

Correspondence to
Dr. Douglass:
laurie.douglass@bmc.org

PEARLS

- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a hereditary form of epilepsy characterized by multiple seizures during stage 2 sleep. It is caused by several different mutations involving the $\alpha 2$, $\alpha 4$, or $\beta 2$ neuronal nicotinic acetylcholine receptor (nAChR) subunit genes. The net effect of these mutations is increased activity of the nAChRs, because of an increased sensitivity to ACh.
- Carbamazepine or oxcarbazepine are effective first-line agents. Up to one third of patients, however, have refractory seizures. Nicotine is a potentially effective alternative treatment, which may work by desensitizing AChRs to acetylcholine.
- Genetic testing for ADNFLE should be considered in children with multiple, frequent, brief nocturnal seizures, strong family history, and normal results on interictal EEG.

OY-STERS

- Nicotine has been reported to be effective in a limited number of studies. However, the efficacy, and potential toxicity, of long-term treatment is unknown.

CASE REPORT The patient presented at age 16 years with nocturnal seizures. Her family frequently noticed restless movements during sleep.

In the first few years, the patient's seizures were well-controlled. At age 19 years, she had normal results on routine EEG recording in wakefulness and stage 1 sleep. Brain MRI at age 20 years was normal.

The patient's medical history was notable for glaucoma, which resolved at age 22 years.

The patient's brother and a paternal cousin had similar seizures since their early teens, confirmed by continuous video EEG monitoring (cVEEG). At age 17 years, her brother started smoking and self-discontinued his anticonvulsant. He believed that he was seizure-free, which was confirmed by normal results on cVEEG. Her father, a heavy smoker, was asymptomatic.

The patient had never smoked, used alcohol, or used illicit drugs. Her developmental history was normal and she completed college without difficulty.

Neurologic examination results were normal, except for difficulty in tandem gait that predated the use of phenytoin.

In the following years, the patient had multiple cVEEG admissions because of increased seizure frequency. cVEEGs revealed clinical and electrical seizures arising out of stage 2 sleep every 10–30 minutes and lasting 30–60 seconds each. They were characterized by version of the head to the left, posturing of one or both upper extremities (right upper extremity more than left), fumbling, and lip-smacking. EEG showed abrupt onset of sharply contoured 9 Hz waves increasing slightly in voltage and evolving into medium voltage 5–6 Hz theta activity, without focal onset or discrete spikes. Sometimes slower activity was seen over the frontal and central regions. There was a paucity of slow wave and REM sleep. The awake background was normal. A sleep study at age 20 years showed absence of slow-wave sleep and reduced amounts of REM sleep, without any evidence of central or obstructive apnea.

Between age 16 and 27 years, the patient tried and failed multiple anticonvulsants: oxcarbazepine, lamotrigine, levetiracetam, zonisamide, valproic acid, acetazolamide, pregabalin, phenytoin, clonazepam, and lacosamide. A vagal nerve stimulator was also implanted without success.

The clinical suspicion of ADNFLE was confirmed by genetic testing at age 24 years. DNA sequencing showed the presence of serine 284 to leucine mutation in the *CHRNA4* gene, which has been reported to be a disease-associated mutation in individuals with ADNFLE.¹ This gene encodes the $\alpha 4$ subunit of the nAChR.

The patient underwent cVEEG again at age 26 years (figure) because she believed her seizures were causing increasing memory impairment, anxiety, and fatigue affecting her work. At that time, she was treated with phenytoin, pregabalin, clonazepam, and lacosamide. EEG initially showed multiple events occurring during stage 2 sleep. These occurred on

From the Departments of Neurology (P.P.P., L.M.D.) and Pediatrics (L.M.D.), Boston Medical Center, Boston University, MA.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure EEG findings during continuous video EEG monitoring at age 26 years

(A) A compressed view of a 40-second seizure prior to nicotine treatment. (B) The first 20 seconds of the same seizure at 30 mm/s. (C) The second 20-second portion of the same seizure at 30 mm/s. (D) REM sleep during treatment with transdermal nicotine. Note the lateral eye movements at F7-8.

average every 60 seconds, lasting on average 6–8 seconds. There were a few seizures lasting up to 60 seconds. The seizures and their electrical correlate were similar to what was seen on prior studies. Due to frequent seizures, there was a paucity of slow-wave sleep and complete absence of REM sleep. On the second day of her hospital admission, a 7-mg nicotine patch was applied about 2–3 hours before bedtime. There was almost complete resolution of clinical and electrical events. The duration of slow-wave sleep increased and REM sleep was recorded. The next morning, the patient felt refreshed and less anxious. A 14-mg patch was tried, but the patient became nauseous. She tolerated transdermal nicotine well, with the exception of myalgia at the site of application, which resolved after the patch was applied to her buttock. She was discharged on a 7-mg nicotine patch, clonazepam, phenytoin, and lacosamide. Two weeks later, she reported that her sleep had improved and her anxiety had resolved. She experienced no side effects from the nicotine patch.

DISCUSSION ADNFLE was first described as a distinct entity in 1995, when 47 patients from 5 families were described.² Age at onset ranged between 2 months and 52 years, with a median of 8 years. Patients reported clusters of nocturnal seizures, with a median frequency of 6 per night, ranging up to 70 per night. Median duration was 60 seconds, ranging from 5 seconds to 5 minutes. In 84% of patients, interictal EEG had normal results. Ictal EEG usually demonstrated bilateral slow-sharp wave discharges in

the anterior quadrants during stage 2 sleep. Carbamazepine was effective in controlling seizures in most patients.

ADNFLE was the first idiopathic focal epilepsy attributed to a receptor mutation, namely the nAChR. Multiple mutations of the $\alpha 2$, $\alpha 4$, and $\beta 2$ nAChR subunit genes have been described. Their net in vivo effect is increased cholinergic neurotransmission.³ Different mutations of the nAChR may exert distinct effects leading to epileptogenesis. In vitro assays of homozygous mutant nAChR subunits lead to decreased ACh-induced currents and increased nAChR desensitization. However, when these receptors were coexpressed with wild-type AChRs, the net effect was increased ACh-induced currents. In vivo studies also show evidence of increased cholinergic neurotransmission.^{3–5} The mechanisms of nicotine's beneficial effects are unclear. It is thought to be due to AChR desensitization after prolonged use.³ Our patient, however, seemed to respond to the nicotine patch after only 1 day of treatment.

Carbamazepine and oxcarbazepine are first-line treatments; however, up to a third of patients have refractory epilepsy.⁶ Outcomes of surgery are poor in frontal lobe epilepsy, possibly due to lack of localizing findings on EEG and imaging in most cases.⁷ Nicotine is a potentially effective treatment of ADNFLE. The sentinel ADNFLE patient treated with transdermal nicotine remained virtually seizure-free during 9 months of treatment, compared to placebo or no treatment.⁸ In another study, tobacco habits of ADNFLE patients from 2 pedigrees were reviewed. Ten out of 14 tobacco users were seizure-free.⁴

Once lesional causes of epilepsy have been excluded, the differential is relatively narrow, including familial partial epilepsy with variable foci, night terrors, periodic limb movement disorder, restless legs syndrome, obstructive sleep apnea, and familial paroxysmal kinesigenic and nonkinesigenic dyskinesia. Such findings, and a positive family history, should prompt the consideration of genetic testing.

As seizures in ADNFLE originate from stage 2 sleep, interictal EEG is usually normal if this stage is not captured. Therefore, EEG should include stage 2 sleep to increase its diagnostic yield.

In this article, a case of refractory ADNFLE responding to transdermal nicotine is presented. The first day of treatment there was dramatic symptomatic improvement and almost complete resolution of clinical and electrical events. The patient's brother has also been seizure-free for many years off treatment after starting smoking. Their father, a heavy smoker, is the likely obligatory carrier, as there is a paternal cousin with the same disorder. He has never experienced seizures but has never had cVEEG.

Our patient had prolonged REM sleep deprivation, confirmed by cVEEG. It is well-established that REM sleep deprivation has multiple effects on the CNS, including emotion, memory, and learning.⁹ Apart from epilepsy, our patient also had anxiety, which almost immediately resolved with the re-emergence of REM sleep.

Despite the clinical success in this patient, there are some concerns regarding long-term nicotine treatment. Studies have failed to demonstrate an increased risk of cardiovascular adverse events¹⁰ with nicotine treatment, but these studies have looked at short-term treatment for smoking cessation, while the effects of long-term nicotine treatment remain unknown. The potential teratogenic effects, as well as the risk of fetal nicotine exposure, should also be considered, as ADNFLE often affects women of childbearing age.¹¹ Even though nicotine seems to be an effective treatment, its long-term efficacy has not been studied. Caution is also needed to avoid the perception that smoking is encouraged, particularly given the fact that ADNFLE often affects adolescents.

ADNFLE is a hereditary form of epilepsy characterized by nocturnal seizures arising from stage 2 sleep. ADNFLE can be caused by different mutations of the neuronal nAChR, ultimately leading to increased cholinergic neurotransmission. Although carbamazepine and oxcarbazepine are often effective first-line treatments, here we report a case of ADNFLE refractory to multiple different treatments, including vagal nerve stimulation. Transdermal nicotine, which ultimately alters cholinergic neurotransmission, may be an effective and well-tolerated treatment for ADNFLE. There are, however, limited data regarding the long-term safety and efficacy of this treatment.

AUTHOR CONTRIBUTIONS

Dr. Pavlakis was involved in the care of the patient and drafted this manuscript. Dr. Douglass was involved in the care of the patient and revised this manuscript. The final version was read and approved by all the authors.

ACKNOWLEDGMENT

The authors thank Dr. Michael D. Perloff for reviewing the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Hirose S, Iwata H, Akiyoshi H, et al. A novel mutation of CHRNA4 responsible for autosomal dominant nocturnal frontal lobe epilepsy. *Neurology* 1999;53:1749–1753.
2. Scheffer IE, Bhatia KP, Lopes-Cendes I, et al. Autosomal dominant nocturnal frontal lobe epilepsy: a distinctive clinical disorder. *Brain* 1995;118:61–73.
3. Bertrand D, Picard F, Le Hellard S, et al. How mutations in the nAChRs can cause ADNFLE epilepsy. *Epilepsia* 2002;43(suppl 5):112–122.
4. Brodtkorb E, Picard F. Tobacco habits modulate autosomal dominant nocturnal frontal lobe epilepsy. *Epilepsy Behav* 2006;9:515–520.
5. Marini C, Guerrini R. The role of the nicotinic acetylcholine receptors in sleep-related epilepsy. *Biochem Pharmacol* 2007;74:1308–1314.
6. Carreno M, Garcia-Alvarez D, Maestro I, et al. Malignant autosomal dominant frontal lobe epilepsy with repeated episodes of status epilepticus: successful treatment with vagal nerve stimulation. *Epileptic Disord* 2010;12:155–158.
7. Englot DJ, Wang DD, Rolston JD, Shih TT, Chang EF. Rates and predictors of long-term seizure freedom after frontal lobe epilepsy surgery: a systematic review and meta-analysis. *J Neurosurg* 2012;116:1042–1048.
8. Willoughby JO, Pope KJ, Eaton V. Nicotine as an anti-epileptic agent in ADNFLE: an N-of-one study. *Epilepsia* 2003;44:1238–1240.
9. Brown LK. Can sleep deprivation studies explain why human adults sleep? *Curr Opin Pulm Med* 2012;18:541–545.
10. Joseph AM, Fu SS. Safety issues in pharmacotherapy for smoking in patients with cardiovascular disease. *Prog Cardiovasc Dis* 2003;45:429–441.
11. Bruin JE, Gerstein HC, Holloway AC. Long-term Consequences of fetal and neonatal nicotine exposure: a critical review. *Toxicol Sci* 2010;116:364–374.

Neurology®

Pearls & Oy-sters: A case of refractory nocturnal seizures: Putting out fires without smoke

Pantelis P. Pavlakis and Laurie M. Douglass

Neurology 2015;84:e134-e136

DOI 10.1212/WNL.0000000000001539

This information is current as of May 4, 2015

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/84/18/e134.full
References	This article cites 11 articles, 1 of which you can access for free at: http://n.neurology.org/content/84/18/e134.full#ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://n.neurology.org/content/84/18/e134.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology All Pediatric http://n.neurology.org/cgi/collection/all_pediatric Antiepileptic drugs http://n.neurology.org/cgi/collection/antiepileptic_drugs EEG; see Epilepsy/Seizures http://n.neurology.org/cgi/collection/eeg_see_epilepsy-seizures
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2015 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.