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DIRECTED AGGRESSIVE BEHAVIOR IN FRONTAL LOBE EPILEPSY: A VIDEO-EEG AND ICTAL SPECT CASE STUDY



Frontal lobe seizures may manifest bizarre behaviors such as thrashing, kicking, genital manipulation, unusual facial expressions, and articulate vocalizations.¹ Aggressive and violent behaviors have also been associated with epilepsy, especially temporal or frontal lobe seizures.² However, this behavior is rare in the ictal state. Aggressive ictal behavior is generally believed to not be goal directed. Interactive behavior with the ability to respond to visual and verbal stimuli is also rare in complex partial seizures. We report the case of a patient with seizures manifesting with interactive directed aggressive behaviors.

Case report. An 18-year-old right handed man was brought in by his mother for a second opinion regarding possible seizures after being suspended from junior college for threatening to shoot his teacher and classmates. The patient had been born prematurely and had a grade 1 periventricular hemorrhage. Motor milestones were delayed by 4 months, but development was otherwise normal. He had a generalized tonic-clonic seizure at age 9, and subsequently had complex partial seizures characterized by confusion, hand automatisms, and drawing up of the legs. These seizures resolved on carbamazepine, which was discontinued after 2 years. At age 15, the patient started having stereotyped episodes characterized by a feeling of “stage fright” and followed by verbal profanities and using his hand as a stylized gun to “shoot” people and objects. The patient never physically struck another person or object during the episodes. He was not postictally confused, was aware that he had a behavioral change, but was amnesic for details of his behavior. He did not respond to trials of zonisamide, carbamazepine, or topiramate. An outside EEG performed during an episode of coprolalia was interpreted as normal and the patient was given a diagnosis of Tourette syndrome (TS). A psychiatrist diagnosed him with obsessive-compulsive disorder but found no evidence for psychosis, anxiety, or mood disorder. Events increased to up to 40 events

daily at time of presentation, despite multiple medication trials to treat TS.

Video-EEG monitoring captured 11 seizures in the awake state and 3 seizures during sleep. All seizures were stereotyped and lasted between 15 and 45 seconds. Three seizures occurred within a 15-minute period in the presence of the attending and resident physician. During these 3 seizures, the patient partially followed simple commands and demonstrated comprehension of spoken language (video 1 on the Neurology® Web site at www.neurology.org), and struck a nonthreatening hand held 2 feet from him (video 2).

During uninterrupted seizures, the patient would speak profane language with threatened aggression, using his hands as stylized guns to track moving people and “shoot” them (video 3). He appeared to alter his actions in reaction to external visual and verbal stimuli. Lip smacking automatisms were present in the latter half of the seizure. The patient was amnesic for the major portion of his seizures, but could accurately identify the person who questioned him during the seizure (video 4). EEG analysis found bifrontal 5- to 6-Hz rhythmic activity during seizures (figure). Ictal SPECT showed areas of hyperperfusion in the right lateral and orbitofrontal cortex. An area of hyperperfusion is also seen in the left medial frontal lobe.

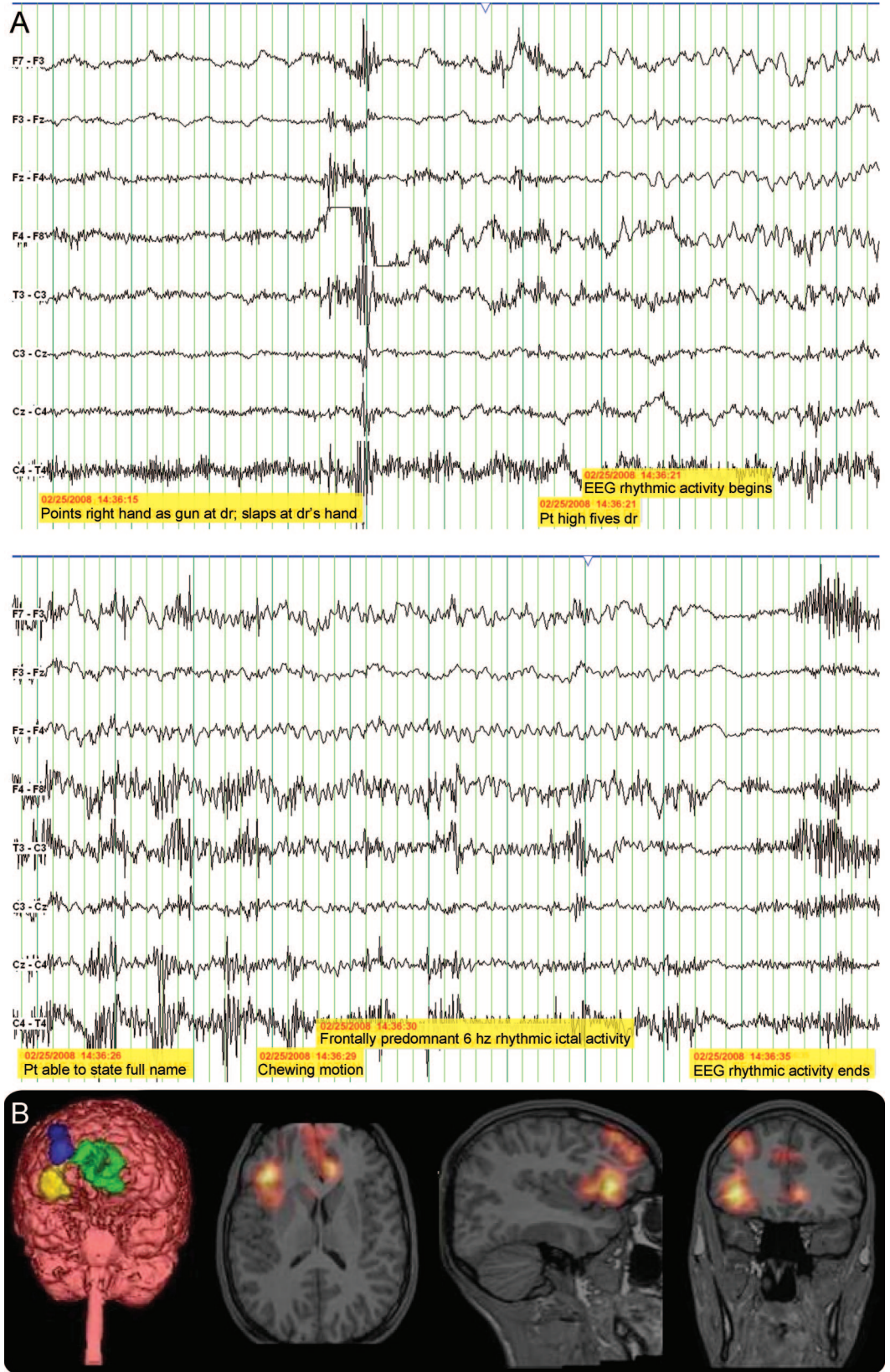
Carbatrol® was instituted at a daily divided dose of 900 mg. His previous highest daily dose of carbamazepine was 600 mg. The patient is seizure-free at 12 months follow-up.

Discussion. More so than seizures arising from other brain locations, frontal lobe seizures may exhibit bizarre and unusual behaviors.³ It is generally agreed among neurologists and epileptologists that well-organized, purposeful, complex, goal-directed behavior is highly unlikely during a seizure.^{4,5} Our patient is an unusual case demonstrating ictal aggressive behavior with complex motor and vocal features that could be misinterpreted as goal-directed actions. While up to 30% of frontal lobe epilepsy patients have articulate vocalizations including swearing,² our patient’s seemingly voluntary actions are likely involuntary, representing complex gestural-hyperkinetic automatisms and vocalizations. The pathophysiology

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Figure Ictal EEG and ictal SPECT results



(A) The electrographic ictal changes on a condensed transverse montage during a seizure. (B) Ictal SPECT showed focal regions of hyperperfusion in the right lateral and orbitofrontal cortex and left medial frontal cortex. Ictal SPECT scan performed using Technetium-99 and superimposed upon interictal SPECT scan and coregistered to MRI (SISCOM).

of this behavior is likely related to activation of circuitry in the primary somatomotor and premotor cortex by epileptic activity.^{6,7} The florid emotional outburst and aggressive behavior could localize to the prefrontal cortex, considered to be connected with higher psychic functions, as well as limbic regions involvement. The fact that he is partially amnesic to the ictal events points toward a complex partial event with possible spread to mesial temporal structures.

This study demonstrates a rare case of directed and interactive aggressive verbal and physical behavior during frontal lobe seizures. This case highlights the potential for certain frontal lobe seizures to cause behavior with significant adverse legal ramifications. The diagnosis of seizures should always be considered in cases of episodic stereotyped behavior.

e-Pub ahead of print on October 21, 2009, at www.neurology.org.

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Disclosure: Dr. Shih serves as a consultant to URL Pharma, Inc., and receives research support from GlaxoSmithKline, NeuroPace, Inc., Eisai Inc., the NIH (ad hoc study section reviewer), and the National Science Foundation. Dr. Leslie Mazwi, Dr. Falcao, and Dr. Van Gerpen report no disclosures.

Received March 21, 2009. Accepted in final form July 22, 2009.

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ENDPLATE DESTRUCTION DUE TO MATERNAL ANTIBODIES IN ARTHROGRYPOSIS MULTIPLEX CONGENITA

Arthrogryposis multiplex congenita (AMC) is defined by congenital contractures of 2 or more major joints¹ and thought to be caused by prolonged fetal immobility, probably regardless of the underlying cause. It is one typical sign of the fetal akinesia deformation sequence (FADS) or Pena-Shokeir syndrome.²

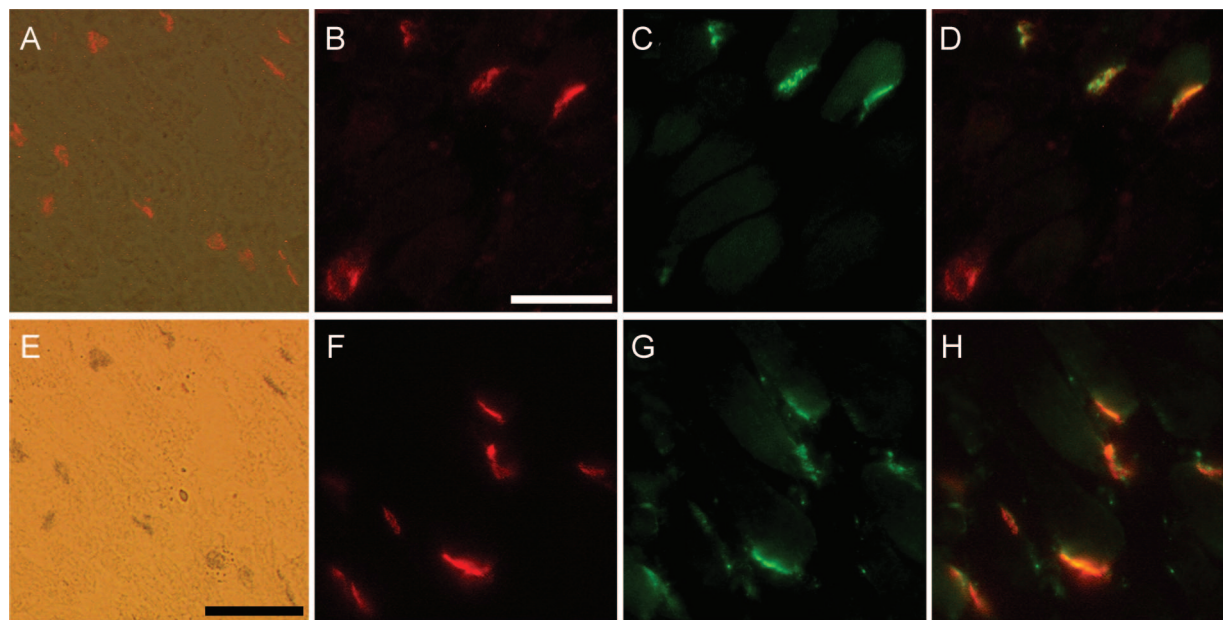
Among the underlying conditions, 2 are known fetal myasthenic syndromes involving the γ -subunit of the fetal nicotinic acetylcholine receptor (AChR): mutations in the *CHRNA3* gene encoding the γ -subunit³ and placental transfer of maternal antibodies specific for γ -subunit-containing fetal AChR.⁴ Because the γ -subunit is replaced by adult-specific ϵ before birth,⁵ these antibodies do not cause myasthenic symptoms in the newborn. The mother may be unaffected if she does not have significant antibodies to the adult AChR.⁶

Case report. Muscle biopsy (vastus lateralis) of a 2-week-old preterm (32nd week) boy was sent for diagnostic evaluation for possible AMC. A previous pregnancy had been aborted at the 26th week due to signs of FADS. Standard histology showed immaturity roughly in accord with gestational age (see e-Methods in appendix e-1 and figure e-1, A and B,

on the *Neurology*[®] Web site at www.neurology.org), without signs of other disease processes. Staining for cholinesterase and with rhodamine-conjugated α -bungarotoxin, reacting with the α -subunit of both adult and fetal AChR, demonstrated normal reactivities at the neuromuscular endplates (figure, A and E). Double immunolabeling with monoclonal antibodies against the AChR γ -subunit and the membrane attack complex (C5b9; e-Methods) detected activated complement deposition at most endplates colocalizing with the fetal isoform of the AChR (figure, B–D). Very high levels of AChR antibodies were detected in mother's serum (commercial test >800 nM, normal value <0.4 nM, detecting both subtypes) with a twofold higher concentration of antibodies against fetal than adult AChR (approximately 800 vs 400 nM; normal values <0.5 nM) (figure e-1C). The mother at the time did not show myasthenic weakness and practiced endurance sports. However, 3 Hz accessory nerve repetitive stimulation revealed a decremental response of >20% compound muscle action potential amplitude, and she developed mild generalized myasthenia gravis (MG) 2 years later. At 4 months, when first tested, the boy's serum was negative for AChR antibodies, as expected due to the natural fall in maternal antibodies.

Typical for FADS, pulmonary immaturity was the crucial problem, but invasive ventilation could be

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(A, E) Serial staining with rhodamine-conjugated alpha-bungarotoxin (A, overlay with diffraction image) and modified bromoindoxyl acetate technique for cholinesterase (E), showing esterase reaction at the AChR positive sites. (B–D) Double immunolabeling with monoclonal antibodies against the γ -subunit of the AChR (B) and the membrane attack complex (C5b9; C) with overlay image (D). The fetal subunits are still present and there is deposition of activated complement at almost all endplates. (F–H) Double immunolabeling with a monoclonal antibody against the α -subunit (F) and a polyclonal against the ϵ -subunit of the AChR (G) with overlay image (H). All endplates show at least some reactivity with anti- ϵ -subunit. Primary magnification for (A and E) was 20 \times , scale bar in (E) indicates 50 μ m. Primary magnifications for (B–D and F–H) was 40 \times , scale bar in (B) indicates 25 μ m. For details on the methods, histomorphology, antibodies, and control stains, see appendix e-1: e-Methods.

withdrawn at the age of 14.5 months. The child now breathes spontaneously via a tracheostomy and has started to crawl.

Discussion. Maternal antibodies against the fetal-specific AChR γ -subunit are likely to be the basis of the boy's impairment. Complement mediated endplate destruction in adult MG with AChR antibodies is well-documented.⁷ Our findings suggest the same process following placental transfer of maternal AChR antibodies as an additional potential mechanism, as well as functional inhibition of the fetal AChR.⁴ The causal relationship between interference with the γ -subunit and AMC is well established.^{3,4,6} However, most MG sera react variably with each subunit and the α -subunit, present in both fetal and adult AChR, is targeted most frequently. As we also detected the ϵ -subunit in our patient's endplates (figure, F–H), it is not possible to assess the extent of complement deposition caused by binding to the fetal AChR alone.

One previous study did not detect the γ -subunit in apparently normal intercostal muscle at the 33rd week,⁵ but we still detected it at the 34th week in this child (figure, B), and in 3 biopsies of diseased limb muscle up to the 38th week (figure e-2, A, C, and G). This may indicate a difference between limb and intercostal muscle development, individual cases, or

greater sensitivity of our techniques. Importantly, none of the other muscles showed anti-C5b9 reactivity at their endplates (figure e-2, B, D, and H).

Complement deposition in the muscle biopsy led to the diagnosis that could have been made by testing the mother's serum as most commercial tests detect antibodies against both adult and fetal AChR. This is safe, specific, and inexpensive. It should be recommended in cases of reduced fetal movements of unknown cause, in particular when a history of previously affected pregnancies is given, as consecutive pregnancies are frequently affected.^{4,6} Differential testing may be helpful for risk assessment in women with known AChR antibody-positive MG, but is not routine. Indeed, frequent monitoring of fetal movements is probably more relevant. If these are reduced, treatments, such as plasmapheresis or immunoadsorption, to reduce the mother's antibodies during the crucial second and third trimesters, can be associated with successful outcomes in future pregnancies (Vincent and Newsom-Davis, unpublished), although reported cases are few.⁶

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Disclosure: Dr. Reimann and Dr. Jacobson report no disclosures. Dr. Vincent serves on scientific advisory boards for the Patrick

Berthoud Trust and the Myasthenia Gravis Foundation of America; serves as an Associate Editor of *Brain*; holds US Patent 7267820 (issued 9/11/07) and filed Patent JA46294P.GBA (10/25/08); receives royalties from publishing *Clinical Neuroimmunology* (Blackwell Publishing, 2005); has received honoraria for lectures or educational activities not funded by industry; performs measurement of AChR antibodies which brings income to her department; receives research support from the European Union (network grant), the NIHR Biomedical Research Centre Oxford, and the Sir Halley Stewart Trust; and receives MuSK antibody royalties from Athena Diagnostics. Dr. Kornblum reports no disclosures.

Received December 1, 2008. Accepted in final form July 27, 2009.

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TREATMENT OF VNS-INDUCED LARYNGOSPASM WITH BOTULINUM TOXIN

Vagus nerve stimulators (VNS) are approved for use in patients with refractory epilepsy. Potential adverse effects include hoarseness, coughing, and dyspnea. Obstructive sleep apnea may occur due to laryngospasm, but treatment of this problem is difficult.^{1,2} We present the first known case in which botulinum toxin effectively treated sleep apnea caused by a VNS device. This is a single observational study without controls (class IV evidence).

Case report. A 16-year-old boy with intractable epilepsy, VNS placement, and cerebral palsy was referred for suspected sleep-disordered breathing. Symptoms included snoring, witnessed apneas, and daytime sleepiness. On the Epworth Sleepiness Scale (ESS), he scored a 16 (significant values >10; maximum 24). Seizures occurred in clusters 2 to 3 times per month.

A polysomnogram (PSG) revealed an apnea-hypopnea index (AHI) of 25, indicating moderate to severe obstructive sleep apnea. The respiratory events resulted in frequent arousals, oxygen desaturations, and significant sleep disruption (sleep efficiency 78%; expected values >90%). The PSG showed periodic chin EMG activity that coincided with airflow limitations. This pattern lasted 30 seconds and repeated approximately every 80 seconds, with normal intervening respiration (figure). Thus, VNS-induced laryngospasm appeared to cause sleep apnea in this patient.

Titration with continuous and bilevel positive airway pressure (CPAP/BPAP) was well-tolerated and prevented significant oxygen desaturations.

However, the AHI remained at 25, indicating the persistence of clinically significant sleep apnea. Therefore, positive airway pressure was unsuccessful in alleviating sleep-disordered breathing.

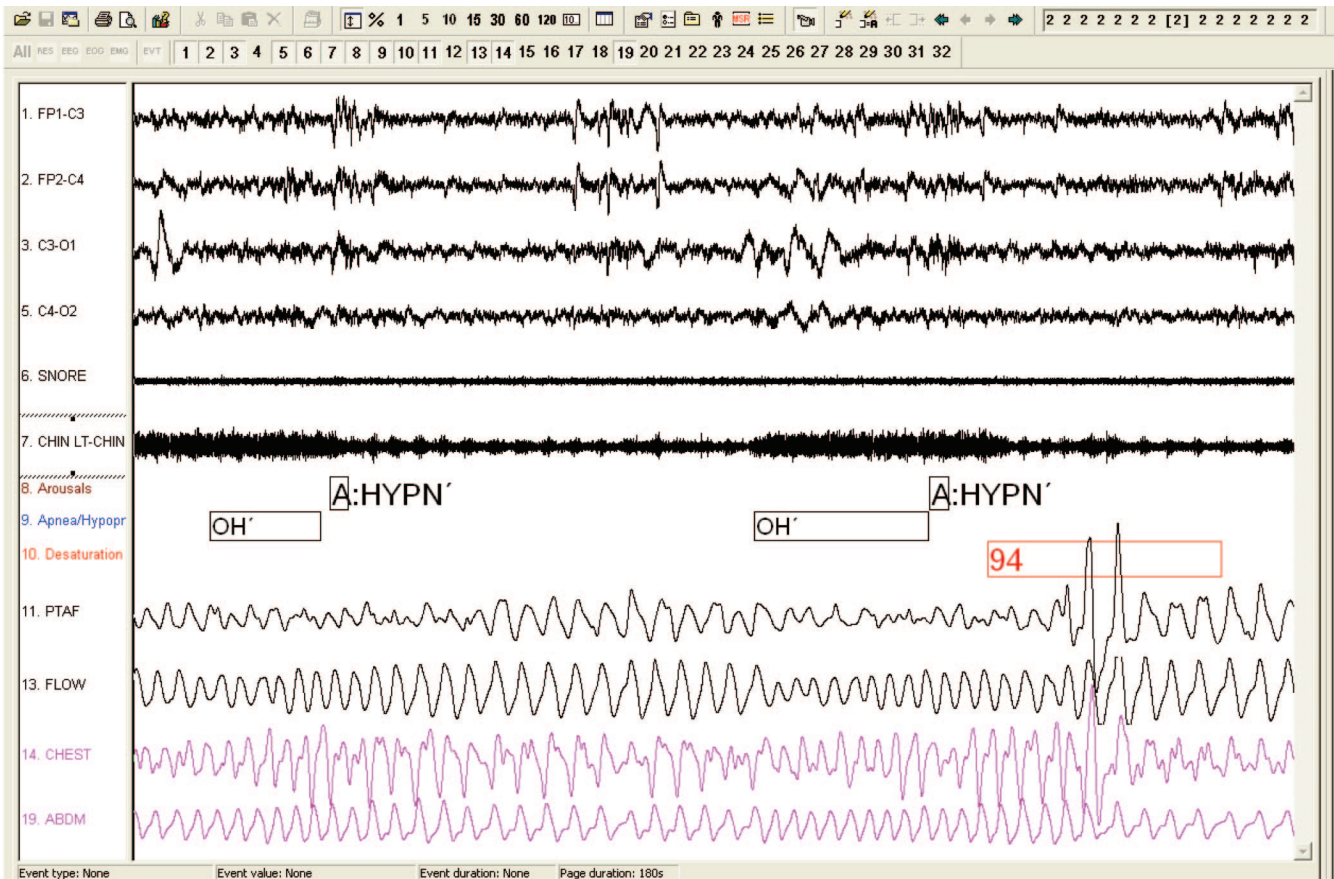
The VNS improved seizure control, making discontinuation of the device impractical. Instead, the pulse width, frequency, and output current of the VNS were decreased. Snoring and witnessed apneas persisted, however, with only mild improvement in daytime somnolence. Additionally, concerns remained about suboptimal seizure control with reduced stimulation settings.

Persistent laryngospasms made VNS adjustment and CPAP/BPAP titration ineffective, requiring use of a different approach. First, direct laryngoscopy verified that the VNS caused the laryngospasms. Following deactivation of the device, the left thyroarytenoid muscle was injected with 0.4 mL botulinum toxin (0.125 U/0.1 mL saline). The VNS was then reactivated.

Within a few weeks, symptoms improved markedly (ESS 11). A PSG performed 1 month after injections revealed an AHI of 3, few oxygen desaturations, and a 90% sleep efficiency. The characteristic EMG artifact seen previously did not occur. Thus, botulinum toxin injections ameliorated sleep-disordered breathing to clinically adequate levels. This effect lasted approximately 4 months, when symptoms recurred (ESS 21).

Discussion. The electrophysiologic findings presented here are characteristic of VNS-induced laryngospasms, but other etiologies may be considered. In general, recurrent upper airway collapse may cause obstructive events to repeat in

Figure Polysomnogram showing obstructive respiratory events due to vagus nerve stimulation-induced laryngospasms



This 3-minute epoch shows the temporal relation between periodic increases in chin EMG activity and obstructive hypopneas (OH). Many of these events caused arousals (A:HYPN) and oxygen desaturations (red numbers; indicate desaturations greater than 3% from baseline). Paradoxical breathing is seen in the chest and abdominal leads. Channels 1, 2, 3, 5: EEG leads; 6: snore channel; 7: chin EMG lead; 8: arousals; 9: apneas/hypopneas; 10: oxygen desaturations; 11 and 13: airflow channels; 14 and 19: respiratory effort channels.

cycles, but chin EMG artifact that occurs synchronously with airflow limitations at fixed intervals distinguishes these events as VNS-induced. Similarly, Cheyne-Stokes respirations occur in a periodic crescendo-decrescendo pattern, but respiratory events are central in nature and are seen primarily during stages 1 and 2. In contrast, VNS devices cause obstructive events that occur during any stage of sleep. Bruxism and catathrenia are less likely, given the lack of accompanying teeth-grinding, groaning, and muscle artifact.

The preferred treatment for sleep-disordered breathing is positive airway pressure.³ Complete resolution of respiratory events may be an unrealistic expectation, however, since laryngospasms may persist as the VNS cycles on and off. Thus, attempts to find a therapeutic pressure may be difficult. Nonadherence and mask intolerance may also limit use of CPAP/BPAP therapy.

VNS devices can be adjusted to alleviate their adverse effects.⁴ Decreasing the output current, pulse width, and signal frequency may reduce laryngo-

spasms, but at the risk of suboptimal seizure control. Therefore, patients should be cautioned about possible increased seizure frequency. Modification of anti-epileptic medications may help maintain a higher seizure threshold, making this a more viable option.

Botulinum toxin may be effective when other modalities fail.⁵ Improvement of symptoms may occur within days following injection and may last several months. Clinicians and patients must consider the risks, including localized infection and bleeding. Additionally, close follow-up for symptom recurrence is imperative. Repeat injections may be needed as the treatment loses effectiveness. Potential benefits include resolution of sleep-disordered breathing and reduced daytime somnolence. Improved sleep quality may contribute to better seizure control, an important consideration in this particular population.⁶

A PSG performed prior to adjustment of VNS or botulinum toxin injection will help evaluate the severity of sleep apnea.⁷ Another PSG performed within a month after treatment is essential to assess effectiveness. Normalization of sleep-

disordered breathing may be difficult to achieve. Therefore, the success of treatment should be measured by a history of symptom improvement in conjunction with polysomnographic data.

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Disclosure: Dr. Kumar reports no disclosures. Dr. Sharafkhaneh serves on scientific advisory boards for GlaxoSmithKline and Pfizer Inc.; has received speaker honoraria from GlaxoSmithKline, Boehringer Ingelheim, Pfizer Inc., and DEY[®]; and has received research support from GlaxoSmithKline, Boehringer Ingelheim, and Novartis. Dr. Edmonds has received honoraria from Cyberonics, Inc. to train surgeons from outside the US. R. Schultz has received royalties from UpToDate (2007–2009) for the topic of Rett syndrome; receives research support from NAPNAP; and has received speaker honoraria from Cyberonics, Inc. and the Texas Neurological Society. Dr. Hopkins has received speaker honoraria from Sleep Consortium and Slack Inc.; receives research support from Autism Speaks; and has received author compensation from BMJ Group and Pediatric Annals.

Received April 6, 2009. Accepted in final form August 3, 2009.

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