CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 18-2013: A 32-Year-Old Woman with Recurrent Episodes of Altered Consciousness

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PRESENTATION OF CASE

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Dr. Jennifer Lyons (Neurology): A 32-year-old right-handed woman was seen in the neurology clinic of this hospital because of episodes of altered consciousness.

She had been well until the age of 24 years, when she began having episodes of "a feeling of walking through a cloud," hearing spoken words without understanding, an inability to speak, and vertigo. A witness described events lasting less than 1 minute, during which the patient would stare at her hands, make gripping movements, and sometimes swear, and then be confused for 2 to 3 minutes. She had little memory of events after the episodes. During several episodes, she lost muscle tone and collapsed. During the next 8 years, episodes recurred at an accelerating rate, sometimes with loss of consciousness, abrupt collapse, and occasional incontinence. The frequency increased 4 to 5 days before menses.

Three months before this evaluation, the patient struck her head during a typical episode. She was admitted to another hospital, where results of magnetic resonance imaging (MRI), electrocardiography (ECG), echocardiography, Holter monitoring, routine and 3-day ambulatory electroencephalography (EEG), and multiple blood tests were reportedly normal; no episodes occurred during monitoring. There was no symptomatic improvement after the administration of triptans or beta-blockers. Subsequently, the frequency of episodes increased to at least daily.

On evaluation at this hospital, she reported no fever, chills, rashes, neck pain, tinnitus, baseline vertigo, palpitations, chest pain, dyspnea, cough, weakness, numbness, gastrointestinal symptoms, or changes in vision, hearing, balance, gait, or bladder habits. Between the ages of 9 and 22 years, she had had occasional episodes of syncope after painful stimuli (such as immunizations or blood draws). She took no medications and had no known drug allergies. She lived with her husband and children and worked in a pharmacy. She drank alcohol infrequently, had stopped drinking caffeinated beverages after the onset of these symptoms, and did not smoke or use illicit drugs. Her mother had a history of headaches and drug abuse, and her father was healthy; there was no family history of neurologic diseases.

On examination, the blood pressure and pulse were normal, with appropriate orthostatic changes. A detailed neurologic examination and the general physical examination were normal. A diagnosis of probable complex partial seizures with secondary generalization was made, and the patient was advised to stop driving. Two months later, a 72-hour ambulatory EEG captured 10 seizures arising from the left temporal lobe, all of which were noted by the patient. Lamotrigine was administered and the dosage was increased to 150 mg twice daily, with reduction in the frequency of events from three times daily to approximately once every 3 days. One month later, MRI of the brain was performed.

Dr. R. Gilberto Gonzalez: MRI was performed with and without the administration of contrast material (Fig. 1), in accordance with an epilepsy protocol. On T_2-weighted images, there is a well-demarcated focus of increased signal intensity in the left inferomedial temporal lobe. The mass does not enhance with gadolinium. It has heterogeneous signal intensity that is predominantly hypointense on T_1-weighted images and hyperintense on T_2-weighted and fluid-attenuated inversion recovery images. The mass involves the occipitotemporal (fusiform) gyrus and causes mild local mass effect. The appearance is most suggestive of a primary brain neoplasm, such as a low-grade glioma. In retrospect, the same finding is present on the study from 6 months earlier, although it is harder to identify because of the positioning of the slices.

Dr. Lyons: During the next 7 months, the patient continued to have staring spells, some of which were associated with sudden loss of postural tone and collapse. Antiseizure medications, including lamotrigine, levetiracetam, oxcarbazepine, and clonazepam, were aggressively adjusted without a clinically significant effect.

Ten months after her initial outpatient evaluation, the patient was admitted to this hospital, and additional diagnostic testing was performed.

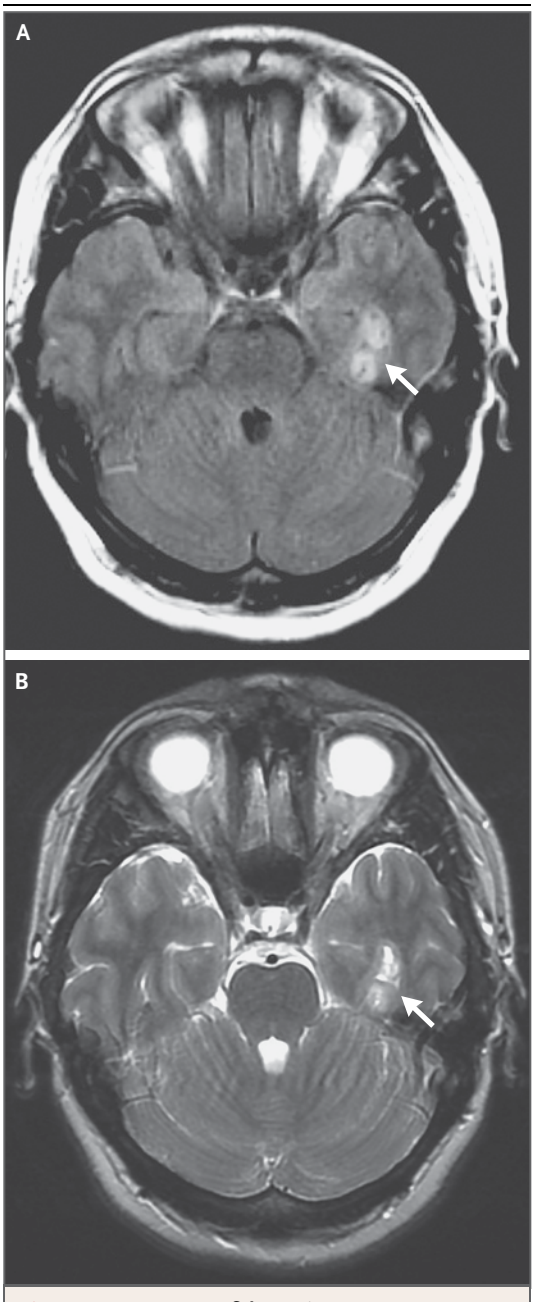

Figure 1. MRI Images of the Brain.
A fluid-attenuated inversion recovery image (Panel A) and a T_2-weighted axial image (Panel B) from an MRI scan obtained at the level of the temporal lobes show a heterogeneous but predominantly hyperintense mass lesion in the inferior left temporal lobe (arrows).

DIFFERENTIAL DIAGNOSIS

Dr. Andrew J. Cole: I am aware of the diagnosis in this case. Paroxysmal, stereotyped neurologic events may be the result of seizures, cardiac dysrhythmia, migraine, vascular disease, toxin ingestion, or psychiatric disease. Typically the diagnosis is strongly suggested by the details of the history, and the principle of parsimony encourages the selection of a single unifying diagnosis.

PAROXYSMAL, STEREOTYPED NEUROLOGIC EVENTS

This 32-year-old woman described an 8-year history of stereotyped self-limited events characterized by the sudden onset of an experiential phenomenon, receptive and expressive dysphasia, diminished responsiveness, and automatic activity lasting minutes and followed by confusion and amnesia for the preceding episode. Some attacks were complicated by sudden loss of muscle tone with collapse, sometimes with resultant traumatic injury. Frank convulsive activity was not described, and incontinence occurred on occasion. Although the patient's history included episodes of neurocardiogenic syncope triggered by painful stimuli, recurrent dysrhythmia was inadequate to explain the semiology (observable manifestations) of the events. Rather, it seems clear that she had recurrent focal seizures. The experiential aura, ictal dysphasia, and automatic activity strongly support localization to the dominant hemisphere, with involvement of the limbic system and adjacent neocortex, as evidenced by the patient's language dysfunction.

Eventually, a 72-hour ambulatory EEG captured 10 of the patient's typical confusional events, proving the proposed diagnosis beyond doubt. Moreover, high-resolution MRI revealed a lesion in the left temporal lobe that was consistent with the clinical localization of the attacks.

LOSS OF MUSCLE TONE WITH FALLS

The patient's history contains one unexplained element that warranted further investigation. In some but not all of the attacks, sudden loss of muscle tone without convulsive activity was described. Patients with complex partial seizures may fall during attacks, but such falls typically consist of stumbling or slumping to the ground. Epileptic drop attacks (also known as temporal-lobe syncope) that are characterized by sudden loss of postural tone are rare in temporal-lobe epilepsy. At one referral center, these attacks occurred in 13% of recorded patients and were associated with bifrontal propagation of epileptic discharge in 74% of affected subjects[1]; 45% of these patients were cognitively impaired and 52% had progressive mental deterioration, neither of which occurred in this patient. Sudden collapse has also been associated with ictal asystole.[2]

To better understand the events leading to falls, the patient was admitted to this hospital for continuous monitoring with video EEG. Medications were reduced to facilitate capture of her typical events. The EEG showed intermittent left-temporal slowing, left-temporal interictal epileptiform discharges, and seven seizures, five of which were localized to the left temporal region. Five events were associated with up to 40 seconds of asystole and resultant electrocerebral silence (Fig. 2), whereas 2 events, similar to the 10 events captured on the ambulatory EEG recording, were not associated with a disturbance in cardiac rhythm. Seizures were characterized by the patient's staring, fidgeting, and reports of nausea, followed by loss of consciousness and collapse if the seizures were associated with asystole.

NEURONAL CONTROL OF CARDIAC RHYTHM

How can we explain the cardiac rhythm disturbance? Cardiac dysrhythmias in epilepsy are not uncommon and have been hypothesized to underlie sudden unexplained death in epilepsy (sometimes referred to as SUDEP), which affects 0.5 to 1.0% of patients with epilepsy each year and accounts for the largest number of deaths associated with this disorder. Both bradyarrhythmias and tachyarrhythmias have been described. Ictal tachycardia is most common, although in one study, 7 of 20 patients had ictal bradycardia in at least one seizure, and 3 of those patients had asystolic events.[3] Only a minority of events recorded from any given patient show bradyarrhythmia, indicating that this phenomenon can be intermittent.

The relationship between seizures and cardiac dysrhythmia may take several demonstrated or hypothetical forms. For example, dysrhythmia can cause seizure (convulsive syncope), seizure can cause dysrhythmia (arrhythmogenic epilepsy), treatment can cause dysrhythmia, or seizure and dysrhythmia can occur as epiphenomena caused by a shared underlying mechanism. To determine the nature of the relationship in a specific case, details of the history and ictal recording are critical. In this patient, cerebral electrographic change preceded bradycardia and asystole, eliminating the possibility of convulsive syncope. Because asystolic episodes recurred while she was on multiple anticonvulsant regimens, it is unlikely that asystole resulted from specific anticonvulsant treatment. In this case, bradycardia followed by asystole favors a disruption of atrioventricular conduction or nod-

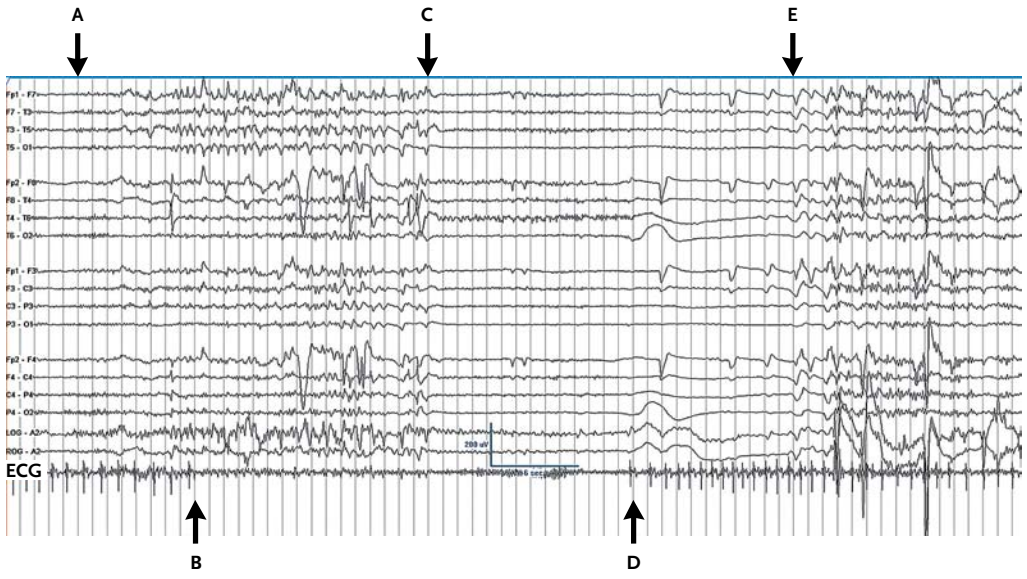

Figure 2. Ictal Electroencephalographic (EEG) Recording.

The first unequivocal ictal EEG change occurs in the left temporal chain (arrow A, top four traces). Within 8 seconds, asystole lasting 30 seconds begins (arrow B). Attenuation is evident after 16 seconds of asystole (arrow C). Resumption of normal sinus rhythm (arrow D) is followed 11 seconds later by the return of delta slowing (arrow E). Gridlines are 1 second apart, the high-frequency filter is 70 Hz, the low-frequency filter is 1 Hz, and original sensitivity before reproduction is 10 μV per millimeter.

al function, rather than a ventricular repolarization mechanism for the arrhythmia. Lacosamide has been associated with prolongation of the PR interval, whereas overdoses of lamotrigine have been associated with complete atrioventricular block; however, this patient was never exposed to lacosamide and had not received high doses of lamotrigine. No reproducible evidence for an effect of anticonvulsant drugs on the corrected QT (QTc) interval has been presented, although drugs known to inhibit the cytochrome P-450 3A4 isozyme may potentiate the effect of coadministered drugs on the QT interval.

ICTAL ASYSTOLE (ARRHYTHMOGENIC EPILEPSY)

Ictal asystole, or arrhythmogenic epilepsy, has been studied at the Cleveland Clinic.[2] In 3700 video EEG studies in which seizures were recorded, ictal asystole was recorded in 16 seizures occurring in 10 patients, 8 of whom had temporal foci and none of whom had generalized seizures. Atonia occurred an average of 42 seconds after the onset of a seizure and 8 seconds after the onset of asystole. Delayed loss of muscle tone after the onset of clinical seizures should raise the clinical suspicion of a secondary cardiac cause.

How might seizures cause dysrhythmia? It is possible that catecholamine release, acidosis, or hyperkalemia resulting from prolonged convulsive activity could induce arrhythmia; however, this patient had early-onset asystole in the context of partial seizures that caused little physiological stress. Alternatively, seizure activity may involve cerebral structures that are important in the regulation of cardiac rhythm, including the amygdala, insula, or hypothalamus. Studies of cortical stimulation in humans indicate that direct electrical stimulation[4] or transcranial direct-current stimulation[5] of the left hemisphere, particularly the insula, may activate parasympathetic descending pathways, leading to bradycardia. Similarly, the infusion of amobarbital into the left carotid artery, resulting in left-hemisphere anesthesia, produces tachycardia, whereas infusion into the right carotid artery produces bradycardia.[6] Case reports of ictal asystole suggest that the onset of seizures occurs predominantly on the left side,[1] but clear cases of onset on the right side have been documented.[2,7] This

patient's lesion was located in the left fusiform gyrus and extended upward toward the insula; it was well positioned to activate structures implicated in bradycardic responses.

This patient's history of neurocardiogenic syncope over a period of many years before the onset of epileptic events and her underlying predisposition for syncope are most consistent with seizures as the cause of asystole. In one series, half the patients with seizure-induced syncope (arrhythmogenic epilepsy) had a positive test when lying in the head-up position on a tilt table.[7]

It is also possible that seizures and dysrhythmia may result from a genetic abnormality shared by excitable cells in the brain and the heart. Dr. Noebels will discuss the molecular mechanisms of epilepsy and arrhythmia and their clinical implications for this patient.

Dr. Jeffrey L. Noebels: This patient had bradycardia and asystole in temporal-lobe epilepsy, a combination that occurs in less than 5% of persons with seizures in this location.[8,9] The presence of a hypothalamic or temporal-lobe mass along with seizures and asystole is especially rare,[10] suggesting the likelihood of a "double hit" in this patient — namely, an epileptogenic lesion coincidentally superimposed on a nervous system primed for vagal hyperreactivity by genetic mutation.

Molecular links between arrhythmias of the heart and brain are emerging that can explain cardiac-associated coexisting conditions in epilepsy and can expand our ability to identify and manage the risk of sudden death beyond simply controlling seizures. It is interesting to consider which genes we might interrogate to explain the seizure-driven bradyarrhythmia and asystole in this patient, and whether treating mutations of such genes might prevent sudden unexplained death in epilepsy.

EXPRESSION IN THE HEART AND BRAIN OF GENES ASSOCIATED WITH THE LONG-QT SYNDROME

There is a growing list of genes influencing cardiac conduction that are directly related to this patient's presentation, beginning with genes associated with the long-QT syndrome. The loci for long-QT syndrome encompass more than 17 genes encoding ion channels, connexins, and transcription factors.[11] Mutations in these genes produce paroxysmal bradycardia and syncope; electrocardiographic features include long and short QT intervals, torsades de pointes, and asystole.[12] Most of these genes show dual expression in the heart and brain, and perhaps additional expression in the autonomic nerves, defining a singular mechanism linking epilepsy, cardiac arrhythmia, and sudden death. Patients with the long-QT syndrome have a high incidence of seizures[13,14]; furthermore, seizures, the long-QT syndrome, and sudden cardiac death occur in transgenic mice carrying human genes with mutations in the most common gene for the long-QT syndrome, establishing the causative link.[15]

There is a second category of genes associated with sudden unexplained death in epilepsy. These genes cause arrhythmias without intrinsic cardiac-conduction disease and could be involved in this patient's condition. Mutation of the gene encoding Kv1.1 is a rare cause of temporal-lobe epilepsy and myokymia in humans; Kv1.1 potassium currents stabilize excitability in hippocampal networks and peripheral nerves but are not found in the myocardium.[16] Other candidates include pacemaker genes that regulate basal heart rate (*HCN1* through *HCN4*, regulating the I_f current, and muscarinic M2- and M3-type G-protein–coupled receptors).[17-20]

ASCERTAINING THE GENETIC RISK OF SUDDEN, UNEXPLAINED CARDIAC DEATH

Gene-directed therapy presents an opportunity to lower the risk of sudden unexplained death in symptomatic persons with epilepsy and the long-QT syndrome.[21] This patient had no clear evidence of a QT-interval abnormality; however, QT-interval prolongation is intermittent and may be difficult to detect, even in persons with known risk-associated DNA variants in the long-QT interval.[22,23] Despite epidemiologic evidence of a high frequency of seizures among patients with the long-QT syndrome, seizures may be underrecognized in the cardiology clinic.[14] Likewise, the incidence of the long-QT syndrome among patients with epilepsy is unknown, since many patients, such as this one, never undergo routine ECGs, even on the initiation of antiepileptic medication targeting ion channels.

Other obstacles forestall accurate risk prediction in such patients. First, detection of a truncation mutation disrupting a key channel protein powerfully predicts loss of current; however, the implications of more frequently encountered missense mutations are less evident.[24] Second,[25-27]

pathogenic variants causing the long-QT syndrome are readily identified by their segregation with affected persons within a mendelian pedigree; however, correctly interpreting the meaning of these variants in patients with sporadic disease, such as this patient, remains challenging. A study profiling 237 ion channels in persons with epilepsy and in those without epilepsy revealed that individual profiles of missense variations associated with neurocardiac diseases were prevalent in both groups at similar levels of complexity, confounding a personal prediction of risk.[28] For these reasons, routine testing of ion-channel genes may not yet be useful in the treatment of patients such as this one.

DR. ANDREW J. COLE'S DIAGNOSIS

Left-temporal-lobe epilepsy due to a tumor in the left fusiform gyrus, most likely a glioma, complicated by ictal asystole in a patient with a predisposition to neurocardiogenic syncope.

DISCUSSION OF MANAGEMENT

Dr. Cole: After the demonstration of asystole, the cardiology staff were consulted for advice on management of this patient's arrhythmia.

MANAGEMENT OF CARDIAC ARRHYTHMIA

Dr. Theofanie Mela: The patient received a temporary transvenous pacemaker and was transferred to the cardiac telemetry unit. She clearly described two different types of symptoms, the first being a long history of combined light-headedness and dizziness that caused her to sit down to avoid syncope. She also had had episodes of syncope after painful stimuli since childhood. These symptoms were strongly suggestive of the vasovagal syndrome and were different from the seizure-related syncope, which she could not prevent by sitting down.

The patient's ECG showed normal sinus rhythm, with no evidence of a long-QT interval (QTc, 406 msec), the Wolff–Parkinson–White syndrome, or any other condition that was suggestive of syncope with a cardiac origin. An echocardiogram was also normal.

The differential diagnosis included seizure-induced asystole in a patient with an underlying component of the vasovagal syndrome, as well as the sick sinus syndrome. The sick sinus syndrome was unlikely, given the patient's young age, structurally normal heart, and absence of bradycardia outside the episodes of seizures.

For management of the condition, a permanent pacemaker could be considered. Permanent pacing in a young patient is not without implications. She would be at a risk for mechanical complications, infection, vascular complications, and the need for numerous replacements of the generator and leads during her lifetime. The patient's inability to undergo MRI of the brain would be a critical problem for her follow-up, since MRI-conditional pacemakers were not available at the time.

In the telemetry unit, no further arrhythmias occurred, and the patient had no requirement for pacing. Although randomized trials involving the study of beta-blockers in vasovagal syncope have yielded mixed results, we recommended the administration of a low-dose beta-blocker for the vasovagal symptoms, which she began.[29]

SURGICAL TREATMENT OF EPILEPSY

Dr. Cole: Indications for surgical treatment of epilepsy include medical intractability, disabling seizures, and a reasonable likelihood that the situation can be improved at an acceptable level of risk. Additional indications are seizures that are immediately life-threatening and the diagnosis and treatment of underlying lesions, usually tumors. Because this patient met all five proposed indications, surgical treatment of the epilepsy was recommended.

Dr. Emad Eskandar: The goals for surgery were as follows: to obtain a diagnosis, to determine whether the lesion was neoplastic and to remove it as needed, to treat or mitigate the epilepsy, and to maintain the ability to perform serial MRI for long-term follow-up. Temporal-lobe surgery has some risks, especially in the dominant hemisphere. The risks included speech dysfunction, memory loss, and disruption of the optic radiations, which would cause a decrease in the visual field. After discussion, we concluded that that area of speech was most likely posterior to the lesion and that we would be able to spare her memory apparatus.

The options were to perform a simple resection of the lesion, a resection with a surgical margin (which would most likely provide better seizure control), or a formal temporal lobectomy, including the hippocampus and the amyg-

dala. The patient had intact memory and speech, and we did not think it was necessary to remove the medial structures, so we planned a resection of the lesion plus a margin.

We performed a small temporal craniotomy with the use of frameless stereotactic guidance. We then removed the lesion plus a small margin and spared the medial temporal structures.

PATHOLOGICAL DISCUSSION

Dr. Declan McGuone: The surgically excised lesion was a low-grade infiltrating oligoastrocytoma (World Health Organization [WHO] grade II of IV) with an ill-defined nodular growth pattern (Fig. 3A). Portions of the lesion consisted of small cells with relatively uniform round nuclei and perinuclear halos that were sitting amid a network of branching capillaries (an oligodendroglial component) (Fig. 3B). A minor component of astrocytic tumor was present. Perivascular accumulation of tumor cells and perineuronal satellitosis were evident. There were few mitoses (Fig. 3C). There was no necrosis or microvascular proliferation. The proliferative index (assessed according to nuclei labeled with Ki-67) was intermediate, at 4.5%.

Immunohistochemical analysis did not provide evidence for the mutant (R132H) form of IDH1, the presence of which confers responsiveness to temozolomide and improved survival in gliomas. The results of SNaPshot tumor genotype analysis (Applied Biosystems), a multiplexed allele-specific assay designed for detecting somatic mutations in tumor DNA, confirmed the tumor to contain nonmutated *IDH1*. The analysis did identify a *BRAF* V600E mutation, which has been described to occur at low frequency in

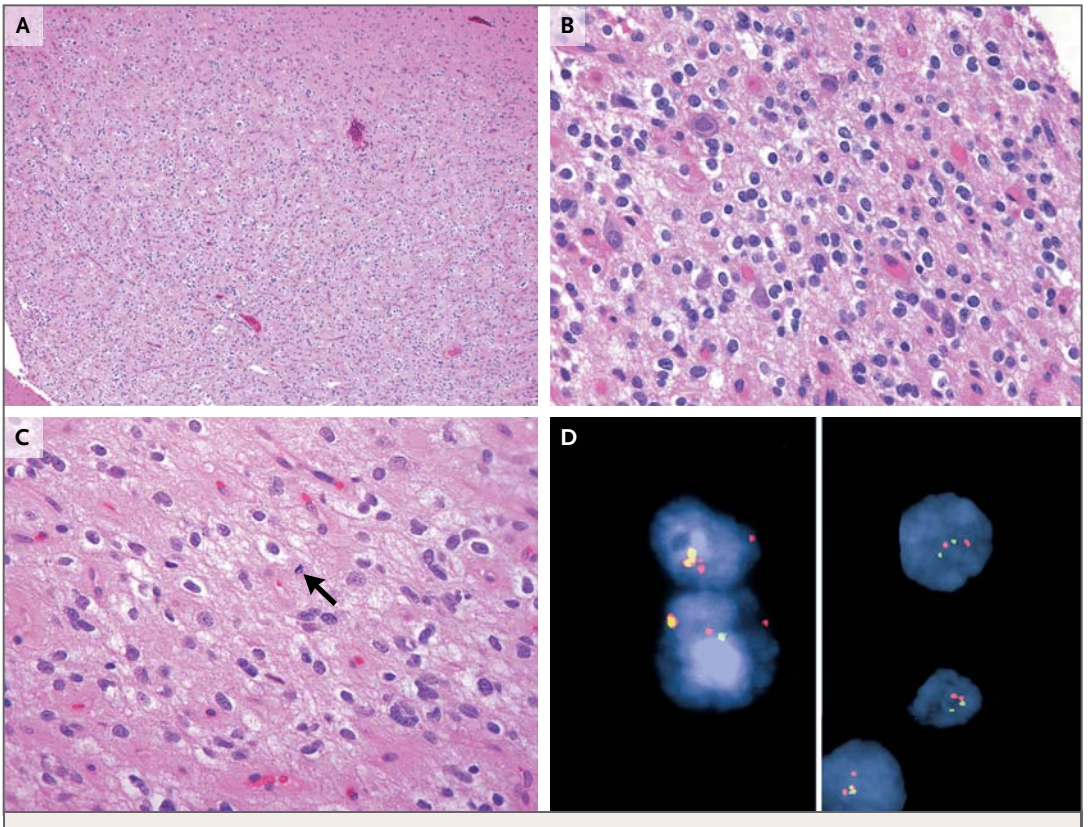

Figure 3. Pathological Examination of a Mass in the Left Temporal Lobe.

A view at low magnification shows brain tissue infiltrated by a tumor with an ill-defined nodular architecture (Panel A). At higher magnification, the tumor consists of oligodendroglial cells with round nuclei and perinuclear halos (Panel B). A tumor cell is in mitosis (Panel C, arrow); there is no necrosis or microvascular proliferation. Fluorescence in situ hybridization analysis (Panel D) shows maintenance of material from chromosome 1p (left side) and chromosome 19q (right side).

oligodendroglioma but is more common in other tumors, such as pilocytic astrocytoma and melanoma.[30] The prognostic significance of the mutation is not known.

Fluorescence in situ hybridization (FISH) showed maintenance of chromosomes 1p and 19q (Fig. 3D), which is associated with a less favorable prognosis than is codeletion of these chromosomes; codeletion of 1p and 19q is commonly observed in oligodendrogliomas. The results of FISH studies that were performed to assess the patient's eligibility for potential clinical trials did not show amplification of the gene locus of platelet-derived growth factor receptor alpha, seen in about one third of glioblastomas. These findings are diagnostic of oligoastrocytoma, WHO grade II of IV.

Dr. Cole: In summary, this patient had asystole and a predisposition to neurocardiogenic syncope, triggered by seizures caused by a glioma in the left temporal lobe. This case raises important issues regarding screening for predisposition to seizure-induced cardiac dysfunction, neurologic mechanisms of cardiac rhythm disturbance, shared molecular mechanisms of brain and heart dysrhythmia, and appropriate strategies for the prevention of sudden unexplained death in epilepsy. The diversity of molecular mechanisms at play in certain persons and an incomplete understanding of genotype–phenotype relationships pose important challenges in the development of appropriate screening strategies in the near future; however, at a minimum, it seems prudent to consider formal 12-lead electrocardiography in patients with epilepsy before and after the administration of anticonvulsant drugs.

Dr. Nancy Lee Harris (Pathology): Drs. Chi and Pathmanathan, would you describe the patient's subsequent treatment and follow-up?

Dr. Andrew S. Chi (Neuro-oncology): This patient had a low-grade oligodendroglial tumor, which was grossly totally resected. I advocated against a permanent pacemaker, given her good prognosis and need for lifelong follow-up MRI. Radiotherapy is standard for low-grade gliomas, but its timing is controversial. The patient's overall risk category was low; therefore I recommended observation. Repeat imaging continues to show only postsurgical changes.

Dr. Jay Pathmanathan (Neurology): At the 24-month follow up, the patient remains free of seizures. She has had some mild memory and word-finding difficulties but remains active. Reduction in her medication dose has not resulted in seizures. Her prognosis is extremely favorable. Freedom from seizures at 2 years in a patient with lesional epilepsy suggests a 74% probability of freedom from seizures at 10 years[31] and suggests an absence of intractability.[32] The risk of seizure recurrence is not affected by discontinuation of antiepileptic medications after 1 to 2 years.[31-33] The patient is quite happy with her treatment outcome.

Dr. Mela: The patient has continued taking atenolol, which she thinks is helpful for persistent vasovagal symptoms, as well as occasional palpitations, which she continues to have during stress or pain. Testing for mutations associated with the long-QT syndrome has not been performed, since the clinical suspicion was low and interpretation of the results can be difficult, for the reasons outlined by Dr. Noebels.

ANATOMICAL DIAGNOSIS

Oligoastrocytoma, WHO grade II of IV, associated with temporal-lobe seizures and ictal asystole (arrhythmogenic epilepsy).

Presented at Neurology Grand Rounds.

Dr. Cole reports receiving consulting fees from Clarus Ventures, Concert Pharmaceuticals, and Sage Pharmaceuticals. Dr. Eskandar reports payment to his institution for a patent on a device for deep-brain stimulation for enhancing learning, motivation, and memory. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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