Misdiagnosis of Epilepsy: Many Seizure-Like Attacks Have a Cardiovascular Cause

Amir Zaidi, MRCP,* Peter Clough, MSc;† Paul Cooper, MD;‡ Bruce Scheepers, MD;†
Adam P. Fitzpatrick, MD, FACC*

Manchester, Cheshire and Salford, United Kingdom

OBJECTIVES
We sought to investigate the value of cardiovascular tests to diagnose convulsive syncope in patients with apparent treatment-resistant epilepsy.

BACKGROUND
As many as 20% to 30% of epileptics may have been misdiagnosed. Many of these patients may have cardiovascular syncope, with abnormal movements due to cerebral hypoxia, which may be difficult to differentiate from epilepsy on clinical grounds.

METHODS
Seventy-four patients (33 men, mean age 38.9 ± 18 years [range 16 to 77]) who were previously diagnosed with epilepsy were studied. Inclusion criteria included continued attacks despite adequate anticonvulsant drug treatment (n = 36) or uncertainty about the diagnosis of epilepsy, on the basis of the clinical description of the seizures (n = 38). Each patient underwent a head-up tilt test and carotid sinus massage during continuous electrocardiography, electroencephalography and blood pressure monitoring. Ten patients subsequently underwent long-term electrocardiographic (ECG) monitoring with an implantable loop recorder.

RESULTS
In total, an alternative diagnosis was found in 31 patients (41.9%), including 13 (36.1%) of 36 patients taking an anticonvulsant medication. Nineteen patients (25.7%) developed profound hypotension or bradycardia during the head-up tilt test, confirming the diagnosis of vasovagal syncope. One other patient had a typical vasovagal reaction during intravenous cannulation. Two patients developed psychogenic symptoms during the head-up tilt test. Seven patients (9.5%) had significant ECG pauses during carotid sinus massage. In two patients, episodes of prolonged bradycardia correlated precisely with seizures according to the insertable ECG recorder.

CONCLUSIONS
A simple, noninvasive cardiovascular evaluation may identify an alternative diagnosis in many patients with apparent epilepsy and should be considered early in the management of patients with convulsive blackouts. (J Am Coll Cardiol 2000;36:181–4) © 2000 by the American College of Cardiology

There is an increasing recognition of the problem of misdiagnosis of epilepsy. The extent of the problem remains unclear, but it is estimated that ~20% of the patients undergoing long-term follow-up in hospital epilepsy clinics do not have epilepsy (1). A recent study of patients referred to a clinic specializing in epilepsy who were taking antiepileptic medication showed a misdiagnosis rate of 26% (2), whereas in a community-based study, 49 (23%) of 214 patients with a primary diagnosis of epilepsy had been misdiagnosed, with the diagnosis of epilepsy disputed in another 26 patients (12%) (3). In both studies (2,3), cardiovascular syncope was the most commonly misdiagnosed condition. Many cardiovascular disorders may cause blackouts complicated by abnormal movements attributable to generalized cerebral hypoxia, particularly reflex forms of syncope, such as vasovagal syncope (4) and carotid sinus syncope (5). These may appear identical to true epileptic seizures, leading to an incorrect diagnosis of epilepsy (6,7). The consequences of an incorrect diagnosis of epilepsy are severe, with implications for driving, occupation and insurance (8,9). In addition, patients may be inappropriately treated with potentially harmful anticonvulsant drugs (10,11).

Although there is a potential for misdiagnosis with any medical condition, it may be a particular problem with epilepsy. There is a specific and sensitive test for the diagnosis of epilepsy—namely, videotelemetry monitoring with electroencephalography—but this may not be widely available or practical in patients with infrequent attacks. The diagnosis is therefore often made on the basis of clinical evidence, but the clinical criteria for epilepsy may not be sufficiently specific to differentiate between ictal and nonictal seizures (12). This article reports the initial results of a more multidisciplinary approach to the investigation of convulsive blackouts, using positive laboratory data from relatively simple provocative tests, rather than clinical history, to confirm the correct underlying diagnosis.

METHODS
Seventy-four consecutive patients (33 men, mean age 38.9 ± 18 years [range 18 to 77]) with recurrent seizure-like episodes were recruited. Each patient had been previously diagnosed as having “epilepsy” on clinical grounds and had

From the *Manchester Heart Centre, The Royal Infirmary, Manchester; †David Lewis Centre for Epilepsy, Cheshire; and ‡Department of Neurology, Centre for Clinical Neurosciences, Hope Hospital, Salford, United Kingdom. Dr. Zaidi received an educational grant from Medtronic, Inc.

Manuscript received August 29, 1999; revised manuscript received December 30, 1999, accepted March 1, 2000.
Abbreviations and Acronyms
ECG = electrocardiogram or electrocardiographic
EEG = electroencephalogram or electroencephalographic

been subsequently referred to the David Lewis Centre for Epilepsy or the Hope Neurosciences Centre for specialist epilepsy care. Thirty-six patients continued to have seizure-like episodes (generalized symmetric limb shaking in 16 patients, asynchronous muscle activity in 12 patients, drop attacks in 6 patients and transient myoclonic twitching 2 patients), despite adequate doses of anticonvulsant drugs (one drug in 21 patients, two drugs in 8 patients and three or more drugs in 7 patients). The most common anticonvulsant drug was carbamazepine (n = 19), followed by sodium valproate (n = 12), phenytoin (n = 8), lamotrigine (n = 7), gabapentin (n = 5), topiramate (n = 3), clonazepam (n = 2) and vigabatrin (n = 2). Another five patients had been treated previously with anticonvulsant drugs with no improvement. The remaining 33 patients had atypical clinical features of epilepsy, including nonconvulsive blackouts (n = 18), features suggestive of a cardiovascular cause such as pallor, sweating, lightheadedness (n = 12) and provocation by standing or noxious stimuli (n = 14), without diagnostic changes on the electroencephalogram (EEG). Patients with suspected psychogenic nonepileptic attack disorder were excluded. The median number of attacks before enrollment in the study was 20, and the median duration of symptoms was 36 months. An interictal EEG was obtained in 66 patients (normal in 53 patients, nonspecifically abnormal in 13 patients), and computed tomography or magnetic resonance imaging of the brain was done in 53 patients (normal in 48 patients, nondiagnostic abnormalities in 5 patients). Rest 12-lead electrocardiograms (ECGs) had been taken in 10 patients, and ambulatory ECG monitoring in 7. The study protocol was approved by the hospitals’ Ethics Committee, and written, informed consent from each patient was obtained. Each patient had a systematic investigation consisting of a rest 12-lead ECG, head-up tilt test and carotid sinus massage. Tilt testing took place between 9 AM and mid-day after an 12-lead ECG, head-up tilt test and carotid sinus massage.

RESULTS
The rest 12-lead ECG was normal in every patient except one who had evidence of a previous inferior myocardial infarction. One other patient had been shown to have episodic Wenckebach second-degree heart block in the past. Nineteen patients (25.7%; six men, mean age 36.8 ± 19 years) experienced their usual symptoms during head-up tilting with profound hypotension or bradycardia, consistent with the diagnosis of vasovagal syncope. The mean time to syncope was 20.1 ± 16.7 min. Marked abnormal movements were reproduced in 12 of these patients (63.2%). All 12 patients developed initial tonic muscle activity consisting of head and body extension with flexion of the arms. Asynchronous multifocal muscle jerking lasting up to 15 s subsequently developed in six patients, whereas bilateral synchronous muscle activity was seen in another two patients. The EEG changes associated with tilt-induced syncope correlated closely with the degree of bradycardia. The development of asystole (n = 7) was typically accompanied by complete loss of EEG activity. However, these changes were not seen in patients with hypotension but a steady heart rate, who characteristically developed excess theta activity on the EEG. Three patients have been successfully treated with permanent pacemakers. One patient declined further treatment, and the remainder are being treated medically (salt supplementation in eight patients, midodrine in six patients, fludrocortisone in one patient). Twelve of the 19 tilt-positive patients (63.2%) were taking anticonvulsant drugs, and treatment has been successfully withdrawn in 10 patients.

One patient had a classic panic attack with hyperventilation, profound sinus tachycardia and hypertension, accompanied by nonepileptiform shaking of the limbs without altered consciousness during the tilt test. One patient developed apparent loss of consciousness without significant alteration of heart rate, blood pressure or EEG recording during head-up tilting, in keeping with an underlying psychogenic cause. Another patient had a typical vasovagal reaction during intravenous cannulation after the tilt test, with reproduction of her typical symptoms. Seven patients (9.5%; six men, mean age 55 ± 14.2 years) had significant ECG pauses during carotid sinus massage, four of whom have undergone permanent pacemaker insertion and two of
whom are waiting for spontaneous symptom–ECG correlation with the insertable loop recorder. Two patients have subsequently been shown to have significant bradyarrhythmias at the time of their seizure-like attacks, using the insertable recorder (complete heart block in one patient and prolonged sinus pauses in the other), and have been successfully treated with permanent pacing. In total, an alternative diagnosis has been found in 31 patients (41.9%), including 13 (36.1%) of 36 patients taking anticonvulsant medication.

After 10.3 ± 6.7 months of follow-up, 19 (61.3%) of 31 patients with an alternative diagnosis for their seizures are symptom-free, and every patient has subjectively improved. Eleven (84.6%) of 13 patients who were taking anticonvulsant medication and for whom an alternative diagnosis was identified have successfully stopped their antiepilepsy drugs.

**DISCUSSION**

The difficulty in distinguishing epilepsy from paroxysmal attacks caused by cardiovascular or psychological disorders has long been recognized (13–15). However, the extent to which incorrectly identified convulsive syncope contributes to the problem of misdiagnosis of epilepsy remains uncertain. Forty years ago, Gastaut et al. (16) estimated that there was an underlying cardiovascular condition in up to one-third of the patients who received an initial diagnosis of epilepsy, whereas Schott et al. (17) identified cardiac arrhythmias in 20% of the patients referred with idiopathic epilepsy. However, most patients with seizure-like episodes are diagnosed as having epilepsy purely on clinical grounds, with no cardiac investigation and often without corroborating EEG evidence (10,18).

**Abnormal movements in syncope.** Reflex forms of syncope appear to be particularly likely to be complicated by abnormal movements. Lin et al. (19) reported that convulsions occurred in 12% of blood donors experiencing vasovagal faints. Lempert et al. (20), using a combination of hyperventilation, orthostasis and Valsalva maneuver, induced syncope in 42 of 59 healthy control subjects. Myoclonic activity was seen in 90% of cases, predominantly multifocal jerking of the limbs. Complete arrest of cerebral circulation has been shown to be highly associated with convulsion (21). It is not surprising, therefore, that tilt-induced vasovagal syncope, which is associated with periods of asystole (22,23), resulted in abnormal movements in 64% of tilt-positive patients in this study. In a study of 15 patients with recurrent, unexplained seizure-like episodes, who were unresponsive to anticonvulsant medication, Grubb et al. (24) induced syncope with tonic-clonic seizure-like activity in 10 patients (67%). After cardiac drug or device therapy, all 10 patients were tilt-negative and free from seizure-like episodes.

Head-up tilt testing clearly has a role in identifying cases of convulsive vasovagal syncope in misdiagnosed "epilepsy." It is known to be safe and well tolerated and has satisfactory sensitivity, specificity and reproducibility (25,26). The role of carotid sinus massage is less clear, but it is noninvasive and has been proven safe (4). Our preliminary results suggest that there may be a significant number of cases of convulsive carotid sinus syncope in older patients with convulsive blackouts.

**Convulsive arrhythmic syncope.** It is more difficult to confirm that convulsive syncope is the result of a cardiac arrhythmia. A 12-lead ECG is typically normal in this group of patients (7). Ambulatory electrocardiography coincides with syncope in no more than 2% to 4% of patients (27,28). However, the recent introduction of the insertable loop recorder, a patient-activated subcutaneous ECG recording device, represents a major advance in the investigation of arrhythmic syncope (29). The device provides retrospective ECG recordings up to 40 min before device activation, allowing accurate correlation of symptoms with cardiac rhythm during an 18-month battery life. Electrocardiographic data can later be retrieved by telemetry. In a multicenter study of 85 patients with recurrent unexplained syncope who received an insertable loop recorder, a positive diagnosis was reached in 59% over a mean follow-up period of 10 months (30).

**Electroencephalography in convulsive syncope.** The EEG characteristics of cerebral anoxia are distinctive. In a study 100 patients with a history of syncope who underwent 10 to 15 s of oculogyric compression, asystole lasting <6 s produced no significant EEG changes (31). However, between 7 and 13 s, there was progressive appearance of theta and delta rhythms, whereas beyond 13 s, there was cortical silence identical to the findings in our asystolic patients (31). The association of asystolic pauses with flattening of the EEG has also been shown in Valsalva-induced syncope (20) and with tilt-induced convulsive syncope (24), but it appears that EEG changes in profound hypotension without complete circulatory arrest are confined to excessive theta activity without EEG flattening (32). These findings suggest that complete loss of EEG activity is attributable to the complete loss of cerebral perfusion during asystole.

**Conclusions.** This study reinforces the difficulty of diagnosing seizure and syncope. More details of these “spells” may help in this problem. This patient group had been carefully selected, but clinicians should be encouraged to consider cardiac issues in any syncopal spell.

**REFERENCES**

2. Smith D, Defalla BA, Chadwick DW. The misdiagnosis of epilepsy