

All Seizures are not Epilepsy: many have a Cardiovascular Cause

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Abstract

Objectives: The aim of this study was to investigate the value of cardiovascular tests to diagnose convulsive syncope in children with apparent treatment-resistant epilepsy and to assess the extent of misdiagnosis of epilepsy in children.

Background: Adult studies have shown that up to 35% of epileptics may have been misdiagnosed. These patients may have cardiovascular syncope, with abnormal movements due to cerebral hypoxia, which may be difficult to differentiate from epilepsy. Studies in children are lacking.

Methods: Thirty-one children (12 male, mean age 10.07 ± 5 years) who were previously diagnosed with epilepsy were studied. Inclusion criteria were continued attacks despite adequate anticonvulsant drug treatment ($n = 17$) or possible epilepsy on the basis of clinical grounds ($n = 14$). Each patient underwent a 12-lead electrocardiogram (ECG), an orthostatic test and carotid sinus massage during continuous ECG and blood pressure monitoring. Ten patients had Holter monitoring.

Results: An alternative diagnosis was found in 19 patients (61.3%), including 8 (47%) of 17 patients taking anticonvulsant medications. Nine patients (29%) developed profound hypotension or bradycardia during orthostatic test, confirming the diagnosis of vasovagal syncope. Seven patients (22.5%) had long Q-T syndrome (LQTS). Two (6.4%) had significant ECG pauses during carotid sinus massage. In these two patients episodes of prolonged bradycardia correlated precisely with seizures by Halter recording, was noted. One patient (3.2%) developed psychogenic symptoms during the orthostatic test.

Conclusion: A simple, non-invasive cardiovascular evaluation may identify an alternative diagnosis in many children with apparent epilepsy and should be considered early in the management of children with convulsive episodes (JPMA 52:116, 2002).

Introduction

Infants and young children cannot describe symptoms of cardiogenic syncope accurately. If the attention in such cases is focused on the seizure activity that may follow, the patient will be treated inappropriately with anticonvulsants¹. Many cardiovascular disorders may cause blackout episodes complicated by abnormal movements attributable to generalized cerebral hypoxia, particularly reflex form of syncope, such as vasovagal syncope², carotid sinus syncope³ and long QT syndrome induced ventricular arrhythmia⁴. There is an increasing recognition of the problem of misdiagnosis of epilepsy in adults. Recent studies in adults have shown that up to 35% of epileptics may have been misdiagnosed. According to an estimate, 20% of adult patients undergoing long-term follow up in epilepsy clinics do not have epilepsy⁵. Smith et al.⁶ demonstrated a 26% misdiagnosis of epilepsy in adult patients referred to a clinic specializing in epilepsy who were taking

antiepileptic medications, whereas in a community based study, 23% of patients with a primary diagnosis of epilepsy had been misdiagnosed, with the diagnosis of epilepsy disputed in another 12% patients⁷. In both studies^{6,7}, cardiovascular syncope was the most commonly misdiagnosed condition. The extent of the problem remains unclear in children. Congenital anomalies, growth spurts and changing metabolic and hormonal requirements make children a biologically novel group as compared to adults. Furthermore, the long term consequences of an incorrect diagnosis of epilepsy are severe, with implications for driving, occupation and insurance in later life^{8,9}. In addition, children may be inappropriately treated with potentially harmful anticonvulsant drugs¹⁰. The diagnosis of epilepsy is often made on the basis of clinical grounds, but the clinical criteria for epilepsy may not be sufficiently specific to differentiate between ictal and nonictal seizures¹¹. Videotelemetry monitoring with electroencephalography (EEG), a specific and sensitive test for the diagnosis of epilepsy may not be widely available or practical in patients with infrequent attacks. There is a need for prospective studies to systematically evaluate the issue of misdiagnosis of epilepsy in children. This study reports the results of a multidisciplinary approach to the investigation of convulsive blackouts in children, using positive laboratory data from relatively simple provocative tests, rather than clinical history, to confirm the correct underlying diagnosis.

Patients and Methods

Thirty-one consecutive patients (12 male, mean age 10.07 ± 5 years) with recurrent seizure-like episodes were recruited during September 1999 to November 2000. Each patient had been previously diagnosed as having "epilepsy" on clinical grounds and had been subsequently referred to the Shifa International Hospital for specialist care. The exclusion criteria were patients with central nervous system or cardiovascular system malformation or disease, metabolic, endocrine or electrolyte abnormalities, abnormal echocardiogram, psychogenic symptoms and strong family history of epilepsy. Seventeen patients continued to have seizure-like episodes (generalized symmetric limb shaking in 9 patients, asynchronous muscle activity in 4 patients, drop attacks in 3 patients and transient myoclonic twitching in one patient), despite adequate doses of anticonvulsant drugs (one drug in 12 patients and two drugs in 5 patients). The most common anticonvulsant drug was sodium valproate (n = 15), phenytoin (n = 3) and phenobarbitone (n = 4). The remaining 14 patients had atypical clinical features of epilepsy, including nonconvulsive blackouts (n = 7), pallor, sweating, lightheadedness (n = 5) and provocation by standing or noxious stimuli (n = 2) without typical diagnostic changes on the EEG. The median number of attacks prior to enrolment in study was 15 and the median duration of symptoms was 24 months. An interictal EEG was obtained in 25 patients (normal in 18 patients, non-specifically abnormal in 7 patients), and computed tomography or magnetic resonance imaging of the brain was done in 10 patients (normal in all 10 patients).

Rest 12-lead electrocardiogram had been taken in 5 patients. The study protocol was approved by the hospital's Ethics Committee and written informed consent was obtained. Each patient had a systematic investigation consisting of a rest 12-lead ECG, orthostatic test and carotid sinus massage. Due to non-availability of head-up tilt test, its modification in the form of orthostatic test was adopted. All cardiovascular medications

were discontinued for at least five half lives before the study. The orthostatic test was performed between 8 AM and mid-day after an overnight fast. After a 15-min rest in supine position, the patient were allowed to stand with support for up to 45 min. Continuous ECG monitoring and phasic blood pressure measured using digital photoplethysmography (Spacelab, Inc. blood pressure monitor, Richmond, Washington), were recorded throughout the study. Patients were returned to the supine position upon completion of the designated test period. Indication for early termination of the test were syncope, or presyncope with a fall in systolic blood pressure >40 mmHg or bradycardia <40 beats/min, or both.

After the orthostatic test, each patient had carotid sinus massage for 5 seconds on each side of the neck in supine position. Carotid sinus hypersensitivity was defined as a pause >3 s. Another ten patients in whom arrhythmias were strongly suspected on the basis of clinical history and ECG features, underwent Holter monitoring (Siemens EH 39 E, Germany).

Results

Nine patients (29%; two male, mean age 12.3 ± 4 years) experienced their usual symptoms during orthostatic test with profound hypotension and bradycardia, consistent with the diagnosis of vasovagal syncope. The mean time to syncope was 15 ± 11.7 min. Marked abnormal movements were reproduced in 5 of these patients (55%). All 5 patients developed initial tonic muscle activity consisting of head and body extension with flexion of arms. Asynchronous multifocal muscle jerking subsequently developed in 4 patients. These patients are being treated medically (salt supplementation in six patients, metoprolol in two patients and fludrocortisone in one patient). Four of the nine orthostatic test positive patients (44%) were taking anticonvulsant drugs and treatment has been successfully withdrawn in all four patients. One patient (3.2%) developed apparent loss of consciousness without significant alteration of heart rate or blood pressure during orthostatic test, in keeping with an underlying psychogenic cause. The rest 12-lead ECG was abnormal in eight patients. Seven patients had long QT syndrome (22.5%; four male, mean age 7.8 ± 3 years, QTc range 460 ms to 510 ms). One patient had occasional benign premature atrial contractions. Five of seven patients had congenital LQTS (Romano-Ward syndrome) and two had idiopathic LQTS. The children with LQTS were experiencing syncope followed by seizures provoked by emotional upset. Subsequently, polymorphic ventricular tachycardia (torsade de pointes) was documented in two patients by ECG during syncope. One of them presented in ER with shock like picture and polymorphic ventricular tachycardia (torsade de pointes) at 280 bpm requiring cardioversion. These patients have been maintained on oral beta blocker treatment. Four of the seven LQTS patients (57%) were taking anticonvulsant drugs and the treatment has been successfully withdrawn in all of them. Two patients (6.4%, one male, mean age 6.4 ± 2.1 years) had significant ECG pauses during carotid sinus massage. They are being investigated for permanent pacemaker insertion. One patient has subsequently been shown to have significantly prolonged sinus pauses at the time of his seizure-like attack, documented by Holter recording. The comparison of baseline characteristics and clinical symptoms/signs of the children with and without a potential cardiac disorder are summarized in Table.

Table. Comparison of baseline characteristics and clinical symptoms/signs of the children with and without cardiac cause of seizures.

Symptoms/Signs	Cardiac cause of seizure	Non-cardiac cause of seizure
1. Pallor, sweating hyperventilation, light headedness and non-convulsive blackouts (n=11)	Yes: - Vasovagal syncope - Sick sinus syndrome	No
2. Lost consciousness and remained completely still "like a dead body" prior to tonic clonic seizures (n=5)	Yes: - Children with *LQTS	No
3. Chest pain, palpitation, pulseless, provocation by standing, emotional stress or noxious stimuli (n=3)	Yes: - Cardiac arrhythmia (Torsade de pointes) - Sick sinus syndrome	No
4. Abrupt onset of seizures while awake or in sleep, no warning of an attack, loss or alteration of consciousness with amnesia tachycardia, bilateral symmetrical motor activity with or without incontinence (n=12)		Yes

*LQTS = Long QT Syndrome

In total, an alternative diagnosis has been found in 19 patients (6 1.3%) including 8 (47%) of 17 patients taking anticonvulsant medications.

After 5 ± 2.2 months follow up, all the patients with an alternative diagnosis for their seizures are symptom-free and each one has subjectively improved. The patients who were taking anticonvulsant medications and for whom an alternative diagnosis was identified have successfully stopped their anti-epilepsy drugs.

Discussion

Although, there is a potential for misdiagnosis with any medical condition, it may be a particular problem with epilepsy. The diagnostic dilemma and distinguishing epilepsy from paroxysmal attacks caused by cardiovascular or psychological disorders in adults has long been recognised¹²⁻¹⁴. However, the extent to which incorrectly identified convulsive syncope accounts for the misdiagnosis of epilepsy in children, remains uncertain. The main reason for diagnostic failure is the young age at which the disease usually presents: young children cannot accurately describe the dizziness, lightheadedness and fainting that may indicate cerebral hypoperfusion caused by cardiac events. Moreover, parents tend to describe only the coma and convulsions that follow these early symptoms. A detailed history and a good description of the events just prior to seizure activity may help to decide whether the episode was cardiac in origin. This study identifies some of the specific clinical characteristics and clinical features which may help to establish a cause and effect relation between cardiac disorder and patient complaint (Table). Schott et al⁵ identified cardiac arrhythmias in 20% of the adult patients referred with idiopathic epilepsy. However, most patient with seizure like episodes are diagnosed as having epilepsy purely on clinical grounds, with no cardiac investigations and often without corroborating EEG evidence.

In the 19th century, neurologists often had trouble distinguishing between syncope and seizures. However, EEG studies have demonstrated unequivocally that, despite confusing

signs of tonic spasms, generalized body jerks and urinary incontinence, syncope is non-epileptic. Lin et al.¹⁶ reported that convulsions occurred in 12% of blood donors experiencing vasovagal faints. Lempert et al.¹⁷, using a combination of hyperventilation, orthostasis and valsalva maneuver, induced syncope in 42 of 59 healthy control adult 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 convulsions¹⁸. It is not surprising, therefore, that orthostasis induced vasovagal syncope, which is associated with periods of asystole^{19,20}, resulted in markedly abnormal movements in 55% of orthostatic test positive patients in this study. In a study of 15 patients with recurrent, unexplained, seizure-like episodes, who were unresponsive to anticonvulsant medications, Grubb et al.²¹ induced syncope with tonic-clonic seizure-like activity in 10 cases (67%). After cardiac drug or device therapy, all 10 were free from seizure like activity.

Head-up tilt or orthostatic test seems to be a reliable method of identifying patients of vasovagal syncope misdiagnosed as “epilepsy”. It has been shown to be safe and well tolerated and has a high degree of sensitivity, specificity and reproducibility^{22,23}. Based on cardiovascular responses just before and during syncope, the type induced is classified as vasodepressor, cardioinhibitory or mixed type²⁴. In brief, the vasodepressor type shows hypotension and tachycardia (or no change in heart rate) during syncope; the cardioinhibitory type shows asystole during syncope (>3 s) and the mixed variety shows hypotension and bradycardia. The role of carotid sinus massage is less clear but it is non-invasive and has been proven safe². Our preliminary results suggest that there may be a significant number of cases of convulsive carotid sinus syncope in children with blackout episodes.

The significance of cardiac arrhythmias occurring interictally is more complex. Due to the extremely low yield, ECG for all patients with “epilepsy” is not routinely obtained. However, in our study, 7/31 (22.5%) patients had significantly positive ECG (LQTS), stressing the importance of this basic cardiovascular test in detection of possible underlying arrhythmias. A history of unexplained syncope or sudden death in a child or young adult, especially during physical exertion or emotional agitation and a history of unexplained drowning or near-drowning, should provoke a suspicion of the possibility of LQTS^{4,25}. Seizures or syncope seemingly precipitated by “fight, flight or fright” has been said to indicate LQTS until proven otherwise⁴. More than one half of the 8,000 sudden unexpected deaths in children may be attributable to LQTS⁴ and the 10-year mortality rate of untreated LQTS may be as high as 50%, making consideration of diagnosis mandatory in some clinical situations. Schwartz et al.²⁶ proposed the first diagnostic criteria for LQTS in 1985. Subsequently, its modifications led to the formulation of new criteria published in 1993²⁷.

Ambulatory electrocardiography coincides with syncope in no more than 2% to 5.3% of patients^{28,29}. However, the recent introduction of the insertable loop recorder, a patient activated subcutaneous ECG recording device, represent a major advance in investigation of arrhythmic syncope³⁰. The device provides retrospective ECG recording 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 5.9% over a

mean follow-up period of 10 months³¹.

The EEG changes are stereotyped in syncope. Gastaut and Fisher-williams³² have recorded EEGs during syncope induced by ocular compression which can induce profound bradycardia or asystole. Following asystole, a characteristic series of changes occur. After 3 to 4 sec, high-voltage slow activity appears in theta range and in the next few seconds it slows into delta range. If asystole persists for 8 to 10 sec, slow activity abruptly disappears and the record appears "flat" unless obscured by tonic EMG activity or movement artifact associated with repeated decorticate jerks. When ventricular contractions resume, brain waves reappear in reverse order from their disappearance. The association of asystolic pauses with flattening of EEG has also been shown in Valsalva-induced syncope¹⁷ and with tilt-induced convulsive syncope²¹. These findings suggest that complete loss of EEG activity is attributable to the absence of cerebral perfusion during asystole³³.

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