

Seizure versus syncope

Andrew McKeon, Carl Vaughan, Norman Delanty

One of the most common but difficult management problems in medicine is that of patients who present with a paroxysmal loss of consciousness. All too often the underlying diagnosis remains elusive. This has a cost both in terms of mortality and ongoing morbidity and in terms of the financial burden associated with hospitalisation and repeated investigations. We describe a practical approach to this clinical dilemma, which is rooted in adherence to basic principles of history taking and examination, formulation of a reasonable differential diagnosis, followed by an intelligent use of specific investigations and selection of an appropriate treatment. We also discuss the effect of sudden unexpected death in epilepsy and sudden cardiac death. Despite a careful and thorough approach to the patient with a “seizure versus syncope” problem, many will require repeated assessment before a diagnosis is made.

Introduction

The assessment of a patient with a transient loss of consciousness can be difficult. These patients fall into two groups: those with seizures, which embrace both epileptic and non-epileptic events, and those with syncope, defined as loss of consciousness and postural tone caused by cerebral hypoperfusion with spontaneous recovery.

On presentation, vital clues are commonly missing because patients may have amnesia and a witness account might not be available, and even after multiple investigations a diagnosis may still be not be possible. There can also be the confounding factor of convulsive syncope, which is a seizure-like reaction resulting from global cerebral hypoperfusion; this happens in around 12% of patients presenting with syncope.¹ A video study of the clinical features of syncopal attacks induced in healthy volunteers showed that myoclonus happens commonly in syncope, and that other movements more commonly seen in epilepsy, such as automatisms and head turning, also occur.² Agreement between physicians as to the nature of the event may also be discordant, making a clinical diagnosis on the basis of one event alone, at times, unreliable.³ Loss of consciousness is a common complaint in accident and emergency departments, with syncope accounting for 3% of visits and 6% of medical admissions.^{4,5} Epidemiological data from the Netherlands have shown the overall incidence of epilepsy to be 30 per 100 000, rising to 62 per 100 000 in people over age 65 years.⁶ Syncope is more common in elderly people; 23% of people over age 70 years experience a syncopal episode over a 10 year period, compared with 15% of those under 18 years. In one prospective study of 650 patients presenting with syncope, there was an 18 month mortality of 9%.⁷ Although syncope has a good prognosis,⁸ patients with underlying cardiovascular disease have a mortality of up to 30% at 1 year.⁹ Many others have recurrent, unexplained syncope. In studies of the diagnostic outcome of patients presenting with syncope, 25–42% were discharged without a diagnosis.^{10–13} When these patients are assessed using valid measures of health status, results suggest a high level of physical, psychological, and social dysfunction.¹⁴

Also, adherence to driving recommendations among patients presenting with syncope may be as low as 7%.¹⁵ Assessment of patients with recurrent unexplained blackouts is expensive, and is cost ineffective unless guided by a good history and examination.¹⁶ In one Austrian study, the median cost of assessment for patients over 4 years in the mid 1990s was €7756,¹⁷ with 38% of these patients discharged without a diagnosis.

Clinical history and examination

The importance of patient histories and witness accounts is paramount. Historical features are very helpful in distinguishing syncope from seizures, and have been proposed as a scoring scheme (table) by Sheldon and colleagues.¹⁸ Their point score is a useful bedside tool, is based on symptoms only, and diagnoses seizures with 94% sensitivity and specificity.

Key clinical features helpful in distinguishing seizure from syncope are also illustrated in figure 1. A patient who describes an epigastric rising sensation, altered taste or smell, or prolonged sense of déjà vu before the onset of the attack is likely to have had a temporal-lobe seizure. The patient might also have had such sensations (auras) previously without any altered consciousness thereafter. A patient who has unformed visual hallucinations before a loss of awareness might have epilepsy with an occipital focus. Palpitations or chest pain are likely to point to an underlying cardiac disorder. Loss of consciousness preceded by

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Department of Neurology, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland (A McKeon MRCPI, N Delanty FRCP); and Department of Cardiology, Mercy University Hospital, Cork, Ireland (C Vaughan FRCP)

Correspondence to: Dr Norman Delanty normandelanty@eircom.net

	Points
Wake with tongue cutting?	2
Déjà vu or jamais vu?	1
Emotional stress associated with loss of consciousness?	1
Head turning during a spell	1
Unresponsive, unusual posture, limb movement, or amnesia of spells? (any one of these)	1
Confusion after a spell	1
Lightheaded spells	–2
Sweating before spell	–2
Spell associated with prolonged sitting or standing	–2

If point score is ≥ 1 the likelihood is seizure or if < 1 the likelihood is syncope.

Table: Questionnaire and scoring system for symptoms pertaining to loss of consciousness¹⁸

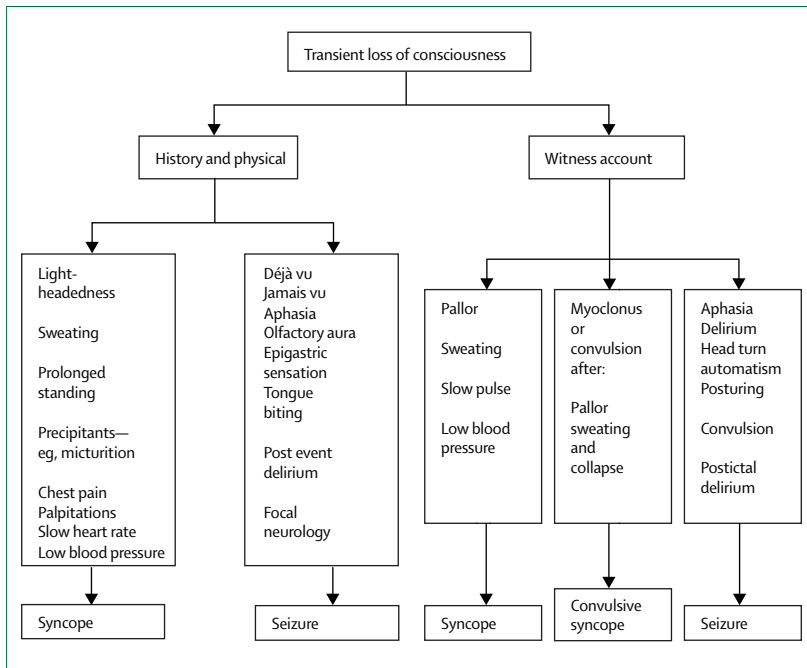


Figure 1: Clinical features distinguishing seizure from syncope

lightheadedness, diaphoresis, nausea, diminution of hearing and vision, or a “faint” feeling, particularly after a prolonged period of standing, is likely to be neurocardiogenic syncope. If the paroxysm of unconsciousness is precipitated by micturition, defecation, or pain, the diagnosis is likely to be situational syncope. Syncope caused by aortic stenosis or hypertrophic obstructive cardiomyopathy might be related to exercise. However, the prodromal symptoms may be non-specific—eg confusion and dizziness. In such cases, witness accounts can be helpful, revealing automatisms, head turning, posturing, or dysphasia. Such focal seizures might be simple partial (awareness retained) or complex partial (awareness altered), and can be followed by secondary generalisation. Differentiating these events from convulsive syncope is crucial, the latter accounting for many patients labelled as having epilepsy. In convulsive syncope, diagnostic clues from the patient might include symptoms such as nausea, lightheadedness, and feeling faint. Diaphoresis and pallor may be seen before the patient loses postural tone and may be followed by a convulsion.

Cardiovascular examination might reveal a valvular or heart-rhythm abnormality, and orthostatic blood-pressure recordings can show postural hypotension. Neurological examination might sometimes reveal a focal abnormality supportive of a possible epileptogenic focus.

Carotid sinus hypersensitivity is a common cause of unexplained falls in elderly people.¹⁹ The key symptom in a patient history is syncope or presyncope on neck

turning, which can be reproduced with carotid sinus massage. As there is a small risk of stroke, this manoeuvre is contraindicated in those with known carotid-artery stenosis and in patients with carotid bruits or recent cerebrovascular events where carotid stenosis has not been excluded. Another factor to consider when taking patients’ histories and obtaining a witness account is amnesia for loss of consciousness. Up to 30% of patients with carotid sinus syndrome who have loss of consciousness do not remember doing so.²⁰ This loss often presents as unexplained falls and is also common in epilepsy, with implications for driving recommendations.

Causes of syncope and seizures are shown in panels 1 and 2. Neurocardiogenic syncope is very common. One study of 641 syncopal patients, who had already been screened for cardiac, metabolic, or neurological causes, showed that 43% of patients had neurally-mediated cardiogenic syncope, with another 5% having a chronic dysautonomic syndrome, such as multiple system atrophy.²¹

Psychogenic non-epileptic seizures and psychogenic pseudosyncope

Psychological illnesses presenting as a seizure or apparent syncopal episode are an important part of the

Panel 1: Causes of syncope

Benign

Neurocardiogenic
Carotid sinus syndrome
Situational: cough; micturition; defecation

Malignant

Postural hypotension
Volume depletion: diuretics; vasoactive drugs; autonomic neuropathy
Cardiogenic

Left ventricular outflow obstruction: aortic stenosis; hypertrophic obstructive cardiomyopathy
Right ventricular outflow obstruction: pulmonary emboli; pulmonary hypertension; tetralogy of Fallot
Obstruction of venous return: superior-vena-cava obstruction; tension pneumothorax; constrictive pericarditis
Atrial tachyarrhythmias: atrial fibrillation; atrial tachycardia; atrial flutter

Heart block: second or third degree
Accessory atrioventricular node pathways: Wolff-Parkinson-White syndrome
Ventricular tachyarrhythmias: ventricular tachycardia; ventricular fibrillation

Long QT syndrome: hereditary channelopathies affecting sodium and potassium channels; acquired

Psychogenic pseudosyncope

caseload of general physicians and specialists; these account for around one third of cases at syncope clinics and up to 30% of patients presenting with “refractory seizures” for video electroencephalogram monitoring.²² The underlying psychiatric disorders are diverse, including factitious, panic, and conversion disorders, as well as malingering. Although a combination of factors can lead to a suspicion for diagnosis of psychogenic non-epileptic seizures—such as attack semiology, personality traits, psychiatric history, and history of trauma or abuse—these suspicions might be confirmed during a routine electroencephalogram or during video electroencephalogram monitoring. Sometimes these events are recorded during tilt-table testing, where there is no change in cardiovascular parameters. Video monitoring or witnessing of an event by an expert physician can also be diagnostic in psychogenic pseudosyncope. Ultimately, psychiatric assessment and early engagement with a behavioural therapist is required for a satisfactory outcome in either disorder.

Investigations

Once a thorough clinical assessment has been completed, appropriate investigations can be selected (figure 2). Management of the patients should not be guided by the specialty under which they were admitted—eg, a patient admitted under neurology only having neurological investigations.²³ One study of clinical-decision making has shown that internists tended toward a broader diagnostic assessment than their cardiology colleagues.²⁴ A prospective assessment of Italian general hospitals has shown how unstratified and variable the evaluation of syncope can be. Carotid sinus massage was done in up to 58% of syncopal patients, and tilt-table testing in up to 50%, with the result of a diagnosis of neurally-mediated syncope made in 10–70% of syncopal patients.²⁵ The setting for evaluation is also important. The European Society of Cardiology Management of Syncope guidelines²⁶ recommend hospitalisation for investigation of any patient presenting with syncope, who has structural heart disease, an electrocardiogram abnormality, syncope causing severe injury, syncope during exercise, or a family history of sudden death. Patients with syncope secondary to arrhythmia, cardiac ischaemia, or with neurally mediated syncope requiring pacemaker implantation will also need admission for treatment. Other patients can be assessed and treated in an outpatient “syncope clinic”. The organisation of such a service is also important. The Newcastle group in the UK have led the way with an integrated multidisciplinary service, with rapid access for accident and emergency staff, allowing more effective assessment and treatment, reduced re-admission rates, and great financial and resource savings.²⁷

Panel 2: Causes of seizures

Epileptic seizure

Idiopathic (genetic): generalised; partial
Symptomatic (acquired): generalised; partial (lesional, non-lesional)

Symptomatic seizures

Tumour: primary; secondary
Vascular: ischaemic stroke; atrioventricular node malformations; cavernous haemangiomas; intracerebral, subarachnoid, subdural haemorrhages
Trauma
Infective: bacterial, fungal, giardiasis abscesses; cerebritis; subdural empyema; HSV encephalitis; bacterial, viral, tuberculous meningitis; HIV; toxoplasmosis; neurocysticercosis; cerebral hydatidosis; cerebral malaria
Neurodegenerative: Alzheimer’s disease
Autoimmune mediated: paraneoplastic limbic encephalitis; cerebral vasculitis; cerebral lupus; neurobehçets; neurosarcoidosis; Hashimoto’s encephalopathy
Febrile seizures
Hypertensive encephalopathy
Electrolyte disturbance: hypo/hypermnatraemia; hypo/hyperkalaemia; hypo/hypercalcaemia; hypo/hypermagnesaemia
Metabolic: hepatic encephalopathy; uraemic encephalopathy; mitochondrial encephalopathy (eg, MERRF, MELAS)
Toxic: alcohol withdrawal; cocaine; amphetamines; ecstasy
Eclampsia

Psychogenic non-epileptic seizures

Basic investigations

Basic laboratory investigations should be done to exclude anaemia, infection, electrolyte disturbances, or renal and liver dysfunction, although routine serum biochemical profiles tend to have a very low yield in this setting.²⁸ Measuring serum prolactin is not a reliable test for distinguishing between epileptic seizures and syncope, but is a useful adjunct for the differentiation of epileptic seizures from psychogenic non-epileptic seizures.²⁹

12-lead electrocardiography is absolutely mandatory when a patient presents with loss of consciousness, providing diagnostic and prognostic information in the evaluation of syncope. Kapoor³⁰ quoted a 33% 5-year mortality for those with cardiogenic syncope. Colvicchi and colleagues³¹ have developed a risk stratification score, which is a simple risk classification system based on clinical history, physical examination, and electrocardiogram findings. Predictors of mortality include age over 65 years, a history of cardiovascular disease, syncope without prodrome, and an abnormal electrocardiogram. Despite the obvious importance of electrocardiogram, a recent study of syncope assessment in emergency departments in the USA, showed that only

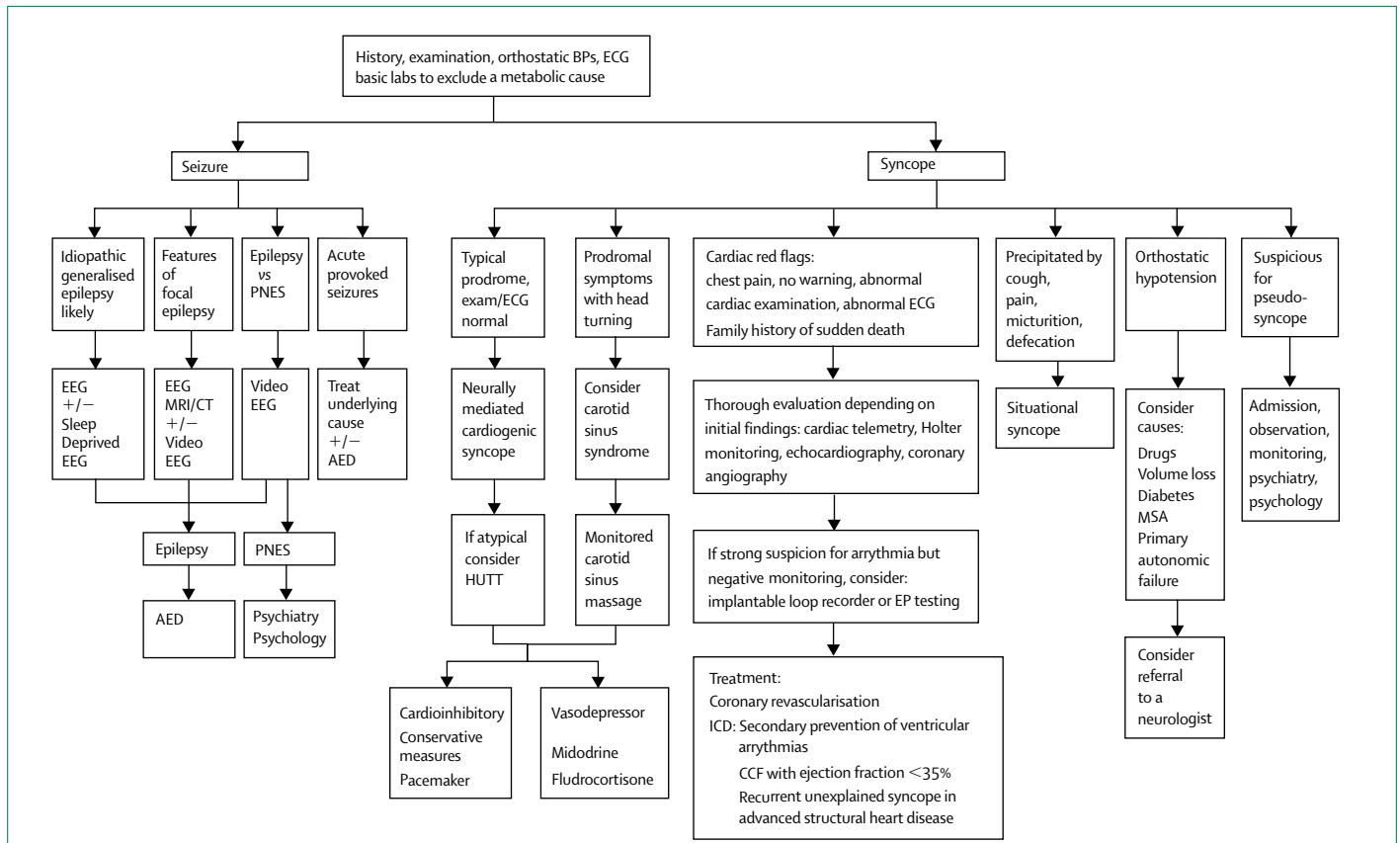


Figure 2: An algorithm of diagnostic considerations in evaluating the patient with a paroxysmal loss of consciousness

BPs=blood pressure, systolic; ECG=electrocardiogram; AED=antiepileptic drug; PNES=psychogenic non-epileptic seizures; EEG=electroencephalography; HUTT=head-up tilt test; EP=electrophysiology; ICD=implantable cardiac defibrillators; CCF=congestive heart failure; MSA=multiple-system atrophy

59% of patients had an electrocardiogram on presentation.³² An electrocardiogram might suggest a specific cause for syncope including bundle branch block, A-V block, pre-excitation, left ventricular hypertrophy, and the long QT syndrome. Also, electrocardiogram-based risk stratification is useful in guiding the use of specialised cardiac tests. In one study,⁸ every patient who had an extensive cardiac work-up, who had a final diagnosis of an arrhythmia had an abnormal baseline electrocardiogram to begin with.

Electroencephalogram

A 30 min interictal electroencephalogram is useful when there is a clinical suspicion of epilepsy.³³ Electroencephalograms are commonly requested for dubious indications—eg, “funny turns”. In one British study³⁴ of electroencephalogram use in a district hospital, 56% of orders were considered to be inappropriate, and only 16% influenced management. A subsequent physician education programme took place and then a prospective study has shown a substantial improvement in use of the electroencephalogram service.³⁴ Timing is also important; 50% of those who present with an assumed generalised convulsion will have an abnormal

electroencephalogram within 24 h of presentation.³⁵ However, if the electroencephalogram is done within the first 48 h, only 21–34% have definite epileptiform activity on electroencephalogram, although many more show slowing which can be helpful in supporting a diagnosis of epilepsy.^{35,36} Younger patients are more likely to have epileptiform abnormalities on electroencephalogram than older patients, who are more likely to have focal or generalised slowing. The yield of epileptiform electroencephalograms in those over age 40 years presenting with a first unprovoked seizure can be as low as 7%. In circumstances where it is difficult to distinguish between convulsive syncope and epilepsy, electroencephalogram during tilt-table provocation might be diagnostic.³⁷ A sleep electroencephalogram or a sleep-deprived electroencephalogram might also increase the diagnostic yield, although there is evidence in some studies that among physicians, and even general neurologists, there is substantial confusion over the usefulness of both.³⁸ Sleep has an activating effect, increasing the yield by 22–25% over the first electroencephalogram. Sleep-deprived electroencephalogram—where the patient is deprived of sleep for all or most of the night—provokes activation beyond that of

sleep alone, with an additional 27–30% yield over a sleep electroencephalogram.^{39–41}

Neuroimaging

In the absence of trauma the use of CT or MRI when assessing patients with transient loss of consciousness should be reserved for patients presenting with a suspected first unprovoked seizure or with a focal neurological deficit. MRI is preferable for looking for neuronal migrational disorders, major malformations, vascular anomalies, and tumours. Those patients with clinical and electroencephalogram features of idiopathic generalised epilepsy do not require a brain scan. In a study by King and colleagues,³⁵ 300 consecutive patients with presentation of first seizure were assessed; 49 of 50 patients with a primary generalised seizure had a normal scan, whereas 26 of 154 patients with a focal onset seizure had potentially epileptogenic foci (diagnostic yield of 17%).

Electrocardiography

Electrocardiography has a role in investigating syncope in the setting of cardiac history or an abnormal cardiac examination, electrocardiogram, or chest radiograph. Sarasin and colleagues⁴² did a prospective observational study, and showed that electrocardiography was normal in all patients with a negative cardiac history and a normal electrocardiogram. However, in those with a positive cardiac history or abnormal electrocardiography, systolic dysfunction was found in 27% of patients, and this finding is highly predictive of an underlying arrhythmia.

Tilt-table testing

Head-up tilt-testing is now widely used in the evaluation of neurocardiogenic syncope,⁴³ although recent guidelines from the European Society of Cardiology recommend the test only in the setting of atypical histories.²⁶ Tilting induces orthostatic stress, causing decreased venous return. Usually, this would result in increased alpha and beta adrenergic tone and avert syncope. However, in neurocardiogenic syncope, the decrease in venous return increases sympathetic tone, with stimulation of cardiac C fibres. Subsequently, the vasodepressor area of the medulla is stimulated, leading to an increase in vagal tone, resulting in bradycardia and a reduction in sympathetic tone causing vasodilatation. For a head-up tilt-test to be positive there must be a reproduction of typical symptoms along with concomitant cardioinhibitory (bradycardic), cardiodepressor (hypotensive), or mixed response. Stimulation with low-dose isoproterenol, improves the yield from around 35% to 60–70%, and also reduces procedural time considerably, with a moderate reduction in specificity.⁴⁴ However, higher doses of isoproterenol can reduce the specificity to around 30%.⁴⁵

Electrophysiological testing

Cardiac-catheter based electrophysiological testing is done in most cases to establish the mechanism for a particular arrhythmia and to guide the selection of treatment. It is also indicated in syncope of undetermined origin. The diagnostic yield and likely diagnoses from an electrophysiological study largely depend on whether the patient has a normal resting electrocardiogram, and normal ventricular function. In patients with cardiac disease, conduction system abnormalities, and sustained ventricular tachycardia are the most common findings. In those with known ventricular tachycardia, the arrhythmia can be induced during an electrophysiological study in around 80% of patients by provocation.⁴⁶ In those without electrocardiography or valvular abnormalities, atrioventricular nodal re-entrant tachycardias and sinus node dysfunction can be found. However, the diagnostic yield of an electrophysiological study in this group can be as low as 12%.⁴⁷ Electrophysiological studies can be particularly helpful in the assessment of elderly patients with recurrent syncope, with a diagnostic yield of 68%.⁴⁸

Cardiac-rhythm monitoring

Standard 24 h Holter monitoring has a sensitivity of only 10%.^{49,50} Extending the monitoring period to 48 h or 72 h can yield a diagnosis in a further 10%.⁵¹ External loop recorders, usually worn for 1–2 months at a time, can improve the detection rate of arrhythmias with a yield of 25%, but the sensitivity is limited by patient tolerance of the dermal electrodes, the relatively short monitoring time, and patient failure to activate the loop recorder at the onset of symptoms.⁵² The yield of monitoring with an implantable loop recorder is high. 25–46% of patients will have an arrhythmia detected, whereas a further 24–42% will have sinus rhythm during recurrent symptoms, hence excluding an arrhythmogenic basis for the symptoms. Many of these patients are likely to have vasodepressor-mediated neurocardiogenic syncope.⁵³ Solano and colleagues⁵⁴ showed that implantable loop recording permitted a diagnosis in 50% of patients with recurrent unexplained syncope but otherwise normal results on cardiac work-up. Patients with asymptomatic arrhythmias during implantable loop recording might benefit from immediate intervention rather than waiting for a clinical event.⁵⁵ Limitations of implantable loop recording are its invasiveness and, in some patients, failure of device activation.

Video monitoring

Video monitoring with electroencephalography can be helpful in determining the nature of a seizure disorder, (ie, epilepsy, convulsive syncope, or psychogenic seizures) in a safe monitoring environment.⁵⁶ Two studies have shown that video electroencephalography can alter the diagnosis in 24–58%^{57,58} of patients, with the greatest yield in reclassifying patients with a diagnosis of

psychogenic non-epileptic seizures, even when the referral base is epileptologists.⁵⁹ Video electroencephalography is commonly thought of as a “last resort” test, although, patients who remain refractory after a trial of an antiepileptic drug or whose seizures remain undiagnosed after clinical assessment might benefit from a period of video electroencephalography monitoring. Video electrocardiogram is also useful in elderly people, who predominantly develop focal epilepsies of vascular aetiology, and can have an effect in management in up to 80–87% of these patients.^{60,61} Video electroencephalography is also useful where non-convulsive status epilepticus is suspected.⁶² Several other non-epileptic events, including cardiogenic syncope, can also be seen on telemetry, accounting for ten of 18 elderly patients in one study.⁶³

Management

Neurocardiogenic syncope

Although the results of pharmacological treatment of neurocardiogenic syncope have generally been disappointing, conservative measures such as education regarding the nature of the disorder, adequate fluid intake, avoidance of predisposing factors, and lying down during prodromal symptoms are useful. Also, isometric contractions of the limb muscles during prodromal symptoms can help stop syncopal attacks by enhancing venous return.^{63,64} Beta blockers are the most commonly used drugs for this disorder. Although there was initial hope that atenolol⁶⁵ or metoprolol⁶⁶ could reduce the number of syncopal attacks in patients with this disorder, the recurrence of neurocardiogenic syncope in patients treated with atenolol is similar to that of placebo,^{67,68} and can be detrimental in the cardioinhibitory forms of neurocardiogenic syncope. The Prevention of Syncope Trial⁶⁹ (metoprolol versus placebo) has shown no difference in syncope-free periods between the treatment groups at 1 year. Midodrine hydrochloride substantially improves orthostatic tolerance during head-up tilt testing in patients with recurrent syncope,⁷⁰ but is of most benefit to those with syncopal symptoms secondary to hypotension, rather than due to cardioinhibition.⁷¹ Fludrocortisone also improves orthostatic symptoms, by reducing the vasodepressor response, and can relieve the symptoms of carotid sinus syndrome,⁷² but larger studies are needed to study this further. Etilfrine hydrochloride, an adrenergic alpha receptor agonist, has also been studied in a double-blind, randomised, placebo-controlled trial and has not shown superiority to placebo.⁷³ Paroxetine has been effective in one placebo-controlled trial but further confirmatory studies are needed.⁷⁴

Permanent cardiac pacing has been studied in neurocardiogenic syncope, with conflicting results. Initial data have shown that there was no benefit with permanent pacing over intervention with drugs.⁷⁵

However a large benefit in favour of pacing with rate-drop response was seen in the North American Vasovagal Pacemaker Study,⁷⁶ resulting in early study closure. This benefit has not been repeated in a subsequent study comparing the recurrence of syncope in those with a pacemaker not actively paced with those with a rate-drop response pacemaker.⁷⁷ However, on balance, it seems that those patients for whom syncope is triggered by a cardioinhibitory event, rather than by hypotension, do benefit from a pacemaker.⁷⁸ However, neurocardiogenic syncope is commonly a benign disorder that does not usually require pacing unless the patient is having frequent or severe cardioinhibitory spells. The implantable loop recorder is useful in identifying such patients with severe cardioinhibitory neurocardiogenic syncope. Patients with cardioinhibitory carotid-sinus hypersensitivity randomly assigned to pacing have a lower incidence of recurrent falls.⁷⁹

Over the past decade implantable cardiac defibrillators have become widely available. The use of these devices is indicated not only for secondary prevention of ventricular arrhythmias,⁸⁰ but also primary prevention of sudden cardiac death in patients with congestive heart failure, of both ischaemic and non-ischaemic causes, and an ejection fraction of 35% or less.^{81,82} Amiodarone has no part to play in the prevention of sudden cardiac death in such patients. Implantable cardiac defibrillator implantation is also indicated in recurrent unexplained syncope in the setting of advanced structural heart disease.²⁶

Antiepileptic treatment

Those patients who are diagnosed with epilepsy can be treated effectively with drugs in most cases. About 50% of patients will become seizure free with the first drug given,⁸³ many doing so at moderate dosing. A further 20% will become seizure free on a second or third drug tried, and the remaining 30% will have intractable epilepsy. In terms of efficacy, many patients have done well on the classically used antiepileptic drugs such as valproic acid, phenytoin, and carbamazepine. Eight more anticonvulsants have come into use over the past 20 years. These drugs are gabapentin, lamotrigine, topiramate, tiagabine hydrochloride, oxcarbazepine, levetiracetam, zonisamide, and pregabalin, all of which have shown efficacy as add-on therapy in refractory epilepsy. The decision which antiepileptic drug to use is based on epilepsy and seizure classification, sex, reproductive status, concomitant medications, and the presence of relevant comorbidity. Recent recommendations from the American Academy of Neurology have identified gabapentin as being effective in the treatment of newly diagnosed partial epilepsy. Lamotrigine and topiramate are effective in mixed populations of both new-onset partial and generalised seizures.⁸⁴

Sudden unexpected death

One of the most compelling reasons to ascertain a diagnosis in a patient presenting with a seizure or syncopal event is to alleviate the rare yet tragic occurrence of sudden unexpected death.

“She rose from Dinner about four O’clock in better health and spirits than she appeared to have been in for some time; soon after which she was seized with one of her usual Fits, and expired in it in less than two minutes without uttering a word a groan or scarce a sigh. This sudden and unexpected blow, I scarce need add has almost reduced my poor wife to the lowest ebb of Misery.”

George Washington wrote these words upon the death of his step daughter Patsy Curtis at age 17 years, in 1773, capturing the devastation of sudden unexpected death in epilepsy.⁸⁵ This type of death is defined as a sudden unexpected non-traumatic, death without drowning in a person with epilepsy, with or without evidence of a seizure, excluding status epilepticus, in which postmortem examination does not reveal a cause of death. The exact incidence of sudden unexpected death in epilepsy (SUDEP) is uncertain. Langan and colleagues⁸⁶ estimated there to be 400 cases of SUDEP per year in England and Wales, but the National Sentinel Clinical Audit of Epilepsy-Related Death (2002) found that number to be much higher at approximately 700 deaths per year.⁸⁷ Walczak and colleagues⁸⁸ found that the incidence of SUDEP is 1.21 per 1000 patient years. Only 8–11% of such events are witnessed.^{89,90}

Risk factors are thought to include sleeping in the prone position, poor seizure control (particularly if there is seizure generalisation), multiple anticonvulsants, heavy alcohol consumption, and mental retardation.^{88–91} The exact mechanism of death in SUDEP is unknown. Respiratory compromise occurs, and may be due to obstructive apnoea or central apnoea (possibly due to epileptogenic spread to the medullary respiratory centres).⁹⁰ SUDEP may also be caused by a cardiac arrhythmia. Epileptic activity itself also induces life-threatening arrhythmias independent of cardiac disease.⁹² There is evidence from video electroencephalography studies that increased autonomic stimulation during seizures, particularly in sleep, may contribute to cardiac dysrhythmia.⁹³ Hilz and colleagues⁹⁴ have speculated that temporal-lobe epilepsy surgery, which reduces sympathetic cardiovascular modulation and baroreflex sensitivity, may contribute to reducing the risk of SUDEP. The National Sentinel Clinical Audit of Epilepsy-Related Death recommended better investigation and certification of epilepsy-related deaths and improved access to epilepsy care.⁸⁷

Sudden death may result as a complication of underlying cardiac disease. The most concerning for the general public in particular is sudden cardiac death in athletes, because of the demise of several high-profile young people. These are rare events in comparison to

sudden death in older people undergoing exertional activity, with an incidence of 1 per 100 000 in young athletes versus 1 in 15 000 for older people. Among the common causes in young athletes are hypertrophic obstructive cardiomyopathy (36%), idiopathic left ventricular hypertrophy, arrhythmogenic right ventricular dysplasia, coronary artery disease, aortic stenosis, myocarditis, and mitral valve prolapse.⁹⁵ Echocardiography is very helpful in detecting the most common of these causes, hypertrophic obstructive cardiomyopathy.⁹⁶ Screening athletes with echocardiography is controversial, as there is a high-false positive rate, necessitating echocardiography in a further 10%. A family history of premature death and of cardiac disease or a personal history of cardiac symptoms or heart disease, and abnormalities on cardiovascular examination warrant further investigation.⁹⁷

Another factor linked to sudden cardiac death is a prolonged QTc interval. This QTc interval is caused by cytochrome P450 isoenzyme 3A4 substrates, including erythromycin, cisapride, and antipsychotics, predisposing to torsades de pointes by blocking the potassium channel I(Kr), hence prolonging cardiac repolarisation.^{98–100} Ventricular arrhythmia tends to happen with concurrent administration of cytochrome P450 3A4 inhibitors such as diltiazem hydrochloride and nitroimidazole antifungal drugs. The hereditary long QT syndrome also predisposes to sudden cardiac death. The genetics of this condition have now been elucidated, with over 250 mutations in seven different genes identified, encoding various subunits of cardiac potassium or sodium channels.¹⁰¹ However, mutations remain unidentified in 30% of families with this disorder. Syncope during exertion warrants a search for hereditary long QT syndrome, including genetic testing if results of cardiac assessment are normal because a normal echocardiography does not exclude this disorder, and the QTc values of carriers and non-carriers overlap.¹⁰² Another potentially fatal arrhythmogenic disorder is the Brugada syndrome, characterised by right bundle branch block and ST-segment elevation of the “coved” type in leads V₁–V₃, predisposing to ventricular arrhythmias or sudden death in up to 8% over a 2 year follow up.¹⁰³

Practical approach to loss of consciousness

The practical approach to the diagnosis of loss of consciousness begins with a hypothesis based on medical history (panels 1 and 2), physical examination, and patient characteristics. This hypothesis should initially drive either a predominantly neurological or predominantly cardiac assessment (figure 2). The basic investigations in nearly all cases will include basic laboratory investigations (full blood count, urea and electrolytes, liver function tests, glucose, calcium, phosphate, and magnesium) and an echocardiogram. Any patient who presents with anything other than a

clear history of an epileptic seizure should also be monitored, initially at least, with cardiac telemetry. Additional investigations can then be determined by the presence or absence of key neurological or cardiac features dictated by the history and physical examination. For example, in patients who have a murmur or an abnormal echocardiogram at presentation, an echocardiogram is essential. By contrast, patients with both normal cardiac examination and echocardiogram do not require routine echocardiography. A cardiac cause of syncope should be strongly suspected in patients with structural heart disease, in particular those with a history of myocardial infarction in whom ventricular tachycardia commonly results in syncope. Many patients in whom the diagnosis is uncertain or remains elusive often undergo extensive cardiac and neurological investigations including Holter monitoring, invasive electrophysiological studies, stress testing, cardiac event recordings, electroencephalography, and sleep deprived electroencephalogram monitoring. Patients with intermittent loss of consciousness in whom a diagnosis cannot be made may benefit from an implantable loop recorder to secure a diagnosis of arrhythmogenic syncope. Empirical treatment with a well tolerated anticonvulsant and close follow-up might occasionally be required, in order to try to bring about a timely therapeutic response in a potentially life-threatening situation. Also, it is important to advise the patient not to drive until a diagnosis is obtained and the symptoms are under control.

Conclusions

The successful diagnostic assessment and management of the patient presenting with a paroxysmal loss of consciousness is rooted in the basic clinical principles of obtaining a detailed patient history and witness account, followed by physical examination and the appropriate use of investigations. This is of vital importance as many of the potential diagnoses are associated with a high mortality, and even recurrent "benign" neurocardiogenic syncope is dangerous and carries considerable morbidity.

Authors' contributions

AM designed and wrote the review and collected the data. CV revised the review for important intellectual content and wrote the "practical approach" section. ND developed the initial idea, contributed to the design of the review, and revised the paper at its different stages of development for important intellectual content.

Conflicts of interest

AM has no conflicts of interest. CV has received speaker's honoraria from Pfizer, Merck Sharpe and Dohme, Bristol Myers Squibb, Novartis, Solvay, and Menarini. ND has received unrestricted educational and research grant support from the following pharmaceutical companies: UCB Pharma, Elan Pharma, GlaxoSmithKline, Janssen Cilag, Pfizer, and Novartis. He is or has also been a member of UCB Pharma Advisory Board (UK), Eisai Advisory Board (Europe), Pfizer Advisory Board (Europe), and the Irish advisory boards of Janssen Cilag, GlaxoSmithKline, and Elan. He has also received speaker's honoraria from UCB Pharma, Janssen Cilag, and Shire. The decision to write and submit this review was entirely his, and was not in any way influenced or initiated by any pharmaceutical company.

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1966 to September 2005. The terms "syncope", "seizure", "epilepsy", "cost", "psychogenic", "ECG", "Holter", "loop recorder", "CT", "MRI", "EEG", "video-EEG", "echocardiography", "tilt-table testing", "electrophysiologic testing", "treatment", "guidelines", "SUDEP", and "sudden cardiac death" were entered. Articles were also identified through searches of the references of articles and the authors' own files. Several references were excluded. Only papers published in English were reviewed. The final list was generated from original references relevant to the topics covered in the review.

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