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Is it possible to accurately differentiate neurocardiogenic syncope from epilepsy?

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Abstract

Global cerebral hypoperfusion resulting in syncope, and asynchronous discharge of cerebral neurons leading to seizure, are two major mechanisms of transient loss of consciousness. They both have a lot in common in clinical and historical settings, although with a high prevalence of incorrect diagnosis, even by well-trained staff. The aim of this review was to try to combine data from both a cardiologist's and a neurologist's perspective (history taking, special questionnaires, serum prolactin, EEG, CT/MRI, tilt-testing, loop recorders). (Cardiol J 2010; 17, 4: 420–427)

Key words: syncope, epilepsy, differential diagnosis

Introduction

Transient loss of consciousness (TLOC) may have many underlying mechanisms. According to the Guidelines of the European Society of Cardiology (ESC), *syncope* is a TLOC due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery [1]. Epilepsy (seizure) is characterized as an excessive asynchronous discharge of cerebral neurons leading to a clinical event [2]. There is one more term: 'convulsive syncope', otherwise known as cerebral anoxic seizure activity secondary to transient global impairment of blood flow, which is no longer recommended for use in clinical practice by the ESC Task Force 'because it carries the risk of increasing confusion between syncope and epilepsy' [3].

Epilepsy and syncope are conditions with prevalence rates in the general population of around 1.5 and 3/100, respectively [4, 5] In the general population, the first episode of syncope usually occurs during childhood, while the second peak is around the age of 65 [1]. In developed countries, age-adjusted incidence of epilepsy ranges from 24–53 per 100,000 individuals [6].

However, epilepsy and syncope are two clinical entities with a high prevalence of incorrect initial diagnosis. Both retrospective and prospective studies suggest that one in four patients with 'epilepsy' are misdiagnosed, based on clinical review and tilt testing [7–12]. Moreover up to 30% of patients have either intractable or uncontrolled seizures or suffer significant adverse side effects secondary to medication [6]. It is well-known that cardiac rhythm can be affected by anticonvulsant drugs, particularly carbamazepine, which may cause an atrioventricular (AV) block.

Even nowadays, psychological reactions to epilepsy remain almost the same as they were in the Middle Ages, with anxiety and fear the commonest emotions (fear of a seizure itself, injury or death pertaining to it, opportunity to lose driving license, lose career, educational restrictions etc) [13].

According to the report published by the All Party Parliamentary Group (APPG) on Epilepsy in June 2007, the human and economic costs of epi-

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Table 1. Syncope *vs* seizures: general differences (adapted from [15, 19–21]).

	Syncope	Seizures
Triggers	Frequent	Rare
Preceding symptoms	Nausea, visual blurring, epigastric sensation, heat, headache, tinnitus	Sensorial, psychic, somatosensory 'auras' or motor phenomena
Position	Usually while standing or sitting; supine very rare	Any
Blanks	'Fading away' in young patients or abrupt loss in elderly persons	Abrupt loss
Fall	Slow, flaccid	Fast, tonic
Skin color	Pale	Sometimes acrocyanosis
Eye deviation	Transient upward or lateral deviation	Sustained lateral deviation
Incontinence	Common	Common
Tongue bite	Uncommon; localization: on the tip of the tongue	Common; localization: on the side of the tongue
Convulsions	Lasts few seconds, arrhythmic, multifocal or generalized	May last few minutes, rhythmic, generalized
Duration	3–30 s	Depends on the type of seizures: up to 5 min for GTCS and shorter for others
Postictal period	Somnolence, headache (no longer than 2 h in most cases)	Confusion, somnolence, headache

GTCS — generalized tonic-clonic seizure

lepsy in England are rather high. They included 400 avoidable deaths per year, 69,000 people living with unnecessary seizures, 74,000 people taking drugs they do not need, and eventually GBP 189 million pointlessly spent each year [14].

Syncope and epilepsy (tonic-clonic seizure especially) have a lot in common in clinical and historical settings. However, making the correct diagnosis can be quite difficult, even for well-trained physicians. There are a lot of outstanding papers devoted to this problem [9–12, 15, 16]. The aim of this review was to try to combine data from both a cardiologist's and a neurologist's perspective.

History

Most patients have their first episode of TLOC between the ages of 10 and 18, although the frequency of syncope is much higher over this period. History obtained from the patient (and witnesses) is often the most important information in establishing the diagnosis in classical cases (Table 1). Syncope is usually triggered, while epilepsy rarely is. Predisposing factors for syncope are: prolonged standing, being in overcrowded/overheated places, pain stimulation or stressful situations, coughing, micturition, defecation. Nevertheless, both disorders may be provoked by excessive fatigue, sleep deprivation, too much watching TV or alcohol abuse. Despite that, epilepsy has its own specific triggers such as flashing lights. In contrast to epilepsy, syncope occurs in the supine position very rarely and only some casuistic cases have been reported [17, 18].

Young patients with syncopal attacks usually describe a lot of preceding symptoms: nausea, vomiting, abdominal discomfort, a feeling of being cold or hot, sweating, blurred vision before the fall. On the other hand, in older patients, loss of consciousness occurs so rapidly that they do not have time to sit down or call for help before they fall down with various injuries. Before epileptic fits, some patients have an 'aura' (e.g. anxiety or fear, unusual sound or taste perception, unpleasant smell perception, rising sensation in the abdomen or stomach-ache with the urge to defecate), but some seizures have no distinct prodromal period. Some authors have reported that the rising sensation may rarely occur in syncope [19].

The first two issues of the ESC Guidelines for the diagnosis and management of syncope gave special attention to the use of the term 'convulsive syncope': 'Myoclonic jerks are very often interpreted as epileptic by physicians as well as eyewitnesses, but not all such movements should be considered as epilepsy. The description of such movements should be neutral, in order to prevent an

immediate connotation with epilepsy'. It is a well-known fact that convulsions are accompanied by syncopal attacks in most cases (usually 70–80%, ranging from 12% up to 100% according to the type of registration) [20–23].

Movements can be present in both epilepsy and syncope. With the latter, they occur only after the fall, and are considered to be an integral component of the brain's response to hypoxia. The duration of epileptical movements is much longer. They can last several minutes, while in syncope they only last a few seconds. The jerks in epilepsy are coarse, rhythmic, and usually synchronous and violent. They can even affect the whole body, whereas those in syncope are usually asynchronous, small, and non-rhythmic. Synchronous jerks can occur in syncope, although they are rare. It should be taken into consideration that eyewitnesses sometimes incorrectly report movements.

Nevertheless, complete flaccidity during unconsciousness argues against epilepsy. The only exception is 'atonic seizure', but this is rare, and occurs without a trigger in children with pre-existing neurological problems.

Complex movements or automatisms (lip-licking, chewing, fumbling, reaching for the head, head raising etc.) rarely occur in syncope. Lempert et al. [21] have provided the only report of automatism in up to 80% of patients with syncope. In contrast to epilepsy, most of these movements were of short duration and solitary rather than repetitive.

Eye movements (nystagmus, upward turning, deviation) also can take place in both epilepsy and syncope, but in everyday life they are often missed by eyewitnesses and doctors. Epileptic eye deviations tend to last longer than syncopal eye turns

The aforementioned definition of syncope implies spontaneous, complete, and prompt recovery of consciousness, for no longer than 30 seconds in classical cases. Thus, any post-ictal disorientation lasting longer than that should automatically suggest an epileptic seizure. However, our data showed that up to one third of patients complained of exhaustion, sleepiness, vomiting, headaches and muscle aches which occurred after syncope [24]. We concluded that post-ictal phenomena may accompany both epilepsy and syncope. Hence, the duration and severity of the post-ictal period is more prominent after generalized tonic-clonic seizures (GTCS), with drowsiness, adynamia and amnesia as the commonest features.

Head injuries and other traumas, as well as urinary incontinence, appear to be equally common in syncope and GTCS. Tongue biting, common in seizures, is very rare in syncope. This occurs on the side of the tongue in epilepsy, and the tip in syncope. It should be noted that observation of such symptoms as convulsions, incontinence, tongue biting and a long post-ictal period with confusion during syncope are usually related to the duration of asystole or severe bradycardia.

Sheldon et al. [25] proposed a simple points score to distinguish syncope from seizures by historical features. A 118-item questionnaire was administered to 671 patients with TLOC referred to three academic centers in Canada and Wales. The causes of TLOC were known satisfactorily in 539 patients and included seizures (n = 102; complex partial epilepsy [50 patients] and primary generalized epilepsy [52 patients]) and syncope (n = 437; tilt-positive vasovagal syncope [267 patients], ventricular tachycardia [90 patients] and other diagnoses such as complete heart block or supraventricular tachycardia [80 patients]). Such features as cut tongue after spells; deja vu or jamais vu before spells; emotional stress as a provocative factor; head turning during a spell; unresponsive or unusual posturing, or jerking limbs during spells; no memory of spells afterwards; all of these were in favor of seizures. On the other hand, a history of lightheaded spells, sweating before spells, and prolonged sitting or standing were identified as provocative factors that supported syncope. The points score, based only on symptoms, correctly classified 94% of patients, diagnosing seizures with 94% sensitivity and 94% specificity.

Later, another points score was proposed to the same group to determine whether syncope was vasovagal in origin, with 89% sensitivity and 91% specificity [26]. In this study, 418 patients with syncope and no overt cardiac disease completed the same 118-item historical questionnaire as in the previous paper. A positive tilt test was used as a 'gold standard'. The causes of syncope were known in most cases and included tilt-positive vasovagal syncope (235 patients) and other diagnoses such as complete AV-block and supraventricular tachycardia (88 patients).

However, when this points score was applied to 380 patients admitted with TLOC to five departments of the university hospital, i.e. Neurology, Cardiology, Internal Medicine, Emergency Department and Cardiac Emergency Room, its sensitivity remained comparable with the one in the original study (87%), but its specificity significantly dropped (32%) [27].

Although a careful history remains key to differentiating seizures from syncope, additional investigations may sometimes help to settle doubt-

ful cases. This is especially true because hypoxic and epileptic mechanisms may interact within one attack, and instrumental diagnostics may be helpful in such situations.

Electroencephalography

Rest electroencephalography (EEG) provides different types of information: confirmation of abnormal electrical activity, type of seizure disorder and location of the focus [28]. Fainting is the commonest reason for referral for EEG, with up to 20% of the population revealing non-specific abnormalities open to misinterpretation [29]. It is recommended to perform electroencephalographic studies 48 hours or more after a suspected seizure, because obtaining an electroencephalogram shortly after a seizure may lead to misleading findings. In half of patients with epilepsy, a single EEG shows no abnormalities.

It is very important to remember that the absence of epileptiform activity on EEG cannot absolutely exclude seizures. If the suspicion of epilepsy is high, another EEG should be obtained after the patient has been deprived of sleep. This approach may reveal abnormalities. Videomonitoring also may reveal evidence of a clinical event or paroxysmal activity. When the etiology of TLOC is doubtful, long term follow-up and videotelemetry with simultaneous EEG and ECG recording is required. After all, in 10% of persons with true seizures, multiple electroencephalographic studies show no abnormalities [28].

EEG findings during a syncopal attack reflect cerebral hypoperfusion. Initially, there may be a slowing of background rhythms, followed by high amplitude delta activity. Persistent hypoperfusion usually leads to subsequent flattening of the EEG, returning to normal in the reverse sequence [30].

Neuroimaging

Computed tomography (CT) and magnetic resonance imaging (MRI) can sometimes be helpful in diagnostics. The American Academy of Neurology has published (and regularly updates) practice guidelines for neuroimaging studies in patients who have had a first seizure. Usually, MRI scanning is preferable to CT because it is more likely to reveal small lesions such as tumors or mesial temporal sclerosis (AAN Guidelines [31]). It is an emergency test in patients with suspected serious structural lesion, fever, recent trauma, persistent headache, or a history of cancer or anticoagulant therapy and those who may suffer from AIDS.

Table 2. Neurological evaluation according to ESC Guidelines [1].

Recommendations	Class	Level
Neurological evaluation is indicated in patients in whom TLOC is suspected to be epilepsy	I	C
Neurological evaluation is indicated when syncope is due to autonomic failure in order to evaluate the underlying disease	I	C
EEG, ultrasound of neck arteries, and CT or MRI of the brain are not indicated, unless a non-syncopal cause of TLOC is suspected	III	B

TLOC — transient loss of consciousness

According to the latest ESC Guidelines, there are no studies evaluating the usefulness of brain imaging for syncope patients and in uncomplicated cases they should be avoided [1]. Indications for neurological evaluation are summarized in Table 2.

Beacher et al. [32] were the first, to our knowledge, to compare patients with neurocardiogenic syncope to matched controls who had never fainted. Associations between brain morphometry (regional gray and white matter volumes) and syncope, resting physiology and anxiety were studied by voxel-based morphometry, a user-independent computerized method of comparing regional brain anatomy. It was shown that patients with a syncopal history had lower regional brain volume within medulla and midbrain. Moreover, lower gray matter volume in contiguous regions of left caudate nucleus predicted increased parasympathetic tone, fainting frequency and anxiety levels. The authors suggest these findings are preliminary evidence of a hierarchical anatomical basis to neurocardiogenic syncope.

Serum prolactin

A prospective study confirmed that plasma prolactin concentration was highly predictive of true epilepsy but barely predictive of syncope or pseudo-seizures [33].

The American Academy of Neurology considered assessment of serum prolactin level to be of limited value in diagnosing epileptic seizures, and distinguishing them from syncope [34]. Published data showed its higher sensitivity for generalized tonic-clonic seizures (60.0%) than for complex par-

Table 3. Differentiation of syncope from epilepsy with head-up tilt-testing [1].

Recommendations	Class	Level
Tilt testing may be considered for differentiating syncope with jerking movements from epilepsy	IIb	C
Tilt testing may be indicated for evaluating patients with recurrent unexplained falls	IIb	C

tial seizures (46.1%), with similar high specificity for both (96%). Elevated serum prolactin, at 10 to 20 minutes after a suspected event, is a useful adjunct for the differentiation of generalized tonic-clonic or complex partial seizure from psychogenic non-epileptic seizure among adults and older children.

A meta-analysis by Ahmad and Beckett [35] also showed the usefulness of raised serum prolactin in diagnosing GTCS in patients presenting to the emergency department after a single episode of TLOC. They concluded that serum prolactin should be measured in patients presenting within an hour of a syncopal episode, unless the cause is immediately obvious. Nevertheless, serum prolactin level does not provide an absolutely clear distinction between epileptic seizures and syncope. Its elevation was observed in patients with tilt-induced syncope in at least two studies [35, 36].

In general, neurological evaluation helps diagnose the neurological disorders that cause syncope or resemble it (summarized in Table 2).

Tilt-testing with/without simultaneous EEG

The role of head-up tilt-testing (HUT) in neurocardiogenic syncope has been established since 1986, in many studies. Current ESC Guidelines recommend tilt-testing to discriminate syncope with jerking movements or unexplained falls from epilepsy. However ,both indications have evidence of IIb class and level C only (Table 3).

In some studies, simultaneous EEG monitoring has been performed during the HUT and most authors showed diffuse brain waves slowing during a syncopal episode [37–41]. Ammirati et al. [39] observed the appearance of theta waves at the onset of syncope, followed by an increase of brain-wave amplitude with the reduction of frequency (delta range) in vasodepressor response. The return to the supine position was associated with restoration of a normal EEG pattern. The onset of cardioinhibitory syncope was characterized by generalized slowing in the theta range, and then in the delta range. A sudden reduction of brain-wave amplitude then ensued, leading to the disappearance of electrocerebral activity (a 'flat' EEG). The return to the supine position did not allow either the immediate resolution of EEG abnormalities or consciousness recovery.

We also studied the prevalence of epileptiform findings and its influence on the result of HUT in neurocardiogenic syncope (NCS) [40]. Epileptiform findings were observed on initial EEG or during the active phase of the HUT in 20 (22%) of 91 patients (nine male/11 female, aged 17–54) with NCS, nine of whom (45%) had been previously diagnosed as epileptic (different forms). HUT was positive in seven of the 20 patients (35%). Among them, mixed (1) type was observed in three patients, vasodepressor (3) type in two, and postural orthostatic tachycardia in two. Of nine epileptic patients, positive HUT was observed in three (one case each for mixed, vasodepressor response, and postural orthostatic tachycardia).

Mercader et al. [41] observed in five of six HUT positive patients slow wave activity that lateralized to the left side of the brain. None of the HUT negative patients exhibited such lateralization. It is noteworthy that lateralization preceded the event by between 5 and 56 seconds (18 ± 21 s). The authors suggest that the central nervous system may play a role in the development of syncope.

Loop recorders

Implantable loop recorders (ILR) have identified serious arrhythmias in patients with repeated syncope [42]. However, their role in distinguishing syncope from seizures is less well-established. Rugg-Gunn et al. [43] observed 20 patients with epilepsy and ILR, and 377 seizures were registered altogether. In 16 patients, median heart rate during habitual seizures exceeded 100 bpm. Ictal bradycardia (< 40 bpm) or asystole occurred in eight (2.1%) recorded events in seven patients. Permanent pacemakers were implanted in four of them later.

Ictal bradycardia/asystole syndrome is mostly related to temporal lobe epilepsy, predominantly in male patients aged older than 50 [44–49]. The diagnosis is based on simultaneous EEG and electrocardiography (ECG) recording with electrographic seizure activity preceding severe bradycardia/asystole or AV-block. A combination of antiepileptic treatment and pacemaker therapy might be required in such patients. The clinical characteristics

Table 4. Major confusing aspects.

Cardiology	Neurology
Inadequacy of trigger factors to the severity of spells	Ineffective 'ex juvantibus' treatment with anticonvulsant drugs
Repeated syncope over a short period of time	Treatment-resistant epilepsy
Fainting in supine position	Active antiepileptic treatment is followed by increase in attack frequency or change in attack characteristics
Pronounced acrocyanosis during syncope	Severe bradycardia or other rhythm disturbances, induced by anticonvulsant drugs
Prolonged drowsiness or/and confusion of consciousness after recovering from a syncopal episode	'True' ictal bradycardia/asystole
Family history for epilepsy	Normal or nonspecifically abnormal EEG
Epileptiform activity on EEG in patients with neurocardiogenic syncope	

of patients with ictal ECG abnormalities are closely similar to those at greatest risk of sudden unexpected death in epilepsy.

Another specific pattern was described on ECG after ILR implantation in the year 2000 [50]. Simpson et al. [50] presented a case report of a 76 year-old man with a history of infrequent episodes of TLOC. Two months after ILR implantation, he was readmitted to the Emergency Department after another fall. His heart rhythm before TLOC was sinus tachycardia, followed by prominent muscle artifact, and restoration of sinus rhythm afterwards with heart rate returned slowly to normal.

Ho et al. [51] revealed identical ILR recordings in all 12 generalized tonic-clonic seizure episodes detected by ILR in six patients with epilepsy. This pattern consisted of a tonic phase (sustained, rapid, high-frequency myopotentials) transitioning to a clonic phase (periodic bursts of high-frequency myopotentials with a decelerating burst frequency from 3–6 Hz to 1–2 Hz) prior to seizure termination. Unfortunately, all episodes had not been automatically detected by ILR and required activation by family members. None of the 76 non-generalized tonic-clonic seizure episodes recorded on the ILR in 14 patients exhibited this stereotypical tonic-clonic pattern.

Petkar et al. [52] presented data from the REVISE trial (Reveal in the Investigation of Syncope and Epilepsy) at the last European Cardiology Congress in Barcelona. The aim of the study was to determine the incidence of misdiagnosis of epilepsy as determined by ILR and the value of tilt testing in this group of patients. Patients misdiagnosed with epilepsy, or where the diagnosis of epilepsy was in doubt, were enrolled in the study. It comprised 32 patients altogether, 21 of them (67.7%) female, mean age 38.2 (17–79 years), with three or more episodes of TLOC in the last 12 months and normal, equivocal or non-diagnostic 12 lead ECG, echocardiogram, 24 hour ECG, standard unprovoked EEG and brain CT/MRI.

ECG-symptom correlation by ILR was achieved in 19 of these (59.4%) patients; specifically: asystole in five (26.3%), muscle artefacts suggestive of tonic-clonic seizures in three (15.8%) and normal sinus rhythm in 11 (57.9%) patients. Four of the five patients with asystole underwent permanent pacemaker implantation, and two of them remained subsequently asymptomatic. The study showed the usefulness of the ILR in diagnosing typical epilepsy by the pattern of muscle artefacts with no correlation found between the results of HUT and ILR in this group of patients.

Other devices manufactured to detect symptoms thought to be due to an arrhythmia are mobile cardiac outpatient telemetry system and external loop recorders [53]. Driver et al. [54] demonstrated the usefulness of noninvasive, mobile, continuous outpatient rhythm monitoring to diagnose seizure-related arrhythmias.

Conclusions

Misdiagnosis of epilepsy remains a major clinical problem. One way forward is for cardiologists, neurologists, and psychiatrists to collaborate in the investigation of fits, faints, and blackouts. This should improve the speed and accuracy of diagnosis and eliminate unnecessary and costly investigation or prolonged, unnecessary, and potentially dangerous treatments. Major confusing aspects are summarized in Table 4 above.

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