Recurrent unexplained syncope may have a cerebral origin: Report of 10 cases of arrhythmogenic epilepsy

Synapses récidivantes inexpliquées d’origine cérébrale : à propos de dix observations d’épilepsie arythmogène

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KEYWORDS
Syncope; Asystole; Temporal lobe epilepsy; Antiepileptic drugs

Summary
Background. — Despite thorough investigation, ∼15–20% of syncope cases remain unexplained. An underrecognized cause of syncope may occur when partial epileptic discharges profoundly disrupt normal cardiac rhythm, including cardiac asystole, the so-called arrhythmogenic epilepsy (AE).

Aim. — To report initial results of observations of AE in patients with recurrent, unexplained, traumatic and/or convulsive syncope.

Methods. — Ten patients aged 49 ± 20 years (median 49.5 years; nine women) underwent complete cardiological (including ambulatory Holter electrocardiogram (ECG), echocardiography and head-up tilt test [plus electrophysiology in four patients]) and neurological (including standard electroencephalogram [EEG], computed tomography [CT] and magnetic resonance imaging scan [MRI]) assessments.

Results. — After initial evaluation, neurocardiogenic syncope was suspected in six patients with tilt-induced hypotension±bradycardia. Further evaluation (prolonged inpatient video-EEG/ECG monitoring) was undertaken because of non-diagnostic syncope or uncertainty about the diagnosis of neurocardiogenic syncope. While monitored in the neurophysiology lab, a syncopal episode similar to the spontaneous episodes recurred in all 10 patients. Cardiac asystole preceded by partial seizure of temporal onset was documented in nine patients; a
Background

Syncope is a fairly common medical disorder that accounts for up to 3% of emergency department visits and ~1–6% of hospital admissions [1]. Numerous studies have delineated the multiple potential causes of syncope, which range from benign to life-threatening conditions [2–4]; those that occur most frequently are cardiovascular (neurally-mediated reflex syncope, arrhythmia) or neurological (seizures, transient ischaemic attack). In most cases, the cause is obvious from the clinical picture [5,6]. Clinical findings that suggest a cardiovascular pathophysiology are dizziness or light-headedness before the event and the regaining of consciousness shortly after resuming the supine position, whereas prolonged confusion and myoclonic jerks are suggestive of epilepsy. Patients with cardiovascular syncope may, however, have myoclonic jerks, tonic spasms or urinary incontinence due to transient cerebral hypoperfusion — the so-called convulsive syncope [7]. These patients do not require antiepileptic drugs, but rather need further evaluation and treatment of their cardiovascular disorder. Conversely, patients with partial seizures may have cardiac arrhythmias, including asystole, which, in turn, can cause syncope — the so-called arrhythmogenic epilepsy (AE) [8–11]. When diagnosed appropriately, these patients may benefit more from antiepileptic medications than from treatment of their arrhythmias, although a pacemaker could be protective for those with asystole whose seizures cannot be controlled.

Cardiac asystole provoked by epileptic seizures is rare [10,11] and only few case reports have been published. Identification of individual patients is challenging because of the therapeutic implications. Indeed, implantation of loop recorders, which provide a symptom-rhythm correlation from a spontaneous episode, is becoming the investigative tool of choice in the setting of recurrent, unexplained syncope [12].

This article reports the initial results of observations of AE in 10 patients referred for evaluation of recurrent, unexplained, traumatic and/or convulsive syncope. All diagnoses were made after documentation of syncope, asystole and electroencephalographic evidence of preceding epileptic activity. These records allowed us to discuss the evidence and consequences of this unusual presentation of unexplained syncope.

second-degree atioventricular (AV) block with a cardiac rhythm of 30 beats per minute preceded by partial seizure of temporal onset was noted in one patient. Eight patients were treated successfully with antiepileptic drugs; two were refractory to antiepileptic therapy and required pacemaker implantation. No patient had recurrent syncope during a median follow-up of 102.5 months (mean 82.2 ± 42; range 16–128 months).

Conclusions. — In patients with recurrent, unexplained, traumatic and/or convulsive syncope, AE should be considered as a possible aetiology.

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Case reports

Initial report, study hypothesis and patient selection

The first, previously reported, case of this series was a 37-year-old woman with no previous medical history, admitted to hospital for the evaluation of unexplained syncope, sometimes associated with generalized fits [13]. Standard, non-invasive, cardiovascular investigation was non-diagnostic. The head-up tilt test induced a presyncopal episode without reproducing the clinical symptoms. In view of the discordance between tilt test-induced and spontaneous symptoms, a neurological point of view was requested. During

Figure 1. Simultaneous EEG/ECG recording in patient #1. a: ↓ partial seizure onset with only electrical abnormalities; the patient is asymptomatic. Recording of spike waves over the left centrotemporal region. The ECG channel shows sinus tachycardia at 120 beats per minute; b: sinus arrest after complete AV block complicated by generalized epilepsy reproducing the clinical symptoms.
described previously[14]. Reproduction of symptoms associ-
head-up tilt test was performed according to a protocol
and echocardiography. A 24-hour Holter ECG documented
All patients had a normal physical examination, 12-lead ECG
evaluation
Initial cardiovascular and neurological
had no cardiac disease. #2, #8 and #9 had a history of mild hypertension; the others
suddenly loss consciousness; they did not look pale and did
turn cyanotic. In patients #3, #4 and #6, a possible his-
history of ‘black-outs’ lasting inferior to 1 min was noted and
patient #7 mentioned a possible history of hallucinations and
oral automatisms. Patient #9 reported transitory aphasia
history of 'black-outs' lasting inferior to 1 min was noted and
in patient #5 and the provocative phase in patients #1, #2,
Patient #7 had a sudden, brief (< 30 s) loss of
related to complete AV block followed by sinus arrest in
patient #1 (Fig. 1) and sinus arrest in patients #2—#8 and
#10 (Figs. 2—4), during which all had syncope with bilateral
tonic spasms and generalized epilepsy, sometimes accom-
panied with suppression of the EEG. A second degree AV
block with a cardiac rhythm of 30 beats per minute was doc-
umented in patient #9. Consciousness was restored after
the heart rhythm returned to normal. Post-ictal disorien-
tation was not prominent. These ictal EEG changes differ
significantly from those recorded in patients undergoing a
long ECG and EEG recordings, and magnetic resonance
imaging (MRI) brain scans in the neurophysiology lab. In-
patient video-EEG/ECG recording was carried out within
48h to 5 days of the initial assessment. Standard ECG
and EEG recording equipment was used, with an addi-
tional digital video camera. EEG monitoring was performed
by using surface electrodes placing according to the
international 10–20 system, with additional T1/T2 or sphen-
odial electrodes and two electrodes for continuous
ECG co-registration [15]. Comprehensive electrophysiol-
gical information obtained from continuous video-EEG/ECG
recordings was analysed.
Ictal EEG activity was evaluated for lateralization, onset,
progression and distribution, to correlate this information
with the onset, duration and type of the co-registered asy-
tolic event, and with semiologic phenomena observed in the
split-screen video monitoring. ECG analysis was done inde-
pendently by a cardiologist and the EEGs were analysed by
an epileptologist.

Clinical presentation and baseline
characteristics of the study population
Patients and witnesses underwent careful interrogation
regarding symptom burden, provocative situations, perisync-
copal symptoms and relevant medical history. The AE
patients were aged 49.3 ± 20 years (median 49.5 years),
were predominantly women and presented with a history of
multiple episodes of abrupt loss of consciousness (median
8) for which no prodrome was reported. Witnesses reported
that the patients appeared completely normal until they
suddenly lost consciousness; they did not look pale and did
not turn cyanotic. In patients #3, #4 and #6, a possible his-
tory of 'black-outs' lasting inferior to 1 min was noted and
patient #7 mentioned a possible history of hallucinations and
oral automatisms. Patient #9 reported transitory aphasia
(< 30 min) only after their last recurrent syncope. Patients
#2, #8 and #9 had a history of mild hypertension; the others
had no cardiac disease.

ECG and EEG correlates during the event, and
therapeutic approach
In all ten patients, prolonged EEG/ECG monitoring captured
unprovoked or provoked partial seizures. Ictal EEG changes
always preceded the clinical onset. Patients #2, #4 and
#6 reported auditory hallucinations and complained of a
strange unease associated with visceral symptoms of nau-
sea and warmth. A left (patients #1, #4—#7, #9 and #10) or
right (patients #2, #3 and #8) temporal EEG discharge ac-
ivity of increasing amplitude and rate was recorded. Within
5–10s of seizure onset, an abrupt, short period of brady-
cardia was followed by prolonged asystole lasting 10–40s,
related to complete AV block followed by sinus arrest in
patient #1 (Fig. 1) and sinus arrest in patients #2—#8 and
#10 (Figs. 2—4), during which all had syncope with bilateral
spasms and generalized epilepsy, sometimes accom-
panied with suppression of the EEG. A second degree AV
block with a cardiac rhythm of 30 beats per minute was doc-
umented in patient #9. Consciousness was restored after
the heart rhythm returned to normal. Post-ictal disorien-
tation was not prominent. These ictal EEG changes differ
significantly from those recorded in patients undergoing a
combined EEG/tilt test for the evaluation of convulsive syn-
cope (Fig. 5). MRI brain scans were always normal except in
patient #2, in whom posttraumatic sequelae were noted.
Patients therefore fulfilled the criteria for the diagnosis of
AE and were treated subsequently with various combinations
of antiepileptic drugs. Table 2 summarizes the ictal cardiac
manifestations of the study patients.
Table 1  Clinical characteristics and initial cardiovascular and neurological evaluations.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex (age)</th>
<th>Syncope duration (yrs)</th>
<th>No. of syncopes</th>
<th>Trauma/injury/convulsion</th>
<th>Baseline ECG</th>
<th>Holter ECG</th>
<th>TTE</th>
<th>60 head-up tilt test</th>
<th>EP study</th>
<th>Standard EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F (37)</td>
<td>4</td>
<td>20</td>
<td>Yes/Yes/Yes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypotension</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>F (77)</td>
<td>5</td>
<td>3</td>
<td>Yes/Yes/Yes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypotension +bradycardia</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>F (47)</td>
<td>2</td>
<td>20</td>
<td>Yes/Yes/Yes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>1st degree AV block</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>F (54)</td>
<td>8</td>
<td>14</td>
<td>Yes/No/No</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypotension</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>M (52)</td>
<td>1</td>
<td>3</td>
<td>Yes/No/No</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypotension +bradycardia</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>F (21)</td>
<td>2</td>
<td>10</td>
<td>Yes/Yes/Yes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Loss of postural tone with normal HR and BP</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>F (29)</td>
<td>18</td>
<td>5</td>
<td>Yes/Yes/No</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>F (83)</td>
<td>3</td>
<td>6</td>
<td>Yes/No/No</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Incomplete RBBB</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>F (59)</td>
<td>2</td>
<td>8</td>
<td>Yes/Yes/No</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Paroxysmal AVB</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>F (34)</td>
<td>0</td>
<td>8</td>
<td>Yes/Yes/Yes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
</tbody>
</table>

During control EEG/ECG monitoring, antiepileptic therapy had no impact on the symptoms of patient #6. For patient #3, only vigabatrin appeared to be effective but was discontinued because of side-effects. A pacemaker was therefore implanted in these two patients and they were maintained on adjusted doses of antiepileptic drugs. After implantation, they had no further recurrence, although patient #3 complained of brief episodes of absence lasting < 30 s. Antiepileptic drugs were the treatment of choice for the other eight patients. After a median follow-up of
Figure 4. Simultaneous EEG/ECG recording in patient #8. a: partial seizure onset in the right temporal region. The ECG channel shows a normal sinus rhythm at 90 beats per minute. The patient is asymptomatic; b: continuous ECG recording showing cardiac asystole; c: secondarily generalized tonic-clonic seizures; d: end of episode.

102.5 months (mean 82 ± 42, range 16—128 months), all 10 patients remained asymptomatic (Table 2).

Discussion

Dysfunction of heart or brain may cause syncope. Both organs are functionally interdependent, which explains the diagnostic difficulties sometimes encountered in clinical practice. For instance, cardiac arrhythmias may lead to decreased circulation to the brain, which can manifest itself as syncope, sometimes with seizures of the myoclonic type. Conversely, alteration of the heart rate during a seizure is a well-known phenomenon, and partial epilepsy can induce bradyarrhythmias and syncope. Therefore, the medical practitioner may easily confuse AE with an authentic cardiac arrhythmia, thus delaying the appropriate diagnosis and therapy. This unusual manifestation of syncope is understood poorly in terms of both its pathophysiological characteristics and prevalence. To the best of our knowledge, we are the first to employ simultaneous video-EEG/ECG in the description of this unusual presentation of recurrent, unexplained syncope.

Since Russell’s observation in 1906 of the cessation of the pulse during a seizure [16], many clinical and experimental studies have shown that cardiac rhythm changes may occur during focal epileptic seizures [8,17—23]. This applies particularly to the anterior hypothalamus and the insular cortex, where stimulation may induce sinus bradycardia and even sinus arrest, with the impulses being transmitted to the heart via the dorsal vagal motor nucleus and the vagal nerve. With greater use of simultaneous EEG/ECG recording, such changes have been subjected to further study. The term AE was used by Pritchett et al. in 1980 [22] and then by Gilchrist in 1985 [17] to report a cardiac arrhythmia with a cerebral origin. Bradyarrhythmias, however, have been reported only rarely in conjunction with partial epilepsy [8,9,23]. Our patients had clinically significant cardiac arrhythmias, despite the absence of a cardiac history, and a normal cardiovascular assessment. In five of eight of the patients, tilt testing elicited hypotension and/or bradycardia, which is probably indicative of a susceptibility to parasympathetic autonomic dysfunction [14]. When compared with patients on whom we have reported previously, who had tilt-test induced asystole, the AE patients were older (49 ± 20 versus 24 ± 15 years, respectively) and had a more severe clinical
Table 2  Recorded ictal cardiac manifestations during prolonged video-EEG/ECG monitoring of unprovoked or provoked seizures in the neurophysiology lab.

<table>
<thead>
<tr>
<th>Patient</th>
<th>EEG localization</th>
<th>Peri-ictal heart rhythm</th>
<th>Mechanisms</th>
<th>Cause of epilepsy</th>
<th>Treatment</th>
<th>Follow-up (months)</th>
<th>Syncoperecurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left TLE</td>
<td>30-second asystole</td>
<td>Complete AV block</td>
<td>Cryptogenic</td>
<td>Vigabatrin + carbamazepine</td>
<td>128</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Right TLE</td>
<td>10-second asystole</td>
<td>Sinus arrest</td>
<td>Posttraumatic</td>
<td>Carbamazepine</td>
<td>124</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Right TLE</td>
<td>30-second asystole</td>
<td>Sinus arrest</td>
<td>Cryptogenic</td>
<td>Carbamazepine + PM</td>
<td>111</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Left TLE</td>
<td>15-second asystole</td>
<td>Sinus arrest</td>
<td>Cryptogenic</td>
<td>Oxcarbazepine + clobazam</td>
<td>110</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Left TLE</td>
<td>30-second asystole</td>
<td>Sinus arrest</td>
<td>Cryptogenic</td>
<td>Carbamazepine</td>
<td>105</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Left TLE</td>
<td>27-second asystole</td>
<td>Sinus arrest</td>
<td>Cryptogenic</td>
<td>Carbamazepine + topiramate + PM</td>
<td>100</td>
<td>No (since PM)</td>
</tr>
<tr>
<td>7</td>
<td>Left TLE</td>
<td>12-second asystole</td>
<td>Sinus arrest</td>
<td>Cryptogenic</td>
<td>Lamotrigine</td>
<td>53</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Right TLE</td>
<td>20-second asystole</td>
<td>Sinus arrest</td>
<td>Cryptogenic</td>
<td>Oxcarbazepine</td>
<td>51</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Left TLE</td>
<td>Bradycardia 30 bpm</td>
<td>2nd degree AV block</td>
<td>Cryptogenic</td>
<td>Lamotrigine</td>
<td>24</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Left TLE</td>
<td>40-second asystole</td>
<td>Sinus arrest</td>
<td>Left hippocampic sclerosis</td>
<td>Carbamazepine + levetiracetam</td>
<td>16</td>
<td>1 syncope during AED titration</td>
</tr>
</tbody>
</table>

AED: antiepileptic drug; AV: atrioventricular; bpm: beats per minute; EEG: electroencephalogram; PM: pacemaker; TLE: temporal lobe epilepsy.
presentation (mean asystole duration $24 \pm 9$ versus $12 \pm 5$ s, respectively) [24]. It is likely that parasympathetic influences mediated the asystole described in our predisposed patients, and probably that described in earlier reports. The hypothesis is that in predisposed patients, partial epileptic discharge triggers vagal discharge, leading to cardioinhibitory, neurally mediated syncope, which, in turn, triggers a generalized convulsion. Therefore, ‘asymptomatic or paucisymptomatic’ partial epileptic patients may be referred for unexplained ‘syncope’ rather than for seizure-like symptoms.

Evidence for cerebral localization of cardiovascular autonomic control is growing. In both animal models and humans, stimulation and recording studies implicate the amygdala in the control of heart rate and blood pressure. The amygdala receives both direct and indirect projections from the autonomic nervous system afferents and also projects into hypothalamus and brainstem centres for autonomic nervous
system homeostasis. Thus, seizures that have their foci in the temporal lobe may propagate easily through these centres. Human cortical stimulation studies have shown that the left hemisphere—particularly the insula—could be important in the generation of parasympathetic cardiac effects, and the right hemisphere is implicated potentially in the regulation of sympathetic function. Oppenheimer et al. reported bradycardia and depressor responses during stimulation of the left anterior insula [19]. The converse applied for right insular stimulation. The many interconnections between the insular cortex, limbic system and hypothalamus led the authors to speculate that this region might represent the centre of cortical arrhythmogenesis. The hemispheric asymmetry is also supported by described changes in heart rate and heart rate variability during the intracarotid sodium amytal test [25] and electroconvulsive therapy [26], and by decreased heart rate following right-sided, intracarotid, amobarbital injection and increased heart rate following left-sided, intracarotid, amobarbital injection [27].

In our study, all patients had temporal lobe epilepsy, consistent with findings from previous reports [8,9,28]. No strong lateralization was observed; however, seven patients had left temporal onset and three had right temporal onset. Although some authors have found lateralization of the cardiac effects of insular cortex stimulation in humans, our personal observations, as well as the review of the literature [8,9,28], do not support the view that similar lateralized differences are present in the AE. However, the proportion of cases of AE with temporal lobe epilepsy must be viewed in light of the fact that more than 60% of patients with epilepsy have partial seizures, most of which arise from the temporal lobe, and it remains uncertain whether our ‘syncope’ patients reflect bias of selection. In our study, women were more often affected by AE, which contrasts with the findings of Reeves et al., who observed an approximate 5:1 ratio of men to women [28]; whether this reflects bias of selection is also uncertain.

There are two groups in which the diagnosis of AE is likely to be missed. The group reported most frequently comprises patients who are known to have partial epilepsy, but in whom episodic loss of consciousness may be attributed only to the cerebral effects of seizures. The group reported less frequently comprises patients in whom syncope may be attributed to an intrinsic cardiac disease, without appreciation that cardiac dysfunction may be the result of a seizure. This distinction is of more than academic interest, as Holter ECG monitoring alone lacks the essential EEG component in the diagnosis of AE. In our present study, the clinical episodes were not typical of generalized epileptic seizures and the usual symptoms and signs of partial seizures were not revealed prominently. Prolonged postictal obtundation was not present. The normal findings on the neurological examination, standard EEG and CT brain scan also made a primary diagnosis of epilepsy unlikely. Patients were referred to our centre because they seemed to present with syncope clinically. They usually present with severe symptoms including trauma and injury due to the absence of prodrôme and cardio-inhibitory reflex, and were referred to the neurophysiology lab after unsuccessful cardiovascular investigation, only based on this criterion. In some reports, a pacemaker was implanted before realization that the patient’s difficulties stemmed from epilepsy [28,29]. We can speculate that cardiac pacing may not be appropriate first-line therapy in the setting of asystole secondary to AE. This supports the conclusion, based on our median follow-up of 102.5 months, that such a disorder can be managed successfully with antiepileptic drugs alone; only a few patients with refractory AE may require dual therapy of antiepileptic drugs and a pacemaker. Although costly, prolonged in-patient video-EEG/ECG monitoring provides a better method of evaluating problematic syncope and should be considered earlier after non-diagnostic standard cardiovascular investigation in patients experiencing severe, recurrent, traumatic syncopal episodes.

Conclusions

The frequency of AE is unknown and its role in recurrent unexplained syncope remains to be confirmed. Our study is small, consisting of 10 patients. Thus, any conclusion drawn from our data must be considered in this context. However, our study has shown that in patients evaluated in the setting of recurrent, unexplained, traumatic and/or convulsive syncope, AE should be considered as a possible aetiology and prolonged video-EEG/ECG monitoring provides the best method for differentiating AE from other diagnoses.

Conflicts of interests

None declared.

References


