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Ictal asystole: A condition between neurology and cardiology

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ABSTRACT

Ictal asystole can appear in patients with focal epilepsy, even in early phases. We present our experience of 7 cases, remarking the electrocardiographic characteristics, the role of apnea, treatment and long-term evolution. Awareness of this entity and collaboration between neurologists and cardiologists are essential for a correct diagnosis and management.

1. Introduction

Cardiac rhythm disturbances in epilepsy were described >100 years ago. However, the development of epilepsy monitoring units during the last decades and the combination of ECG monitoring during the EEG have allowed diagnosing a wide variety of seizure-related arrhythmias. Sinus tachycardia is the most common finding, but extreme bradycardia or asystole involve a rare but more serious situation. Ictal asystole (IA), either sinus pauses or atrioventricular block (AVB) has been described in focal seizures [1,2]. The clinical meaning and underlying mechanisms are still unknown. The treatment can include a pacemaker so both neurologists and cardiologists must be aware and recognize this entity. We present our clinical experience remarking some gaps still misunderstood.

2. Methods

We recruited patients from the epilepsy monitoring unit (Fundación Jiménez Díaz, Madrid, Spain). The patients were retrospectively included since January 2006 to June 2013 and prospectively added since July 2013 to April 2018. They were included when a definite diagnosis of IA was made by an ictal asystolic event (sinus pause or AVB) recorded during a video-EEG. The asystole was defined as an RR interval longer than 3 s due to sinus pause or AV block. The definite diagnosis of IA could be obtained before or after implanting the pacemaker.

We present a series of 7 patients with a confirmed diagnosis of IA (Table 1). The mean age at diagnosis of IA was 46 years (range 28–67) and 57% of the patients were male. Five of them had a previous diagnosis of focal impaired awareness seizures (FIAS) with a mean time of 8,2 years since the diagnosis of epilepsy until the IA was firstly diagnosed. All except one patient had non lesional epilepsy and two patients also associated focal to bilateral tonic clonic seizures. Interictal EEG showed epileptiform anomalies in 85% of cases. The 5 patients with a history of epilepsy had used 1–3 antiepileptic drug in spite of which they had recurrent seizures and falls. Most of the seizures occurred in the absence of falls. The 2 patients without previous diagnosis were admitted to the cardiology department because of repeated syncope and diagnosed of sinus pause and paroxysmal AV block by loop recorder and ECG monitoring (Fig. 1). The final diagnosis of IA was made after implanting the pacemaker, when symptoms preceding syncope persisted, even with a longer duration and allowed to identify the typical manifestation of FIAS (automatism, staring). A video-EEG confirmed epilepsy-induced asystole followed by pacemaker activation in these two patients, meeting criteria for definite IA.

Sinus pause was the most common finding except in one case who presented paroxysmal AVB (Fig. 2). Sinus pause was preceded by slight bradycardia but not tachycardia. An electrophysiological study was performed in the two patients without a previous diagnosis of epilepsy and showed normal sinus and atrioventricular conduction properties.

All patients received a pacemaker, five of them because of refractory FIAS and recurrent symptomatic IA and two of them because of syncope and asystole documented with cardiac monitoring but still unsuspected epilepsy at that time.

During a mean follow-up of 57 months (range 4–145 months), all except one patient continued presenting focal seizures but without syncope or falls disappeared. One patient remained seizure and syncope free with AED.

3. Discussion

Ictal asystole has been diagnosed along the last three decades but its clinical meaning, prognosis and treatment are on debate. IA is defined as the absence of heart beat for a minimum of 3 s [3]. The final diagnosis requires the combination of an EEG-ECG, confirming that conduction disturbances are triggered by focal seizures. There are multiple case reports and short series describing this entity but a consensus of management is missing [3–11]. There are important uncertainties around this entity: 1) What are the mechanisms s of IA?; 2) Does the apnea add a worse prognosis?; 3) Is the pacemaker indicated in early stages; 4) What is the relation to SUDEP?

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Table 1
Patients and asystole characteristics.

N	Age epilepsy	Age syncope	Age IA	Previous epilepsy	Type	Lobe	Aura	Semiology	Intercritical EEG	N° syncope	MRI	Diagnosis IA	IA duration	ECG finding
1	52	55	56	YES	Partial	R - Temp	Ascending Feeling	Smacking, dystonia	Abnormal	4	Normal	EEG	7	Sinus pause
2	43	68	69	YES	Partial	R - Temp	Dizziness	Bubbling in throat	Normal	1	Normal	EEG	8	AV block
3	32	32	33	NO	Partial	L - Temp	Pallor, ascencing epigastric feeling	Peribucal automatism	Abnormal	>10	Not done	ECG	6	Sinus pause
4	67	67	76	YES	Partial	L - Temp	Epigastric feeling	Smacking,	Abnormal	9	Normal	EEF	13	Sinus pause
5	43	43	48	YES	Partial	Insula	Pallor, ascencing epigastric feeling	Peribucal automatism	Abnormal	>10	Normal	EEG	6	Sinus pause
6	60	60	61	NO	Partial	R - Fronto-temp	Pallor, ascencing epigastric feeling	smacking,	Abnormal	3	Not done	ECG	5	Sinus pause
7	28	37	37	YES	Partial	R - Temp	Feeling	hands rubbing, oral automatisms	Abnormal	2	Heterotophy	EEG	56	Sinus pause

The reported incidence of IA is very low, around 0,2–0,4% of patients with FIAS undergoing an EEG, however it could be underestimated. When a loop recorder was implanted in patients with refractory FIAS, a potentially fatal asystole was documented in 16% of patients [9–14].

The brain areas responsible of central autonomous system control are the insular cortex, amygdala, cingulated gyrus, hypothalamus and brainstem and prefrontal cortex, so an epileptic seizure affecting these areas is supposed to affect the heart rhythm. There are two hypotheses:

- The "lock-step phenomenon" describes the synchronization between the central autonomic centers and the postganglionic autonomic activity. Experimental studies and intra-surgical stimulation of these specific areas demonstrated rhythm disturbances [15,16].
- The second hypothesis is a "vasovagal reflex". As intense emotions can trigger a vasovagal (VV) response via hyperstimulation of the limbic system, seizures arising or involving this center could induce a similar response. Schuele et al. demonstrated a similar heart rate pattern during a provoked VV syncope than during a seizure induced asystole [17].

Sinus pauses in epilepsy have been classically related to central apnea during generalized seizures, however, respiratory centers are not usually affected in FIAS. Nevertheless, there are some cases reporting central apnea coexisting with the IA [9,18,19]. In addition, in many cases there is no mention to oxygen saturation or respiratory pattern [19]. So, we cannot exclude that central apnea could take a role in IA, as a coexisting phenomenon or as a cause. If this combination entails a worse prognosis has never been studied.

3.1. Characteristics: clinical, EEG and ECG

IA is usually described in long-term or refractory epilepsy, however it has also been described as an early or isolated symptom in unknown or recently diagnosed patients [20,21,22], like two of our cases.

It frequently appears as typical focal seizures involving the temporal lobe (epigastric ascending feeling, sweating, facial grimacing, hands rubbing, repetitive automatisms, autonomic symptoms) associated with impaired awareness but followed by a loss of consciousness and atonia (syncope), which is not expected in this kind of seizures. The latency between the beginning of the seizure and the syncope is variable, being so short in some cases that recognizing ictal manifestations can be challenging.

Most cases involve the temporal lobe where autonomic system structures lie, however seizure's beginning can be extratemporal or unknown, suggesting that is not the origin but the propagation of the electrical activity through specific heart rate control areas what determines the occurrence of IA. Accordingly, seizure's laterality is variable and there is a broad range of latency between seizure's beginning and the asystole (from −3 to 268 s) [22]. Other characteristics reviewed by Tényi included an abnormal interictal EEG in 75%, a normal neuroimaging tests in 55% and no relation with specific antiepileptic drugs.

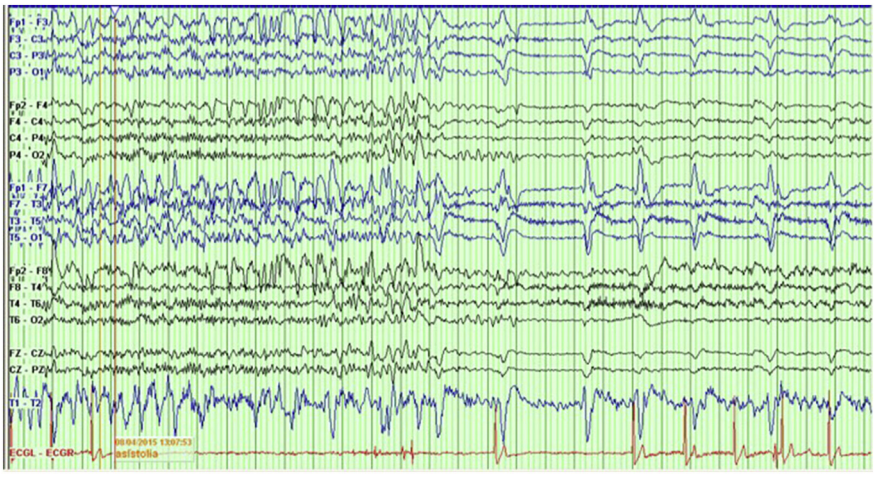

Fig. 1. Patient number 5: ictal asystole with sinus pause of seconds.

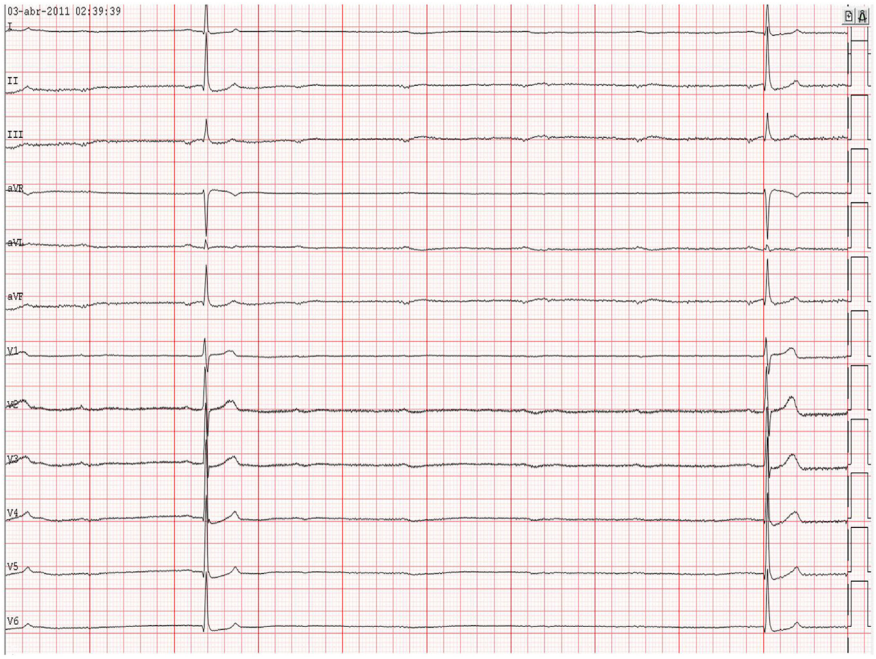

Fig. 2. Patient number 2: ictal asystole with paroxysmal AV block.

Sinus pause is the most common finding on the ECG tracings but paroxysmal AVB have also been described [22]; this distinction is seldom included in the literature and the meaning is unknown. The duration spreads from 3 to 96 s, independently of the type of seizure, duration of epilepsy and presence of antiepileptic drugs. Bestawros published a cut off value of 6 s to consider IA as clinically remarkable event and proposed it as indication of pacemaker [9].

3.2. Clinical implications

Clinical consequences of IA are repetitive, unexpected and unpredictable falls and traumatisms, when muscular tone should be preserved in common FIAS. Taking into account that around 30% of epilepsy is refractory to treatment, the risk of falls in IA is not negligible. However, the great interest lies on the possible association to sudden death in epileptic patients (SUDEP). Previously described risk markers for SUDEP are long-term, refractory focal to bilateral tonic-clonic seizures and the combination of several AED, which are not the typical profile of IA/FIAS.

The MORTEMUS study registered some cases of SUDEP during a V-EEG. A cardiorespiratory arrest was documented as a post-ictal event in tonic-clonic seizures in relation to a generalized EEG suppression [23]. As opposed to this post-ictal phenomenon, IA is a direct consequence during seizure activity. It is suggested that asystole-induced cortical hypoperfusion can even stop the seizure and/or the neural afferent signals, shortening the seizure duration [6,24]. By now, there is no clear evidence of IA as cause of sudden death, however cases of very prolonged asystole as one of our cases of 56 s, AV block or coexisting apnea are disturbing [26].

3.3. Diagnosis

The gold standard is the ECG-EEG demonstrating a seizure-induced asystole.

In the clinical practice, there are two possible scenarios to suspect IA: First and most common is a patient with focal epilepsy and sudden falls. The second and most difficult scenario is a patient without previous diagnosis of epilepsy who suffers recurrent syncope. The clinical history is essential to get the right diagnosis, being mandatory to search clues such as atypical VV syncope (no prodromal or trigger), previous automatisms or autonomic signs, age of appearance, normal ECG, normal electrophysiological study. We found in half of our patients that falls and syncope appeared “in clusters”, that means multiple falls within the same day. This finding is in line with the high rate of recurrent episodes of IA (up to 40%) described by Hampel, which were symptomatic in >60% of cases [26].

In cases with high suspicion index, AED withdrawal or a long-term ECG-Holter could be useful to document the asystole.

3.4. Treatment

Since the relation between IA and death has not been demonstrated, all treatments are aimed to reduce symptoms. As asystolic events are consequence of epilepsy, an optimal seizure control must be the immediate target, based on drugs and/or surgery.

In our experience, as in other series, the pacemaker can help to prevent syncope recurrences. Patients have remained syncope free after the pacemaker in spite of recurrent seizures with impaired awareness (FIAS).

Cardiac pacing has been a matter of debate, existing data showing syncope disappearance by intensifying the antiepileptic treatment without pacemaker and data in favor to an early device implant [18,22].

Although pacing therapy has demonstrated to decrease the number of syncope, its risks and consequences are not negligible, mainly in young people (pneumothorax, infection, lead fracture, repeated replacements…) A consensus about the indication and the appropriate timing for pacemaker implant is still missing.

In our opinion, a pacemaker is clearly indicated in patients with recurrent falls unable of achieving seizure control. A more conservative approach could be recommended in young and untreated patients. The device could be avoided or delayed until an optimal treatment is achieved. An ECG-loop-recorder could help during the optimization to monitor the presence of short or asymptomatic IA.

4. Conclusions

Ictal asystole is a relatively new entity with an increasing rate of diagnosis. The presence of uncertainties in physiopathology and prognosis

and the lack of consensus in treatment make it a challenge. A higher suspicion rate and a deeper knowledge by cardiologists are mandatory. The pacemaker clearly decrease syncope in refractory epilepsy, but the indication in asymptomatic asystole or in recently diagnosed patients is unknown. Collaboration between neurologists and cardiologists is needed for a better management.

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