■ Electroclinical reasoning report

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Epileptic Disorders

Low-grade tumour over the left temporal neocortex and ictal asystole: network and surgical implications

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ABSTRACT

We describe a patient with focal epilepsy characterized by ictal asystole episodes and low-grade tumour over the left temporal neocortex. Non-invasive presurgical evaluation showed an epileptogenic zone extended beyond the low-grade tumour. This extension was confirmed by intraoperative electrocorticography. One-stage surgery with anterior temporal lobe resection was performed. The patient was seizure-free after one year of follow-up. Detailed electroclinical and therapeutic reasoning with hypotheses defining epileptogenic and symptomatogenic networks are discussed.

Key words: ictal asystole, epilepsy surgery, epilepsy networks, temporal lobe, SUDEP

Patient details

The patient, a 15-year-old, right-handed male, presented with medically uncontrolled epilepsy that began at the age of nine. Clinical seizures consisted of behavioural arrest with impaired awareness followed by looking around aimlessly, preservative or *de novo* upper limb automatisms (sometimes nose wiping and oroalimentary automatisms were associated) and pharaphasic errors with anomia.

Post-ictal confusion followed each seizure. Aura was not reported. His seizures occurred once or twice weekly and always lasted less than two minutes. Less than five syncope episodes per year during the aforementioned episodes were reported. Following treatment with a combination of clobazam and carbamazepine, a major reduction in seizure frequency was obtained (2-3 per month), with disappearance of the syncopes.

During the first outpatient visit, the parents presented a home-video showing the reported syncopes (*video sequence 1*).

The patient's medical history was significant for many syncopes per year, starting at the age of five; cardiological evaluation and the first awake EEG were normal, while neuropsychological evaluation showed mild emotional-affective difficulties.

He had developed normally with good school results. The family history was negative for seizures or cardiological disease.

His general and neurological examinations were normal.

VIDEOS ONLINE

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Hypothesis 1

The patient had a family history that was negative for epilepsy and a personal history characterized by many syncopes per year that started at the age of five, apparently not associated with heart dysfunction. The awake EEG was reported as normal.
At nine years, seizures with likely temporal lobe semiology started. The appearance of both upper limb and oral automatisms at the onset of seizures and post-ictal confusion suggested a mesial rather than neocortical epileptogenic zone. Paraphasic errors with anomia during seizures suggested a probable involvement of the dominant hemisphere.
A drop attack observed on a home video excluded vaso-vagal reflex syncope since it occurred abruptly and without the classic fainting prodrome.
Given this symptomatology, a complete cardiological evaluation with non-invasive epilepsy presurgical evaluation was performed.

Non-invasive investigations

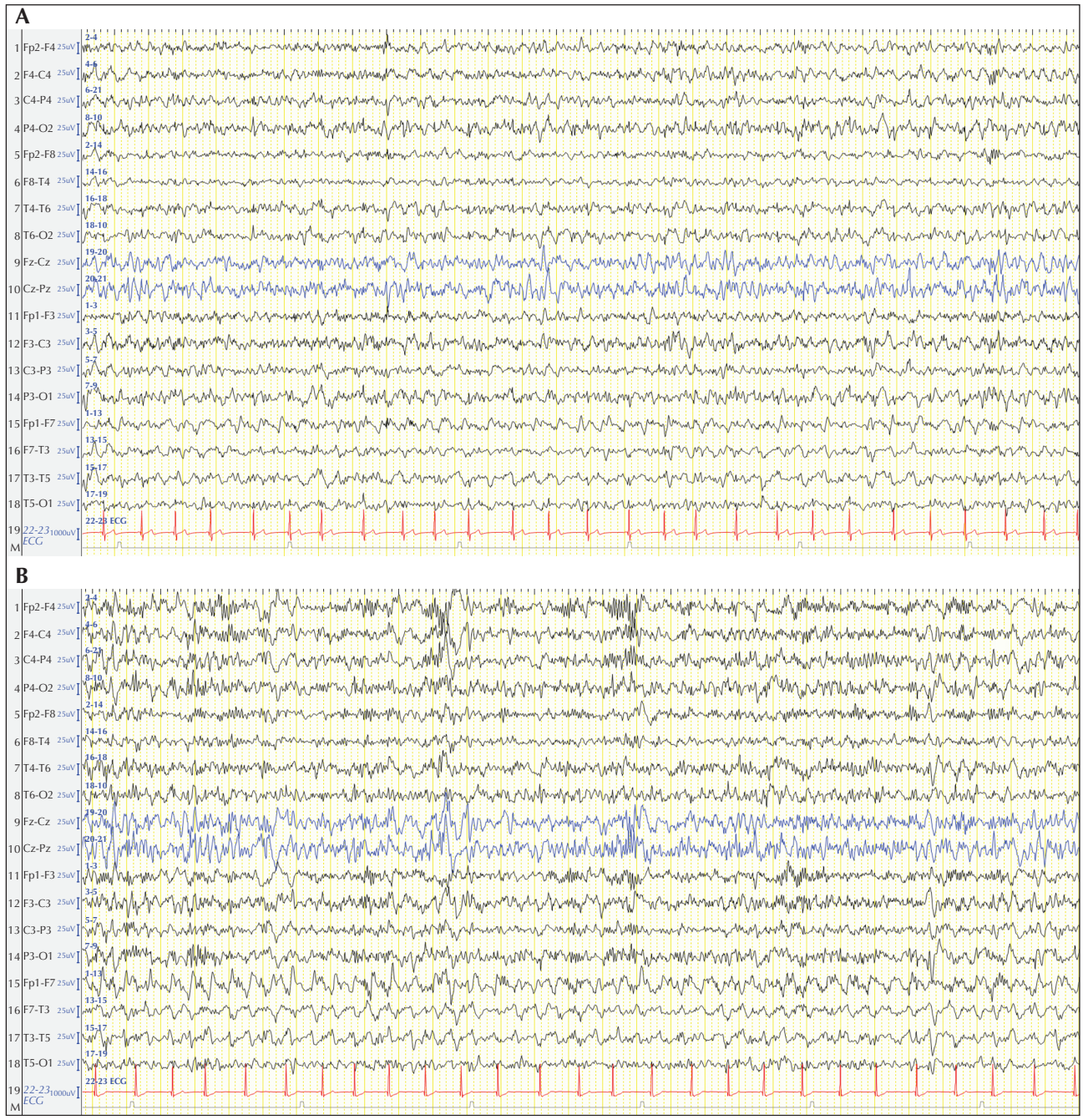
Polygraphic video/EEG long-term monitoring revealed normal background activity with intermittent polymorphic medium-amplitude theta activity over the left temporal region (*figure 1A*). Sometimes, this slow activity became rhythmic (*figure 1B*), without any observed clinical change.
Several electro-clinical seizures were captured, revealing a seizure onset over the left temporal region. In one of these seizures, cardiac arrest appeared (*video séquence 2*). *Figure 2* shows a detailed EEG description of the seizure with ictal asystole (IA).
Anatomical brain MRI (*figure 3*) revealed an area of magnetic signal modification over the middle temporal gyrus up to the sulcus, between the middle and inferior temporal gyrus. Brain MRI T1 sequences revealed blurring and reduced volume of the left temporal pole, compared to the right one, as well as peri-lesional hyperintensity on FLAIR sequences. The posterior left hippocampus was also likely to be small (*figure 4A*), with normal volume of amygdales (*figure 4B*).
Brain FDG-PET superimposed on brain MRI showed diffuse left antero-mesial temporal lobe hypometabolism (*figure 4C*).
Functional MRI revealed lateralization of receptive and expressive language to the left hemisphere and appropriate contralateral representation of the left and right sensorimotor functionality. The activation of the visual cortex was bilateral and symmetrical.
Neuropsychological investigations revealed adequate intellectual functioning (Wechsler Intelligence Scale for Children -IV, Full Scale Intelligence Quotient: 105) with slight verbal memory and emotional-affective difficulty.
Cardiological evaluation with 24-hour ECG and ultrasound were negative, also excluding Brugada syndrome.

Hypothesis 2

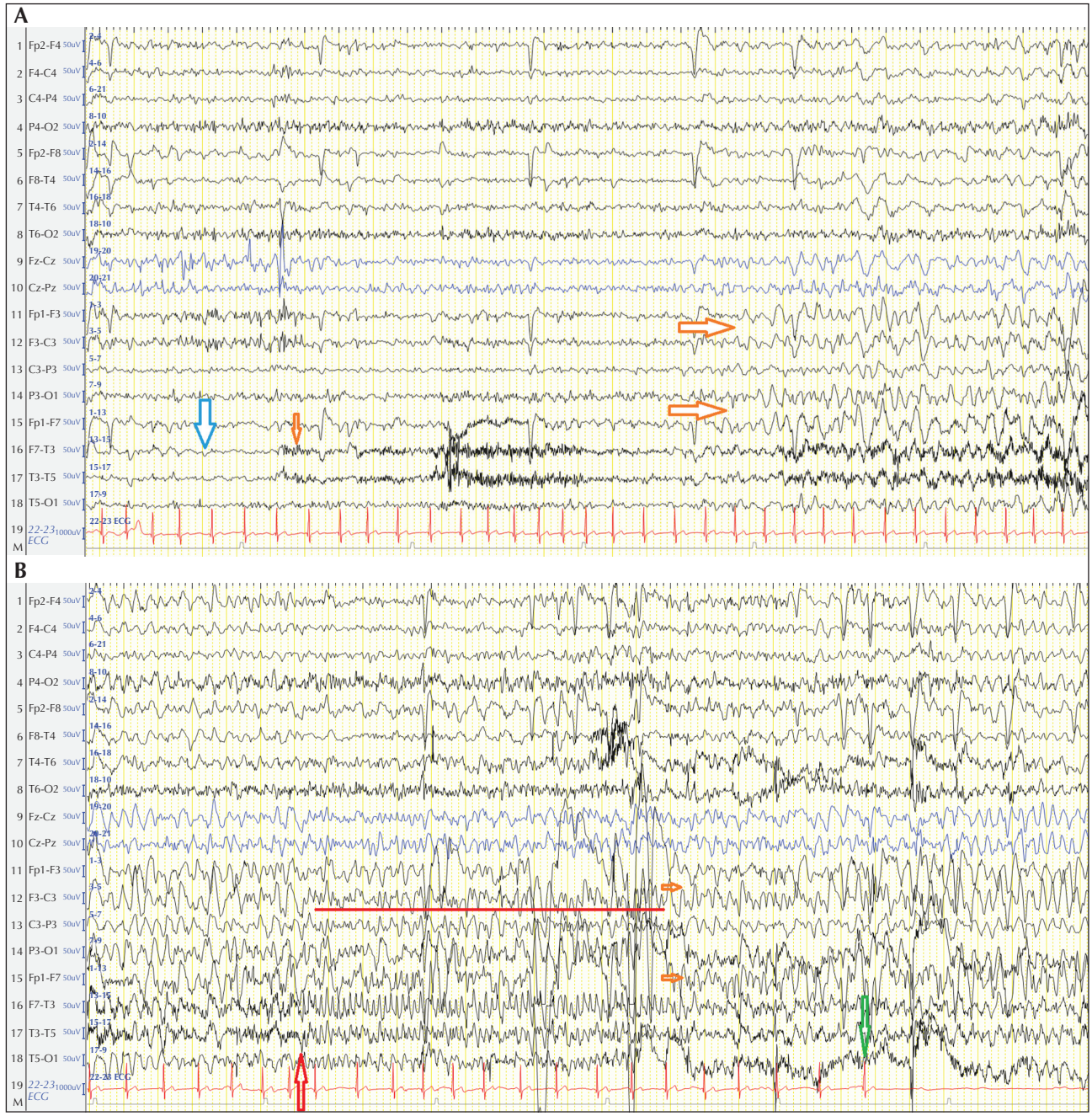
The electroclinical and neuroimaging data were consistent with a left temporal epileptogenic zone.
Brain MRI showed a likely low-grade tumour over the middle temporal gyrus and signs of likely focal cortical dysplasia (temporal pole hypoplasia with blurring on T1 and peri-tumour hyperintensity on FLAIR sequences).
Interictal EEG showed slow activity over the left temporal region with likely subclinical seizures involving the left temporal region.
Ictal EEG showed a likely epileptogenic zone over the left temporal region, possibly close to the lesion located on the left middle temporal gyrus. The discharge spread over the left temporal pole and sometimes over the hippocampus, involving the central autonomic network with the appearance of cardiac arrest.
A substantial involvement of the hippocampus was supported by PET hypometabolism, the suspected small size of its posterior region on MRI, the seizure semiology (as discussed above) as well as the neuropsychological evaluation revealing verbal memory difficulties.

Action taken

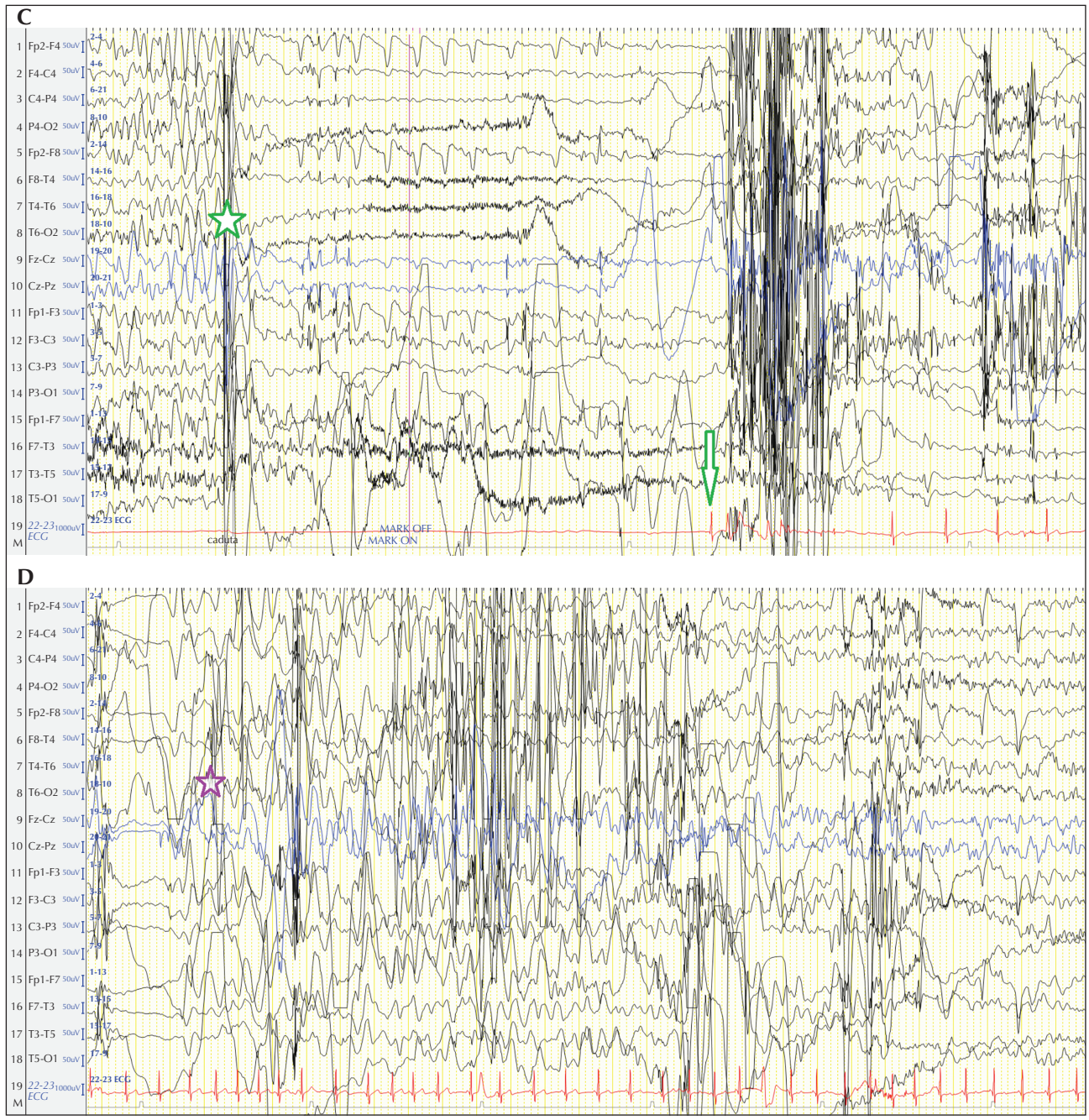
Based on the results of the non-invasive epilepsy surgery evaluation, one-stage surgery was conducted [1]. Considering the unclear involvement of the hippocampus and the temporal pole on brain MRI, the diffuse left antero-mesial temporal lobe hypometabolism on FDG-PET and the seizure semiology suggesting propagation of the discharge towards the central autonomic network, we performed intraoperative electrocorticography (ECoG) to define the resection boundaries more confidently with the aim of ensuring minimal resective surgery. EcoG showed medium-high-amplitude fast activity over the left temporal pole and high-amplitude spikes over the hippocampus. The hippocampal abnormal activity was recorded even after the left temporal pole resection.
These findings indicated a probable large epileptic network hub, extending from the low-grade tumour (likely primary pacemaker) to the whole temporal pole and to the hippocampus (likely secondary pacemakers).



■ **Figure 1.** Sleep interictal EEG. (A) Normal background activity with intermittent polymorphic medium-amplitude theta activity over the left temporal region. (B) Medium-high-amplitude rhythmic slow activity over the left temporal region (likely a subclinical seizure).



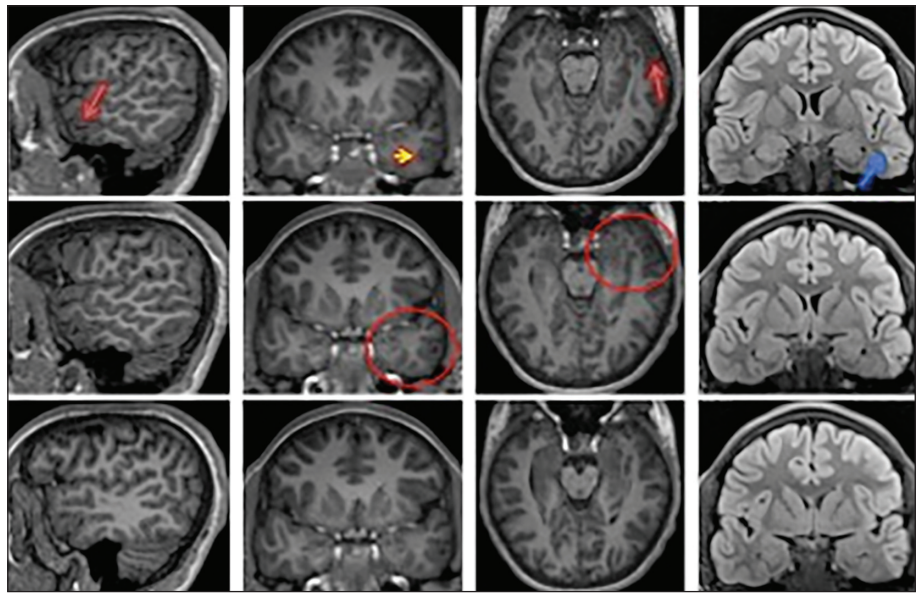
■ **Figure 2.** (A-D) Awake ictal EEG. Seizure onset characterized by background flattening over the left temporal region (large blue arrow), followed by a fast recruiting activity (small blue arrow); the latter is difficult to see because of muscular artifact covering the brain activity. Subsequently, a medium-high-amplitude polymorphic and rhythmic theta-delta activity over the antero-mesial left hemisphere appears (large orange arrows). After 30 seconds, a medium-amplitude monomorphic and rhythmic fast activity over temporal electrodes is observed (red arrow), with which a clear change of both associated ipsi- and contralateral hemispheric activity (horizontal red line).



■ **Figure 2.** *(continued)*. At the end of this last recruiting discharge, the activity preceding it returns over the antero-mesial left hemisphere (small orange arrows) and after four seconds, cardiac arrest occurs (green arrow). After 10 seconds from the cardiac arrest, a widespread EEG suppression appears (red star) and after another 14 seconds, the cardiac rhythm reappears (green arrow). Fourteen seconds after cardiac rhythm recovery, the brain background activity reappears (violet star).

Based on the findings of non-invasive and intraoperative investigations, an anterior temporal lobe (ATL) resection was performed (*figure 5*).

Neuropathology based on the excised tissue specimen showed a morphology and strong CD34 positivity consistent with a diagnosis of polymorphic low-grade neuroepithelial tumour (PLNTY type) with associated focal cortical dysplasia type I, representing focal cortical dysplasia type IIIb.



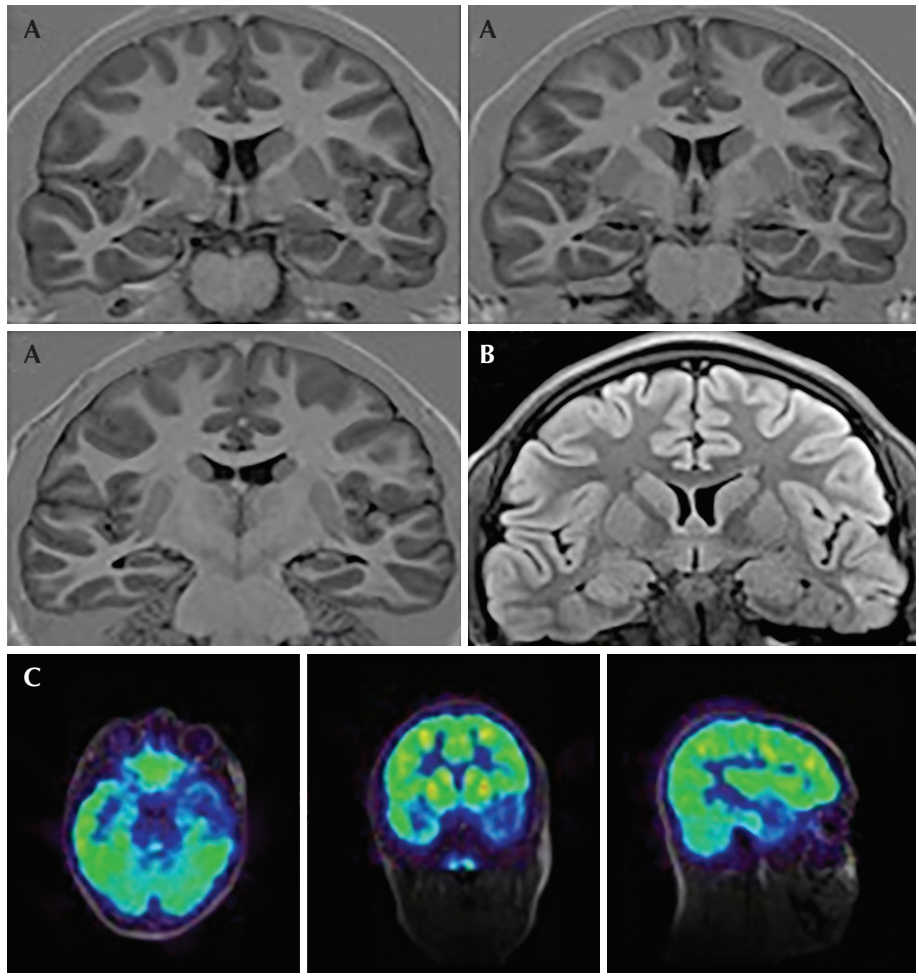
■ **Figure 3.** Coronal T1 brain MRI showing magnetic signal modification over the middle temporal gyrus (red arrows), up to the sulcus between the middle and inferior temporal gyrus (yellow arrow), with signs of blurring and reduced volume on the left temporal pole compared to the right (red circles). Coronal FLAIR brain resonance image showing peri-tumour hyperintensity.

Follow-up

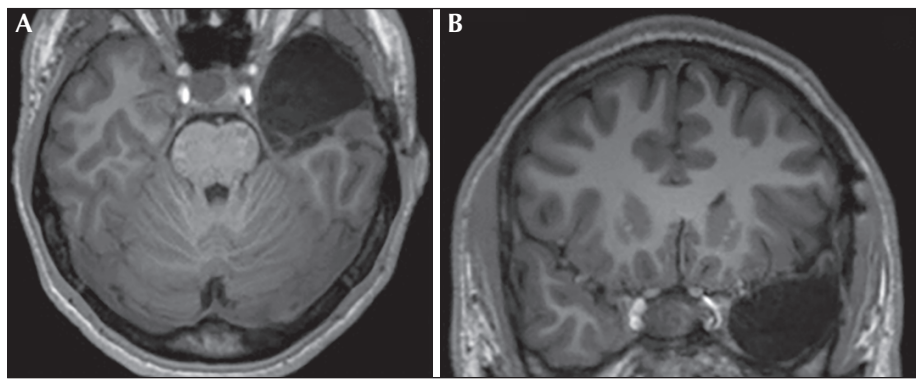
The patient has been seizure-free for one year and has been without antiepileptic therapy for six months. He is attending high school in Italy with good performance.
His neuropsychological follow-up confirmed a slight verbal memory deficit and emotional-affective difficulties.

Discussion

The first description of the association between epilepsy and autonomous cardiovascular control dates back to 1906, when Russel demonstrated the disappearance of a patient's pulse rate during an epileptic seizure [2]. After more than one century, the exact IA mechanism is still not fully understood [3], however, the involvement of the central autonomic network, which controls parasympathetic and sympathetic output, or an excessive vagal tone mediated at cortical level are the main implicated pathways [4-6]. An experimental study on animals showed that cardiac vagal discharges were intermittently synchronized 1:1 with chemically induced epileptic activity [7].
In the clinical setting, the diagnosis of IA is very challenging because patients may not show pulse disappearance at each seizure and polygraphic video-EEG long-term monitoring is required [8, 9].
Usually, IA appears one year after epilepsy onset, however, IA has also been observed at epilepsy onset [10], making the diagnosis of epilepsy difficult.
In our case, vaso-vagal syncopal episodes were reported from the age of five. At epilepsy onset, there may still be diagnostic pitfalls if we consider that in most IA cases, IA occurs subsequent to temporal lobe epilepsy (TLE) [6]. Symptoms and signs of TLE can be very similar to those of syncope since both paroxysmal events may present with pallor, oral automatisms, sweating and fixation [8].
In our patient, the sudden fall to the ground in the absence of fainting prodrome, the longer duration compared to vaso-vagal or cardiac syncope, and the long-lasting postictal phase were suggestive of a seizure [11].
On the basis of these considerations, we could speculate that the suspected syncope episodes that appeared at five years old were most likely seizures.
The home video during the first outpatient visit (*video sequence 1*) revealed a drop attack strongly suggesting heart rhythm involvement; for these reasons, polygraphic video-EEG long-term monitoring and cardiological evaluation were mandatory. A further diagnostic challenge is that not all focal seizures of the same patient are necessarily associated with IA [6, 12], as observed in our patient.



■ **Figure 4.** (A) Coronal T1 brain MRI showing a possibly slightly smaller size of the posterior left hippocampus. (B) Coronal FLAIR brain MRI showing normal amygdales. (C) Brain FDG-PET superimposed on brain MRI showing diffuse left antero-mesial temporal lobe hypometabolism.



■ **Figure 5.** Surgical resection area on coronal T1 brain MRI (A) and axial T1 brain MRI (B).

Seizures with IA generally show a substantially overlapping EEG sequence. About 30 seconds after seizure onset, a sinus pause, lasting for about 10 seconds, subsequently occurs. At that point, ictal EEG abnormalities either continue or are interrupted by widespread slowing (during which the patient is atonic) and/or EEG suppression. In the suppressive EEG model, EEG activity restarts after about 10 seconds from the resumption of cardiac activity [9]. The seizure of our patient showed the same sequence, with a suppressive EEG pattern.

Asystole must last for >six seconds in order to establish that the symptoms of cerebral hypoperfusion are due to parasympathetic activation [9, 13-16]. This then leads to a discussion regarding the following three questions: (1) does a link exist between IA and sudden unexpected death in epilepsy (SUDEP)? (2) is the pacemaker useful in patients with IA? (3) should carbamazepine be discontinued?

Several authors have shown that IA was not associated with death or permanent brain damage, even when asystole duration was >30 seconds [10]. Our patient had an asystole episode of about 25 seconds. The suggested link between IA and SUDEP is rather weak for several reasons. In the MORTality Epilepsy Monitoring Unit Study (MORTEMUS), all monitored cases of SUDEP or near SUDEP showed that asystole preceding death was always postictal, associated with focal to bilateral tonic-clonic seizures, and preceded by apnoea and widespread EEG suppression ("electrocerebral shutdown") [12, 18, 19].

On the contrary, in our patient, asystole occurred during a focal seizure, was not preceded by apnoea and occurred about 10 seconds before the electrocerebral shutdown. EEG suppression occurred during the ictal period and was the consequence of a reversible cerebral hypoperfusion [20]. Therefore, the distinctive EEG signs of cerebral hypoperfusion can be identified regardless of the aetiology of syncope, and their severity depends on the duration of parasympathetic activation [9]. IA related to parasympathetic activation should be treated as benign, as non-ictal vaso-vagal syncope, as suggested by Nguyen-Michel et *al*. [9]. IA should also be considered as self-limiting, as the end of the seizure is caused by cerebral hypoxia [6, 8, 20].

Based on these observations, it seems unlikely that IA is an important factor contributing to SUDEP [9].

The second question is whether a pacemaker could be useful in patients with IA. Different studies have reported that patients with IA without a pacemaker survived with an average follow-up of four years and no cardiac resuscitation required for any of the patients, even in the presence of prolonged IA [8, 15, 21-24].

Furthermore, ictal parasympathetic activation can cause not only negative cardiac chronotropic effects leading to asystole, but also vasoplegic effects on the circulation. If the vasoplegic effect prevails over the cardiac effect, pacemaker implantation could paradoxically have negative effects [24].

Finally, non-negligible risks and consequences associated with pacemaker implantation, especially at childhood age (pneumothorax, infection, lead fracture, repeated replacements and others), should also be considered.

All these observations limit pacemaker application to a minority of cases with IA in accordance with the therapeutic algorithm proposed by Strzelczyk *et al*. [24], in which priority is given to drugs and epilepsy surgery [20, 24-26].

The third question is whether carbamazepine (CBZ) should be discontinued.

The arrhythmogenic potential effect of antiepileptic drugs may be responsible for SUDEP [21, 27-30]. The drugs may not only increase the QT interval on the electrocardiogram (ECG) [29], but they also may reduce heart rate and blood pressure responses to factors of physiological stress [17], thus preparing for SUDEP.

CBZ is commonly prescribed in patients with focal seizures. The exact CBZ mechanism of action is not fully understood, but evidence suggests that it could act as a sodium channel blocker [31, 32], stabilising the channel in the inactivated state. As a result, the refractory period of an action potential could last longer [33, 34]. In addition, CBZ could have negative chronotropic and dromotropic effects [35, 36]. Nevertheless, CBZ administered for 12–32 months in patients with focal epilepsy has been shown to have no detectable effect on cardiac AV conduction, depolarization and repolarization, or on measures of short- and long-term variation of ECG time intervals [34]. Furthermore, several authors shown that CBZ can be safely used in the absence of pre-existing cardiac pathologies [34]. Due to the aforementioned reasons and considering that our patient was a good candidate for epilepsy surgery, CBZ was not discontinued.

At the end of our presurgical evaluation, the decision between a tailored or a more extensive resection was the final step of our diagnostic-therapeutic pathway.

IA typically occurs during a focal seizure involving the left temporal lobe [6, 9, 37], but may occur with extratemporal or unknown onset [38-43]. More likely, the propagation of electrical activity through specific heart rate control areas induces the occurrence of IA rather than triggering the seizure hub of the brain network. This assumption could explain the broad latency intervals described between seizure onset and IA [10].

This also explains why in Panayiotopoulos syndrome, a life-threatening cardiorespiratory arrest may occur if the seizure discharge engages an occipito-temporal network that determines propagation of the discharge in the heart rate control areas [44-48].

The brain areas responsible for controlling the autonomic nervous system are the insular cortex, amygdala, cingulate gyrus, prefrontal cortex, hypothalamus and brainstem [10, 15, 49, 50]. These areas are part of a dynamic network and for the generation of IA, a specific pattern of activation of this network must be engaged during a seizure [25, 51, 52].

It is now common knowledge that the generation of epileptic seizures, cognitive dysfunctions and response to treatment are underpinned by extensive dynamic networks involving cortical and subcortical structures [53-56]. These extended networks are made up of regions responsible for seizure onset and propagation (hubs) as well as features (nodes) that are involved only remotely [57, 58]. This conceptual framework is of fundamental importance for the surgical approach as seizure freedom is unlikely to be obtained without removing the hub region of the epilepsy network. Although hub resection is important for seizure outcome, the definition of surgical completeness remains elusive within the poorly-defined framework of an epileptogenic dynamic network; in fact, authors have reported that patients become seizure-free after incomplete resection or have Engel Class III/IV outcome following an apparent complete resection [59].

Conclusions

From a practical standpoint, in our case, electroclinical data suggested a likely epileptogenic zone over the left temporal lobe close to or into the low-grade tumour (likely primary pacemaker, epileptic network hub) with rapid propagation of the discharge over the left temporal pole and subsequently through the hippocampus (likely secondary pacemakers, epileptic network hub). This epileptic discharge led to a specific activation pattern of a dynamic network involving specific cortical and subcortical regions (likely epileptic network nodes) responsible for the appearance of IA. The neuroimaging data confirmed the electroclinical findings.

Since the patient was a candidate for epilepsy surgery, we excluded the hypothesis of pacemaker implantation, which in our opinion should only be used in patients with long-lasting IA, drug-resistant epilepsy and not candidates for surgery.

Based on all the observations reported, an ATL resection was indicated as the best therapeutic option for our patient. ■

Legends for video sequences

Video sequence 1

Drop attack with awareness is likely impaired. During the video, the father calls the patient saying "Lorenzo", but he does not reply and after closing the door, he suddenly falls on the ground.

Video sequence 2

Video-EEG recording during a seizure with ictal asystole. The video begins with the patient starting to clean a cell phone screen. Psychomotor arrest of a few seconds appears with gaze turned to the lower right. After a few seconds, he resumes cleaning the phone as before the psychomotor arrest. At some point, the mother asks him simple questions, but the patient answers with paraphrases and shows purposeless automatisms of the upper limbs. The neurophysiopathological technician, as soon as he observes the seizure on the EEG unit monitor, approaches the patient and tests his awareness. The patient answers with paraphasic errors and anomia. After a few seconds, he has a drop attack. Post-ictal confusion follows the seizure.

Key words for video research on www.epilepticdisorders.com

Phenomenology: ictal asystole
Localization: temporal lobe
Syndrome: structural epilepsy
Aetiology: low grade tumour

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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TEST YOURSELF

(1) What is the mechanism associated with ictal asystole?

(2) What are the main differences between asystole in SUDEP and ictal asystole?

(3) When would a pacemaker be useful in patients with IA?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.