

Supplementary material

Illustrative case: Patient 3 (*supplementary table 1*)

A 40-year-old right-handed man without any known comorbidities presented with recurrent seizures since the age of 25 years. The semiology was characterized by aura of a ringing sound in both ears followed by darkness of vision, followed by loss of consciousness and tonic-clonic movements of all limbs.

Birth and development were normal. There were no antecedents such as febrile seizures, meningoencephalitis or head injury. Family history was negative for epilepsy or for any other neurological condition. The seizures did not respond to multiple trials of AEDs. At presentation, despite being on optimum doses of a combination of levetiracetam and clobazam, he was having 2-3 secondary generalized seizures per month.

Interictal EEG showed focal slowing over the right posterior head region with epileptiform abnormalities. Four electroclinical events were recorded during the scalp VEM period. All of them had very focal ictal onset characterized by rhythmic fast spike activity over T6 to T4/O2, evolving into repetitive spike-waves, and then into a monomorphic delta rhythm (*figure 1A*). The patient developed ictal bradycardia followed by asystole with mean latency of 22.4 seconds and mean duration of 28.7 seconds during all the events (*figure 1B, C*). 3T brain MRI did not show any structural abnormalities.

Brain fluorodeoxy-positron emission tomography (FDG-PET) showed doubtful focal hypometabolism over the right parietal region (*supplementary figure 1A*). Magnetoencephalography (MEG) showed no significant dipole clustering (*supplementary figure 1B*). The anatomic-electroclinical hypotheses generated favoured ictal onset zones in relation to the right parieto-temporal neocortex, temporo-occipital neocortex, posterior insula, posterior cingulate, or precuneus.

As non-invasive presurgical investigations did not reveal a structural lesion in the suspected areas, the patient underwent stereo-EEG (SEEG).

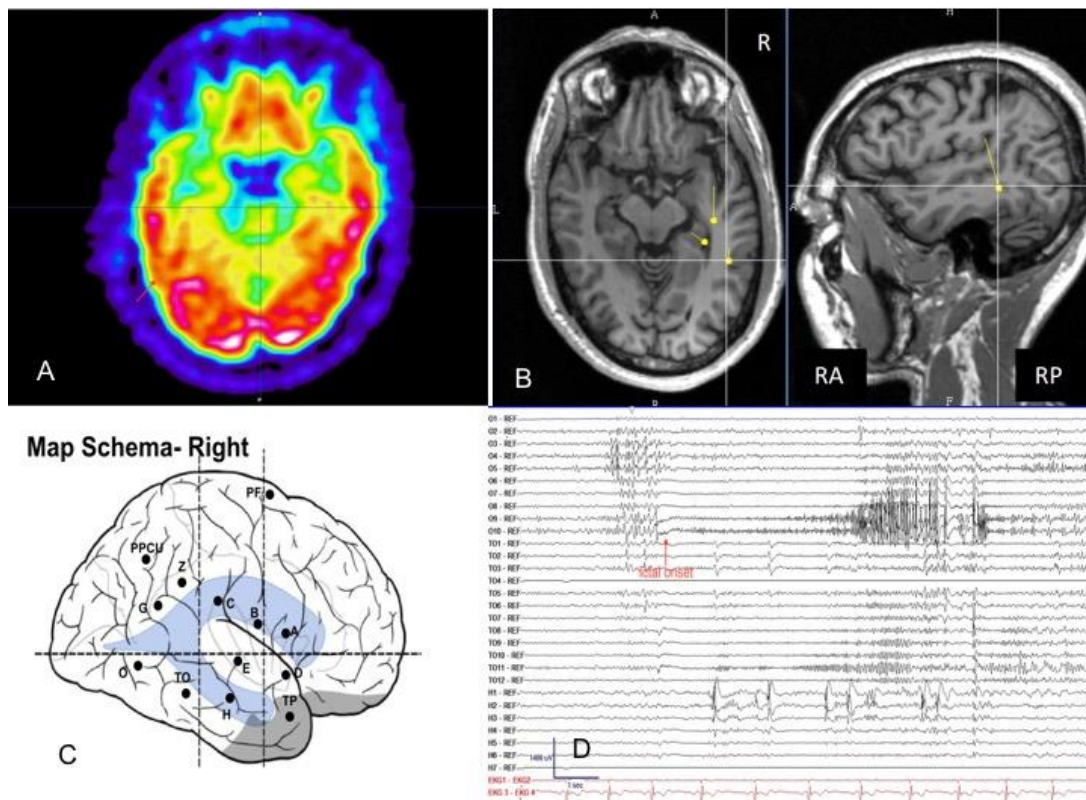
Depth electrodes were implanted over the suspected regions which are mentioned above with ROSA guidance including the occipital polar, angular gyrus, and posterior frontal area and hippocampus (*supplementary figure 1C*). Eleven electroclinical seizures were recorded and all of them had focal onset from occipital and temporo-occipital contacts (*supplementary*

figure 1D). Ictal asystole was not recorded during any of the seizures during the SEEG monitoring.

The patient underwent right posterior-inferior temporal focal cortical resection on March 19, 2018. Histopathological examination of the resected cortex showed non-specific gliosis without any evidence of focal cortical dysplasia. He was seizure-free when seen last at six months after surgery.

Figure legends

Supplementary figure 1. (A) Brain PET showing mild focal hypometabolism over the right posterior temporal region (red arrow); (B) MEG showing scattered dipoles over the right temporal region; (C) SEEG electrode positions; and (D) ictal SEEG onset characterized by low-amplitude fast activity over O9 and O10 contacts which subsequently evolved into high-amplitude multiple spikes over the same region (SEEG electrode positions: A: anterior insula; B: mid-insula; C: posterior insula; D: antero-inferior insula; E: postero-inferior insula; TP: temporo-polar; H: hippocampus; TO: temporo-occipital; O: occipital; G: angular gyrus; PPCU: parietal precuneus; Z: posterior cingulate; and PF: posterior frontal).



Supplementary table 1. Characteristics of individual patients with ictal asystole.

Patient number	Age (year)/gender/handedness	Age at onset of epilepsy (year)	Duration of epilepsy (year)	Seizure frequency per month	AED therapy	Presurgical evaluation findings and conclusions	Treatment/outcome
1	45/M/Right	43	2	4-5	Valproate and clobazam	Left temporal onset, diffuse cerebral atrophy on MRI. ILR over one year recorded one asymptomatic asystole and 5 bradycardia episodes (possibly related to subclinical seizures).	Modification of AED by increasing the dose of clobazam. Free of overt seizures during the last year.
2	36/F/Right	5	31	3-4	Phenytoin, primidone, and zonisamide	Right temporal seizure onset, right parieto-occipital and left parietal gliosis on MRI	Right parieto-occipito-temporal disconnection; Engel Class II outcome
3	40/M/Right	25	15	2-3	Levetiracetam and clobazam	Right posterior temporo-occipital seizure onset, normal MRI, PET and MEG - inconclusive, SEEG - right occipital and temporo-occipital seizure onset	Right temporo-occipital focal resection; Engel Class I outcome
4	17/F/Right	11	6	2	Oxcarbazepine and levetiracetam	Left parietal onset, left parietal gliosis on MRI	Lost to follow-up
5	29/F/Ambidextrous	6	23	300-600	Levetiracetam, lamotrigine and perampanel	Midline central and to left onset, left parietal FCD on MRI	Left parietal FCD resection under ECoG guidance; Engel Class III outcome

AED: antiepileptic drug; F: female; ILR: implantable loop recorder; FCD: focal cortical dysplasia; MRI: magnetic resonance imaging; ECoG: electrocorticography; SEEG: stereoelectroencephalography; PET: positron emission tomography; M: male; MEG: magnetoencephalography.

Supplementary table 2. Characteristics of individual patients with cardiac asystole.

Patient number	Age (year)/gender	Age at onset of syncope (year)	Prior cardiac disease	AED therapy	Cardiac evaluation/cardiac diagnosis	Treatment/outcome
1	30/F	28	No	Oxcarbazepine, Lacosamide	High-grade AV block, intermittent 2:1, 3:2 Wenckebach block and AV nodal conduction defect	Permanent pacemaker implanted; no further syncope
2	16/F	12	No	Nil	Structurally normal heart, sick sinus syndrome	Permanent pacemaker implanted; no further syncope
3	59/M	57	No	Nil	Structurally normal heart, intrahisian conduction defect bifascicular AV block (RBBB + LPFB), intermittent high-grade AV block	Permanent pacemaker implanted; no further syncope
4	63/M	63	Yes	Valproate	Sick sinus syndrome	Pacemaker implantation planned
5	49/F	12	No	Oxcarbazepine, Clobazam	Double vessel coronary artery disease, high-grade AV block	Permanent pacemaker implanted; no further syncope
6	74/M	74	No	Nil	Triple vessel coronary artery disease, paroxysmal AV block with phase IV AV block (triggered by ventricular premature complexes)	Permanent pacemaker implanted; no further attacks
7	85/M	84.5	No	Levetiracetam	Sinus bradycardia with first-degree AV block and complete RBBB	Pacemaker implantation planned
8	65/M	62	No	Valproate, Phenytoin, Phenobarbital	LBBB with prolonged PR interval, trifascicular block	Pacemaker implantation planned
9	46/M	25	No	Levetiracetam, Clonazepam	RBBB, sick sinus syndrome	Permanent pacemaker implanted; no further attacks
10	44/F	38	Yes	Valproate, Levetiracetam	Inducible ventricular tachycardia due to Brugada pattern after flecainide	ICD implanted
11	74.5/M	74	No	Nil	Cough syncope with asystole, structurally normal heart	Antitussive and bronchodilator medications
12	22/M	20	Yes	Nil	Sick sinus syndrome, structurally normal heart	Permanent pacemaker implanted; no further attacks
13	40/F	30	Yes	Phenytoin, Levetiracetam	Sick sinus syndrome, structurally normal heart	Pacemaker implantation planned

AV: atrio-ventricular; F: female; ICD: implantable cardioverter defibrillator; LBBB: left bundle branch block; LPFB: left posterior fascicular block; M: male; PR interval: interval between beginning of P wave until beginning of QRS complex in the ECG; RBBB: right bundle branch block.