■ Electroclinical reasoning report

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Ictal fear during parietal seizures

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ABSTRACT

Ictal fear is characterized by a subjective sensation of fear and consistent clinical manifestations during seizures. This phenomenon is rarely observed in parietal seizures. We report anatomical electroclinical correlations between an SEEG-recorded seizure and prominent fear semiology. The seizure onset zone was quantified using the Connectivity Epileptogenicity Index (cEI) method. Occurrence of fear during seizures was related to the involvement of the left inferior parietal cortex and the superior temporal gyrus without amygdala involvement. Our case confirms that parietal seizures can produce ictal fear without concomitant involvement of the limbic temporal network.

Key words: SEEG, Ictal fear, focal seizures, parietal lobe

Ictal fear describes the experience of a fearful emotion and related clinical signs at the beginning of, or during, an epileptic seizure. Seizures with fear as a prominent feature reflect the transient perturbation of brain regions involved in fear regulation and/or expression. Amygdala is a key structure of this network and is under the regulation of prefrontal structures (orbital frontal cortex [OFC], dorso-lateral prefrontal cortex and anterior cingulate cortex) [1, 2]. According to different series, ictal fear is reported by 10-13% of patients with focal seizures [3-7]. It is usually observed in temporal lobe seizures involving the amygdala, but more dramatic presentation (such as terror behaviour) is related to ventromedial prefrontal involvement [8, 9]. In contrast, ictal fear has been rarely reported as the main feature of parietal lobe seizures. Alemayehu *et al.* [10] described two patients with fear and panic attacks as ictal manifestations, originating from the parietal lobe, without implication of the amygdala. Here, we report a patient with seizures in which fear was the main clinical manifestation. Stereoelectroencephalography (SEEG) revealed an origin in the left inferior parietal lobule without involvement of the amygdala or prefrontal regions.

Case study

A 25-year-old, right-handed man had a 24-year history of drug-resistant structural focal epilepsy. His perinatal history was notable for birth by Caesarean, with respiratory distress due to meconium aspiration that required reanimation. The patient first presented with isolated cyanotic episodes at the age of one month and a half, then with a febrile seizure at 24 months of age, and a first non-febrile seizure occurred 10 months later. His seizures became gradually more frequent and were rapidly resistant to various antiepileptic drugs. His initial psychomotor development was normal, however, a developmental delay with learning difficulties was noticed since his early childhood.

He reported that seizures started with a sudden, unexplained, initially isolated, sensation of fear. After this aura, other symptoms occurred, including a perception of coloured round shapes

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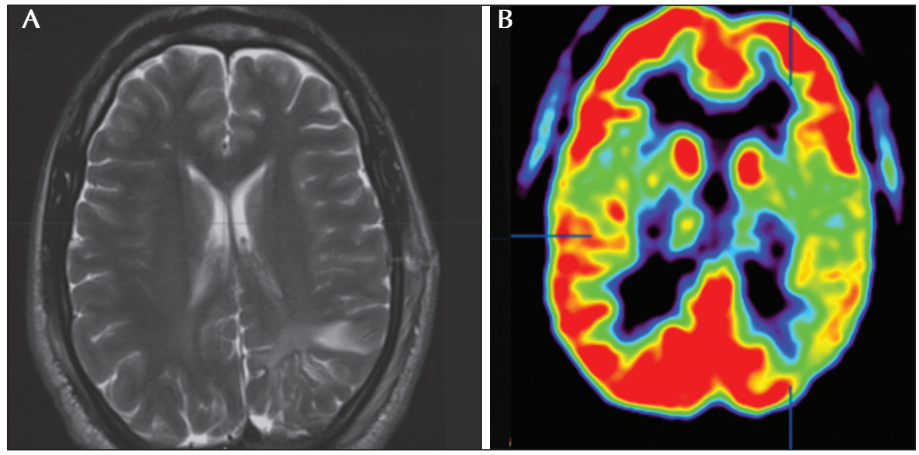
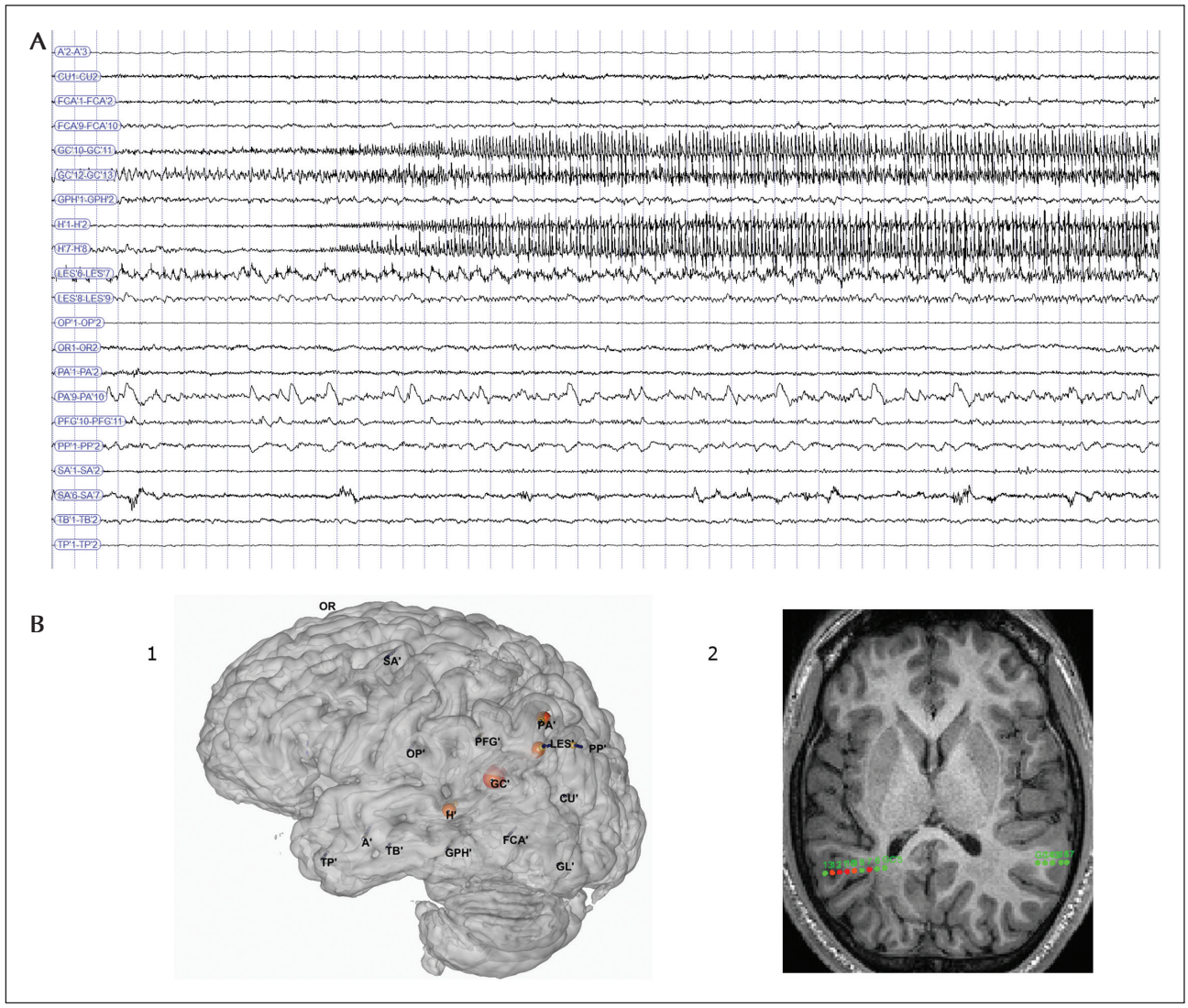
moving in the right visual field, a thoracic sensation, palpitations, followed by oculocephalic version to the right, then by a loss of contact, with right hemifacial clonic jerks and hypersalivation. Seizures with bilateral motor manifestations were frequent. Video-EEG recording of the patient's two habitual seizures confirmed this consistent pattern. Ictal EEG changes were characterized by rhythmic theta waves over P3-O1 electrodes, which then diffused on the adjacent posterior parietal and temporal electrodes. Magnetic resonance imaging (MRI) showed slight left hemispheric atrophy, with a subcortical white matter T2 and FLAIR hypersignal within the left parieto-temporo-occipital junction, suggestive of a gliotic scar (*figure 1A*). FDG-PET examination revealed hypometabolic areas, mainly distributed over the left posterior regions (*figure 1B*). Neuropsychological evaluation revealed a significant global cognitive deficit with visual-verbal dissociation (better in verbal). Stereo-EEG exploration was performed with the aim of defining the epileptic zone (*figure 2*). The patient was informed that his data might be used for research purposes and signed consent was obtained. Eighteen intracerebral multiple contact electrodes (Alcis, Besançon, France; 10-15 contacts; length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) were implanted according to Talairach's stereotactic method. A postoperative computerized scan (CT) was performed in order to verify the absence of bleeding and the position of each recording lead. Subsequently, CT/MRI data fusion was performed in order to accurately identify and locate each contact along the electrode trajectory using specific in-house software (Gardel, available at: http://meg.univ-amu.fr/wiki/GARDEL:presentation) [11].

Ictal recording revealed semiology centred on fear without major language disturbance. Electrical seizure onset was characterized by a long-lasting pattern of slow rhythmic activity evolving to polyspikes, initially focalized on the lateral leads towards the left supramarginal gyrus (GC' electrode). Two minutes later, the same slow rhythmic pattern of activity appeared over the lateral contacts towards the posterior aspect of the left superior temporal gyrus (H'electrode) (*figure 2A*), followed by involvement of the superior and inferior parietal lobules (PA' and LES' electrodes) within the next two minutes. After these changes, affecting the parieto-temporal junction, the patient announced a seizure, while complaining of fear, vertigo and palpitation. There was no concomitant involvement of the amygdala or prefrontal regions. Objective clinical semiology comprised an anxious facial expression, piloerection all over his body and tachycardia. Later, left tonic oculocephalic version shortly preceded bilateral motor manifestations.

The SEEG signal was quantified using the Connectivity Epileptogenicity Index (cEI), recently developed and validated by our group [12]. The cEI is a novel approach, combining the original Epileptogenicity index (EI) [13] and a directed functional connectivity measure ("out-degrees") by non-linear regression coefficient h2 in a single quantity. The EI combines analysis of both spectral and temporal features of SEEG signals, respectively, related to the propensity of a brain area to generate fast discharges (12.4-127 Hz), and to the timing of involvement of this area in the seizure. A normalized EI value is used, ranging from 0 to 1. If there is no involvement of the brain structure, the EI is equal to 0 (no epileptogenicity), whereas if the brain structure generates a rapid discharge and the time to seizure onset is minimal, the EI is equal to 1 (maximal epileptogenicity). The cEI was calculated by



■ **Figure 1.** (A) T2-weighted axial MRI showing sequelae lesions, prominent in the white matter of the left parietal region. (B) FDG-PET showing hypometabolic areas in the left posterior region.



■ **Figure 2.** (A) SEEG trace showing the emergence of ictal activity on electrodes GC′ (contact 10-11 and 12-13 in the inferior parietal lobule) and H′ (contacts 1-2 in the Heschl gyrus and 7-8 in the lateral temporal cortex). Note the absence of involvement of the amygdala (A′ 2-3). A′2-3: left amygdala; CU1-2: right cuneus; FCA′1-2: left lingual gyrus; FCA′9-10: left anterior occipital sulcus; GC′10-11; 12-13: left supramarginalis gyrus; GPH′ 1-2: left parahippocampal gyrus; H′1-2: left Heschl gyrus; H′7-8: lateral posterior aspect of the left superior temporal gyrus; Les′7-8; 8-9: left angular gyrus; OP′1-2: left posterior insular cortex; OR 1-2: right orbitofrontal cortex; PA′1-2: left precuneus; PA′9-10: left intraparietal sulcus; PFG′10-11: posterior aspect of the left supramarginalis gyrus; PP′1-2: posterior aspect of the left superior parietal lobule. (B1) SEEG representation with projection of the left-side electrodes on a 3D MRI mesh. The red spheres indicate the regions with maximal Connectivity Epileptogenicity Index (cEI) values (left inferior parietal lobule and superior temporal gyrus). (B2) Representation of the Connectivity Epileptogenicity index (cEI) values estimated based on different contacts of the electrode GC′ and visualization of this electrode in the patient's anatomy showing maximal epileptogenicity in the inferior parietal lobule.

using an in-house cEI Matlab plugin (https://meg.univ-amu.fr/wiki/AnyWave:Plug-ins) [14]. For connectivity analysis, signals were filtered in the beta-gamma range (12-45 Hz). A non-linear regression analysis was computed between all pairs of channels based on the h2 index. The directionality of the link was determined based on the delay of the highest h2 value across directions. We used a 3-second sliding

window with a step of 0.5 seconds, and a maximum lag of 0.1 seconds. A threshold of 0.2 was applied to the connectivity matrix at each time window, yielding a binary connectivity matrix for each step. The out-degree value for each time window was calculated by computing the number of outgoing connections (out-degrees). The median values of out-degrees were computed across all time windows for each SEEG channel. The normalized values of the h2 out-degrees and the normalized EI were then added together for each channel. Normalization was performed by dividing all measures by the maximum value of the sum across all channels, resulting in a combined index [12]. The cEI values were then represented within the patient's individual 3D brain map (*figure 2B*). The cEI was estimated over a 50-second period, starting 20 seconds before the first clinical symptoms.

The maximal cEI values were found in the left supramarginal and the posterior superior temporal gyrus (*figure 2B*). Electrical stimulation did not trigger any seizure. At the end of the SEEG exploration, thermocoagulations were performed on the electrodes H'2 to 8, GC' 10 to 13, LES' 3 to 8, leading to a significant (more than 90%) decrease in the frequency of seizures. At the last follow-up visit, four years after thermo-SEEG, the patient remained improved, experiencing two seizures per year. For this reason, he declined the proposal of a cortectomy centred on the left inferior parietal region.

Discussion

This case illustrates a rare example of parietal lobe seizure in which fear was the most prominent symptom. Fear occurred while the epileptic discharge affected the inferior parietal cortex and the lateral temporo-parietal junction with no concomitant involvement of the amygdala or prefrontal regions.

A variety of brain structures are implicated in the expression and regulation of fear. It has long been known that amygdala plays a central role both in the processing of emotionally relevant stimuli and in mediating the emotional responses, in particular those of fear and anxiety [1, 2]. As part of the fronto-temporo-limbic network, the prefrontal and orbito-frontal cortices exhibit top-down control over the emotional processing and emergence of behavioural responses [15, 16]. Fear is one of the most common auras reported in mesial temporal lobe seizures [17]. In such seizures, patients often experience a fearful sensation or anxiety, while in frontal or temporo-frontal seizures, the clinical presentation may be dominated by dramatic manifestations of intense fear or a panic behaviour can be observed [5, 18, 19].

Notwithstanding, fear remains a rare manifestation in seizures associated with other localizations. In one study reporting on patients with early ictal symptoms of fear, 82.6% of patients had a temporal lobe focus and 17.4% had a frontal lobe focus, whereas only 13.2% had a parietal and 7.6% had an occipital lobe focus [3]. However, different studies reviewed for this report determined the epileptogenic regions with variable accuracy, some using only scalp EEG. Thus, the precise involvement of brain structures was not investigated. So far, only two patients have been reported with panic attacks as ictal manifestations of parietal lobe seizures, documented by invasive recordings [10]. However, in these cases, it remained uncertain whether fear was correlated with a discharge strictly limited to the parietal cortex, since the temporal and frontal lobes were poorly explored. Furthermore, the epileptic discharges of these patients originated from the right hemisphere, whereas a left hemispheric seizure origin was reported in the present case. Our findings thus differ from the available literature data suggesting that the right hemisphere would be more involved in fear response than the left hemisphere [3, 20]. Based on an SEEG study from our group, investigating 17 patients with parietal lobe seizures, ictal fear was found in three cases (17%) [21]. Seizures originated from the superior parietal cortex in two cases and from the inferior parietal lobule in one case. Propagation to the amygdala was observed in only one case. In our case, since the implantation was mainly unilateral, we cannot totally exclude propagation to the contralateral amygdala. The role of the parietal lobe in emotional processing is not well known. Stimulation of the parietal cortex does not lead to emotional manifestations, unlike stimulation of the temporo-mesial regions [20]. The parietal lobe participates in recognition of facial expressions together with the occipito-temporal cortex, amygdala, orbitofrontal cortex and basal ganglia [22].

A study investigating patients with focal brain lesions revealed that lesions in the right somatosensory-related cortices were associated with impaired recognition of facial expressions [23]. Furthermore, a recent functional imaging study demonstrated that processing of facial expressions was characterized by activation of the inferior parietal lobule [24].

Another mechanism for fear may also be discussed. Ictal fear could be a fear of the seizure and its traumatic context. Several studies reported a high prevalence of anxiety disorders in patients with refractory epilepsy [25, 26]. Recently, a new term has been proposed for patients with epilepsy, suffering from a specific kind of post-traumatic stress disorder (PTSD): post-epileptic seizure PTSD [27]. Chung and Allen support this hypothesis by showing that 81% of patients with epilepsy reported PTSD symptoms associated with

their traumatic epileptic seizures and 51% of patients were diagnosed with post-epileptic seizure PTSD [27]. In another study, 64% of patients with difficult-to-treat epilepsy reported that seizures evoked helplessness and intense fear or horror and 5% had PTSD related to a traumatic seizure [28]. Finally, in our case, both mechanisms might have contributed to the emergence of fear symptoms. ■

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

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TEST YOURSELF

(1) Which brain structures are involved in fear and its regulation?

(2) What are the main aspects of epileptic seizures with fear?

(3) What is the incidence of fear in parietal seizures?

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