










## SHORT RESEARCH ARTICLE

# Anti-GAD65 musicogenic epilepsy: Bilateral and independent mesial temporal seizures revealed by foramen ovale electrodes

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## Abstract

Musicogenic epilepsy (ME) is characterized by seizures triggered by music. The epileptogenic focus in this rare reflex epilepsy is often in the temporal lobe, although the precise localization is still unclear. A correlation between ME and the presence of GAD65 antibodies indicates a potential immunological pathogenic mechanism. We evaluated a 32-year-old woman with drug-resistant temporal lobe epilepsy as a candidate for epilepsy surgery. In the absence of clear clinical lateralizing signs, video-EEG monitoring with intracranial electrodes inserted through the foramen ovale was performed to record from the amygdalo-hippocampal regions. The foramen ovale electrodes revealed bilateral, asynchronous, and independent seizure onsets in the mesial temporal regions triggered by music. Testing for GAD65 antibodies confirmed high-titer positivity. The efficacy of epilepsy surgery in antiGAD65-positive ME patients remains limited. We highlight the use of semi-invasive recording with foramen ovale electrodes in ME, as it can reveal bilateral seizures of mesial origin that contraindicate surgery and support the consideration of immunotherapy options.

**Plain Language Summary:** Musicogenic epilepsy is a type of epilepsy in which music triggers seizures. Our understanding of its origin and cause is still limited. We assessed a patient with music-induced seizures to see if surgery was an option. Since noninvasive tests before surgery were not clear, we used a minimally invasive method with electrodes inserted through a small opening in the skull called the foramen ovale to record the seizures. Thus, we found that the seizures

Roberta Di Giacomo and Giulia Maccanti contributed equally to this study.

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started independently from both temporal lobes, contraindicating epilepsy surgery. We also found high levels of GAD65 antibodies indicating an immunological pathogenic mechanism.

**KEYWORDS**

antiGAD65, autoimmune-associated epilepsy, foramen ovale electrodes, musicogenic epilepsy, temporal lobe epilepsy

## 1 | INTRODUCTION

Musicogenic epilepsy (ME) is a rare form of epilepsy (prevalence of 1 per 10000000) characterized by seizures triggered by specific sounds or music<sup>1</sup> ranging from simple tones to complex symphonic compositions. The triggering stimulus often has an affective or emotional component.<sup>2</sup>

Given the complexity and variability of the stimuli, the pathogenesis of ME remains unclear. It has been suggested that ME primarily originates from the temporal lobe (TL), with a predominance on the right side.<sup>1,2</sup> However, the exact localization is a subject of debate, particularly regarding whether the epileptogenic zone is localized in lateral<sup>3</sup> or mesial TL areas.<sup>4</sup> Furthermore, the literature has identified a correlation between ME and the presence of anti-GAD65 antibodies,<sup>5</sup> suggesting a potential immunological mechanism underlying the condition.

We report a case of medically refractory anti-GAD65 epilepsy with musicogenic seizures, in which video-EEG monitoring with intracranial electrodes inserted through the foramen ovale demonstrated bilateral involvement of mesial temporal regions.

## 2 | CASE PRESENTATION AND METHODS

A 32-year-old left-handed woman has been experiencing brief paroxysmal episodes since the age of 29. These episodes were characterized by feelings of anxiety and fear, sometimes described as sensation of heat rising from the epigastrium to the head, accompanied by a feeling of “fullness” in the head and a loss of awareness. The episodes occurred several times per day, occasionally in clusters, and were sometimes triggered by music or songs. No lateralizing gestural automatisms or dystonic postures were observed.

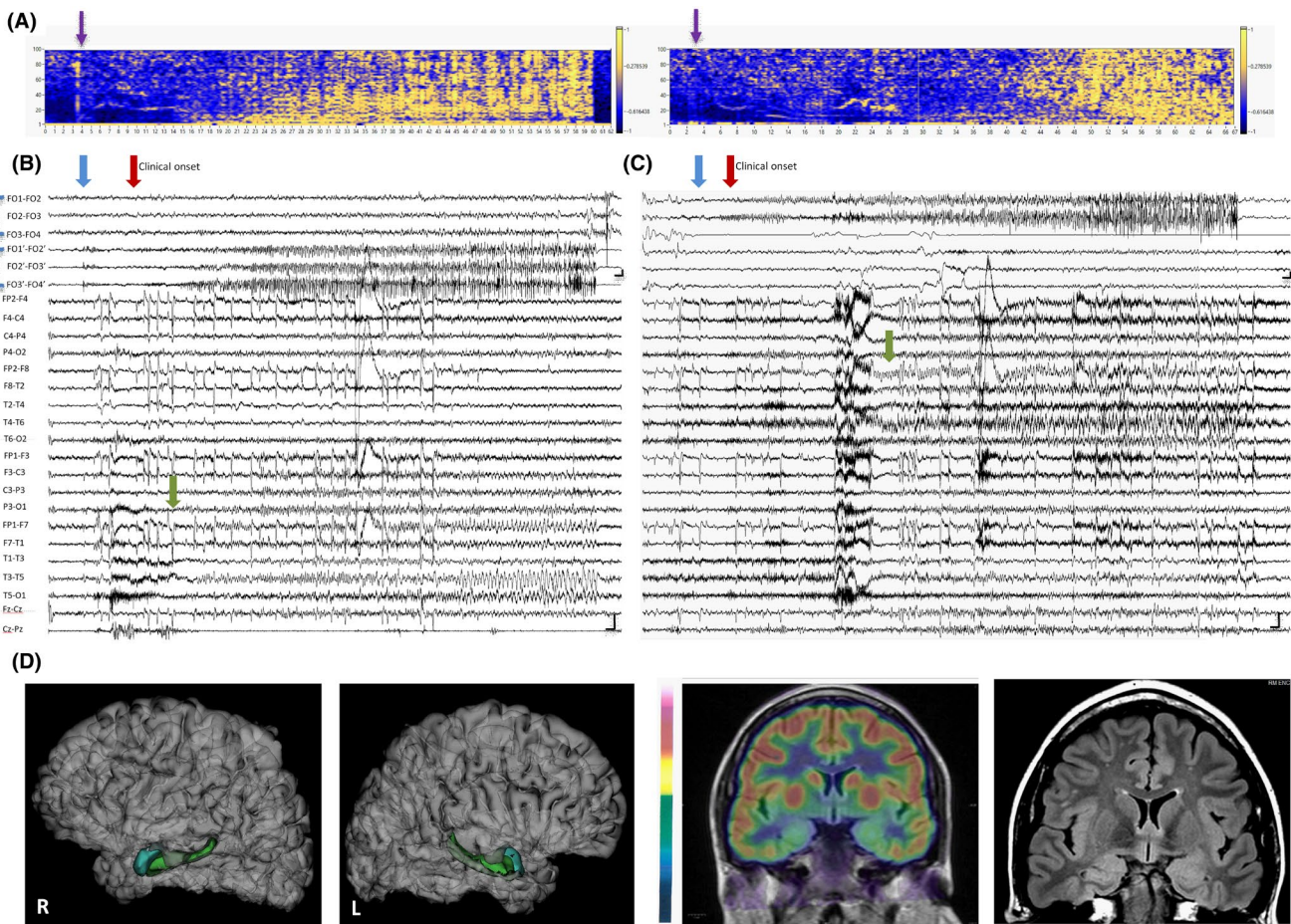
There was no reported history of CNS infection, febrile seizures, significant head trauma, or perinatal complications. After ineffective treatment with several antiseizure medications (levetiracetam, topiramate, carbamazepine, and zonisamide), the patient underwent a noninvasive pre-surgical evaluation at our Epilepsy Center. Routine

**Key points**

- Musicogenic epilepsy (ME) is characterized by seizures triggered by music.
- The epileptogenic focus is often located in the temporal lobe, although its precise localization remains unclear.
- Foramen ovale electrodes revealed bilateral and independent seizure onsets in the mesial temporal regions in a patient with ME and GAD65 antibodies.
- A correlation between ME and GAD65 antibodies suggests a potential immunological pathogenic mechanism.

biological tests and neurological examinations were normal, but neuropsychological assessments revealed bilateral involvement with long-term deficits in both visual-spatial and verbal memory. Brain 3T-MRI showed mild enlargement of the left amygdala. Language functional MRI demonstrated left-hemisphere dominance, while brain FDG-PET revealed no asymmetry in brain metabolism. Prolonged scalp-video-EEG (electrodes in 10–20 System positions) identified bitemporal asynchronous interictal epileptiform discharges (IEDs), with a predominance on the left side. We recorded one habitual spontaneous focal seizure without impaired awareness: the patient reported a subjective sensation of warmth rising from the epigastrium to her head, without motor features or aphasia. The ictal EEG displayed a late discharge (about 15 seconds) localized to the left temporal region, with subsequent involvement of the left centro-parieto-occipital regions.

In the absence of clear clinical lateralizing signs with poorly localizing scalp seizure onset, bilateral neuropsychological deficits, and mild neuroimaging abnormalities, the patient underwent video-EEG monitoring with intracranial electrodes inserted through the foramen ovale to identify early involvement of mesial structures at seizure onset.<sup>5</sup> Two FOEs (ADTech FO04K-SP05X-000), each



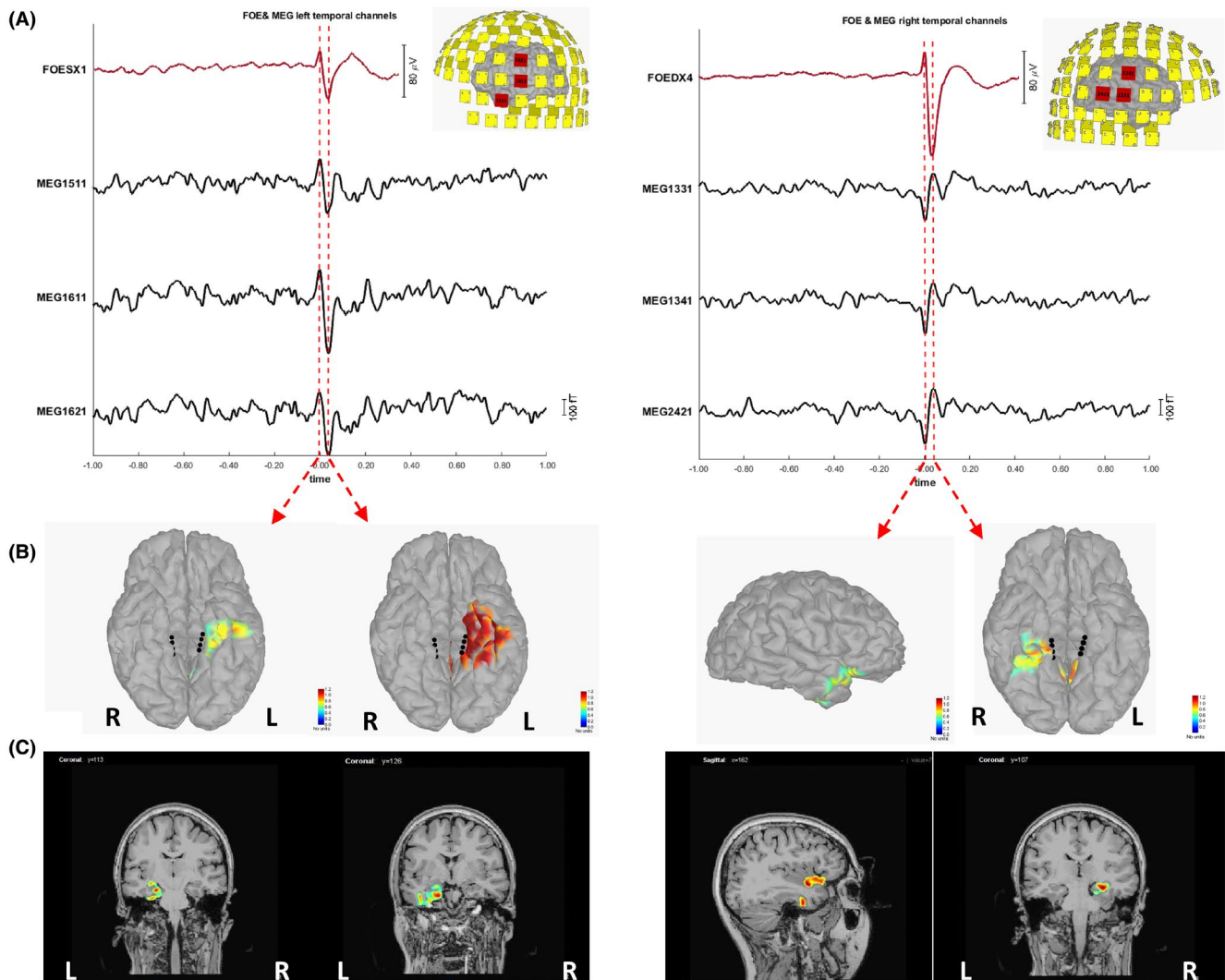
**FIGURE 1** (A) Spectral analysis of seizures demonstrated chirp seizure onset, with the ictal seizure recorded on the scalp and shown in Panel B. Chirps are characterized by high-power fast activity at  $>80\text{Hz}$ , which gradually decreased in frequency within 5–10s. Due to similarity to the sonographic pattern recorded during birds' vocalization, these brief signals with rapid frequency content changes were defined by physicists as “chirps.” Elpho-EEG software was used for EEG spectral analysis ([www.elpho.it](http://www.elpho.it)). Chirps are marked with purple arrows. (B) The left FOE (grouped under “L” in the figure) leads showed mesial temporal discharge with low-voltage fast activity after music listening. PZ was deamplified to remove artifacts. (C) The right FOE (grouped under “R” in the figure) leads showed mesial temporal discharge with low-voltage fast activity after music listening. FO4 was deamplified to remove artifacts. In both panels, the EEG recordings use a longitudinal montage (blue arrow indicates seizure onset, red arrow indicates first clinical event and green arrow indicates scalp seizure onset). Calibration: Vertical line  $100\mu\text{V}/\text{cm}$ , horizontal line 1s. (D) Neuroimaging: On the right side, brain magnetic resonance imaging fluid-attenuated inversion recovery (FLAIR) demonstrated a mild enlargement of the left amygdala; in the center, an FDG-PET scan showed no alterations; on the left side, a pre-implantation T1 volumetric MRI, analyzed with the free-surfer pipeline, segmented the mesial TL structures (hippocampal formation in green and amygdala in blue) and generated pial surfaces.

carrying four contacts, were bilaterally positioned in the cisterna magna medial to the amygdalo-hippocampal regions. Interictal EEG confirmed the presence of bilateral temporal IEDs; while ictal EEG recorded one seizure originating from the right mesial TL and two from the homologous contralateral regions. In both seizures, discharges initially appeared on FOE leads as low-voltage fast activity with *chirp* ictal biomarker<sup>6</sup> (Figure 1A) and subsequently emerged on homolateral scalp temporal regions after a few seconds (Figure 1).

Two of the seizures, one on the right and one on the left occurred 2–3 min after listening to specific Italian pop and rap songs, with identical seizure semiology. Interictal

magnetoencephalography yielded results similar to those from interictal video-EEG, with spike propagation limited to the homolateral TL (Figure 2).

Given the bilateral temporal involvement, late-onset epilepsy, seizure facilitation by music listening, and amygdala alteration, autoantibodies were tested. The serum anti-GAD65 concentration was  $329\,750\text{IU}/\text{mL}$  (using an enzyme-linked immunosorbent assay) (ELISA–Medizym®antiGAD cod 3802). Other screening tests were negative. Based on these findings, a diagnosis of drug-resistant autoimmune-associated epilepsy with anti-GAD65 positivity was established, the hypothesis of surgical treatment was suspended.



**FIGURE 2** (A) Averaged interictal spikes on left and right FOEs (red). Interictal activity is also visible on temporal MEG channels. (B) MEG source localization of the spikes at the first peak and the second (propagation). The Brainstorm toolbox (<http://neuroimage.usc.edu/brainstorm>) was used for MEG data analysis and source estimation with dSPM. In the left hemisphere, mesial origin and propagation are observed, while in the case of the right FOE spike the source localization at the first peak is in the anterior temporal lobe, with propagation to inferior temporal and mesial regions. For visualization purposes, the maps were thresholded at 80% of the maximum activation in radiological display convention. (C) The same localizations as in panel B, mapped on subject's MRI in neurological display convention.

### 3 | DISCUSSION AND RESULTS

ME is a rare form of epilepsy characterized by its wide range of triggers, which vary among individuals and evolve over time. Emotional factors further complicate the condition, adding to its complexity.<sup>1</sup>

In our case, the patient did not exhibit identifiable triggers, such as a definite type of music. She was unfamiliar with which songs, harmonies, or rhythms served as triggers, which is often expected in reflex seizures. While ME is commonly localized to the TL, defining the specific epileptogenic area responsible for seizure onset and propagation remains a significant challenge. This highlights the importance of invasive EEG recordings

in diagnosis and treatment planning, a concept already emphasized by various authors.<sup>3,4</sup> Nagahama et al. conducted a literature review, identifying 10 cases of ME where invasive EEG was utilized to localize the epileptogenic region. Among these cases, eight showed focal unilateral TL seizure onset (six in the right TL, two in the left TL), while two cases exhibited bilateral mesial temporal onsets. Specifically, the lateral temporal cortex was involved in three cases, mesial temporal structures in three cases, the planum temporale in one case, and both lateral and mesial structures in one case.<sup>3</sup> In contrast, Pelliccia et al., using Stereo-EEG recording, demonstrated the predominant role of the mesial region of the TL in one patient with ME.<sup>4</sup>

Patients with autoimmune-associated epilepsy are not generally evaluated by semi-invasive methods for pre-surgical purposes, making our findings valuable. We employed an intracranial recording technique using FOfs, offering a cost-effective and minimally invasive approach. FO recording provides several advantages: superior spatial resolution compared with noninvasive methods (scalp T1/T2) and semi-invasive approaches such as sphenoidal electrodes; rapid interpretation in comparison to subdural recordings and Stereo-EEG; easier and quicker placement and explantation compared with SEEG, with a lower incidence of major complications. Additionally, this method is generally better tolerated, allowing for extended recording durations beyond typical limits. Importantly, it is associated with a lower cost than SEEG, making it a valuable option even in resource-limited settings.<sup>7,8</sup>

The application of this technique allowed for the identification of early bilateral involvement in mesial TL. Furthermore, our case confirmed the correlation between temporal epilepsy with asynchronous and independent seizure onset from the mesial regions triggered by music and the presence of GAD65 autoantibodies. As emphasized in the literature, it is crucial to conduct the anti-GAD65 assay in cases of bitemporal epilepsy, given the established link between high antibody titers and the manifestation of neurological symptoms.<sup>9-13</sup> Notably, none of the 10 cases of musicogenic epilepsy (ME) reported in Nagahama review underwent anti-GAD65 sampling. This assessment is important for prognosis, considering autoimmune-associated epilepsy's tendency to become drug-resistant.<sup>10,11</sup> Treatment options include a combination of antiseizure medications and immunotherapy, such as intravenous methylprednisolone, intravenous immunoglobulins, or plasma exchange, extending to cyclophosphamide or rituximab. Additional therapies may include surgery, deep brain stimulation of thalamic nuclei, and vagus nerve neurostimulation. However, the response to these treatment modalities is generally poor.<sup>14-18</sup> Regarding surgery, for patients with drug-resistant ME who are potential candidates for resective surgery, it has been suggested that measuring anti-GAD65 may be useful in predicting seizure freedom due to the risk of bitemporal involvement. In Malter's study, two out of three patients who underwent surgery experienced a reduction in seizure frequency, but none achieved complete seizure freedom.<sup>15</sup> Similarly, Dimova described a patient who underwent amygdalohippocampectomy after failing medication, resulting in class IIIa Engel outcome with worsening neuropsychological function.<sup>17</sup> In a recent 2024 study, Zao-Fleming et al. evaluated the outcomes of 95 patients with drug-resistant focal epilepsy associated with high titers of anti-GAD65. Among these patients, six underwent VNS implantation with limited

and unsustainable benefits. Seven received surgical resection, and two patients underwent both interventions. Only one surgical patient achieved seizure freedom; this patient had an alternative etiology related to epilepsy (temporal cavernoma), prompting discussions about the relevance of anti-GAD65 positivity.<sup>18</sup>

Among our cohort of 22 patients with antiGAD65 TL epilepsy, we performed surgery on three patients with unilateral temporal involvement, all of whom achieved class I Engel's classification outcome (data not published).

## 4 | CONCLUSION

ME involves a neuronal network that is not yet fully understood. Its manifestation likely depends on specific triggers that activate certain circuits more than others. To the best of our knowledge, this is the first report utilizing FOE to reveal bilateral and independent mesial temporal seizure onset in autoimmune-associated ME linked to anti-GAD65. Experience with epilepsy surgery for anti-GAD-positive ME and TL epilepsy remains limited, and treatment indications should be tailored to the individual patient.

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## CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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