■ Clinical commentary

Epileptic Disord 2021; 23 (5): 754-759

Epileptic Disorders

Musicogenic epilepsy in paraneoplastic limbic encephalitis: a video-EEG case report

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Received December 27, 2020;
Accepted April 01, 2021

ABSTRACT

Musicogenic epilepsy (ME), a peculiar form of reflex epilepsy, represents a neurological rarity and yet another demonstration of the extraordinary power of music on the human brain. Despite the heterogeneity of the reported musical triggers, patients' emotional response to music is thought to play a crucial role in provoking seizures. Accordingly, the mesial temporal structures (especially of the non-dominant hemisphere) appear most involved in seizure generation, although a more complex fronto-temporal epileptogenic network was documented in some cases. Autoimmune encephalitis has been recently included among the many possible aetiologies of ME based on a few reports of music-induced seizures in patients with anti-glutamic acid decarboxylase 65 antibodies. Here, we describe the case of a 25-year-old man, educated in music over a long period of time, who had suffered from drug-resistant temporal lobe epilepsy following seronegative limbic encephalitis related to non-Hodgkin lymphoma. Along with spontaneous events, the patient also developed musicogenic seizures later in the disease course. After detecting five music-induced episodes via 24-hour ambulatory EEG, we performed prolonged video-EEG monitoring during which the patient presented a right temporal seizure (characterized by *déjà-vu*, piloerection and gustatory hallucinations) while listening to a hard rock song through headphones (which he had not previously heard). This observation allowed us to confirm the provoking effect of the music on our patient's seizures, despite the lack of any emotional drive, which suggests that a "cognitive" trigger was more likely in this case. Our report further highlights that autoimmune encephalitis should be investigated as a novel potential cause of musicogenic epilepsy, regardless of autoantibody status.

Key words: musicogenic seizures, autoimmune epilepsy, paraneoplastic limbic encephalitis, video-EEG

VIDEO ONLINE

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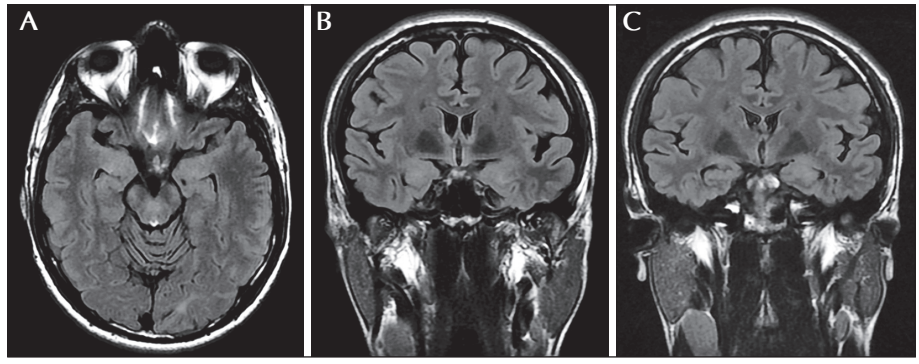
doi:10.1684/epd.2021.1322

Musicogenic epilepsy (ME) is an exceedingly rare form of reflex epilepsy, defined by the occurrence of seizures consistently evoked by "sounds in melodic or harmonic combination" [1], ranging from simple sounds or pure vocals to much more elaborate musical pieces. Not only listening to music, but also playing, dreaming or thinking about it can serve as a trigger, as well as singing. ME stands out among other forms of auditory-induced epilepsy regarding the heterogeneity of the provoking stimuli, which vary among different subjects and often within the same individual, as well as the latency

between the musical trigger and seizure onset, reportedly up to several minutes [2]. ME usually affects young adults and is characterized by the recurrence of music-evoked focal and focal-to-bilateral tonic-clonic seizures, the electro-clinical features of which support the diagnosis of temporal lobe epilepsy (TLE) in 75% of the patients [3]. As to aetiology, although an underlying cause cannot be found in most subjects, trauma, cerebrovascular accidents, focal cortical dysplasia, brain tumours, hippocampal sclerosis and demyelinating lesions have been reported in association with ME, along with a few genetic conditions (*i.e.* autosomal dominant lateral temporal lobe epilepsy and Dravet syndrome) [2]. Recently, music-evoked temporal lobe seizures have also been described in three patients with autoimmune encephalitis (AE) related to anti-glutamic acid decarboxylase (GAD) 65 antibodies (Abs) [4, 5]. Herein, we report the case of a young man diagnosed with seronegative paraneoplastic limbic encephalitis who later developed treatment-resistant musicogenic seizures, suggesting that AE might represent a novel (or overlooked) potential cause of ME, regardless of antibody specificity.

Case study

In August 2016, the patient, a 21-year-old, previously healthy, ambidextrous boy, abruptly developed recurrent spells characterized by "goose bumps", *déjà vu* and an unpleasant metallic taste, sometimes followed by awareness impairment and oral automatisms. Soon afterwards, he started complaining of difficulties in recalling past episodes of his life. EEG recordings performed at the time documented bilateral asynchronous temporal lobe seizures, and brain MRI showed T2 hyperintensity involving both mesial temporal structures, prominent on the left side (*figure 1*). Slight pleocytosis (10 white blood cells/mm^3) and oligoclonal bands were detected in the CSF, whereas Abs against onconeuronal and neuronal surface antigens were absent in both CSF and serum. A diagnosis of definite autoimmune limbic encephalitis was made, according to the criteria by Graus *et al*. [6]. Contrast-enhanced whole-body CT, performed at the time, was also unremarkable. The patient was started on corticosteroids (intravenous methylprednisolone followed by oral prednisone), and subsequently a course of intravenous immunoglobulin, before switching to azathioprine, without clinical benefit. The appearance of a skin rash and generalized lymphadenopathy about three months later revealed aggressive mature B-cell lymphoma, for which the boy received chemotherapy and eventually underwent autologous hematopoietic stem cell transplantation. Despite complete remission of his haematological malignancy, the patient continued to experience weekly/daily seizures that proved resistant to numerous therapeutic regimens (carbamazepine, lacosamide, levetiracetam, zonisamide and topiramate, in various combinations). In late 2018, brain MRI confirmed the previously documented alterations involving both mesial temporal lobes, whereas CSF analysis was normal; once again, no specific Ab was detected in either CSF or serum. At that time, the boy also started noticing that his seizures were more and more often evoked by listening to music, which struck him particularly since he was an avid music fan and a skilled guitarist (he had been playing both classical and electric guitar for over 14 years, routinely practicing and performing live with a local band). The patient reported that different musical pieces (instrumental and vocal), even unknown to him, might represent a trigger, regardless of their emotional content. He also stated that, given his specific training, he was particularly prone to "mentally analysing" musical



■ **Figure 1.** Brain MRI at onset using fluid-attenuation inversion recovery (FLAIR) for axial (A) and coronal (B, C) sections showing bilateral mesial temporal hyperintensity, and a slight increase in hippocampus and amygdala volume on the left side.

tracks whenever he heard one, specifically regarding the music content, whereas lyrics generally meant little to him. During a 24-hour ambulatory EEG (AEEG), performed when the patient was 25, he reported five seizures, four of which occurred while listening to music (with a latency ranging from 8 to 53 minutes), and another arose 37 minutes into a guitar solo. A clear-cut ictal EEG pattern was documented in three out of five episodes, showing left temporal onset in two cases and right temporal onset in another. In order to confirm such an interesting observation, the patient underwent prolonged video-EEG monitoring during which musical stimuli were delivered through headphones. Songs belonging to different genres were randomly played on his mobile phone, for about five minutes at a time, with 15-second intervals. After 14 minutes from the start, and 57 seconds into a hard rock song, that he had never heard before but which he immediately liked, the boy experienced one of his typical seizures, characterized by *déjà-vu*, followed by piloerection on his right arm (*figure 2A*) and a "lightness" of the right side of his body, later associated with a strongly unpleasant metallic taste in his mouth and nose and subtle oral automatisms (*video sequence 1*). Throughout his seizure, the patient was fully aware but appeared rather overwhelmed, especially by the displeasing metallic taste, although he denied any feeling of anxiety or fear. The concomitant EEG tracing showed an ictal pattern arising from the right middle temporal derivations, soon spreading to the ipsilateral central-parietal-occipital region, which started a few seconds before the patient's signal and stopped about one minute before complete clinical remission (*figure 2B*). Before seizure occurrence, occasional interictal epileptiform discharges (IEDs) could only be detected on the left temporal derivations and exclusively during periods of somnolence and non-rapid eye movement (NREM) sleep, whereas after seizure termination, a few right temporal IEDs were observed as well (bilateral asynchronous IEDs during sleep are shown in the *supplementary figure*).

Discussion

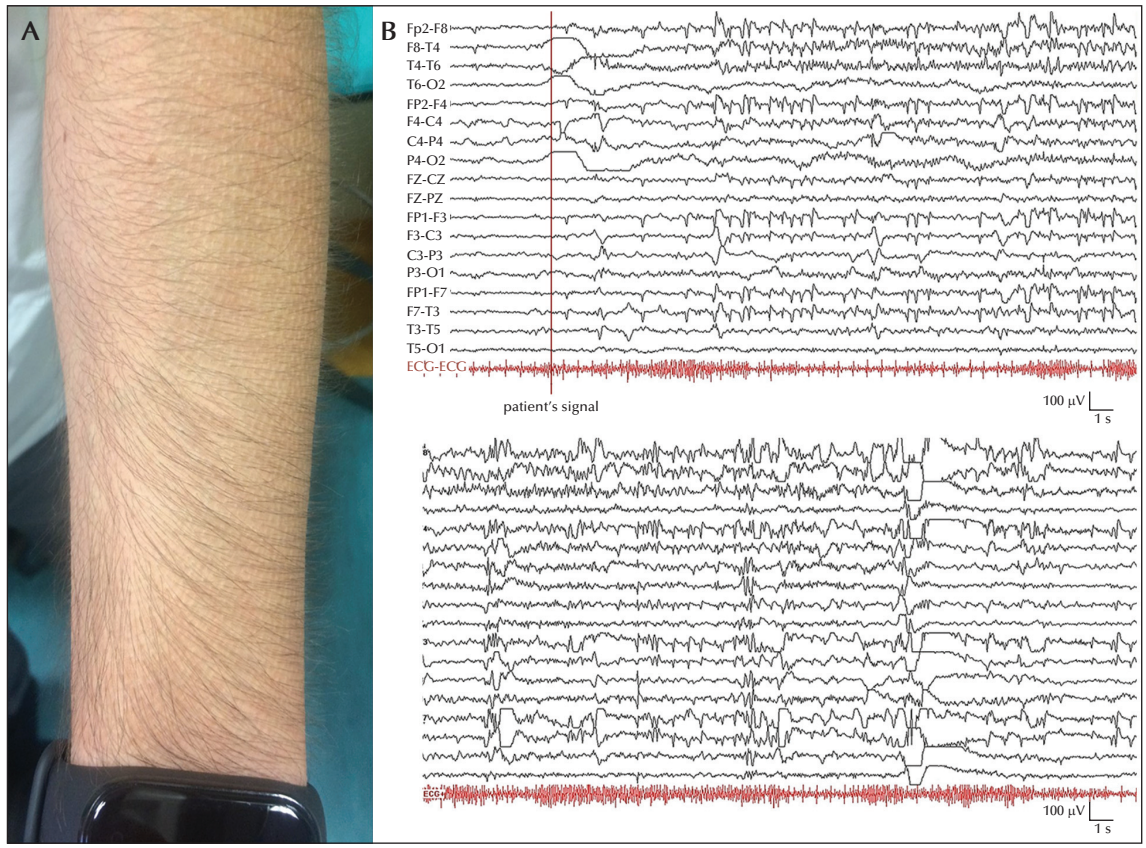
ME is a rare form of reflex epilepsy, first described by Critchley in 1937 [7], and has since been a subject of debate due to its peculiar features. A complex fronto-temporal network is thought to be involved in generating musicogenic seizures, with the mesial temporal structures playing a "driving" role, as suggested by intracranial EEG [8] and effective connectivity studies [9]. Several underlying aetiologies have been reported in the literature, and AE was recently included among them based on evidence of music-induced seizures in three subjects with anti-GAD65 Abs [4, 5].

The young patient described herein suffered from drug-resistant TLE following seronegative limbic encephalitis related to non-Hodgkin lymphoma, and developed focal seizures evoked by musical stimuli later in the disease course, although spontaneous episodes also persisted. The concomitant occurrence of both provoked and unprovoked seizures has been reported in over 50% of cases [10], and represents one of the main criticisms to the definition of ME as a reflex epilepsy [11]. Conversely, the delay between the onset of epilepsy and that of musicogenic seizures has been described only in a minority (5%) of patients [10], and might be related to a "kindling" effect of the early spontaneous seizures on the complex network underlying music processing, especially at cognitive and emotional levels.

After recording five seizures, apparently evoked by listening to/playing music, via AEEG, we attempted to recreate similar conditions during video-EEG monitoring in our neurophysiopathology laboratory, where the patient presented a typical seizure 14 minutes after initiation of musical stimulation. This provides another example of the prolonged interval commonly observed between musical trigger and seizure onset, which has led some authors to question – once again – the very reflex nature of ME [12]. In fact, such a prolonged delay could be justified by the crucial role in seizure provocation played by either the powerful emotional response to music or (less commonly) its higher-order cognitive processing. The 14-minute latency period observed in our case was a little longer than the intervals reported in the literature (and previously documented during our patient's own AEEG), but this might be a mere consequence of the way music was delivered, *i.e.* with 15-second interruptions at approximately every five minutes.

The right temporal seizure recorded in our laboratory was triggered by a hard rock song that the patient was not familiar with, although he appreciated it. Moreover, his daily seizures were induced by various kinds of musical pieces that did not affect him emotionally. Therefore, we suppose that in this case specific features other than the emotional content of music – *e.g.* regarding rhythm, harmony or melody – might represent the real ("cognitive") trigger. This may also be supported by the patient's long-term music education, which might have made him more prone to develop ME in the first place, as already reported [10].

Regarding ictal lateralization, our patient presented with bitemporal asynchronous reflex seizures, a rather uncommon occurrence in ME. In fact, the emotional aspect of music has been hypothesized to drive most



■ **Figure 2.** (A) Ictal piloerection, showing horripilation on the patient's right arm during his seizure. (B) Ictal EEG recording. The EEG tracing shows the appearance of a single sharp wave on the right mid-temporal derivations, followed by a brief global attenuation and then onset of a rhythmic theta (4-5-Hz) activity, intermingled with spikes and sharp waves, rapidly spreading to the ipsilateral central-parietal-occipital region and the posterior region of the contralateral hemisphere (less evident). The theta activity (mixed with movement and muscular artifacts) briefly increases in frequency and then abruptly stops, well before the end of the patient's symptoms, which gradually fade. The red line marks the patient's warning about seizure onset. EEG settings: 21-channel digital recordings, bipolar longitudinal montage, HFF: 70 Hz, LFF: 1.6 Hz, sensitivity: 100 µV/mm.

musicogenic seizures, accounting for their commonly reported right predominance [10]. However, Tseng *et al*. recently suggested that the right hemisphere also subserves the perception of pitch, timbre and melody, whereas the left hemisphere is likely involved in the recognition of music and its sequential and analytical aspects [13]. Therefore, musicogenic seizures could actually originate from either side of the brain based on the specific musical element inducing them. The fact that our patient had provoked seizures, independently arising from both hemispheres, may be somewhat related to the "triggering" role of different musical features from time to time. However, the fact that the boy was ambidextrous makes any attempt at anatomo-clinical correlations even more challenging.

Besides, bitemporal asynchronous unprovoked seizures have been recorded since the acute stage of AE, and the mesial temporal structures of both hemispheres are certainly affected by the immune-mediated process, as demonstrated by MRI findings. Therefore, it is likely that both temporal lobes, to date, equally tend to "seize", either spontaneously or in response to music. Whether seizures arising from different sides of the brain are actually triggered by different stimuli (*i.e.* specific musical features) is an interesting question without a conclusive answer.

Finally, the semiology of our patient's seizures clearly indicated ictal involvement of the medial temporal lobe since the very onset; the first symptom was *déjà vu*, which has been recently hypothesized to depend

on an increased synchronization among different mesial temporal structures, *i.e.* rhinal cortices, amygdala and hippocampus, that might disrupt the recognition memory system [14]. However, some of the patient's ictal manifestations, in particular the unilateral horripilation, are more likely to reflect his epilepsy-specific aetiology, given the consistent association between ictal piloerection and AE [15, 16].

In conclusion, we believe this case is interesting since it provides further evidence that ME may develop in patients with AE, regardless of autoantibody specificity. The prominent involvement of the limbic system in this immune-mediated disease might be responsible for this, but other factors, specifically related to the underlying inflammatory process, should be investigated. Music-evoked seizures may be overlooked due to the prolonged latency between musical trigger and seizure onset, therefore they should be actively sought in this particular patient population. ■

Legend for video sequence

The video shows the patient experiencing a seizure while listening to music through headphones. The boy warned the examiner about the beginning of his typical ictal symptoms (*i.e. déjà vu*, as he would later recall), and then touched his right arm as he felt a sensation of "lightness" on the right side of his body, along with "goosebumps" (actual piloerection). At first, the patient would not answer to the examiner's question due to the music still playing ("I can't hear you. . .just let me turn this off", he stated), but after that he appeared perfectly aware, and he was able to name objects and follow commands. Later on, he complained of a strange bad taste in his head, nose and mouth, which he found rather disturbing, associated with slight oral automatisms. The ictal symptoms slowly and gradually faded (resolving almost a minute after the end of the first part of the video). In the second part, the patient recalls the various symptoms experienced during his seizure.

Key words for video research on www.epilepticdisorders.com
Phenomenology: reflex seizure
Localization: temporal (bilateral)
Syndrome: temporal lobe epilepsy
Aetiology: autoimmune

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

Disclosures.
None of the authors have any conflicts of interest to declare.

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TEST YOURSELF

(1) Which of the following is a potential trigger in musicogenic epilepsy?

A. Complex instrumental musical pieces
B. Emotional popular songs
C. Pure vocals
D. All of the above

(2) Where is the most common onset of musicogenic seizures?

A. Parietal lobe
B. Temporal lobe
C. A + B
D. No localized onset can be identified

(3) The reflex nature of musicogenic epilepsy was often questioned due to:

A. the variability of the musical trigger
B. the prolonged period of latency between musical stimulus and seizure onset
C. A + B
D. none of the above

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