A case of musicogenic epilepsy with high level of anti-glutamic acid decarboxylase antibodies

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Musicogenic epilepsy is an extremely rare type of reflex epilepsy triggered by listening to music. A 27-year-old woman began to recognize auras of déjà-vu approximately once a month when listening to a ballad since she was 23 years of age. She experienced a total of 5 episodes of aura followed by tonic-clonic seizure, and was referred to our department. We strongly suspected the patient as having musicogenic epilepsy based on electroencephalography findings and symptomatological features, although there were no obviously abnormal findings on cephalic magnetic resonance imaging performed during the interval between seizures. The seizures were controlled by antiepileptic drug. Type 1 diabetes mellitus with a high level of anti-glutamic acid decarboxylase antibodies (GAD-ab) developed approximately 3 years after epilepsy onset, which resulted in triggering of the aura without listening to music.

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Introduction

Musicogenic epilepsy, first reported in 1937 by Critchley [1], is a type of simple or complex partial seizure typically triggered by listening to certain styles of music [2]. It is extremely rare, with a prevalence of 1 in 10 million of the general population, and is classified as reflex epilepsy [2, 3].

In recent years, anti-glutamic acid decarboxylase antibodies (GAD-Ab)-positive epilepsy has often been discussed in relation to autoimmune epilepsy cases. Here, we report a case of musicogenic epilepsy with high level of GAD-Ab and type I diabetes mellitus. We modified the personal details to protect personal information.

Case Report

The patient was a right-handed, 27 year-old woman. She reported no previous episodes of central nervous system disease including febrile seizure. Her medical history of other physical diseases and family history were unremarkable.

The patient was the second born of two siblings and a high achieving student. After graduation from university, she obtained a job in the service sector and later changed employment. Currently, she is working in the car manufacturing industry and her living habits are irregular due to night shift work. The patient sometimes goes to karaoke with friends and has a characteristic of music appreciation.

In one evening two years prior to presentation to our department, she lost consciousness after experiencing an aura of déjà-vu that persisted for a few seconds, which occurred when listening to a ballad sung by her favorite Japanese male singer. Subsequently tonic-clonic seizure developed that lasted for approximately 2 minutes. She was transported to the emergency department of a near-by hospital, where cephalic magnetic resonance imaging (MRI) and electroencephalography (EEG) examinations revealed no abnormal findings. The patient was diagnosed with epilepsy based on the symptoms, and medication was started with 2000 mg/day of levetiracetam. However, once or twice a month, she continued to experience repeated auras of déjà-vu induced when she felt emotional while listening to a ballad sung by the same singer. Since spring of one year prior to presentation to our department, the auras were especially triggered by high-pitched phrases sung by unspecified singers regardless of gender.

Subsequently, twice a year, the patient experienced tonic-clonic seizures following a few seconds of déjà-vu as she became emotional when listening to a ballad.

At presentation to our department, hematological and biochemical findings were as follows: white blood cell count 7800/μl, red blood cell count 405 × 10^6/μl, hemoglobin 12.3 g/dl, platelet count 27.4 × 10^5/μl, total protein 7.2 g/dl, albumin 4.5 g/dl, aspartate aminotransferase 21 IU/l, alanine aminotransferase 19 IU/l, alkaline phosphatase 234 IU/l, lactate dehydrogenase 155 IU/l, blood urea nitrogen 9.3 mg/dl, creatinine 0.46 mg/dl, sodium 142 mEq/l, potassium 3.9 mEq/l, chloride 106 mEq/l, blood sugar 79 mg/dl. There were no abnormal hematological or biochemical values. The blood level of levetiracetam was 22.89 μg/ml.

On interictal EEG, the background waves were normal α waves at a frequency of 11 Hz as the basic rhythm with occipital dominance,
and some spikes were recorded in the right anterior temporal electrode (Figure 1). Carbamazepine 100 mg/day was added to levetiracetam. We also instructed the patient to avoid listening to seizure-inducing music. On day 16 after starting carbamazepine, hematological examination showed that her platelet count was reduced to 93,000/µl. Thus, administration of carbamazepine was suspended, which resulted in a gradual recovery of platelet count. However, because the patient again experienced a tonic-clonic seizure when she heard ballad-like music by chance at her workplace, topiramate at 50 mg/day was started. Although no additional tonic-clonic seizure occurred, she continued to have auras induced by musical phrase once or twice a month.

One year after presentation to our department, the patient developed nausea, dry mouth, polyposia, and polyuria. At that time, glucose 3+ was found in urine during a routine checkup at work. She was referred to the department of diabetes of our hospital, and admitted for close examinations and treatment. A blood examination at that time showed fasting blood sugar of 458 mg/dl, HbA1c 10.6%, glutamic acid 42.1%, GAD-ab 470,000 U/ml, C-peptide 0.4 ng/ml, insulin antibody < 0.4 U/mol, and antinuclear antibody 1:40.

Based on these results, the patient was diagnosed with acutely developed GAD-ab–positive type 1 diabetes mellitus, and intensive insulin therapy was started. To investigate the high GAD-ab level, cephalic MRI and whole-body CT scanning were performed to examine for the presence of neurological disease, endocrine disease, and paraneoplastic syndrome, although no abnormal findings were detected. She was discharged after a 1-month hospitalization.

At present, the patient continues to receive insulin injections. Following previous discharge from the department of diabetes, she had been attempting to avoid exposure to music as much as possible by refraining from listening to music and karaoke, and even avoiding shops and restaurants with music playing continuously. Since 3 months after the occurrence of the diabetic attack, auras were also triggered not only by singing, but also by trumpet performances and a variety of other types of music that the patient encountered by chance. Moreover, in rare occasions, auras of déjà-vu began to be recognized even without induction by music. After the start of topiramate, she has not experienced tonic-clonic seizure but she continues to avoid exposure to all music as much as possible.

**Discussion**

Musicogenic epilepsy is a type of reflex epilepsy typically triggered by specific musical stimuli [2, 4, 5]. The main factor for inducing epilepsy in affected patients is music, and most cases are classified as temporal lobe epilepsy [6] with 60% originating from the right temporal lobe [3]. In the present patient, some spikes were recorded at the right anterior temporal electrode on EEG. This case was diagnosed as musicogenic epilepsy because all the déjà-vu experiences were triggered by ballad-like music causing an emotional response and because every tonic-clonic seizure was preceded by the aura of these déjà-vu experiences.

In most patients with musicogenic epilepsy, an epileptic seizure is triggered by music con-
taining specific elements, although a previous report noted that seizure was triggered by music in only 17% of the cases [3]. As for the present patient, during the first 3 years after onset of epilepsy, the aura emerged only when she listened to a specific kind of music. Thereafter, she developed type 1 diabetes mellitus and auras started even without musical stimuli. Recently, limbic encephalitis mediated by autoantibodies to a variety of nerve cell membrane antigens has been reported in some cases of intractable epilepsy, which has drawn attention to treatable encephalitis that responds to immunotherapy [7]. The mechanism involving the GAD-ab in neural disease is largely unknown. Further, GAD-ab is also well known to be involved in the development of type 1 diabetes in some cases. GAD is present mainly in gamma-aminobutyric acid (GABA) secretory neurons and pancreatic β cells, and catalyzes the conversion of glutamic acid to GABA. However, when the autoantibody inhibits GAD activity to reduce GABA secretion, the resulting marked decline of GABA level in the motor cortex of the brain leads to an imbalance of agitation control, thus inducing neural discharge. Meanwhile, it has been speculated that insulin secretion may be inhibited in the pancreas [8]. The GAD-ab level is normally lower than 100 U/ml in patients with type 1 diabetes, while it can frequently exceed that level in patients with neurological signs [9]. In the present patient, the auras appeared initially only as a sequel to listening to ballad-like music and was well controlled by antiepileptic medication, but later emerged even without musical induction when the GAD-ab level became elevated to as high as 470,000 U/ml. Falip et al. [10] reported 3 (0.0019%) pa-
tients with musicogenic epilepsy from the database of 1510 patients with epilepsy, and the prevalence of musicogenic epilepsy in patients with epilepsy and GAD-ab was 2 of 22 cases (9%). They concluded that musicogenic epilepsy is a characteristic seizure type in patients with epilepsy and GAB-ab. Because our patient had high level of GAD-ab at the onset of diabetes mellitus and thereafter showed transformation of epilepsy symptoms, we considered that the appearance of GAD-ab was involved not only in diabetes but also in autoimmune mechanisms in epilepsy. Based on our findings, treatment policy for such patients have to be considered carefully, taking into account the possibility of autoimmune epilepsy.

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**References**