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Case Report

A case of autoimmune epilepsy associated with anti-leucine-rich glioma inactivated subunit 1 antibodies manifesting electrical shock-like sensations and transparent sadness

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ABSTRACT

Autoimmune epilepsy is an isolated phenotype of autoimmune encephalitis, which may be suspected in patients with unexplained adult-onset seizure disorders or resistance to antiepileptic drugs (AEDs). Antibodies against leucine-rich glioma inactivated subunit 1 of the voltage-gated potassium channel (VGKC) complex, recently termed anti-LGI-1 antibodies, are one of the causes of autoimmune epilepsies. Bizarre symptoms with extremely short duration and high frequency are clues to the possible presence of autoimmune epilepsy with anti-LGI-1 antibodies. Precise diagnosis is important because autoimmune epilepsy is treatable and the prognosis can be predicted.

1. Introduction

Autoimmune encephalitis is a group of syndromes with the subacute onset of amnesia, confusion, and often prominent seizures [1]. The spectrum of autoimmune encephalitis is widening. Recent retrospective studies have shown an association between antivoltage-gated potassium channel (VGKC) antibodies and the development of a new onset, unexplained seizure disorder in patients with autoimmune limbic encephalitis symptoms [2]. Some patients with isolated seizure syndromes, including drug-resistant epilepsy and temporal lobe epilepsy (TLE), have low titers of anti-VGKC-complex antibodies in their sera [2,3]. Identification of an immune basis is important because adjunctive immunotherapy may improve the clinical conditions in these patients [4].

We report a case of autoimmune epilepsy with a high titer of anti-VGKC-complex antibodies (>400 pM). Bizarre symptoms of brief and frequent limbic seizures were the clues suggesting autoimmune epilepsy.

2. Case report

A 53-year-old university professor was referred to our department for investigation of seizures. He had nephrotic syndrome in childhood. There was no history of trauma, inflammation, infection, psychiatric disease, or medication use. He had no relevant past medical history including risk factors for malignancy. His family history was unremarkable. Stereotyped paroxysmal episodes started approximately two years before presentation. In November 2009, he repeatedly experienced an extremely short (<0.5 s) and unexplained sensation like an electric shock in the head. Thereafter, the same sensation recurred several times a day and was triggered by startle stimulus. In December 2009, the electric shock-like sensation increased to 20 to 30 times a day. He experienced unexplained sadness, which he described as “transparent sadness”, for a few minutes while watching a play. Thereafter, unexplained sadness occurred when he listened to a certain piece of music. Listening to the same phrase of the music induced the same unexplained sadness. He avoided listening to music. In January 2010, he had a feeling of falling and sensed the odor of burned rubber at the same time. Although the feeling of falling and the sensing of the odor of burned rubber disappeared after only one day, the electric shock-like sensation continued.

He experienced a hot sensation in his lower left arm and lower leg momentarily, followed by pressure behind his left ear and sharp ringing and fullness in the left ear 10 to 20 times a day. He visited several medical and psychiatric departments, but the cause could not be identified. He consulted an epilepsy specialist in a hospital. Epilepsy was suspected, although an electroencephalogram (EEG) showed no epileptic discharge. Treatment with 300 mg of carbamazepine (CBZ) was

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started, and the electric shock-like sensation and hot sensation in his lower left arm and lower leg disappeared. Because of adverse reactions, CBZ was discontinued, and treatment was switched to zonisamide (ZNS). The electric shock-like sensation recurred 20 to 30 times a day. MRI showed no abnormality. In June, water dribbled from the right corner of his mouth while drinking. On the next day (June 24 X−, he had twitching in the right corner of his mouth for a few seconds, which was triggered by eating. Zonisamide was discontinued, but twitching continued. In July, he bit the right edge of his tongue during sleeping. After starting lamotrigine (LTG) and clonazepam (CZP), the electric shock-like sensation and twitching in the right mouth corner disappeared. In September, while on business travel, he was short of medication, and the electric shock-like sensations recurred. In January 2011, LTG was discontinued because of drowsiness, and treatment was switched to levetiracetam (LEV). The electric shock-like sensations recurred and increased to 10 times a day. Adding phenytoin (PHT) was not effective. He had a tactile sensation starting from the fingers on his right hand and spreading to the shoulder, which lasted a few seconds. He saw a bolt of lightning with jagged edges several times. In April, while he was traveling on a short-distance train, a generalized convulsion occurred when he was awakened by the alarm clock that he set on his cellular phone. He sustained a compression fracture of the lumbar spine as a result of the seizure. The tactile sensation disappeared after the generalized convulsion.

In June 2011, he was referred to our hospital. General and physical neurological examinations were unremarkable. He was alert, oriented, and highly intelligent. His Mini-Mental State Examination score was 30 out of 30. Although he had several bizarre symptoms that lasted very short durations, all the symptoms were repetitive and stereotyped, and epileptic seizures were suspected. Intraindividual seizure variability and unusually high seizure frequency observed in this patient suggested autoimmune epilepsy.

Full blood workup included routine tests to assess electrolytes, liver and renal function, vitamins B_1 and B_{12}, and autoimmune-related antibodies. All the test results were within normal ranges. Cerebrospinal fluid (CSF) examination showed no abnormality. The EEG showed no epileptiform discharges or slow waves (Fig. 1). A magnetic resonance imaging (MRI) (3T) scan was normal. 2-Deoxy-2-[^{18}F] fluoro-d-glucose (^{18}F-FDG) positron emission tomography/computed tomography (FDG-PET/CT) of the brain and body showed no hyper- or hypometabolism (Fig. 2). Although there were no other features to support an autoimmune etiology, we examined autoantibodies including anti-VGKC complex antibodies and intracellular autoantibodies (anti-Hu, Yo, Ri, Ma2/Ta, and amphiphysin). Serum anti-VGKC complex antibodies were elevated to 2493 pM (normal: <100 pM). The target antigen of VGKC complex antibodies was LGI-1.

Since the patient had no other subjective symptoms including memory impairment, he was observed without initiating immunotherapy. Occult cancer was excluded with whole body FDG-PET/CT.

In November 2011, he became seizure-free. During follow-up over one year, serum concentrations of anti-VGKC complex antibodies declined (768 pM), and the patient remained seizure-free with no memory impairment. In August 2014, anti-VGKC complex antibodies became negative. He became seizure free without antiepileptic drugs.

3. Discussion

Autoimmune encephalitis is characterized by seizures, memory disturbance, and/or psychiatric symptoms with or without inflammation revealed by CSF examination and/or MRI. In contrast to the encephalitic-type phenotype of autoimmune encephalitis, the new concept of autoimmune epilepsy is an isolated phenotype of autoimmune encephalitis that lacks a typical “limbic encephalitis” phenotype and resistance to antiepileptic drugs [5]. Recent case series have reported neuronal autoantibodies in approximately 10% of patients who have epilepsy without cognitive or psychiatric features [6]. Normal laboratory and imaging findings (particularly normal CSF analysis and MRI) do not exclude autoimmune encephalitis. Prompt diagnosis and treatment with immunosuppressive therapies improve or even reverse symptoms. If left untreated, retrospective case series show that these conditions can lead to irreversible cognitive deficits, ongoing seizures, and death [7–9]. Bien and Elger suggested that limbic encephalitis should be considered a differential diagnosis in any adult patient with newly developed temporal lobe epilepsy and/or a rather quickly progressing amnestic disturbance [10]. Toledano et al. proposed valuable clinical clues to diagnose autoimmune epilepsy: intraindividual seizure variability or multifocality, an unusually high seizure frequency, antiepileptic drug (AED) resistance, subacute onset, personal or family history of autoimmunity, and recent or past history of neoplasia [11]. Our case manifested multifocal seizure types. We suspect that the electrical shock-like sensation in the head was a cephalic aura originated from the mesial temporal lobe, although the semiology is atypical for temporal lobe epilepsy. Sadness triggered by specific music probably originated from the amygdala and the odor of burned rubber from the uncus. In addition to the temporal lobe seizures, he had other types of seizures including mouth twitching, hot sensation, tactile sensation,

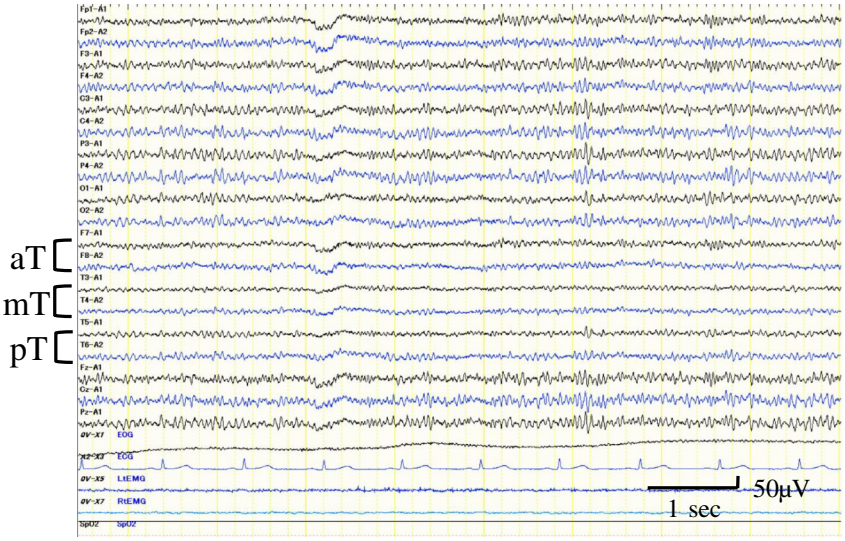

Fig. 1. Interictal EEG.The EEG shows epileptiform discharges or slow waves.

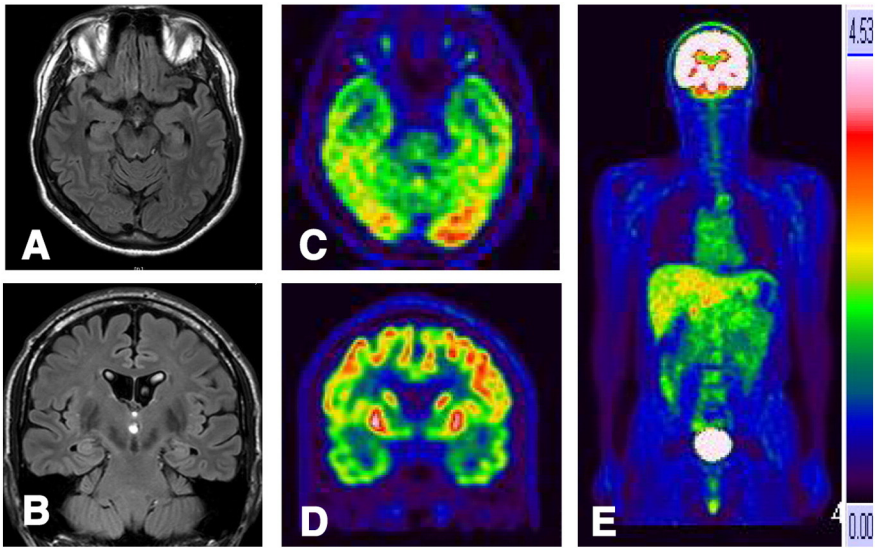

Fig. 2. Imaging studies. A: Brain MRI with fluid-attenuated inversion-recovery (FLAIR) sequence, transaxial view. B: Brain MRI with FLAIR sequence, transcoronal view. C: Brain ^{18}F-FDG PET/CT, transaxial view. D: Brain ^{18}F-FDG PET/CT, transcoronal view. Brain images (A, B, C, and D) show no abnormalities. E: Whole body ^{18}F-FDG PET/CT shows no abnormal uptake and excluded underlying paraneoplastic syndrome.

and lightning bolt with jagged edges. We assumed that these seizures originated from the extratemporal lobes. The seizures were frequent and resistant to AEDs. Extremely short duration of seizures was characteristic for this patient, although it was not reported in previous papers [7–9,11]. The frequent and short seizures (FSS) of our case resembles faciobrachial dystonic seizures (FBDS). Faciobrachial dystonic seizures are multiple, brief (<3 s) episodes of simultaneous facial grimacing and arm dystonia with a high frequency of attacks. Faciobrachial dystonic seizures are highly specific for anti-LGI-1 limbic encephalitis and are important for its recognition and diagnosis [12]. Our case report suggests that frequent and short seizures might be an important feature of autoimmune epilepsy associated with anti-LGI-1 antibodies.

In our patient, symptoms disappeared completely without immunotherapy and underwent spontaneous remission. Irani et al. reported that FBDS often preceded the cognitive impairment observed in anti-VGKC-complex antibody-associated limbic encephalitis [13]. Immunotherapy shortened the time to recovery and might prevent subsequent development of cognitive impairment [13]. A few cases of anti-VGKC antibody-associated limbic encephalitis that improved without immunosuppressive therapy have been reported [14–16]. Butler et al. reported that patients with VGKC-associated limbic encephalitis often recovered substantially with immunotherapy despite broad cognitive dysfunction in the acute phase but might have residual permanent anterograde amnesia [17]. Our case showed no cognitive dysfunction and became seizure-free with LTG, although his seizures might have improved earlier with immunotherapy than without immunotherapy. This case demonstrates that high titers of anti-VGKC complex antibodies are not always related to a severe, progressive clinical course.

Autoimmune epilepsy is one of the epilepsies that improves with immunotherapy. Physicians should pay attention to clinical clues such as subacute onset, intraindividual seizure variability or multifocality, AED resistance, personal or family history of autoimmunity, and recent or past history of neoplasia. In addition, FSS might be additional features in autoimmune epilepsy associated with anti-LGI-1 antibodies.

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Conflict of interest

None of the authors have any conflicts of interest to report.

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