Seizures associated with amphiphysin antibody

Tüzün E, Bebek N, Gürses C, Akman-Demir G, Gökyiğit A
Istanbul University, Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey

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Introduction

Anti-amphiphysin antibody was first identified in a woman with breast cancer and stiff-person syndrome [1]. Subsequent reports indicated that this antibody was associated with a variety of neurological syndromes including limbic encephalitis, encephalomylitis, cerebellar degeneration and polyneuropathy [2]. We describe a patient presenting with a rare syndrome and tumor combination, extending the spectrum of amphiphysin autoimmunity.

Differential Diagnosis

A 58-year-old male presented with generalized tonic clonic status epilepticus, which had initiated as secondarily generalized seizures with a left-sided focal onset on the same day. His family members reported no previous seizures, amnesia or psychiatric symptoms. Seven months prior to initiation of seizures, he had undergone a radical urinary bladder surgery due to stage III transitional cell bladder cancer. Initial neurological examination was normal.

Complete blood count, blood chemistry analysis, thyroid function tests and cranial MRI were normal. CSF analysis showed no lymphocytes, red cells or atypical cells, normal protein and glucose content. Initial interictal EEG examination showed slow waves involving the right frontotemporal region, which within weeks spread first to the anterior part of the hemispheres and then to all brain regions in repeat EEG recordings. Ictal and interictal EEGs displayed no epileptic discharges. Serological tests for several central nervous system infections including HSV, HHV-6, HIV and syphilis were negative. Paraneoplastic panel revealed serum IgGs reacting with a 128 kDa band on immunoblotting of human neuroblastoma (SH-SY5Y) cells and recombinant amphiphysin protein (1:3200). Serum sample was negative for antibodies directed against other onconeural or epilepsy-associated antigens (Hu, Yo, Ri, Ma, CV2, glutamic acid decarboxylase (GAD), voltage-gated potassium channel (VGKC) and N-methyl D-aspartate receptor (NMDAR)). (18F)-Fluorodeoxyglucose positron emission tomography (PET) examination did not reveal any abnormality in the glucose metabolism of the brain. However, it showed a hypermetabolic lesion in the right acetabulum, which was considered as the bone metastasis of bladder cancer and consequently radiotherapy was started.

A complete seizure control could only be achieved within the next three weeks by gradual administration of four antiepileptics (phenytoin, oxcarbazepin, phenobarbital and levetiracetam). Since amphiphysin-specific antibodies were detected after the cessation of seizures, no immunosuppressive treatment was initiated. Neurological examinations and neuropsychological tests performed during the interictal periods and after the termination of the seizures and normalization of EEG were all normal. During the follow-up period, the patient did not show any psychiatric or behavioral symptoms. After the control of the seizures, he was followed under phenobarbital treatment for 10 months with no additional seizures.

Discussion

Several autoantibodies including anti-GAD, VGKC and NMDAR have been associated with unexplained new-onset epilepsy that might occur during the course of autoimmune encephalopathies [3-5]. While, amphiphysin antibody is one of the well recognized paraneoplastic antibodies, there are only a handful of reported patients presenting with seizures in association with this antibody. The ages of these patients range between 55 and 63, two of them were males and one was a female. They had not only presented with seizures

*Corresponding author: Erdem Tüzün, M.D., Department of Neurology, Istanbul University, Istanbul Faculty of Medicine, 34390, Çapa, Istanbul, Turkey. E-mail: drerdem@yahoo.com
but also with additional encephalopathy symptoms such as delirium, cognitive dysfunction, psychosis or choreoathetosis. Different from our patient, the MRI examination and/or CSF analysis yielded pathological results. Small cell lung cancer was identified in two patients. Notably, in addition to amphiphysin antibody, Hu or VGKC antibodies were detected in two of the patients [2,6,7].

Apart from other factors, the underrepresentation of seizures in amphiphysin autoimmunity might be at least partially due to the fact that amphiphysin antibody is usually not included in the diagnostic work-up of seizures of unknown cause. Our patient differs from previously reported cases by preservation of the memory functions and lack of psychiatric symptoms throughout the follow-up period, exclusively presenting with seizures. Moreover, while bladder cancers are occasionally associated with paraneoplastic neurological syndromes [8], they have never been reported in relation with seizures or amphiphysin antibody.

Unilateral clinical presentation and EEG findings at the onset and monophasic course of the convulsions suggest that seizures of our patient might have started as a result of a focal and self-limited paraneoplastic encephalitis caused by amphiphysin antibodies. Indeed, in contrast with many other paraneoplastic antibodies, amphiphysin antibodies have been shown to exert harmful effects on neurons in an animal model [9]. Also, amphiphysin knock-out mice exhibit severe and intractable convulsions [10] suggesting that antibody mediated inhibition of amphiphysin functions might plausibly generate epileptic seizures. In this context, other than being a neurological rarity, our patient’s clinical features suggest that the spectrum of anti-amphiphysin associated neurological syndromes is larger than previously thought and that amphiphysin antibody should be regularly screened in epilepsy patients of unknown cause.

**Conflict of Interest**
None to declare.

**References**