ELSEVIER

A Patient With Epilepsia Partialis Continua With Anti-Glutamate Receptor ε2 Antibodies

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This report concerns a 6-year-old female with epilepsia partialis continua. Autoantibodies against amino- and carboxyl-terminal regions of the *N*-methyl-D-aspartate receptor subunit glutamate receptor ε2 were detected in the serum and cerebrospinal fluid. The anti-glutamate receptor ε2 subunit antibodies have been demonstrated in the serum and cerebrospinal fluid in some patients with chronic progressive epilepsia partialis continua of childhood and those with Rasmussen's encephalitis. The patient, however, did not develop any neurologic deterioration or intractable seizures. Therefore, anti-glutamate receptor ε2 subunit antibodies are not specific for chronic progressive epilepsia partialis continua of childhood and Rasmussen's encephalitis.

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Introduction

Epilepsia partialis continua (EPC) is a rare type of localization-related motor epilepsy. Among many diseases with EPC, chronic progressive EPC of childhood and Rasmussen's encephalitis are characterized by progressive neurologic deficits and focal intractable seizures. In 1994, Rogers et al. [1] were the first to identify the presence of antibodies to α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor subunit glutamate receptor3 (GluR3) in patients with Rasmussen's encephalitis. Inoculation of animals with GluR3 protein induced symptoms mimicking Rasmussen's encephalitis. Subsequently, Andrews et al. [2] reported that serum levels of anti-GluR3 antibodies correlated with the severity of symptoms associated with Rasmussen's encephalitis and that plasmapheresis resulted in transient improvement of seizure severity and neurologic function. On the other hand, Takahashi et al. [3] reported that antibodies to the *N*-methyl-D-aspartate (NMDA) receptor subunit glutamate receptor ε2 (GluR ε2) were detected in the serum of patients with chronic progressive EPC of childhood, but not in any patient with West syndrome, Lennox-Gastaut syndrome, and localization-related partial seizure with transient EPC. Thus, chronic progressive EPC of childhood and Rasmussen's encephalitis are regarded as autoimmune disorders. Wiendl et al. [4] reported that anti-GluR3 antibodies were detected in the serum of patients with not only chronic progressive EPC of childhood and Rasmussen's encephalitis but also other forms of epilepsy.

Described here is a patient with EPC who did not manifest any neurologic deterioration or intractable seizures, although anti-GluR ε2 antibodies were detected in the serum and cerebrospinal fluid.

Case Report

A previously healthy 6-year-old female was admitted to the hospital because of continuous myoclonic jerks in the right thumb. There was no family history of neurologic disorders. Medical history indicated no perinatal problems and normal psychomotor development. Eight days before hospitalization, she developed high fever (39.7°C), which remitted the next day. Four days after the febrile event, she developed myoclonic jerks in the right thumb, and 2 days later, the jerks became persistent, with periods of 5 seconds to 5 minutes separating the events. Two days later, she developed tonic-clonic seizures in the right upper limb, with myoclonic movement at the right corner of the mouth and eyelids for at least 30 seconds. On the day of admission, she developed continuous myoclonic jerks in the right thumb, sometimes including a tonic component in the other fingers of the right hand and right wrist. These events were not associated with muscle paralysis.

On admission, physical examination revealed no abnormalities. The patient manifested persistent jerks in the right thumb with intermittent cessation, associated with occasional tonic convulsions in the right upper

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Table 1. Laboratory data

Blood		Cerebrospinal Fluid	
WBC	6700/μL	Cell count	1/mm^3
Hb	12.9 g/dL	Protein	167 mg/dL
Plt	24.7 × 10^4/μL	Glucose	57 mg/dL
TP	7.4 g/dL	Oligoclonal band	Negative
Alb	4.7 g/dL	Myelin basic protein	< 0.5 pg/mL
Na	139 mmol/L	Neuron specific enolase	25 ng/mL
K	3.7 mmol/L	IgG	10.5 mg/dL
Cl	106 mmol/L		
Ca	9.6 mg/dL		
P	4.0 mg/dL		
CRP	0.12 mg/dL		
IgG	1333 mg/dL		
IgA	150 mg/dL		
IgM	257 mg/dL		
Adeno3 (NT)	< × 4 (< × 4)		
Adeno7 (NT)	< × 4 (< × 4)		
Influenza H1N1 (HI)	× 80 (< × 10)		
Influenza H3N2 (HI)	× 160 (< × 10)		
Japanese encephalitis (HI)	× 20 (< × 10)		
*Measles IgM (EIA)	0.24 (< 0.80)	Measles IgM (EIA)	0.16 (< 0.80)
*Measles IgG (EIA)	42.7 (< 2.0)	Measles IgG (EIA)	1.06 (< 0.20)
HSV IgM (FA)	< × 10 (< × 10)	HSV IgM (EIA)	0.44 (< 0.80)
HSV IgG (FA)	< × 10 (< × 10)	HSV IgG (EIA)	< 0.20 (< 0.20)
CMV IgM (EIA)	0.30 (< 0.80)	HSV DNA (PCR)	Negative
CMV IgG (EIA)	< 2.0 (< 2.0)		
Anti-GluR ε 2 Abs		Anti-GluR ε 2 Abs	
IgG Ab	Positive	IgG Ab	Positive
IgM Ab	Positive	IgM Ab	Positive

Normal values are in parentheses. Abnormal values are underlined.
* The patient was vaccinated against measles at age 1 year 3 months.

Abbreviations:

Ab	= Antibody	Ig	= Immunoglobulin
Alb	= Albumin	K	= Potassium
Cl	= Chloride	Na	= Natrium
CMV	= Cytomegalovirus	NT	= Neutralization
CRP	= C-reactive protein	P	= Phosphorus
EIA	= Enzyme immunoassay	PCR	= Polymerase chain reaction
FA	= Indirect fluorescent antibody	Ptl	= Platelet
Hb	= Hemoglobin	TP	= Total protein
HI	= Hemagglutination inhibition	WBC	= White blood cell
HSV	= Herpes simplex virus		

limb, but the latter were not accompanied by any loss of consciousness. Forced use of the right hand resulted in exacerbation of the jerks. Laboratory data, including complete blood cell counts and levels of serum electrolytes and C-reactive protein, were normal. Serum IgM level was elevated (257 mg/dL), while IgG and IgA levels were normal. Serum levels of antibodies to influenza H1N1, influenza H3N2, and measles (IgG type) were elevated (Table 1). Lumbar puncture revealed elevated protein level (167 mg/dL) but normal cell count (1/mm^3) and glucose level (57 mg/dL). Oligoclonal band, myelin basic protein, and neuron specific enolase results were negative. However, cerebrospinal fluid levels of IgG and IgG-type measles antibody were elevated (Table 1). Anti-GluR ε2 antibodies (IgG type) against N- and C-terminals of GluR ε2 were detected in the cerebrospinal fluid. Serum immunoassays for anti-GluR ε2 antibodies were positive; both IgG-type and IgM-type autoantibodies against carboxyl-terminal fragment of GluR ε2 were detected. Brain magnetic resonance imaging, including T_1-weighted, T_2-weighted, proton-weighted, and fluid-attenuated inversion recovery images and ^{18}F-deoxyglucose-positron emission tomography studies revealed no abnormal findings. Electroencephalography demonstrated focal spikes over the right central region, which were independent of the myoclonic jerks of the right thumb. According to the above clinical and laboratory findings, she was diagnosed with EPC. Seizures did not respond to intravenous phenytoin but to clonazepam and carbamazepine. EPC disappeared about 1 week after the initiation of treatment. The patient continued to manifest the jerks, but these were not continuous and their frequency diminished to two to three series daily. About 2 weeks after the initiation of treatment, the jerks disappeared completely and the patient was discharged from the hospital. One month after discharge, myoclonic jerks reappeared in the right thumb and gradually increased to one series lasting for a few minutes to 1 hour daily at 2 months after the discharge. Increasing the dose of clonazepam and carbamazepine resulted in a gradual decrease in seizure frequency. One year and 7 months after the onset, IgM antibodies against GluR ε2 were negative, but IgG antibodies were still positive in serum. Two years and 3 months after the onset, she has been seizure free for 9 months and manifests no neurologic deterioration or abnormal brain magnetic resonance imaging findings.

Methods

Detection of Autoantibodies Against GluR ε2

With a tetracycline-induction system [5], stable NIH3T3 transformant cell lines expressing the NMDA-type GluR ε2 subunit were established.

Cell extracts of the transformants were transferred to the nitrocellulose membrane to detect the presence of antibodies against GluR ε2. The membrane was reacted with sera or cerebrospinal fluid from the patient and was stained by alkaline phosphatase-labeled second antibodies [6].

Epitope Analyses

Four sequences of complementary deoxyribonucleic acid of GluR ε2 gene (an N-terminal-fragment, and 3 C-terminal fragments) were inserted into bacterial fusion protein vectors (pGEX: Pharmacia Biotech AB, Uppsala, Sweden, and pMAL: New England Biolabs, Beverly, Massachusetts, USA). The production of those bacterial fusion proteins was induced by isopropyl-β-D-thiogalactopyranoside. For Western blot analysis, the bacterial fusion proteins composed of GluR ε2-fragments were transferred to the nitrocellulose membranes. The membranes were incubated with sera or cerebrospinal fluid from the patient and were reacted with IgG-type secondary antibodies coupled to alkaline phosphatase [7].

Discussion

Ionotropic glutamate receptor channels are classified into three subtypes: NMDA, AMPA, and kainate [8]. The NMDA receptor channels have been implicated in synaptic plasticity and synaptic localization, which are associated with neural development and learning [9]. Overactivation of NMDA receptor channels leads to excitotoxic neuronal cell death [10]. Antibodies to the GluR ε2, which is a subunit of the NMDA receptor channel, are estimated to contribute to the EPC in patients with chronic progressive EPC of childhood [3]. In this patient, antibodies to the C-terminal region of the GluR ε2 subunit were detected. That region is known to play an important role in efficient clustering and synaptic localization of the NMDA receptor channel [10]. Therefore, this patient was expected to develop progressive neurologic deterioration, including dementia, intractable seizures, and movement disorders. However, she developed neither of them, indicating that the antibodies may not necessarily cause neurologic deterioration. The phenotype of the patient is different from Rasmussen's encephalitis or chronic progressive EPC of childhood in the following aspects: (1) seizures responded to antiepileptic drugs, (2) brain magnetic resonance imaging (T_1-weighted, T_2-weighted, proton-weighted and fluid-attenuated inversion recovery images) did not reveal any abnormalities during the course of the illness, and (3) lack of any neurologic deficit. Bancaud [11] classified electroencephoalogram into two types; the EPC type 1 is nonprogressive classic Kojewnikow's syndrome, and EPC type 2 is Rasmussen's encephalitis. According to the normal background electroencephalogram with paroxysmal discharges from the central area, nonprogressive neuroradiologic and clinical features and lack of neurologic deficits indicate that this patient could be classified as EPC type 1.

The exact etiology of EPC could not be identified in the patient. The high levels of protein and total IgG in CSF suggest the cause of EPC was probably an encephalitic process. One possible explanation is the introduction of a foreign body, by an unknown mechanism, which shares a common epitope with that of GluR ε2. Such antigen could have resulted in elevation of anti-GluR ε2 antibodies, which crossed the blood-brain barrier that had become permeable because of encephalitis. Subsequently, the antibodies caused excitotoxic damage of the brain, leading to the seizures. Another explanation is that the EPC was caused by measles encephalitis, as indicated by the high titer of measles IgG-antibody in the serum and cerebrospinal fluid, although the patient did not develop measles clinically during the course of the illness, and she was vaccinated against measles at age 1 year. Subacute sclerosing panencephalitis is another possible diagnosis, but the patient manifested neither neurologic symptoms other than seizures nor electroencepholographic findings that are characteristic to this disorder, such as periodic complexes. The relationship between subacute sclerosing panencephalitis and anti-GluR ε2 antibodies is unknown; however, the antibodies could probably render the brain more vulnerable to seizures caused by encephalitis.

The presence of anti-GluR ε2 antibodies has been proposed to contribute to the seizures in chronic progressive EPC of childhood and Rasmussen's encephalitis [3]. That this patient manifested anti-GluR ε2 antibodies without developing progressive EPC indicates that not only Bancaud's type 2 EPC but also type 1 EPC is associated with anti-GluR ε2 antibodies. At this stage, however, the patient, whose phenotype is currently compatible with EPC type 1, could develop type 2 EPC phenotype. Therefore, a long-term follow-up of this patient is necessary to clarify the clinical nature of this disorder and its relation to the anti-GluR ε2 antibody.

In this patient, only autoantibodies to GluR ε2 were examined because the assay system for autoantibodies to GluR3 has not been established. In another two patients with chronic EPC and autoantibodies to GluR ε2, autoantibodies to GluR3 were examined in another institute, but the results were negative. Recently, besides autoantibodies against GluR3 and GluR ε2, autoantibodies against neuronal acetylcholine receptor α7 subunit [12] and munc-18 [13] have been reported in patients with Rasmussen's encephalitis. It is therefore suggested that patients with Rasmussen's encephalitis or chronic EPC might have heterogeneous autoantibodies. GluR3 and GluR ε2 might be involved some other way in the pathophysiology of Rasmussen's encephalitis or EPC. However, further study is necessary to elucidate the relationship between the autoantibodies and the phenotypes of the diseases.

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