Type 1 Diabetes Mellitus and Epilepsia Partialis Continua in a 6-Year-Old Boy With Elevated Anti-GAD65 Antibodies

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ABSTRACT. A 6-year-old boy presented with epilepsia partialis continua 6 months after diagnosis of type 1 diabetes. Anti-glutamic acid decarboxylase 65 antibodies were found in his serum and cerebrospinal fluid. Antiepileptic agents did not improve his seizures. High-dose steroids, plasmapheresis, and intravenous immunoglobulin resulted in decreased anti-glutamic acid decarboxylase 65 antibody levels and resolution of his seizures. ***Pediatrics*** **2002;109(3). URL: http://www.pediatrics.org/cgi/content/full/109/3/e50;** ***GAD65 antibody, type 1 diabetes mellitus, Rasmussen encephalitis, seizure, plasmapheresis, autoimmunity.***

ABBREVIATIONS. GAD, glutamic acid decarboxylase; GABA, γ amino butyric acid; SMS, stiff-man syndrome; EPC, epilepsia partialis continua.

Glutamic acid decarboxylase 65 (GAD65) is a protein found both in the central nervous system, where it converts glutamic acid to γ amino butyric acid (GABA), and in the β-cells of pancreatic islets. Antibodies to GAD65 are found in 70% to 80% of patients with new-onset type 1 (autoimmune) diabetes mellitus.[1] They are also found in patients with certain neurologic conditions, particularly, stiff-man syndrome (SMS); however, the antibody titers are 10- to 1000-fold higher than the titers usually seen in type 1 diabetes mellitus.[2] This is the first report of a patient with both type 1 diabetes mellitus and epilepsia partialis continua (EPC) associated with extremely elevated levels of anti-GAD65 antibodies.

CASE REPORT

The patient is a previously healthy 6½-year-old adopted black boy who developed simple partial seizures involving the right hand 6 months after receiving the diagnosis of type 1 diabetes. He progressed rapidly over 3 days to have continuous multifocal right-sided seizures involving the hand, the face, and the leg (EPC). He stabilized transiently after 1 week, but 2 weeks after the initial seizure he became aphasic and obtunded. An electroencephalogram revealed frequent left-sided epileptiform discharges and slowing. He was treated with continuous but changing antiepileptic medications for the first 17 days after onset of seizures, at which time high-dose corticosteroids (2 mg/kg/d intravenous prednisolone) were added. Acyclovir was used for 4 days at the time of presentation but was discontinued when herpes simplex virus polymerase chain reaction and cultures were negative. Intubation and midazolam coma were used between day 17 and day 25 after seizure onset. None of these modalities resulted in improvement of the seizures.

His evaluation included cerebrospinal fluid studies that were negative for herpes simplex virus, tuberculosis, fungus, cryptococcal antigen, and routine viral and bacterial pathogens. Serology was negative for herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, and *Mycoplasma*. Coagulation studies, including protime, partial thromboplastin time, protein C and protein S, and antithrombin III, all were normal. Rheumatologic studies, including lupus anticoagulant, antinuclear antibodies, anti-DNA antibodies, and rheumatoid factor, were also normal. Thyroid function, serum ammonia, lactic acid, amylase, lactate dehydrogenase, and liver enzymes were also normal.

Results of magnetic resonance imaging of the head were normal on admission to the hospital. However, repeat scans 6 and 16 days after presentation with seizures showed a nonenhancing left cerebellar lesion (Fig 1A). A subsequent scan 26 days after presentation revealed lesions of the gray matter involving the occipital and frontal cortex bilaterally and left insular region, which resolved within 2 weeks of initiating therapy as described below (Figs 1B and 1C).

Serum anti-GAD65 titers measured at the time of diagnosis of type 1 diabetes were 3484 U/mL (positive >4.0 U/mL), and islet cell antibodies were reported as negative (both tests performed in Barcelona, Spain, by Guillem C. Cuatrecasas, MD, PhD). Six months later, at the time of diagnosis of EPC, serum anti-GAD65 titers were 19 610 U/mL (positive >1.0 U/mL) and cerebrospinal fluid anti-GAD65 titers were 3325 U/mL (both performed at Endocrine Sciences, Calabasas Hills, CA, by Dr Michael Moxness). Islet cell antibody titers at this time were positive at 10 240 Juvenile Diabetes Foundation Units (reference range: negative. Test performed at University of Florida Diagnostic Referral Laboratories, Gainesville, FL, by William E. Winter, MD).

The patient was treated with a combination of high-dose corticosteroids (2 mg/kg/d intravenous prednisolone), intravenous immunoglobulins, and plasmapheresis. The intravenous immunoglobulin was initiated on day 26 after seizure onset, and plasmapheresis treatments were started on day 27. Plasmapheresis treatments consisted of single-volume plasma exchanges with either 5% albumin alone or 5% albumin plus fresh-frozen plasma as replacement fluids. Treatments were initially performed daily for 5 days. After the initial plasmapheresis treatments, anti-GAD65 antibody levels fell to 4491 U/mL (Endocrine Sciences). The patient became seizure-free and able to communicate. Over the course of 2 months, the interval between cycles of plasmapheresis was increased from daily to twice weekly to bimonthly. He returned to baseline neurologic status within 3 months of initiation of plasmapheresis. One month later, plasmapheresis was stopped. Oral prednisone was tapered to 2 mg/d. Although initial anti-GAD65 antibody titers fell as low as 1821 U/mL, they began to rise to the 5000 to 6000 U/mL (tests performed at Endocrine Sciences) range within 1 month of stopping plasmapheresis and have remained in this range to the present (Fig 2). The patient's diabetic condition remained unchanged throughout therapy with hemoglobin A1c levels of 9% to 10%.

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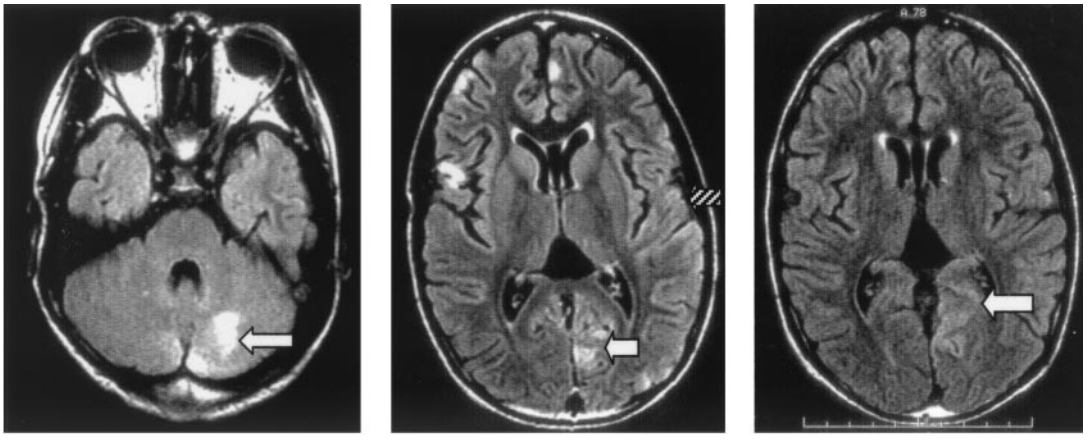

Fig 1. Magnetic resonance imaging (FLAIR sequences) shows brain lesions at various times in the course of the patient's hospitalization. A, Two weeks after seizure onset, scan shows hyperintense lesion in the cerebellar gray matter at a time when the child remained conscious and interactive but still had nearly constant right hand and face seizures. B, Ten days after image A, scan shows additional lesions in both cerebral hemispheres. Note particularly the left mesial occipital lesion (white arrow) and subtle, more diffuse increased signal in the left central region (hatched arrow). C, Two weeks after image B, the lesions in the cerebral hemispheres had resolved.

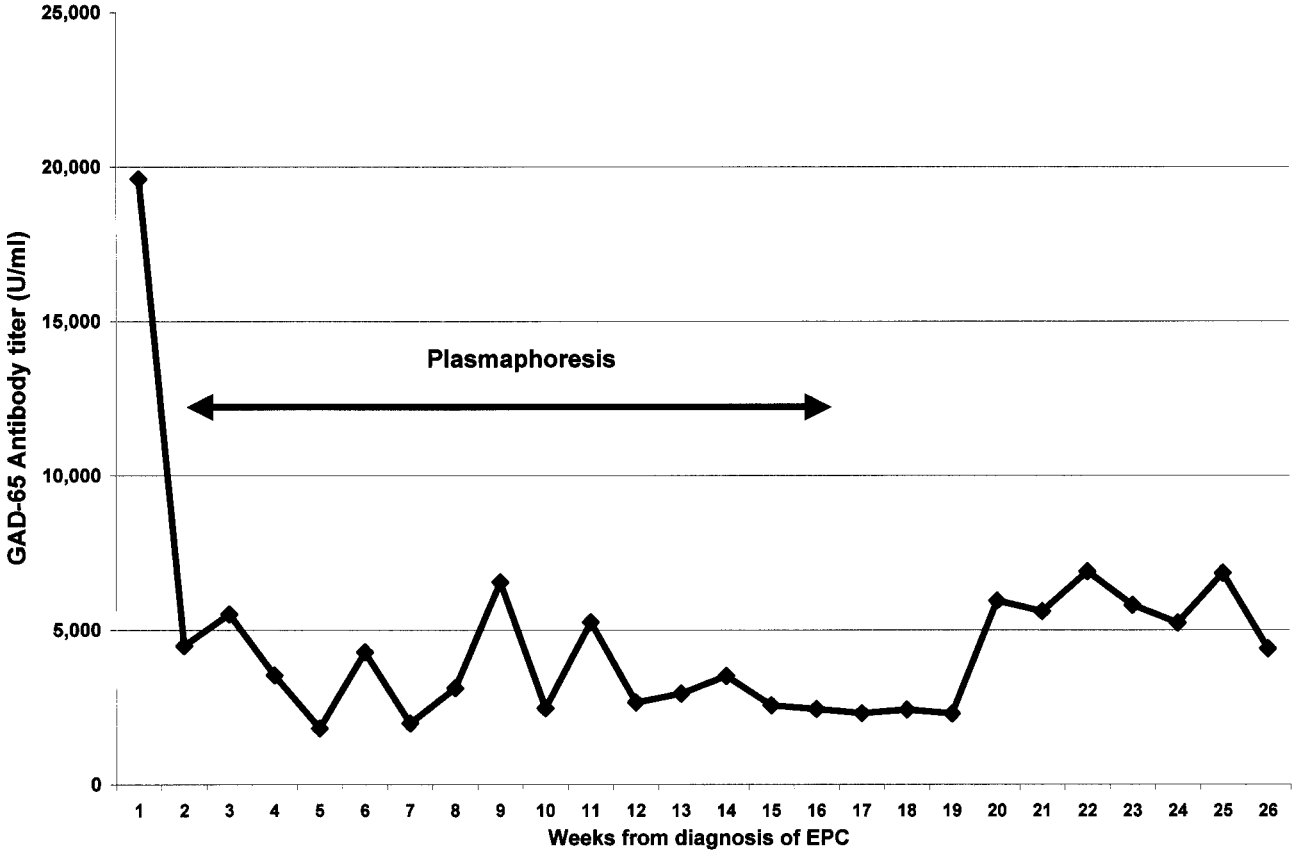

Fig 2. Anti-GAD65 antibody titers in U/mL are shown over time. The initial decline occurred after the start of plasmapheresis. When 2 values are reported for the same day, they were obtained before (higher titer) and after (lower titer) plasmapheresis treatment.

DISCUSSION

EPC can be a devastating seizure disorder and is associated with multiple causes. The causative role for anti-GAD65 antibodies in this patient is supported by his remarkable response to therapies aimed at decreasing both anti-GAD65 antibody titers and production.

The numerous possible causes of EPC all were unlikely in this patient on the basis of his evaluation and response to therapy. Recognized viral causes, including cytomegalovirus, herpesviruses, Epstein-Barr virus, and human immunodeficiency virus, and bacterial and fungal causes were not detected.[3,4] Metabolic disorders reported to cause EPC include

Kuf disease, myoclonic epilepsy lactic acidosis and stroke, Leigh syndrome, NADH-coenzyme Q reductase deficiency, and nonketotic hyperglycinemia. Our patient did not have elevations of his serum ammonia or lactic acid levels, and his magnetic resonance imaging findings were not consistent with any of these metabolic disorders.

Other causes of EPC include paraneoplastic syndromes, cerebrovascular disease, congenital brain malformations, multiple sclerosis, and Rasmussen encephalitis.[5] It remains uncertain how presumably generalized processes such as Rasmussen encephalitis, paraneoplastic syndromes, and now elevated anti-GAD antibodies precipitate partial seizures. Recently, an autoimmune mechanism was reported for some patients with Rasmussen encephalitis, and treatment directed against the abnormal antibody, plasmapheresis, and intravenous immunoglobulin have produced at least transient improvement in some patients.

GAD is also expressed in the cytoplasm of the β-cells of the pancreatic islets. Although the function of GAD in the pancreas is unclear, it may be involved in paracrine signaling between pancreatic α- and β-cells.[6] Anti-GAD65 antibodies are found in the majority of patients with recent-onset type 1 diabetes. In prediabetic individuals, they can be detected years before clinical onset of disease.[7]

GAD antibodies have been associated with epilepsy on rare occasion.[8] When detected, elevations in GAD antibodies are usually no greater than 3 times normal.[9] Our own review of 8 children with explosive onset of intractable partial seizures (including 1 with diabetes) revealed no elevations of anti-GAD antibodies. More common, GAD antibodies have been associated with SMS, cerebellar ataxia, and myoclonic encephalopathy. Of these, the most frequent association is with SMS, a disorder of increased muscle tone, difficulty moving, and painful spasms.[10] Sixty percent of people with SMS have elevated GAD antibody titers, but only approximately 30% of individuals with SMS have type 1 diabetes. Our patient did not have neurologic findings suggestive of SMS.

Several immunologic differences may be important in the pathogenesis of the 2 diseases. Although several autoantibodies, including GAD65, are found in type 1 diabetes, the autoreactive T-cell response seems to be the major mediator of disease.[11] In contrast, SMS is associated with extremely high anti-GAD65 antibody titers that likely cause a direct functional impairment of GABAergic neurons that leads to a lack of inhibition of nerve stimulation.

Our patient had extremely elevated GAD antibody levels at the time of initial testing consistent with levels previously reported in SMS (GAD65 titer from Barcelona). The GAD65 titers presented in Fig 2 all are from the same laboratory, however, and show the decline in antibody titer with plasmapheresis. These titers, however, remain extremely elevated compared with titers followed serially in type 1 diabetes.[12] The provocation of seizures by the presence of GAD antibody is supported by the fact that GAD is a critical enzyme for synthesis of the inhibitory neurotransmitter, GABA. Stopping plasmapheresis and intravenous immunoglobulin treatment has resulted in a slow rise in GAD65 antibody levels. So far, however, our patient's neurologic condition has remained stable. This is the first report of a patient with both type 1 diabetes mellitus and EPC associated with extremely elevated levels of anti-GAD65 antibodies.

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