Encephalitis Associated With Glutamic Acid Decarboxylase Autoantibodies in a Child

A Treatable Condition?

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Objective: To increase the recognition of glutamic acid decarboxylase autoantibodies–related encephalitis in childhood.

Design: Case report and review of the literature.

Patient: A 6-year-old girl who had developed refractory seizures, developmental regression, and type 1 diabetes mellitus at age 25 months.

Interventions: Blood analysis, electroencephalogram, cerebral magnetic resonance imaging, positron emission tomography scan, lumbar puncture, and measurement of glutamic acid decarboxylase activity were performed. Treatment with repeated plasmapheresis and rituximab, with concomitant antiepileptic drugs, was administered.

Results: Highly elevated titers of glutamic acid decarboxylase autoantibodies were found in the serum, as well as in the cerebrospinal fluid. Major clinical improvement in parallel with a decrease in the levels of serum and cerebrospinal fluid antibodies was observed with treatment.

Conclusions: Encephalitis associated with glutamic acid decarboxylase autoantibodies is a severe epileptic disorder that occurs in young children as well as adults. It may be partially reversible with aggressive immunomodulatory treatment, including plasmapheresis and rituximab. Studies are warranted to determine whether early treatment leads to complete remission.

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GLUTAMIC ACID DECARBOXYLASE (GAD) is an enzyme implicated in the anabolism of γ-aminobutyric acid (GABA), which is one of the most important inhibitory neurotransmitters. This enzyme is expressed in GABAergic neurons as well as in pancreatic β cells. In addition to their role in type 1 diabetes mellitus (T1DM), GAD autoantibodies (GADAs) are associated with various neurologic conditions, such as stiff person syndrome, cerebellar ataxia, limbic encephalitis, myasthenia gravis, and epilepsy, described mainly in adults. There are rare observations in children, without long-term follow-up. We report the case of a 6-year-old patient who had developed refractory epilepsy, developmental regression, and T1DM, in association with elevated plasma and cerebrospinal fluid (CSF) GADAs, at age 25 months and describe her significant improvement after treatment.

REPORT OF A CASE

This 6-year-old girl was born at term after an unremarkable pregnancy. Early developmental milestones were attained without delay. At 25 months, the patient progressively developed 20 to 30 focal seizures per day (behavioral arrest, fearful gaze, eye and head version, and tachycardia), with frequent secondary generalization. These were refractory to treatment with 10 antiepileptic drugs, the ketogenic diet, intravenous immunoglobulins, thiamine hydrochloride, pyridoxine hydrochloride, and coenzyme Q10. From the age of 30 months, progressive development of drooling, gait instability, muscular weakness, and lack of interest in the environment was noted. An extensive diagnostic workup was conducted before the child was referred to our center. Laboratory analyses included normal lactate to pyruvate ratios and negative routine blood test results for metabolic diseases, unremarkable electroneuromyographic find-
ings, and normal muscle biopsy results. When the child was aged 3 years, an oral glucose tolerance test revealed transiently elevated postprandial glucose values, which progressed to T1DM. Laboratory testing showed autoantibodies to insulin, pancreatic islet cells, tyrosine phosphatase IA2, and GAD. At 29 months, an electroencephalogram (EEG) showed multifocal discharges and right frontal electroclinical seizures. Results of brain magnetic resonance imaging at 31 months were normal. However, by the time she was 5 years old, bilateral (predominantly right) hippocampal, cortical, and cerebellar atrophy had appeared (Figure 1).

We first evaluated this patient when she was 6 years old. Focal seizures were observed 10 times daily; treatment was topiramate and clobazam. Three of 10 seizures were secondarily generalized. Neurologic examination showed neck and mouth weakness, gait instability, and limb ataxia; head circumference was 52 cm. Neuropsychological examination was difficult to perform because of global developmental delay, fatigability, poor attention span, and linguistic barrier. The child tended to manipulate objects without a specific aim. Expressive speech was characterized by word-finding difficulties, as well as poor lexical evocation and grammatical structure. Oral comprehension was restricted to simple structured sentences. Short-term memory was severely impaired.

Highly elevated serum levels of GADAs were present (highest value, 3400 IU/mL; reference, <10 IU/mL). Additional autoantibodies linked with various types of encephalopathies were not analyzed. When the child was 6 1/2 years old, a spinal tap was performed. In addition to blood-brain barrier dysfunction, the CSF samples showed high levels of GADAs (13 U/mL; reference, <1 U/mL), type 2 oligoclonal bands, and an elevated CSF to serum GADA immunoglobulin G ratio (11; reference, <1.5), suggestive of specific intrathecal GADA synthesis.

A 5-day course of intravenous methylprednisolone, 23 mg/kg/d, was initiated; no effect was observed on seizure frequency, EEG abnormalities, or neurologic symptoms. Consequently, while the child was receiving treatment with oral prednisone, 1 mg/kg/d, started immediately after the intravenous treatment, we used plasmapheresis (1 exchange/d during 5 consecutive days, followed by 3 exchanges/wk for 1 wk, 2 exchanges/wk for 4 wks, and then 1 exchange/wk).

A dramatic decrease in the serum GADA level was observed 2 weeks after the first plasmapheresis. These low levels were maintained (<300 IU/mL) with a combination of oral prednisone and 2 plasmapheresis sessions per week (Figure 2). Increased weakness and seizure frequency occurred after the frequency of plasmapheresis was reduced to once per week 6 weeks after its initiation; this increase was accompanied by an elevation in GADA levels during a 2-month period (highest value, 460 IU/mL). Because of decompensated T1DM and weight gain, prednisone therapy was stopped and immunomodulatory drugs were introduced 3 weeks after initiation of plasmapheresis. Treatment with mycophenolate mofetil, 600 mg/m² twice a day, did not yield any clinical improvement. However, a continuous drop in serum GADA levels was noted in parallel with the use of rituximab (given as 2 doses of 375 mg/m², with a 1-week interval, and 2 doses 4 months later). In parallel, with concomitant clobazam (up to 0.8 mg/kg/d) and stripentol (up to 30 mg/kg/d), progressive reduction in the frequency and severity of seizures was observed. Twelve months after initiation of plasmapheresis, the CSF GADA level had dropped to 1.8 U/mL, our patient had an average of 2 to 4 complex partial seizures per day and 1 to 3 short (<60 seconds) tonic seizures per week, and the EEG abnormalities had markedly diminished (Figure 2B). The child ate without assistance, colored with more precision, played symbolic games, and used a richer vocabulary. At 8 years, her gait was normal and the weakness had disappeared. She was able to use short sentences and to understand her parents’ speech. Her serum glucose concentration was controlled with subcutaneous insulin therapy.

The hemoglobin A₁c level decreased progressively, from 5.7% to 4.9%. There was no further progression of cerebral atrophy shown on magnetic resonance imaging performed 1 year after initiation of plasmapheresis (Figure 1).

Glutamic acid decarboxylase autoantibodies epitope-specific recognition was determined, and enzyme activity inhibition was measured in blood and CSF samples before and 1 year after the start of plasmapheresis and immunomodulatory therapy. The antibodies were GAD65-specific and showed no reactivity to GAD67. The enzyme activity inhibition in the serum samples was reduced from 64% before treatment to 36% after treat-
ment (these could not be measured in CSF samples). The technical details of the laboratory methods have been described5-10 and are summarized online (see the supplementary Appendix; http://www.archneurol.com).

The 2 previous reports3,4 on GADA-related encephalopathy in children suggest that this potentially treatable entity is insufficiently recognized in this age group. A correlation between clinical improvement and a decrease in plasma GADA titers was noted in one of these children.4 The second child returned to his normal state 3 months after disease onset, despite persistently high values of plasma GADAs,3 whereas our patient, although showing marked improvement, still experiences seizures and cognitive impairment despite significantly decreased levels of GADAs.

The mechanisms by which the circulating antibodies interact with GAD, an intracellular enzyme, are still debated. Some argue11 that the presence of GADAs indicates a nonspecific generalized immune process; for example, these antibodies are present in 60% of all isolated cases of T1DM. However, GABA synaptic transmission impairment due to GADAs was demonstrated in vitro,12 and low cortical GABA levels were recently reported13 in patients with high levels of serum GADAs. In addition, serum GADA levels are usually higher in neurologic diseases than in the typical isolated cases of T1DM.14 Glutamic acid decarboxylase autoantibodies related to neurologic conditions also seem to be qualitatively different from those involved in T1DM, as indicated by lack of staining of cerebellar granular neurons by GADAs from the serum of patients with uncomplicated T1DM.15 Moreover, the characteristic inhibition of GAD enzyme activity is not observed for GADAs in T1DM.15 Finally, GADAs in neurologic diseases often recognize GAD epitopes that differ from those bound by GADAs in T1DM (e.g., recognition of the b78 epitope is rare among patients with T1DM).16 Glutamic acid decarboxylase–specific monoclonal antibody b78 inhibits GAD enzyme activity, b96.11 does not.17 We found that, prior to treatment, our patient’s GADAs recognized epitopes associated with T1DM (b96.11) and neurologic diseases (b78).7,17 After treatment, however, the T1DM-related antibody specificity remained and the epitope related to neurologic diseases was no longer recognized.

Encephalopathy associated with GADAs may be reversible with immunotherapy. Plasmapheresis was the most effective treatment in decreasing GADA levels in our patient, whereas intravenous immunoglobulin and intravenous and oral corticosteroids had no effect on GADA levels or seizure frequency. In a recent review18 of 53 patients (aged 17-80 years) with epilepsy and GADAs, treatment with intravenous immunoglobulin, corticosteroids, or cyclophosphamide did not improve seizure control. The use of rituximab may have been effective in our patient and may be of interest in treatment of autoimmune neurologic diseases.19 This anti-CD20 monoclonal antibody causes selective destruction of B lymphocytes and decreased production of antibodies.20-22 Interestingly, rituximab has been recently demonstrated23 to partially preserve β-cell function when used at the onset of T1DM.

The reason for our patient’s improvement remains unclear. For instance, time may have contributed to the de-

![Figure 2. Evolution of glutamic acid decarboxylase autoantibodies (GADAs), with drug treatment indication, electroencephalographic findings, and average number of seizures per day from the time of initial plasmapheresis (PLEX). MMF indicates mycophenolate mofetil.](image-url)
crease of GADA levels in the CSF, and additional auto-
antibodies, not analyzed in our patient but recently reported11 as causing various types of encephalopathies, may have been influenced by our therapeutic approach. In addition, stiripentol and clobazam act on the GABA-
ergic system and may have influenced seizure control. However, the rapid decrease of seizures and improve-
m ent in behavior that paralleled the decrease and stabili-
zation of GADA levels during plasmapheresis and im-
munomodulating therapy was dramatic in our patient. Our observations, as well as those from other recent re-
ports,12-16 support the presence of a causal effect of GA-
DAs in this form of encephalitis; this remains to be veri-
fied. Multicenter prospective studies may determine whether earlier treatment with plasmapheresis and ri-
tuximab allows an even better outcome than that achieved with our patient.

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Author Contributions: Dr Korff had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Korff and Siegrist. Acquisition of data: Korff, Parvex, Wilhelm-Bals, Hampe, Schwitzgebel, Michel, and Lalive. Analysis and interpretation of data: Korff, Parvex, Cimasoni, Hampe, Schwitzgebel, Siegrist, Lalive, and Seeck. Drafting of the manuscript: Korff, Cimasoni, and Wilhelm-Bals. Critical revision of the manuscript for important intellectual content: Korff, Parvex, Wilhelm-Bals, Hampe, Schwitzgebel, Michel, Siegrist, Lalive, and Seeck. Administrative, technical, and material support: Parvex, Hampe, Lalive, and Seeck. Study supervision: Korff, Schwitzgebel, and Lalive.

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