Anti-GAD antibody syndrome with concomitant cerebellar ataxia, stiff person syndrome, and limbic encephalitis

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Practical Implications

Multiple neurologic syndromes can occur with anti-glutamic acid decarboxylase antibodies, and these can coexist in a single patient.

A 42-year-old man initially presented at age 38 with progressive vertigo, leg stiffness, dysarthria, diplopia, and ataxia. Lumbar puncture revealed 1 red blood cell and 9 nucleated cells (96% lymphocytes) with normal protein and glucose. Anti-glutamic acid decarboxylase (GAD) antibody testing was strongly positive at 1,050 nmol/mL (November 2009 by immunoprecipitation assay, Mayo Clinic, reference range (RR) ≤ 0.02 nmol/mL). MRI brain was unremarkable. He was diagnosed with stiff person syndrome (SPS), autoimmune cerebellar ataxia (CA), type 1 diabetes mellitus (DM1), and Hashimoto thyroiditis. He was treated with high-dose methylprednisolone for 3 days, IV immunoglobulin (IVIg) 2 g/kg divided over 2 days, and monthly IVIg for 3 months, with persistently high anti-GAD antibody level after treatment (1,070 nmol/mL in February 2010).

Despite treatment, his symptoms worsened. He received 4 plasmapheresis treatments and 5 infusions of rituximab over 15 months. His diplopia and dysmetria improved after the first few treatments of rituximab. His gait began responding after the third rituximab treatment, and he no longer needed a cane by his fifth treatment. His anti-GAD levels initially fluctuated but then steadily decreased to 300–400 nmol/mL by August 2010 (see figure 1). After therapy he continued to have dysarthria, nystagmus, dysmetric saccades, increased tone, dysmetria, and stiff posture, although he was able to walk unassisted. He was lost to follow-up for 3 years, with no maintenance immunotherapy during that time.

Three years later he presented with labile mood and multiple 1–2 minute episodes of drooling, staring, and difficulty speaking. He continued to display examination findings consistent with SPS and CA. MRI showed increased signal in the mesial temporal structures and insular cortex (figure 2). Video-EEG monitoring revealed frequent electroclinical seizures originating in the right hemisphere. Lumbar puncture was normal. Anti-GAD antibodies in serum and CSF were 148.3 U/mL (radioimmunoassay, Labcorp, RR 0.0–1.5 U/mL) and 10.0 nmol/L (immunoprecipitation assay, Mayo Clinic, RR ≤ 0.02 nmol/L), respectively. Serum and CSF paraneoplastic

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Figure 1 Serum anti-GAD antibody titer in relation to immunomodulatory treatment

There was no change in anti-glutamic acid decarboxylase (GAD) antibody titers with methylprednisolone (methylpred) or IV immunoglobulin (IVIg), and only a transient change after plasma exchange (PLEX). There was sustained reduction in anti-GAD titer with rituximab treatments.

panel including voltage-gated potassium channel antibodies was negative. He was treated with divalproex sodium, phenytoin, and levetiracetam, and his seizures stopped. He received 5 sessions of plasmapheresis over 10 days concurrently with high-dose methylprednisolone for 5 doses for a diagnosis of limbic encephalitis (LE). His cognitive and physical function returned to baseline, and 3 weeks later his serum anti-GAD titer was 138.2 U/mL. He was discharged with plans for outpatient rituximab therapy. He deferred formal neuropsychological testing.

DISCUSSION

Anti-GAD antibodies are implicated in a number of neurologic syndromes, including SPS, CA, and LE. High titers have also been detected in some patients with treatment-resistant localization-related epilepsy.¹ Anti-GAD antibody is detected in 80% of patients with newly diagnosed DM1, although at lower titers and against different epitopes from those seen in neurologic disease.² Patients with neurologic manifestations of elevated anti-GAD levels are more likely to have organ-specific autoantibodies, including anti-TPO (occurring in 50%–60% of patients), anti-gliadin, and others.^{3,4} Other autoimmune conditions such as pernicious anemia and psoriasis have been reported.^{3,4} Our patient had both personal and family history of several autoimmune diseases, in keeping with previously described associations.

The pathogenic role of anti-GAD antibodies in neurologic disease is unclear.^{2,4} Titers of anti-GAD antibody do not necessarily correlate with the severity of neurologic manifestations.⁵ In our patient, there was at least a modest correlation between titers and clinical improvement in response to immunomodulation, both during his initial presentation with SPS and CA and during his episode of LE. Unfortunately, the titers during these 2 episodes were reported from different labs using different techniques, and there is no way to directly compare them.

Combinations of the major features of anti-GAD antibody syndrome—DM1, SPS, CA, seizures, and LE—have been reported in individual patients, but our patient presented with all of these clinical syndromes.

There is no consensus about appropriate treatment for these patients. Case reports and series have reported variable responses to corticosteroids, IVIg, plasmapheresis, rituximab, and cyclophosphamide. There is one randomized trial of IVIg for the treatment of SPS that demonstrated efficacy compared with placebo,⁶ but there are no randomized trials for treatment of other disorders associated with anti-GAD antibodies. LE associated with anti-GAD antibodies may

Figure 2 MRI brain demonstrating evolution of limbic encephalitis

Upper images show axial fluid-attenuated inversion recovery (FLAIR) sequences for this patient at initial presentation (A), 1 week after corticosteroids and plasmapheresis (B), and at 4-month follow-up (C). Lower images show coronal postgadolinium T1 sequences for the same time points. There is FLAIR hyperintensity and contrast enhancement in the mesial temporal lobes and insulae, right-greater-than-left, which resolves with treatment.

be less responsive to corticosteroids than LE secondary to other autoantibodies.⁷ In our patient, a combination of plasmapheresis and rituximab proved effective, but without ongoing immunomodulation he relapsed years later with a new neurologic syndrome.

Clinicians must be cognizant of the broad spectrum of clinical presentations associated with anti-GAD antibodies in order to promote early diagnosis, as these patients often require aggressive treatment to achieve symptomatic improvement.

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