Clinical/Scientific Notes

Melissa Heiry, MD
Pegah Afra, MD
Fumisuke Matsuo, MD
John E. Greenlee, MD
Stacey L. Clardy, MD, PhD

Neurol Neuroimmunol Neuroinflamm 2015;2:e142; doi: 10.1212/NXI.0000000000000142

IMPROVEMENT OF GAD65-ASSOCIATED AUTOIMMUNE EPILEPSY WITH TESTOSTERONE REPLACEMENT THERAPY

OPEN

Treatment response in autoimmune epilepsy is variable. Achieving seizure reduction is often dependent on the specific neuronal antibody.[1,2] Glutamic acid decarboxylase 65 (GAD65)-associated epilepsy is among the most challenging of the autoimmune epilepsies to treat, often requiring multiple antiepileptic drugs (AEDs) and aggressive immunotherapy to attain a reduction in seizure frequency.[3]

There have been reports of improvement in seizure frequency in nonautoimmune epilepsy following administration of testosterone.[4–6] However, the association between sex steroids and autoimmunity is not clear, with no established association of sex hormone responsiveness in cases of autoimmune epilepsy. We present a case of immunotherapy- and AED-resistant GAD65-associated autoimmune epilepsy demonstrating sustained improvement with exogenous testosterone replacement.

Classification of evidence. This report provides Class IV evidence. It is a single observational study with no controls.

Case report. A 47-year-old Caucasian man developed transient episodes of piloerection initially involving the right face with progression to the right and left upper extremity. The episodes were associated with positive visual phenomena, as if "looking through water." Episodes lasted 30–60 seconds and occurred up to 20 times daily. There was no associated loss of consciousness. He could hear during events but was unable to interact. Auras included a metallic taste in the mouth, diaphoresis, and/or fatigue.

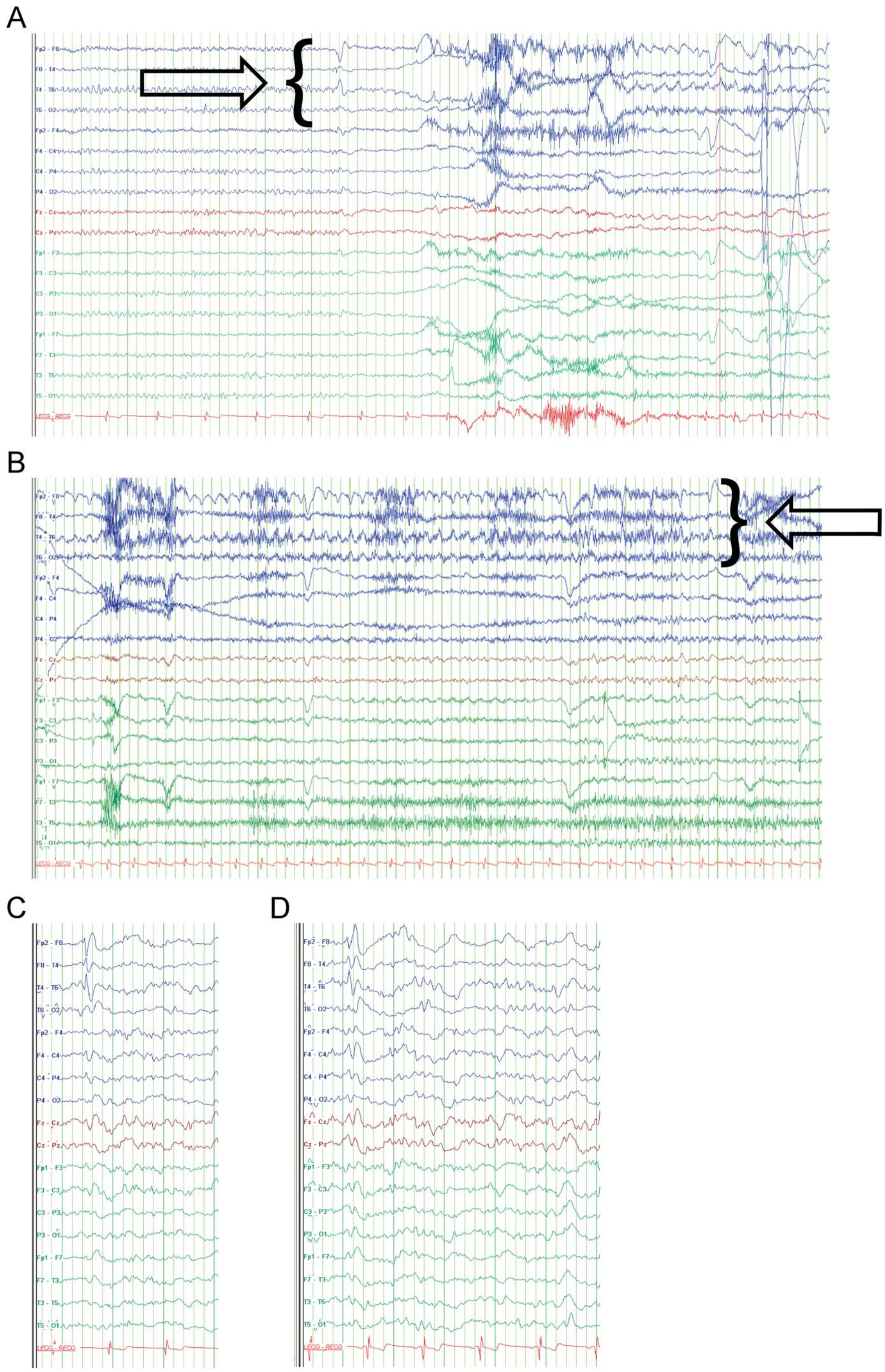
Past medical history was notable for hypothyroidism, a remote left varicocele repair, and remote removal of a benign testicular growth. CSF analysis was notable for positive GAD65 antibodies (>250 IU/mL). Serum evaluation was repeatedly positive for GAD65 antibodies (>250 IU/mL) and notable for low testosterone (226 ng/dL; reference range 240–950 ng/dL). EEG revealed paroxysmal single sharp waves over the right temporal lobe. MRI of the brain with contrast was unremarkable. Whole-body PET CT demonstrated decreased uptake in the bilateral temporal lobes, right greater than left.

The patient was treated with varying regimens of IV methylprednisolone, IV immunoglobulin, and plasma exchange. Throughout his course, he was on varying doses of oral prednisone ranging from 20 mg to 100 mg, depending on seizure severity. He was able to tolerate only low-dose mycophenolate mofetil. He experienced brief improvement in his symptoms with many of these regimens, without sustained benefit. Both oxcarbazepine and levetiracetam were trialed separately for treatment of the seizures, with no significant improvement noted. Clonazepam caused paradoxical agitation.

During the course of treatment, the patient was diagnosed with primary hypogonadism based on small testes bilaterally, reduced libido, reduced testosterone, and mildly elevated follicle-stimulating hormone. Testosterone replacement therapy (200 mg IM every 14 days) was initiated, and the patient subsequently noted improvement in seizure frequency and duration and an improved level of functioning. He reported increased seizure frequency (returning to 15–20 seizures daily) at a testosterone level <600 ng/dL. At a level >700 ng/dL, however, he experienced only 1–4 seizures daily.

He was admitted for long-term EEG monitoring to objectively verify his observations given the risks of ongoing testosterone replacement therapy. Testosterone therapy was discontinued the week prior to admission, but he was otherwise maintained on his home regimen of immunosuppression and AEDs, including prednisone 15 mg daily, mycophenolate mofetil 500 mg bid, and lamotrigine 200 mg bid, none of which were changed in the several months prior to admission. During the 15-day admission, 43 of 46 captured episodes (31 partial seizures and 22 electrographic seizures) lateralized to the right and localized to the broad right fronto-temporo-central areas and at times the entire right hemisphere (figure 1). Three of 46 captured episodes were characterized as auras with no apparent electrographic correlate but may have represented simple partial seizures subject to the detection limitations of scalp EEG. There was an increase in seizure frequency with

Figure 1 Ictal and interictal EEGs

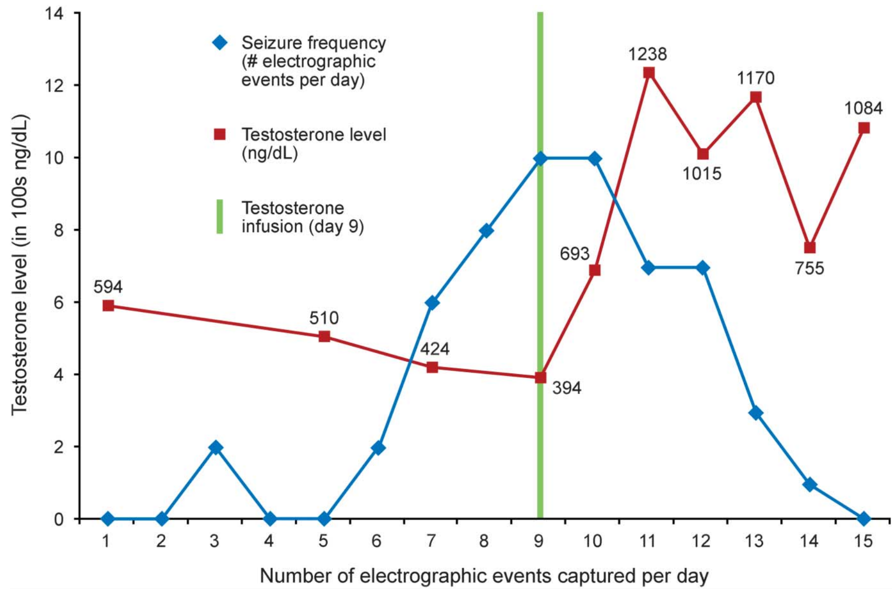


(A, B) Electrographic seizure of 26-second duration. Clinically, the patient reported having a difficult time interacting or communicating, with associated piloerection. Electrographically, ictal onset (A, arrow) consisted of single right frontotemporal sharp and slow waves followed in 2 seconds by a run of right frontotemporal sharp waves that built up to 3 Hz and then evolved to 2 Hz before ictal termination (B, arrow). (C, D) Interictal epileptiform discharges. Right frontotemporal sharp and slow waves (C) and right frontotemporal sharp and slow waves followed by right frontotemporal delta slow activity (D).

decreasing testosterone levels. As a result, on day 9 (testosterone level 394 ng/dL), 200 mg of IM testosterone was administered, with a subsequent dramatic reduction in both electrographic seizure frequency and duration correlating with increasing serum testosterone levels (figure 2). The reduction in seizure frequency and severity on testosterone replacement has been sustained for more than 1.5 years.

Discussion. In this case, long-term EEG monitoring established a correlation between increasing serum testosterone levels and a sustained reduction in

Figure 2 **Serum testosterone level and seizure frequency**



There was a dramatic reduction in both electrographic seizure frequency and duration after testosterone infusion on day 9, correlating directly with increasing serum testosterone levels.

seizure frequency and intensity. The mechanism whereby testosterone mediated this effect for this patient is unclear, but androgen deficiency with reduced testosterone levels and low fertility has been documented in men with epilepsy.[7] There have also been reports illustrating an improvement of nonautoimmune epilepsies following administration of testosterone.[4–6,8]

Mechanistically, testosterone metabolism involves production of 2 metabolites, dihydrotestosterone (DHT) and estradiol (E2), with proposed opposing effects. DHT has been shown to block NMDA transmission, reducing glutamatergic transmission and overall reducing excitability through metabolism via the 5a reductase pathway.[9] Conversely, E2 has demonstrated varying properties, including both proconvulsant and antiseizure effects. Proposed blockade of conversion to E2 with aromatase inhibitors (such as testolactone) has been shown to reduce seizure frequency to a greater extent than testosterone therapy alone in men with refractory complex partial seizures and hypogonadism.[8,10] Given the risks associated with exogenous testosterone replacement, routine testosterone replacement in the absence of documented testosterone deficiency is not recommended, nor is the use of exogenous testosterone as an antiepileptic agent. Further understanding of the relationship between sex hormones and epilepsy is necessary.

This case highlights the need for increased attention to the possible role of endocrinologic abnormalities in patients with autoimmune epilepsy and the need to address such abnormalities because they may play a role in worsening the epilepsy, particularly in autoimmune epilepsies that are less responsive to immunosuppressive therapy.[3]

From the Department of Neurology (M.H., P.A., F.M., J.E.G., S.L.C.), University of Utah, Salt Lake City; and Department of Veterans Affairs Medical Center (J.E.G., S.L.C.), Salt Lake City, UT.

Author contributions: All authors made substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; were involved in drafting the work or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Study funding: This study was funded by a research grant from the Western Institute for Biomedical Research awarded to Stacey L. Clardy.

Disclosure: M. Heiry reports no disclosures. P. Afra is on the speakers' bureau for UCB Pharma and Sunovion; received research support from UCB Pharma, Sunovion, and Cyberonics; and is on the editorial board for Austin Journal of Neurological Disorders & Epilepsy. *F. Matsuo reports no disclosures. J.E. Greenlee is an associate editor for* MedLink *and* Clinical Neurology and Neurosurgery, *receives royalties from MedLink and Merck, has been a course director and faculty for American Academy of Neurology, and received research support from United States Department of Veterans Affairs. S.L. Clardy received research support from Western Institute for Biomedical Research. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by the authors.*

Received May 22, 2015. Accepted in final form July 1, 2015.

Correspondence to Dr. Clardy: stacey.clardy@hsc.utah.edu

1. Quek A, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 2012;69:582–593.
2. Vincent A, Irani SR, Lang B. The growing recognition of immunotherapy-responsive seizure disorders with autoantibodies to specific neuronal proteins. Curr Opin Neurol 2010;23:144–150.
3. Dubey D, Konikkara J, Modur PN, et al. Effectiveness of multimodality treatment for autoimmune limbic epilepsy. Epileptic Disord 2014;16:494–499.
4. Frye C. Hormonal influences on seizures: basic neurobiology. Int Rev Neurobiol 2008;83:27–77.
5. Herzog AG. Psychoneuroendocrine aspects of temporolimbic epilepsy. Part II: epilepsy and reproductive steroids. Psychosomatics 1999;40:102–108.
6. Frye C. The role of androgens in epilepsy. Expert Rev Neurother 2006;6:1061–1076.
7. Bauer J, Blumenthal S, Reuber M, Stoffel-Wagner B. Epilepsy syndrome, focus location, and treatment choice affect testicular function in men with epilepsy. Neurology 2004;62:243–246.
8. Harden C, MacLusky NJ. Aromatase inhibition, testosterone, and seizures. Epilepsy Behav 2004;5:260–263.
9. Pouliot WA, Handa RJ, Beck SG. Androgen modulates N-methyl-D-aspartate-mediated depolarization in CA1 hippocampal pyramidal cells. Synapse 1996;23:10–19.
10. Herzog AG, Klein P, Jacobs AR. Testosterone versus testosterone and testolactone in treating reproductive and sexual dysfunction in men with epilepsy and hypogonadism. Neurology 1998;50:782–784.

Neurology®
Neuroimmunology
& Neuroinflammation

Improvement of GAD65-associated autoimmune epilepsy with testosterone replacement therapy

Melissa Heiry, Pegah Afra, Fumisuke Matsuo, et al.

Neurol Neuroimmunol Neuroinflamm 2015;2;
DOI 10.1212/NXI.0000000000000142