LETTER TO THE EDITOR

To The Editor

Segmental Myoclonus and Epilepsy in a Child with GAD 65 Antibodies

Keywords: GAD 65 antibodies, Child, Myoclonus, Epilepsy

Glutamic acid decarboxylase (GAD) is a rate-limiting enzyme for the synthesis of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. It is widely distributed in the central nervous system but is also present in other organs, especially the pancreas. Elevated GAD 65 antibodies have diverse clinical associations, including stiff person syndrome (SPS), cerebellar ataxia, limbic encephalitis, epilepsy, ocular motor disorders, type 1 diabetes mellitus,[1,2] and rarely myoclonus.[3–6] GAD 65 antibody-associated neurological syndromes, mostly SPS or epilepsy, are rarely reported in pediatrics.[2,7] Many patients improve after immune therapy and some, whose presentation includes seizures, become seizure free.[1] Elevated GAD 65 antibodies may be associated with tumors. However, such an association is rare in children.[1]

A 7.5- year-old-girl, previously healthy and intellectually normal, presented with a few days history of self-limited right-sided throbbing headache and a new-onset focal tonic–clonic seizure with bilateral spread lasting 5 min. She concurrently developed right sided then bilateral continuous, high frequency, semi-rhythmic facial muscle twitching, consistent with myoclonus, most prominent on the right face and upper lip (Video). The myoclonus was present during wakefulness and sleep. Six weeks later, the myoclonus spread to her right thumb and tongue. She did not develop myoclonus anywhere else. She did not feel the myoclonus. The myoclonus responded partially to treatment with clonazepam. Levetiracetam was started following a second, 2.5 min focal unaware seizure, 10 d after the first seizure. There were no signs of encephalopathy, cognitive decline, or regression. She could eat, drink, and speak normally.

Pregnancy, delivery, development, and past medical history were unremarkable. Parents are non-consanguineous. There was no family history of seizures, autoimmune, or movement disorders. The patient's full neurological exam was normal apart from the myoclonus.

Blood tests were normal including CBC, extended electrolytes, glucose, liver and thyroid function, uric acid, copper, ceruloplasmin, ESR, CRP, C3, C4, immunoglobulins, rheumatoid factor, ANCAs, anti-TPO, and phospholipid (cardiolipin and β2-glycoprotein) antibodies. ANA screen was positive (low titers at 1:40 for speckled and 1:80 for nucleolar antinuclear antibodies detected by immunofluorescence), but dsDNA and extractable nuclear antigens were negative. Urinary vanillylmandelic acid and homovanillic acid were negative.

CSF investigations revealed normal glucose and lactate, with a slightly elevated protein (0.29 g/l, normal range: 0.12–0.24) and cell count (8 cells, 97% lymphocytes). Oligoclonal bands were present in the CSF with no corresponding bands in the serum. GAD 65 antibodies were 'highly positive' in CSF and serum as tested by a cell-based immunoassay (CBA: Euroimmun AG, Luebeck, Germany), performed by MitogenDx, Calgary, Canada. Serum level of anti-GAD 65 as tested by an enzyme-linked immunosorbent assay (ELISA) was >250 IU/ml (normal range < 5 IU/ml). Other autoimmune encephalitis and paraneoplastic antibodies (CBA and line immunoassay, respectively: Euroimmun) including NMDA, DPPX, VGKC, Anti$GABA_B$ receptor profile, AMPA antibodies were negative. Neoplastic work up was negative including chest, abdomen, and pelvic MRI at presentation and 1 year later.

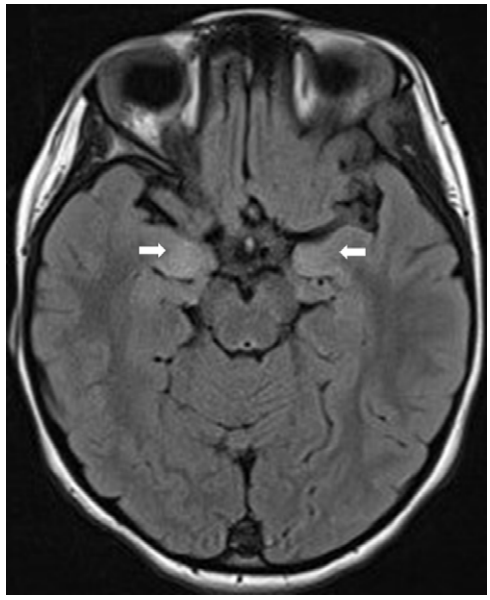

Figure 1: *Axial FLAIR brain MRI (TR 9890, TE 90) demonstrating bilateral asymmetric (right > left) hyperintense signal abnormalities (arrows) within the uncus and adjacent parahippocampal gyri 3 months after presentation, which improved 9 months later and resolved 2 years after presentation.*

The first brain MRI showed an asymptomatic Chiari I malformation with no other abnormalities. Follow-up MRI 6 and 10 weeks later showed sequential development of left then right mesial temporal lobe hyperintensities (Figure 1). Whole-body positron emission tomography (18 F FDG-PET) to further look for potential neoplasm showed intense asymmetric activity, right > left, in the nasopharynx and oropharynx from the myoclonus. Intense uptake was seen in thenar muscles of the right hand. No other abnormality was identified in the brain or elsewhere.

The initial EEG captured continuous 7–9 Hz muscle artifacts from the myoclonus during wakefulness, which decreased during sleep, becoming more prominent on the right side, and not associated with epileptiform discharges. An EEG 7 weeks later showed left hemisphere slowing and multifocal epileptiform discharges with interictal left temporal epileptiform activity occurring in runs at times and infrequent left frontal and bilateral frontopolar interictal epileptiform activity (Figure 2).

Surface and needle EMG showed bilateral semirhythmic facial muscle discharges consistent with a subcortical origin.

The patient was diagnosed with GAD 65 antibody-associated neurological disease. Four months after presentation, she was started on immunosuppressive therapy according to the BrainWorks protocol (http://www.sickkids.ca/PDFs/Research/BrainWorks/63976-Antibody%20IBrainD.pdf): IV methylprednisolone

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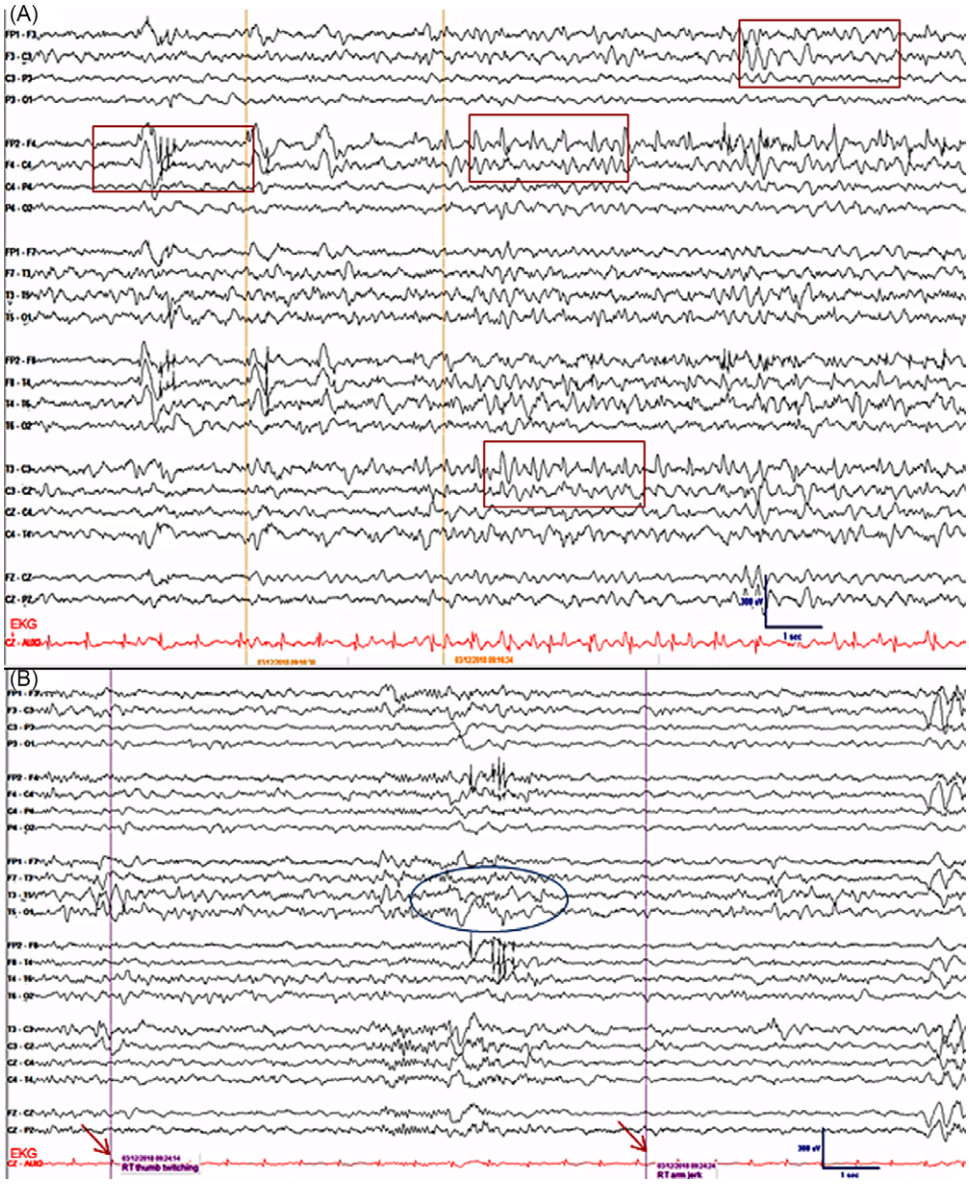

Figure 2: *Scalp video EEG (bipolar montage) during stage II sleep performed 7 weeks after the initial presentation. (A) There are multifocal sharps and spikes in the left temporal, left frontal pole, and right frontal pole/frontal regions interictally (boxes). (B) Slowing in the left temporal region is shown (ellipse). Patient had right thumb/arm twitching (arrows) that had no EEG correlate.*

pulse therapy for 5 d (30 mg/kg), followed by oral taper of prednisone over 5 months (initial dose 2 mg/kg), 8 courses in total (5 biweekly then 3 monthly) IV immunoglobulins (2 g/kg/course), and 2 doses of rituximab (500 mg/m^2) 2 weeks apart.

Treatment response was assessed by myoclonus change over time, seizure control, EEG findings, and MRI changes. Her response to the immunosuppressive therapy across all the aforementioned domains appeared favorable for well over 2 years. Four more focal seizures with bilateral spread occurred 8, 30, 30.5, and 31 months after her initial presentation. At 32 months follow-up, the facial and right thumb myoclonus remained mild, occurring intermittently daily, and treated with clonazepam. She also developed new events consistent with insular lobe epilepsy 31 months after her presentation. They consisted of intense pain in her throat, feeling strangulated with spasms in her pharynx, dysphonia, fear, abdominal pain, and vomiting followed at times by lethargy and sleepiness. Initially, four such events occurred once per week, lasting 20 min each. Subsequently, they occurred once or twice per day, lasting 1–2 h each. The events had no EEG correlate on video-EEG telemetry but their semiology was consistent with insular lobe epilepsy. They occurred randomly while she was awake. She was started on divalproex sodium with rapid full resolution. She continues to take levetiracetam. A disease flare up was suspected 31 months after her presentation, because of her seizures' recurrence. This prompted repeat investigations: (1) A 24-h EEG showed intermittent right temporal epileptiform activity with spread to the right frontal or parietal regions during sleep; (2) a repeat MRI showed new signal hyperintensities over the right more than the

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left mesial temporal lobes, hippocampi, and parahippocampal gyri. These changes occurred after resolution of all prior MRI hyperintensities with no atrophy 2 years after her initial presentation; (3) repeat CSF cell count and protein were unremarkable but oligoclonal bands were present in the CSF with no corresponding bands in the serum, and GAD 65 antibodies were 'highly positive' in the CSF and serum; (4) other autoimmune encephalitis and paraneoplastic antibodies in the CSF and blood were negative; and (5) repeat blood autoimmune screen revealed positive ANA screen (nuclear antibody homogeneous pattern titer at 1:320 and nuclear antibody centromere pattern titre at 1:640), elevated centromere protein B (4.2, normal range: 0–0.9) and myeloperoxidase (3, normal range: 0–0.9) antibodies, with no clinical correlate. Other nuclear, anti-TPO, and phospholipids antibodies were negative. Immunosuppression therapy was started according to BrainWorks protocol for her disease flare up.

The patient did not develop limbic encephalitis, encephalopathy, memory loss, behavioral difficulties, SPS, ataxia, or type 1 diabetes mellitus.

We report a novel association of elevated GAD 65 antibodies in a child with seizures, segmental myoclonus, and bilateral transient temporal lobe hyperintensities on MRI without clinical limbic encephalitis. Initial and subsequent body imaging did not reveal the presence of an associated neoplasm.

Diverse disorders can cause abrupt onset myoclonus and seizures including electrolytes disturbance, liver/renal failure, infections, intoxication/drugs, inflammation/demyelination, autoimmune (systemic or CNS)/paraneoplastic diseases, trauma, vascular brain injury, structural brain abnormalities, and neurodegenerative diseases. Investigations in our patient ruled out most etiologies, including antithyroid and antiphospholipid antibodies, reported occasionally in association with epilepsy,[8] especially when myoclonus is present. However, progressive neurological disorders, such as those causing progressive myoclonic epilepsy, for example mitochondrial disorders, remained high up on the differential diagnosis until long-term clinical follow up revealed that the patient never regressed or developed new findings.

Epilepsia partialis continua was initially considered as a cause of her abnormal facial and right hand movements. However, the lack of rhythmicity, the absence of an EEG correlate of the myoclonus and its persistence during sleep, were supportive of a subcortical origin.

Axial, palatal, or lower limb myoclonus have been reported rarely in adults with GAD 65 antibodies.[2–6] GAD 65 antibody-associated neurological disease, and specially extrapyramidal movement disorders, is rarely reported in children.[1,2,7,9] 'Continuous involuntary movements' (without further details) and intractable myoclonic epilepsy were reported in a 9-month old developmentally delayed boy,[9] who had normal brain MRIs 2 months apart. Seizures and epileptiform EEG abnormalities, usually involving the temporal lobes, have been documented,[2,10] while limbic or extralimbic encephalitis appears to be uncommon.[11] The pathogenesis of GAD 65 antibody-associated disease is poorly understood.

The presence of systemic autoantibodies has been reported in patients with elevated GAD 65 antibodies as in our patient, including antithyroid, antinuclear, and anti-RNP antibodies, reflecting widespread immune dysregulation.[12,13] Our patient did not have specific clinical or radiological evidence of diseases associated with these autoantibodies. We are following her up closely for symptoms of other autoimmune and/or lymphoproliferative disease.

Based on anecdotal reports, immunosuppression can be effective, especially when initiated early and may lead to better outcomes.[1,7,10] Our patient's myoclonus and seizure control improved significantly and her brain MRI abnormalities resolved following the initiation of clonazepam, levetiracetam, and immunosuppressive therapy until her disease relapse more than 2 years later. We can only speculate on the effectiveness of her immunosuppressive therapy.

In conclusion, myoclonus and epilepsy may be associated with antineuronal autoantibodies in children without encephalopathy. Antineuronal antibody testing including anti-GAD 65 should be included in the work up of children with compatible clinical presentations. A high index of suspicion is important in facilitating early diagnosis and treatment. This case expands the clinical spectrum of GAD 65 antibody-associated neurological disorders in children, adding another phenotype to its more commonly recognized associations with SPS, epilepsy, and cerebellar ataxia.

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Conflict of Interest

The authors declare that there are no conflicts or competing interest relevant to this work.

Statement of Authorship

MS conceived writing the case report. He was involved in the organization and execution of the project. He did the literature search, produced the first draft, and edited the manuscript several times. QX contributed the EEG figure and its legend, wrote part of the case description and discussion, and edited (review and critique) the manuscript. MB contributed the MRI figure and its legend, and edited (review and critique) the manuscript. WI did the EMG, contributed to the case description, and edited (review and critique) the manuscript. KG did part of the literature search, contributed to the case description and discussion, and edited (review and critique) the manuscript. SU contributed the video and its legend, and edited (review and critique) the manuscript

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.21.

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