

Case Report

Non-N-methyl-D-aspartate Autoimmune Encephalopathy and Catatonia Treated With Electroconvulsive Therapy: A Pediatric Case Series and Treatment Guidelines

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Introduction

Autoimmune encephalitis (AE) in pediatric patients is becoming increasingly recognized as a clinical entity that should be included in the differential diagnosis for new-onset psychosis.^{1,2} With increasing attention and recognition come the challenges of guiding patients and their families through a highly complex treatment process. The approach to autoimmune-associated catatonia, even in the pediatric population, is not inherently different from treating catatonia because of other specified medical causes.³ As in adults, when medication treatments for catatonia fail or if the condition is imminently life-threatening, electroconvulsive therapy (ECT) should be considered, given the ameliorating nonspecific effect of ECT on catatonia.⁴ Some idiosyncrasies related to autoimmune conditions in pediatric populations deserve special attention when considering ECT as a part of the treatment plan. There are several case reports related to the use of ECT as an augmentation strategy within anti-N-methyl-D-aspartate (NMDA) receptor AE.⁴ While NMDA receptor antibody-associated AE is the most common one in the literature, there are numerous other autoimmune causes of catatonia in which ECT may also be efficacious. The Grauss criteria describe features that may be used for the diagnosis of possible, probable, or definite AE.^{1,2} Symptom onset in AE must be acute to subacute (less than 3 months), with multiple domains impacted (i.e., cognitive symptoms, psychiatric symptoms,

neurological symptoms). In addition, abnormalities of cerebrospinal fluid (CSF) to include pleocytosis or oligoclonal banding, electroencephalography (EEG) changes such as temporal slowing, and/or magnetic resonance imaging (MRI) findings (i.e., multifocal or temporal lobe-restricted hyperintensities) are required for diagnosis. High-titer antineuronal auto-antibodies must be seen in serum or CSF to definitively diagnose AE because of a specific auto-antibody. Psychiatric symptoms without neurologic symptoms, or vice-versa, make the likelihood of an AE diagnosis much lower. Cases with clinically suggestive features should optimally be referred to a specialty center with initial workup including, but not limited to, EEG, MRI of the brain with and without contrast, CSF cytology, CSF infectious panel, CSF AE panel, serum AE antibody panel, and other serum antibody titers (antinuclear antibody, antithyroid antibody panel, anticardiolipin, anti-beta-2-glycoprotein, anti-Smith/Ro/La, anti-DNAse B, anti-Streptolysin-O [ASO]) as suspected.

Here, we report on 4 cases, either primary seronegative AE or with a secondary AE associated with

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autoimmune brain disease other than anti-NMDA receptor encephalitis, with disease onset before the age of 18 years. All were treated successfully with ECT when used as an augmentation to the immunomodulatory medication regimen and benzodiazepines.

Case A

Ms. A is an African-American female with a history of presumptive seronegative AE. She experienced first-episode psychosis with abrupt onset at the age of 15 years. She was found to have cognitive decline, memory impairments, vivid visual hallucinations, disorganized behavior, paranoia, and catatonia. Initial evaluation revealed an abnormal EEG and oligoclonal bands in her CSF. Unfortunately, her initial CSF sample was lost in transport to an outside laboratory. Later repeat lumbar puncture after partial treatment was negative for known autoantibodies on the AE panel. She met criteria for probable AE¹ and was treated initially with intravenous (IV) steroids with recovery of symptoms. She experienced a mild flare of symptoms when compliance with monthly infusions of IV steroids was delayed but symptoms resolved with escalation to the use of concurrent IV steroids and IV immunoglobulin (IVIG).

At 17 years of age, she presented with acute mental status changes and re-emergence of catatonia. Bush-Francis Catatonia Rating Scale (BFCRS) score was 13, and she had autonomic instability. Computed tomography (CT) of the head, EEG, and head MRI were unremarkable. She was started on IV lorazepam with pulse IV steroids, rituximab, IVIG, memantine, and melatonin, but only experienced mild improvement. Given symptom progression to malignant catatonia, recommendations were given for emergent initiation of ECT. With family consent and concurrence by 2 independent psychiatrists, ECT treatment began on hospital day 9 with bitemporal electrode placement. She was treated in her hospital room on stepdown status. We achieved an adequate seizure on the first stimulus ([Supplementary Figure 1](#)) with prolonged EEG seizure activity terminated by 2 mg of midazolam. She also experienced mild hypotension successfully treated with IV hydrocortisone and phenylephrine. She was transferred to a pediatric ICU for the second treatment. Her symptoms rapidly remitted with a BFCRS score of 0 after the second treatment. She was discharged from the hospital after the fifth session, receiving a total of 6 index ECT treatments and 4 maintenance ECT

treatments, tapering to monthly. She continued to receive biweekly dexamethasone and monthly IVIG for several months with maintenance rituximab. She graduated from high school and is now pursuing undergraduate studies.

Case B

Mr. B is an African-American male with a history of Sjogren's syndrome (anti-Ro, anti-nuclear antibody positive, positive lip biopsy), chronic inflammatory demyelinating polyneuropathy, protein energy malnutrition, and sickle cell trait. At the age of 17, he was hospitalized with acute mental status changes with progressive cognitive decline and memory impairments. He exhibited acute onset of psychosis with disorganized behaviors, auditory and visual hallucinations, and expressive speech changes. Initial workup showed diffuse parenchymal loss on cranial CT and unremarkable CSF and EEG studies. He further decompensated with tachycardia, fevers of unknown source, significant proteinuria, and elevated inflammatory markers despite IVIG treatment. MRI showed subtle areas of enhancement within the deep basal ganglia, posterior perisylvian regions, right posterior frontal lobe, and global cerebral atrophy. He was subsequently transferred to our tertiary care institution for further management.

His symptoms remained refractory to medication treatment including IVIG, IV steroids, mycophenolate, and rituximab. Repeat MRI of the head was significant for worsening basal ganglia enhancement and global intracranial atrophy. EEG demonstrated intermittent left temporal slowing. Serum findings were remarkable for antimicrosomal thyroid antibodies, anti-Sm, anti-Ro, and anti-La, along with a positive anti-nuclear antibody (speckled pattern). CSF findings were unremarkable. IV lorazepam treatment was started at 0.5 mg every 6 hours with an initial BFCRS score of 17 with autonomic instability and mutism. He was only partially responsive to lorazepam and immunosuppressants.

With family consent and concurrence by 2 independent psychiatrists, bitemporal ECT treatment began on hospital day 30 given continued autonomic instability and imminent need for parenteral nutrition. He demonstrated significant improvement after the second ECT with the BFCRS score decreasing to 4. Between treatments 2 and 3, there was a 5-day gap, and his BFCRS score increased

to 15. However, after the completion of 10 index ECT treatments, he showed sustained remission. Notably, he was able to avoid a gastrostomy tube and was able to complete all activities of daily living independently. He was discharged on hospital day 52 and continued to receive monthly maintenance ECT for 4 months. At follow-up visits, he had weight gain of 35 pounds, returned to school, and ECT was discontinued.

Case C

Ms. C is a Caucasian female with autism spectrum disorder secondary to SHANK3 genetic mutation, learning disability, and attention deficit hyperactivity disorder. She was diagnosed with probable seronegative AE diagnosed at 12 years of age based on acute onset of behavior changes, seizure-like episodes, an abnormal EEG, and CSF pleocytosis. She responded to immunotherapy with marked improvements back to 75% of her baseline. She was managed as an outpatient with maintenance immunosuppressants, aripiprazole, lorazepam, sertraline, methylphenidate, and melatonin.

However, at 18 years of age, she presented with agitated catatonia, obsessive-compulsive features with marked perseveration, profound psychomotor restlessness, agitation, disorganized thinking, and profound insomnia. Her initial BFCRS score was 31 with autonomic instability requiring pediatric ICU admission. Workup in the pediatric ICU included brain MRI, an electrocardiogram, an EEG, and serum studies that were unremarkable. There was significant improvement with a dexmedetomidine infusion and IV lorazepam 2 mg every 4 hours, but the benefit was not sustained and she was unable to be weaned on either agent. Given concern for an evolving malignant catatonia unresponsive to increased lorazepam, ECT was recommended. Additional treatments included lithium, zolpidem, clonidine, mycophenolate, and IVIG.

With consent from her legal guardian and concurrence by 2 independent psychiatrists, bitemporal ECT treatment began on hospital day 10. First treatment produced prolonged seizure activity terminated by 3 mg of midazolam plus 4 mg of lorazepam and 50 mg of propofol. With increased stimulus intensity, subsequent treatments did not produce prolonged seizure activity. She was able to be moved to a step-down unit on hospital day 21 with significant improvement after the fifth and sixth ECT treatments. By the seventh ECT, Ms. C's catatonia symptoms had

remitted. She was discharged on hospital day 32 after a total of 10 index ECT treatments. Medications at discharge included clonidine, lithium, lorazepam, zolpidem, quetiapine, and trazodone as needed. Her outpatient treatment plan also included immunotherapy and maintenance ECT treatments, now at 1-month intervals after 8 months. She is back in school and functioning near her premorbid baseline.

Case D

Ms. D is a Caucasian female with a history of international adoption, and rheumatic fever with associated encephalopathy. She was diagnosed with rheumatic fever at age 15, and she had concurrent onset of memory impairments, hallucinations, catatonia, chorea, ataxia, and migratory arthritis. Evaluation revealed ASO and anti-DNase b titers. She was initially refractory to IVIG, IV steroids, and rituximab and risperidone but showed marked symptom improvement with the addition of tocilizumab. She was subsequently maintained with tocilizumab, mycophenolate, and IVIG. She was able to attend college, but at the age of 21, a wean of mycophenolate and a streptococcal infection resulted in relapse. Her primary symptoms were one month of severe cognitive decline, hallucinations, and catatonia. She had marked psychomotor retardation, mutism, and stupor. Examination showed arthritis and elevated ASO and anti-DNase B. She initially demonstrated mild improvement with IVIG, steroids, and increased tocilizumab dose. However, one month later, she was admitted with continued weight loss and features of catatonia despite maximal immunosuppressant therapy. Serum findings included elevated Anti-Ro, IgG, ASO, and complements (C3 and C4). Her initial BFCRS score was 18 without autonomic instability. She was partially responsive to IV lorazepam 1 mg every 6 hours with a BFCRS score of 8. However, she rebounded to a BFCRS score of 16 after attempted conversion to oral dosing.

She was referred for ECT for refractory catatonia on hospital day 7. She started bitemporal ECT treatment on day 9 with consent of her legal guardian and concurrence by 2 independent psychiatrists. Catatonia features improved greatly after the sixth treatment and remitted after the seventh treatment. After the ninth treatment, she was able to perform all independent activities of daily living. After completion of 10 index ECT treatments and 32 hospital days, she was discharged on oral lorazepam 1.8 mg every 8 hours and

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risperidone 0.25 mg as needed every 12 hours for hallucinatory phenomena and agitation. She was weaned to once every 6 weeks maintenance ECT and remains in remission after 6 months.

Discussion

Here, we present 4 cases of autoimmune encephalopathy-associated catatonia with onset in the pediatric period. Ultimately, catatonia in these cases failed to fully respond to treatment with medications. With ECT, we obtained significant improvements in catatonia in all cases. In 3 cases, families considered the treatment to be life-saving. Across these 4 cases, we encountered special considerations that were specific to pediatric autoimmune catatonia, including, appropriateness of treatment, use of anesthetics and muscle relaxants, adrenal suppression from prior immunomodulatory treatments, and ethical/legal considerations for transitional age youth.

Medical Considerations

Several treatments were completed in the pediatric ICU setting because of severe autonomic instability from malignant features of catatonia. When the condition improved after initial treatments, we were able to safely transport the patients to our ECT treatment suite.

In all 4 of these cases, we induced anesthesia with the barbiturate drug, methohexital ([Supplementary Figure 2](#)) (trade name Brevital; Par Pharmaceutical, Chestnut Ridge, NY), which is the first-line anesthetic for patients in our ECT program. The use of ECT anesthetics was discussed in a recent review of anti-NMDA encephalitis cases, suggesting avoidance of agents such as ketamine or nitrous oxide that act via the NMDA receptor.⁴ One patient exhibited prolonged immobility with muscle wasting. We used the non-depolarizing skeletal muscle relaxant rocuronium rather than succinylcholine to avoid risk of hyperkalemia. In one case, we held steroids the morning of treatment, which led to significant hypotension after the first ECT that was treated with bolus IV steroids and phenylephrine, highlighting the risk of adrenal suppression. The presence of AE conferred an increased risk of prolonged seizures, but only twice did we see a seizure longer than 180 seconds, successfully terminated

with 2 mg of midazolam and 3 mg of midazolam/4 mg of lorazepam/50 mg of propofol, respectively.

Ethical and Legal Considerations

In each of these cases, we found ECT treatment to be ethically sound because of the very poor prognoses of the patient(s) and the relatively increased but manageable risks of adverse events related to ECT itself. In all cases, documented consent from the patient (if they are aged ≥ 18 y) and/or legal guardian (if they are aged < 18 y or lack capacity) as well as assent from the patient's family (if they are aged ≥ 18 y) or the patient (if they are aged < 18 y) is considered standard of care. Here, we described 2 patients who became adults either during their initial illness or during the hospital stay in which ECT was used. In one case, the acute risk of morbidity/mortality was sufficiently high to warrant designation of an "emergency intervention," signed by 2 independently consulting psychiatrists, one of which was a child-adolescent specialist and one of which was an ECT specialist. In this case, we required the filing of emergency guardianship paperwork simultaneous to the start of ECT. Some states have specific legal requirements for the practice of ECT which were reviewed by Shenai et al.⁵

In general, we recommend following established practice parameters,^{2,6} with the following modifications for patients with autoimmune-associated catatonia:

1. Indications
 - a. Catatonia unresponsive to benzodiazepines and augmenting agents (memantine, zolpidem)
 - b. Catatonia with autonomic instability (fever, tachycardia, hypertensive emergency)
 - c. Severe psychosis symptoms unresponsive to medications and augmenting agents
 - d. Severe affective symptoms that include acute suicidal ideation
2. Relative contraindication
 - a. CNS lesions with mass effect (increases the risk of brainstem herniation)
3. Assessment (adapted from the study by Mooneyham et al.,² with permission).
 - a. Multidisciplinary approach with consultation to neurology and rheumatology
 - b. Laboratory biomarkers for autoimmune and inflammatory causes (complete blood count with

- differential, anti-nuclear antibody, erythrocyte sedimentation rate, C-reactive protein, serum AE antibody panel, antithyroid antibody panel, anticardiolipin, anti-beta-2-glycoprotein, anti-Smith, anti-Ro, anti-La, anti-DNase B, ASO)
- c. CSF studies (opening pressure, cell count, glucose, protein, gram stain, culture, ACE level, CSF AE antibody panel, oligoclonal bands/IgG index, infectious workup [varicella-zoster virus, herpes simplex virus, human herpesvirus-6])
 - d. Neuroimaging to evaluate structural (MRI hyperintensities) and possibly functional (positron emission tomography hypometabolism) changes
 - e. Routine or prolonged EEG to characterize any seizure activity if present
 - f. Standardized cognitive assessment for working memory and executive function (ex. Montreal Cognitive Assessment, Trails A, Hopkins Verbal Learning Test)
4. ECT procedure
- a. Treat in the intensive-care setting for patients who are medically unstable or with malignant catatonia.
 - b. Hold antiepileptics (except benzodiazepines) night before and day of ECT. If not possible due to seizure disorder, taper antiepileptics to the minimum effective dosage.
 - c. Hold benzodiazepines the morning of ECT if possible and/or pretreat with flumazenil 0.5–1 mg immediately after administration of anesthetic agent to reverse benzodiazepine effect on seizure threshold, rather than aggressive tapering of benzodiazepines.⁷
 - d. Use a nondepolarizing relaxing agent such as rocuronium for patients with severe muscle wasting or diffuse muscular rigidity to avoid hypokalemia.
 - e. Recommend bitemporal ECT over unilateral ECT and brief-pulse (1.0 ms) over ultrabrief pulse (0.3–0.5 ms) due to likely greater speed to response.⁸
 - i. Use a stimulus dose-titration procedure at initial treatment to establish an estimated seizure threshold (our protocol used 50% stimulus charge increments with successive restimulation).
 - ii. If first seizure shows inadequate EEG seizure morphology or duration, administer a second stimulus at a further 50% increment in stimulus charge during the first session. Administer additional anesthetic and relaxant if needed. Wait for 1–2 minutes if additional anesthetic is used.
 - iii. Stimulus for further sessions should be delivered at 2 additional 50% increments in stimulus charge, with further increases at successive treatments as needed for inadequate seizures or poor clinical response.
 - iv. Monitor closely for vital sign abnormalities immediately after treatment. Patients with concurrent steroid treatments may require bolus steroids after ECT.
 - f. During the index course, treat at least 3 times per week, avoiding gaps of more than 3 days to limit intertreatment regressions. In this regard, given the urgency of need for definitive response, daily ECT for the first 3 treatments should be considered if logistically feasible.
 - g. Once an adequate response is obtained, continue maintenance ECT to prevent relapse, starting weekly and tapering to every 4–6 weeks as tolerated.
 - i. Consider discontinuing ECT after 6 months without signs of recurrence.
 - j. Recommend continuous follow-up with multidisciplinary team

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.psych.2019.12.005>.

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