Seizures in a Young Woman Due to *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis With Unremarkable Imaging Evaluations:

A Proposed Treatment Algorithm

David R. Spiegel, MD; Abbey Mclean, MD; Megan Ralston, MS; Alim Osman, MS; Pavan Suryadevara, MS; Jason Bard, BS; Trevor Schlecht, MS; and Jake Whitley, BS

The most common and first described autoimmune encephalitis syndrome is anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.[1] An underlying tumor is found in 25%–40% of patients and corresponds to ovarian teratoma (OT) in 90% of these tumors[2]; however, negative imaging results can occur.[3] Thus, we present a patient with this scenario and the dilemmas involved in treatment.

Case Report

The patient was a 27-year-old Black woman, with no prior medical, psychiatric, or substance misuse history, who presented to the emergency department (ED) following an unwitnessed seizure at home and a recurrence in the ED. Although the patient was unable to provide a history due to altered mental status, her mother reported that she was in her usual state of health until 3 days prior to admission when she complained of fatigue, dizziness, and a worsening headache over the ensuing days prior to presentation. Due to confusion and agitation, our team was consulted.

On examination, the patient was oriented × 1, endorsed no hallucinations or delusions, and scored positive for delirium on the Confusion Assessment Method.[7] We began olanzapine 5 mg 3 times daily with no improvement in agitation; however, she subsequently manifested orofacial dyskinesias without ictal activity on electroencephalogram. Shortly thereafter, the patient was intubated and transferred to the intensive care unit wherein dexmedetomidine and propofol were initiated (Figure 1[4–6] and Table 1).

On hospital day 71, the patient was discharged with the following medications: carbamazepine 200 mg twice daily, lacosamide 300 mg twice daily, and valproate 875 mg twice daily. Three weeks later, the patient had an outpatient neurology follow-up. At that time, she reported continued apraxia and short-term memory impairment though without further seizures on carbamazepine monotherapy. After this visit, the patient was lost to follow-up.

Discussion

Anti-NMDAR encephalitis is characterized by a constellation of neurologic and psychiatric features along with positive NMDAR antibody. Given that about 80% of patients with anti-NMDAR encephalitis are women, and up to 60% have a concomitant tumor, typically OT, tumor screening is imperative.[8] As there is no serum tumor marker for OT, recommended screening includes ultrasound and pelvic computed tomography and magnetic resonance imaging.[9] The best management of women with anti-NMDAR encephalitis and high clinical probability of OT but negative imaging studies is unclear. The options include immunotherapy without further search for OT, repetitive screening for OT (eg, every 6 months), explorative laparoscopy, and blind oophorectomy.[9] Notably, while exploratory laparoscopies and blind oophorectomies demonstrate OT in some patients, no tumor may be detected in others.[1]

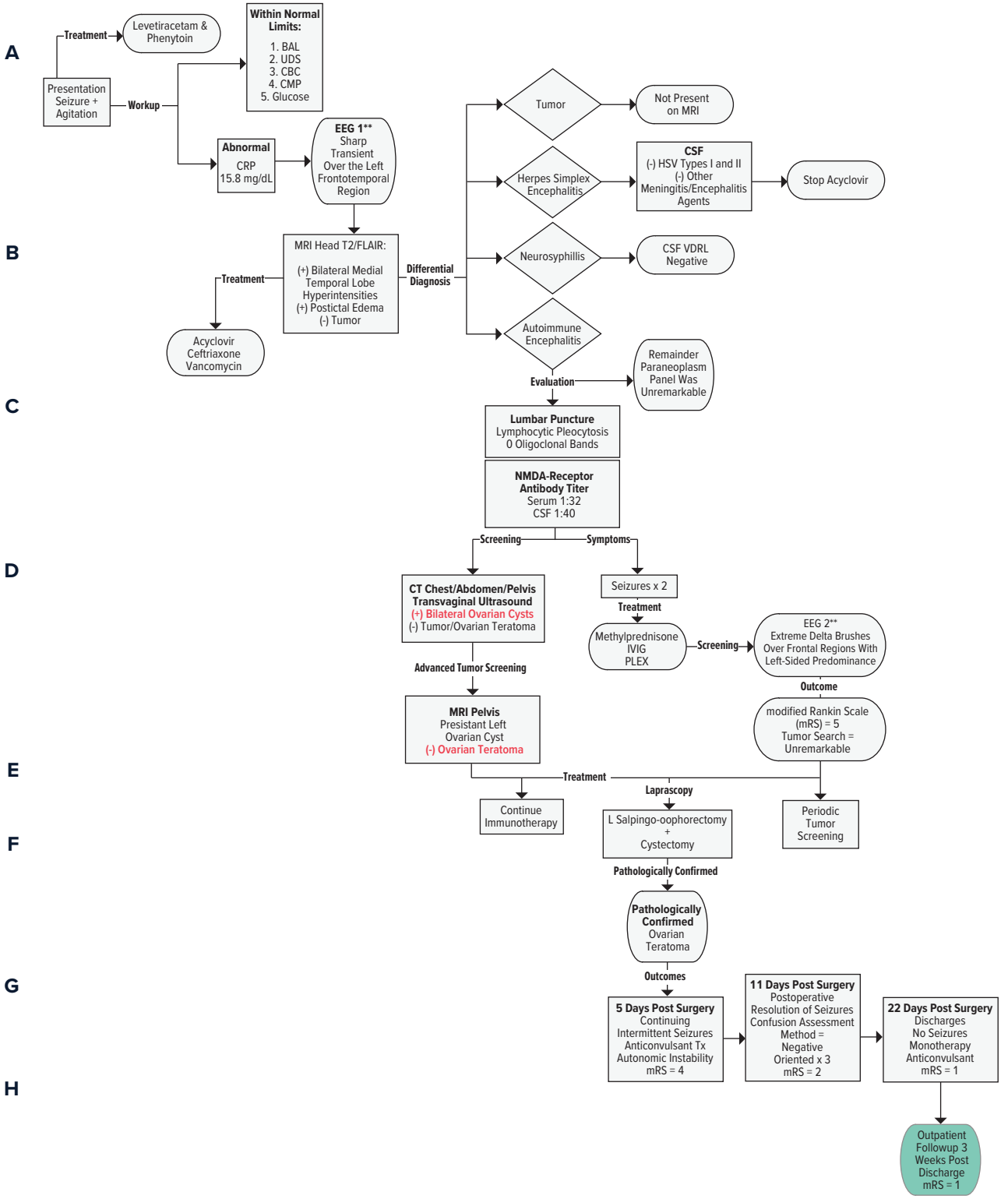
The detection of an underlying tumor is dependent of age (≥ 18 years), sex (female), and ethnic background (Black women).[1] Known independent predictors of poor outcome include the higher severity of anti-NMDAR encephalitis and delayed initiation of both immunotherapy and tumor removal.[10] Furthermore, patients whose tumors are resected have a better outcome (modified Rankin Scale score ≤ 2)[11] and decreased risk of relapse compared with those patients whose tumor was not removed.[1,8] Based on the above, our patient's demographics and risk factors were predictive of a poor outcome without further treatment. Thus, the gynecology service decided to proceed with a left salpingo-oopherectomy (see Figure 1/Table 1 algorithm steps E and F).

Conclusion

Cases of "microteratomas" not previously identified by any imaging modalities, as in our patient, have been reported.[9,12,13] Fortunately, unilateral

Figure 1.

Evaluation and Treatment of the Patient's Symptoms of Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis



Abbreviations: BAL = blood alcohol level, CBC = complete blood count, CMP = complete metabolic profile, CRP = C-reactive protein, CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalogram, FLAIR = fluid-attenuated inversion recovery, HSV = herpes simplex virus, IVIg = intravenous immunoglobulin, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, mRS = Modified Rankin Scale, NMDA = N-methyl-d-aspartate, NMDAR-e = NMDA receptor encephalitis, OT = ovarian teratoma, PLEX = plasmapheresis, POD = postoperative day, Tx = treatment, UDS = urine drug screen, VDRL = venereal disease research laboratory.
Symbols: (+) present, (-) not present.

Table 1.

Description of Algorithm Steps in the Evaluation and Treatment of the Patient

Algorithm Step	Evaluation/Treatment	Results and Treatment for Our Patient	Considerations
A	Altered mental status with subsequent generalized tonic-clonic seizure[4]	Hospital Day 1	Metabolic, toxic, infectious etiologies of seizure and altered mental status ruled out
	Physical examination/vital signs/tests: BAL, UDS, CBC, CMP/STAT glucose, CRP, thyroid function tests (including antithyroid peroxidase), severe acute respiratory syndrome coronavirus-2 polymerase chain reaction, urinalysis, chest x-ray, vitamin B_{12}, folate, thiamine	Results unremarkable, except for CRP: 15.8 mg/dL	
	Anticonvulsant therapy	Began levetericetam and phenytoin	
	Meningitis/encephalitis prophylaxis	Began acyclovir, ceftriaxone, vancomycin	
B	Neurologic evaluation:	Hospital Day 2	Differential diagnosis for etiology of seizure: (1) primary cerebral tumor, (2) HSE/neurosyphilis/other infectious, (3) autoimmune encephalitis
	EEG	Remarkable for sharp transients over left frontotemporal regions	
	MRI of the head	Increased hyperintensities in bilateral medial temporal lobes on T2/FLAIR, initially concerning for herpes simplex encephalitis	Options a–b: essentially ruled out, acyclovir discontinued
	CSF analysis	Hospital Day 3 Unremarkable for VDRL, HSV I and II, West Nile virus, Lyme disease, other infectious etiologies of meningitis, and encephalitis	
C	Autoimmune encephalitis evaluation:	Hospital Day 1–3	Remainder of serum/CSF paraneoplastic panel unremarkable
	Serum antithyroid peroxidase, thyroglobulin antibody, complement 3 and 4, double-stranded deoxyribonucleic acid antibody, antinuclear antibodies, antineuronal antibody	Results unremarkable	
	Serum NMDA antibody	Titer = 1:32	NMDA receptor antibody encephalitis working etiology of both seizures and altered mental status
	CSF analysis	Mild lymphocytic pleocytosis, normal protein and glucose, no oligoclonal bands detected	
	CSF NMDAR antibody	Titer = 1:40 (result returned on hospital day 25)	
D		Hospital Day 14	NMDA receptor antibody encephalitis continues to progress
	Tumor screening: CT chest, abdomen, pelvis; transvaginal ultrasound	Remarkable solely for bilateral ovarian cysts (ie, no evidence of neoplasms)	
	Advanced tumor screening (MRI pelvis)	Hospital Day 30 (-) ovarian teratoma	
	Evolution of anti-NMDA receptor encephalitis: additional EEG	Hospital Day 33 Extreme delta brush over frontal regions with left-sided predominance	
	Begin immunotherapy: methylprednisone 1 g daily x 5 days, subsequent IVIg and PLEX for 9 days	Hospital Day 30–44 Developed 2 additional seizures, continued to require intensive care/mechanical ventilation, mRS = 5	
E	Options for Further Treatment (1) immunotherapy without further search for ovarian teratoma, (2) repetitive screening for ovarian teratoma (eg, every 6 months), and/or (3) explorative laparoscopy and/or blind oophorectomy	Hospital Day 46 Diagnostic laparoscopy	High clinical probability of ovarian teratoma but imaging negative
F	Diagnostic laparoscopy Unilateral/left salpingo-oophorectomy with cystectomy	Hospital Day 46 Did not demonstrate ovarian teratoma Ovarian teratoma pathologically confirmed (result returned hospital day 54)	Consent obtained from next of kin Left-sided procedure chosen in attempt to spare fertility[5] with persistent left ovarian cyst
G	Status post left salpingo-oophorectomy with cystectomy	Postoperative Day 5 mRS = 4 Postoperative Day 11 No longer demonstrated ictal activity, delirium resolved, mRS = 2 Postoperative Day 22 Patient was discharged, symptoms of anti-NMDAR-e were no longer present; discharge medications were carbamazepine, lacosamide, and valproate	Residual short-term memory deficits were present
H	3-week neurology outpatient follow-up	Asymptomatic except for cognitive deficits, MMSE[26] score = 25	MMSE remarkable for short-term memory deficits (0/3 on recall)

Abbreviations: BAL = blood alcohol level, CBC = complete blood count, CMP = complete metabolic profile, CRP = C-reactive protein, CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalogram, FLAIR = fluid-attenuated inversion recovery, HSV = herpes simplex virus, IVIg = intravenous immunoglobulin, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, mRS = Modified Rankin Scale, NMDA = *N*-methyl-D-aspartate, NMDAR-e = NMDA receptor encephalitis, OT = ovarian teratoma, PLEX = plasmapheresis, POD = postoperative day, Tx = treatment, UDS = urine drug screen, VDRL = venereal disease research laboratory.
Symbols: (+) present, (-) not present.

salpingo-oopherectomy identified an OT in our patient; however, in cases in which imaging fails to identify a teratoma, some investigators advocate for bilateral oophorectomy, especially if patients do not respond to immunotherapy.[1,14] While the latter approach may be the best opportunity for survival, we advocate for further research in potential fertility-sparing options in these cases.

Article Information

Published Online: January 11, 2024. https://doi.org/10.4088/PCC.23cr03510

Prim Care Companion CNS Disord 2024;26(1):23cr03510

Submitted: February 13, 2023; accepted June 15, 2023.

To Cite: Spiegel DR, Mclean A, Ralston M. Seizures in a young woman due to *N*-methyl-D-aspartate receptor antibody encephalitis with unremarkable imaging evaluations: a proposed treatment algorithm. *Prim Care Companion CNS Disord.* 2024;26(1):23cr03510.

Author Affiliations: Department of Psychiatry and Behavioral Sciences, Eastern Virginia Medical School, Norfolk, Virginia (all authors).

Corresponding Author: David R. Spiegel, MD, Eastern Virginia Medical School, Department of Psychiatry and Behavior Sciences, 825 Fairfax Avenue, Norfolk, Virginia 23507 (spiegedr@evms.edu).

Relevant Financial Relationships: Dr Spiegel is in the speaker's bureau for Allergen, Alkermes, Otsuka, and IntraCellular but has no conflict of interest in preparation of this manuscript. The remainder of the authors have no disclaimer/conflict of interest to report.

Funding/Support: None.

Patient Consent: Consent was verbally received from the patient to publish the case report, and information has been de-identified to protect anonymity.

References

1. Linnoila JJ, Rosenfeld MR, Dalmau J. Neuronal surface antibody-mediated autoimmune encephalitis. *Semin Neurol*. 2014;34(4):458–466.
2. Nougaret S, Cunha TM. From ovary to brain: Specific imaging features of ovarian teratomas associated with anti-*N*–methyl-D-aspartate receptor encephalitis. *Diagn Interv Imaging*. 2021;102(7–8):403–404.
3. Vargas RJ, Farid H, Goldenson RP, et al. Ovarian teratomas and anti–*N*-methyl-D-aspartate receptor encephalitis: why sonography first? *J Ultrasound Med*. 2016;35(4):852–854.
4. Steriade C, Britton J, Dale RC, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. *Epilepsia*. 2020;61(7):1341–1351.
5. Flannery P, Yang I, Keyvani M, et al. Acute psychosis due to anti- *N*–methyl-D-aspartate receptor receptor encephalitis following COVID-19 vaccination: a case report. *Front Neurol*. 2021;12:764197.
6. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
7. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the Confusion Assessment Method: a new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941–948.
8. Dai Y, Zhang J, Ren H, et al. Surgical outcomes in patients with anti–*N*-methyl-D-aspartate receptor encephalitis with ovarian teratoma. *Am J Obstet Gynecol*. 2019;221(5):485.e1–485.e10.
9. Cirkel C, Cirkel A, Royl G, et al. On the quest for hidden ovarian teratomas in therapy-refractory anti-NMDA receptor encephalitis: a case report. *Neurol Res Pract*. 2022;4(1):15.
10. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12(2):157–165.
11. Rankin J. Cerebral vascular accidents in patients over the age of 60, II: prognosis. *Scott Med J*. 1957;2(5):200–215.
12. Maramattom BV, Jacob A. *N*–methyl-D-aspartate receptor encephalitis: a new addition to the spectrum of autoimmune encephalitis. *Ann Indian Acad Neurol*. 2011;14(3):153–157.
13. Cleverly K, Gambadauro P, Navaratnarajah R. Paraneoplastic anti- *N*–methyl-D-aspartate receptor encephalitis: have you checked the ovaries? *Acta Obstet Gynecol Scand*. 2014;93(7):712–715.
14. Bartolini L. Practice current: how do you treat anti-NMDA receptor encephalitis? *Neurol Clin Pract*. 2016;6(1):69–72.