A Case of Ovarian Teratoma–Induced *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis Presenting With Psychosis and Catatonia, Progressing to the Minimally Conscious State and Successfully Treated With Adjunctive Zolpidem

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The identification of *N*-methyl-D-aspartate receptor (NMDAR)–antibody encephalitis (AE) recognized that some patients with rapidly progressive psychiatric/cognitive symptoms, seizures, abnormal movements, autonomic dysfunction, hypoventilation, and coma of unknown cause had an autoimmune disease. Tumors, usually ovarian teratoma (OT), are a known trigger of NMDAR autoimmunity.[1,2]

Pleomorphic in nature, psychosis and acute behavioral changes (ie, agitation, disorganized behavior) are the most frequently reported psychiatric manifestations of NMDAR-AE, although depressed level of consciousness and catatonia are also common.[3] Importantly, about 80% of patients improve with immunotherapy and, if needed, tumor removal.[2]

We present a young woman who developed acute-onset behavioral changes accompanied by psychosis and catatonia, ultimately determined to have NMDAR-AE. Despite prompt treatment, symptoms progressed, including development of a minimally conscious state (MCS).

Case Report

Our patient, a 21-year-old woman with no prior psychiatric or medical history, presented to the emergency department due to "behavioral outbursts." Four days prior to admission, the patient developed auditory hallucinations/delusions, disorganized speech, and agitation but had limited recall of autobiographical events over the preceding 2 weeks. Physical examination, including vital signs, was unremarkable. The patient denied alcohol and illicit substance use, and blood alcohol level/urine drug screen were both negative. We were consulted on admission to the medical unit.

Our patient's longitudinal course while hospitalized is summarized in Table 1,[4–8] including symptoms, evaluation, treatment, and procedures. The transvaginal ultrasound results are provided in Figure 1. Ultimately confirmed by cerebrospinal fluid antibody positivity, our patient was treated for NMDAR-AE, initially with tumor excision and, subsequently, intravenous immunoglobulin (IVIg)/plasmapheresis. Eleven days after surgery, dexmedetomidine/other sedation was discontinued, yet our patient remained in a stupor for 6 additional days. Forthwith, all acute symptoms abated, with the patient developing the MCS. The latter ultimately resolved after 8 days of zolpidem treatment.

In the post-acute phase, our patient's Montreal Cognitive Assessment[7] score was 25 (5 points lost in short-term memory recall), and on hospital day 50, she was transferred to a rehabilitation facility, without immunotherapy but maintained on zolpidem.

Discussion

The frequency of NMDAR-AE in cases with OT involvement ranges from 30% to 60%.[9] Furthermore, while autoimmune encephalitis is increasingly considered in patients with psychiatric symptoms, as it is potentially treatable with immunotherapy, autoimmune encephalitis is much less common than primary psychiatric disease, for instance, accounting for less than 1% of first episode of psychosis.[10]

At our initial evaluation, our patient's illness had rapidly progressed to unresponsiveness with catatonic features. In addition, her acute onset (4 days) of psychosis with lack of prodromal symptoms of schizophrenia and lack of personal and family psychiatric/substance use history prompted our evaluation for possible nonpsychiatric/autoimmune etiologies.[11] Despite uncovering our patient's OT, female patients with OT-triggered NMDAR-AE reportedly account for only 1.17%–3.07% of OT patients.[12,13]

While our patient's phenotype, save prodromal flu-like symptoms, was consistent with NMDAR-AE, her paraclinical features, save mild pleocytosis, were unremarkable.[2] Interestingly, during its post-acute phase, neuropsychological dysfunction is experienced by most patients recovering from NMDAR-AE. Commonly observed deficits occur in the domains of episodic memory (as in our patient) and executive functioning.[14]

Finally, after treatment with IVIg/plasmapheresis, her unresponsiveness only progressed to the MCS, albeit without catatonic features. Yet, in the context of post-acute NMDAR-AE, zolpidem treatment for MCS was effective. In brief, zolpidem, a selective agonist at the ω_1 subtype receptor of γ-aminobutyric acid–A receptor complex, has been posited to potentially aid in recovery of MCS by restoring normal function in frontocortico-striatopallidal-thalamocortical circuitry vis-a-vis inhibiting areas that are inhibitory.[15,16]

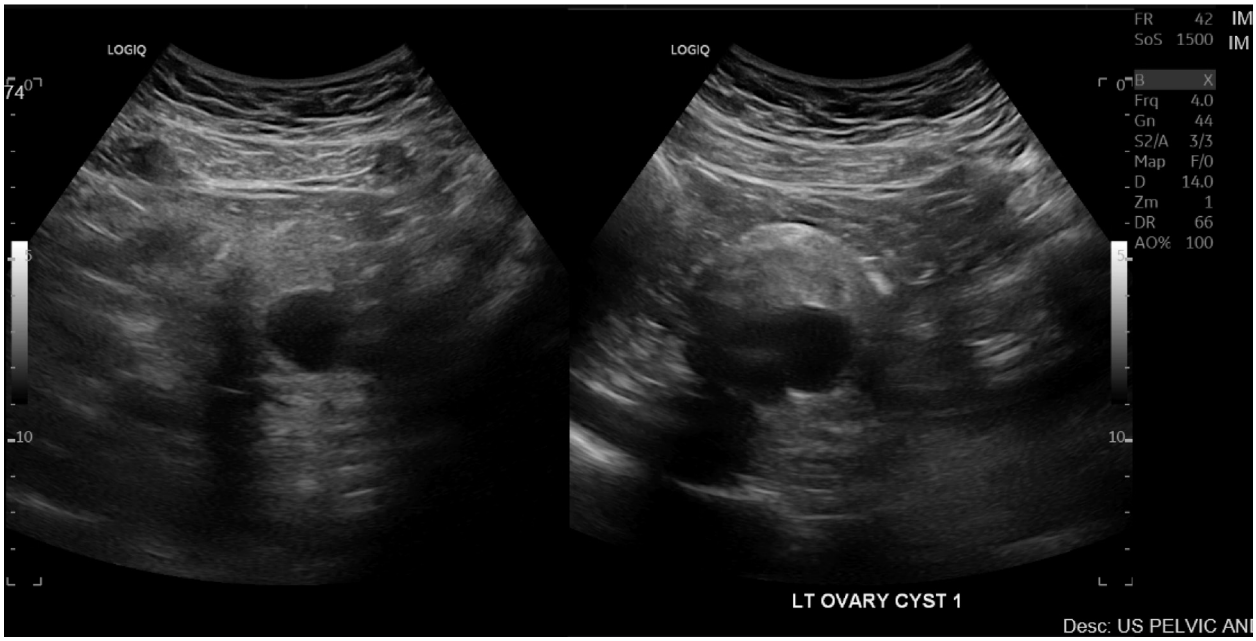
In conclusion, we believe our case emphasizes the importance for clinicians to consider (1) NMDAR-AE for

Table 1. Longitudinal Course of the Patient's Hospitalization

Hospitalization Day Number	Symptoms	Treatment	Outcome
Admission	Delusions, auditory hallucinations, agitation for 4 preceding days		CBC, CMP, CXR, Ua: WNL; B-HCG: (–); SARS-CoV-2 PCR (–); BAL/UDS: (–); folate, thiamine, vitamin B_{12}, serum angiotensin converting enzyme: WNL
1	Onset of catatonia: immobility/stupor, mutism, staring, with additional symptoms—BFCRS[4] score = 23; Later in day, onset of seizures	CT head Transvaginal ultrasound Lumbar puncture Clonazapam and valproic acid began	No acute intracranial abnormalities Large left mature ovarian dermoid cyst, uterus and right ovary are within normal limits (see Figure 1) CSF glucose: 63 mg/dL; CSF protein: 20.7 mg/dL; CSF WBC = 22/cumm: lymphocytes: 97%; albumin: 11 mg/dL (7–29 mg/dL); ACE: < 1.5 u/L IgG index: 0.8; myelin basic protein 1.2 ng/mL; oligoclonal bands = 3 CSF gram stain/fungal culture, meningitis panel: no demonstration of organisms CSF HSV 1/2 PCR, VDRL, lyme DNA PCR: not detected
3	BFCRS = 23	CT abdomen/pelvis MRI head S/P left salpingo-oophorectomy	(+) Probable left ovarian teratoma Tiny focus of gliotic change in right midcentrum ovale and right parietal lobe; (–) evidence of medial temporal lobe hyperintensities Subsequent intubation
4	Admitted to intensive care units for airway protection, RASS[5] score = 4	**Dexmedetomidine initiated**	
5	RASS score = –4	MRI head	Extubated to noninvasive ventilation No changes from prior MRI. No new parenchymal signal abnormalities. No abnormal signal in the mesial temporal lobes or within the cortex
6	Orofacial dyskinesias, choreoathetoid movements of the arms	EEG	Slowing of the background was consistent with nonspecific encephalopathy There was no EEG evidence for active epileptogenic issues
8	RASS score = –4; abnormal movements continue; onset of dysautonomia	Intravenous immunoglobulin treatments begins	Patient reintubated
11	Day 8 symptoms continue		Dysautonomia increasing in severity
12	Day 8 symptoms continue	Intravenous immunoglobulin treatments end	No change in symptoms
13	Day 8 symptoms continue	Plasmapheresis is initiated	CSF anti-NMDA receptor antibody ratio returns: 1:160
14	Day 8 symptoms continue	**Dexmedetomidine discontinued**	No change in symptoms
20	CRS-r[6] score = 15: MCS	Final plasmapheresis treatment	Tracheostomy placed; no further involuntary movements noted; dysautonomia ceased
25	CRS-r = 15	Zolpidem 5 mg/d	No change in MCS
27	CRS-r score = 16	Zolpidem 5 mg/d	MCS Improves
28	CRS-r score = 20	Zolpidem 5 mg 4 times daily	MCS improves
33	CRS-r score = 23	Zolpidem 5 mg 4 times daily	MCS resolves; No reemergence of catatonia or psychosis
39	Residual cognitive symptoms: MoCA[7] score = 25, losing all 5 points on short term memory; CAM[8]: negative	MRI head	Previously noted right frontoparietal white matter lesions are either smaller or unchanged, as described, nonspecific. No new lesions are seen. The brain otherwise looks normal
50	MoCA score = 25; BFCRS score = 2; CAM: negative	Patient discharged on zolpidem 5 mg 4 times daily	Patient discharged from the hospital

Abbreviations: ACE = angiotensin-converting enzyme, BAL/UDS = blood alcohol level/urine drug screen, BFCRS = Bush- Francis Catatonia Rating Scale, B-HCG = β-human chorionic gonadotropin, CAM = Confusion Assessment Method, CBC = complete blood cell count, CMP = complete metabolic profile, CRS-r = Coma Recovery Scale-Revised, CSF = cerebrospinal fluid, CT = computed tomography, CXR = chest x-ray, EEG = electroencephalogram, HSV = herpes simplex virus, IgG = immunoglobulin G, MCS = minimally conscious state, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, NMDA = *N*-methyl-D-aspartate, RASS = Richmond Agitation Sedation Scale, SARS-CoV-2 PCR = severe acute respiratory syndrome coronavirus 2 polymerase chain reaction, S/P = status post, Ua = urinalysis, VDRL = Venereal Disease Research Laboratory, WBC = white blood cells, WNL = within normal limits.
Symbols: (+) = present, (–) = not present.

Figure 1. Transvaginal Ultrasound: Left Ovarian Teratoma



those patients, especially female, with an acute and rapidly progressive pleomorphic psychiatric presentation and (2) the potential effect zolpidem can have on patients with MCS.

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