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Clinical Observations

Clinically Significant Response to Zolpidem in Disorders of Consciousness Secondary to Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis in a Teenager: A Case Report

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ABSTRACT

BACKGROUND: Anti-*N*-methyl-D-aspartate receptor encephalitis has been associated with a prolonged neuropsychiatric phase that may last for months to years. **PATIENT:** We report the case of a 16-year-old girl who was diagnosed with anti-*N*-methyl-D-aspartate receptor encephalitis resulting from left ovarian mature teratoma 2 weeks after presentation with psychosis. Following tumor removal and immunotherapy, recovery from a minimally conscious state was accelerated significantly by zolpidem that was used for her sleep disturbance. Our patient was discharged home 8 weeks after admission with marked improvement in her neurological function. Zolpidem has been reported to improve arousal in disorders of consciousness but there are no previous reports of its benefit among patients with anti-*N*-methyl-D-aspartate receptor encephalitis. **CONCLUSION:** Zolpidem would be a reasonable consideration as an adjunctive treatment in anti-*N*-methyl-D-aspartate receptor encephalitis after tumor removal and immunotherapy to accelerate recovery and rehabilitation.

Keywords: anti-*N*-methyl-D-aspartate receptor encephalitis, minimally conscious state, zolpidem, disorders of consciousness, neurorehabilitation

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Introduction

Since its first description in 2005, anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis has been reported increasingly in the literature, although its exact incidence is unknown.[1] A recently published California Encephalitis Project report found that NMDA encephalitis is a more common cause of encephalitis among patients younger than 30 years of age than individual viruses such as herpes simplex virus-1, West Nile virus, varicella zoster virus, and enterovirus encephalitides.[2] Antibodies against the NMDA receptor are associated with the clinical syndrome of a nonspecific prodrome of headache and upper respiratory tract infection typically followed 2 weeks later by the onset of psychiatric symptoms and neurological manifestations including seizures and movement disorders. The initial presentation leads to a stage of decreased responsiveness alternating with agitation. The clinical symptoms often respond to immunotherapy involving plasma exchange, intravenous immunoglobulin therapy, and/or steroids concomitant with identification and removal of a tumor, usually an ovarian teratoma. Previous case series and reviews have documented a prolonged hospitalization course both for the acute illness followed by several months of physical and behavioral rehabilitation.[1,3,4] Zolpidem is a short-acting nonbenzodiazepine hypnotic of imidazopyridine class that binds to ω_1 type of gamma amino butyric acid ($GABA_A$) receptor at the same location as benzodiazepines and is effective in initiating sleep. We report the case of a 16-year-old girl with anti-NMDA receptor encephalitis who presented with acute psychosis, followed by a prolonged phase of minimally conscious state even after tumor removal and immunotherapy who improved serendipitously after addition of zolpidem for sleep.

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Case report

Our patient is a 16-year-old, right-handed girl with no prior illnesses who was evaluated for headache and low-grade fever and was suspected to have a viral infection. Four days before admission, she began to exhibit bizarre behavior. She seemed anxious and was perseverative in her speech and thought content. In the subsequent days, she became increasingly agitated, with episodes of auditory hallucinations and combativeness toward her parents. At another facility, a computed tomography study of the head and a urine drug screen were negative. Her parents noted that her symptoms waxed and waned through the day with worsening of symptoms toward the evening. On the day of admission, she exhibited combative behavior and was evaluated by neurology and psychiatry in our emergency room and given haloperidol for agitation without significant benefit. A lumbar puncture showed cerebrospinal fluid pleocytosis with a total cell count of 87, nucleated cells of 73, and red blood cells of 14. Differential count on the cerebrospinal fluid revealed 96% lymphocytes, 3% monocytes, and 1% neutrophils. She was started on meningitis doses of antibiotics including vancomycin, cefotaxime, azithromycin, and acyclovir and was admitted with a presumptive diagnosis of viral encephalitis. A brain magnetic resonance imaging study with and without contrast showed an incidental Chiari I malformation, but was otherwise normal.

Cerebrospinal fluid analysis of an arbovirus panel was negative. Her cerebrospinal fluid culture was negative for bacterial growth. Polymerase chain reactions of a cerebrospinal fluid sample were negative for herpes simplex virus, varicella zoster virus, Epstein-Barr virus, enterovirus, cytomegalovirus, mycoplasma pneumoniae, parechovirus, and toxoplasmosis. A nasal swab culture for respiratory syncytial virus, human meta-pneumovirus, adenovirus, influenza, and parainfluenza viruses also was negative, as were blood and urine cultures.

Her symptoms continued to wax and wane, fluctuating between agitation and catatonia with worsening symptoms toward the evening that were treated unsuccessfully with haloperidol. She exhibited autonomic instability with fluctuating blood pressure, urinary incontinence, tachycardia, and fever. On day 5 of hospitalization, she required transfer to intensive care unit when she became comatose. A repeat brain magnetic resonance imaging scan revealed no new changes. An electroencephalograph showed generalized slow waves indicative of diffuse cerebral dysfunction without epileptiform discharges. With the infectious workup uninformative, additional testing centered on a possible paraneoplastic process. A computed tomography scan of her chest, abdomen, and pelvis revealed a left adnexal mass with fat and calcification, and the lesion was removed 2 days later. Cytology of the mass showed a mature ovarian teratoma. A repeat cerebrospinal fluid study showed a strongly positive NMDA antibody titer of 1:1280 (Mayo Clinic Laboratories, Rochester, MN), whereas the rest of the CSF paraneoplastic panel was negative. After tumor removal (hospitalization day 8), she underwent immunotherapy with seven cycles of plasmapheresis (hospitalization days 8 to 22), followed by intravenous immunoglobulin (2 g/kg) on hospitalization day 23. She was given a course of high-dose steroids on hospitalization days 12 through 16 (methylprednisolone 1 g for 5 days followed by a 1-month taper).

She was transferred after immunotherapy to the neurology floor on hospitalization day 27 for behavioral and neurorehabilitation. Her rehabilitation course was limited by periods of lucidity that lasted for about 20 minutes to 1 hour. She continued to exhibit autonomic instability and orolinguofacial dyskinesias. A serum NMDA titer sent after tumor removal and immunotherapy was negative. As part of intensive inpatient neurorehabilitation service, she received twice-daily physical, occupational, and speech therapy. To optimize her sleep–wake cycle for participation in therapy services, we introduced zolpidem 10 mg at bedtime on hospitalization day 42, after which her parents noticed a sudden improvement in duration of lucidity. After receiving the bedtime dose of zolpidem, she would engage in age-appropriate conversations and exhibit insight into her condition. These periods of lucidity would last for 2 to 4 hours, after which she would become confused and then stuporous. Her parents videotaped how she behaved before and after taking zolpidem. Our review of these videos prompted a trial of the medication on hospitalization day 45 during daytime therapy hours with resultant significant improvement in level of function. Her Functional Independence Measurement for Children score (WeeFIM) was 18 to 19 during her course in the pediatric intensive care unit and remained at that minimal level at the time of transfer to the neurology floor. WeeFIM assesses functional independence in 18 tasks encompassing self-care, mobility, and cognition. Performance on each item is assigned one of seven levels of an ordinal scale that represents range of function from complete and modified independence (levels 7 and 6) to modified and complete dependence (levels 5 to 1). The minimum possible total rating is 18 (total dependence in all skills); the maximum possible rating is 126 (complete independence in all skills). Her WeeFIM scores rose to 87 within 1 week after adding zolpidem. She was discharged home 55 days after admission, months ahead of her initial anticipated discharge date. Her WeeFIM score was 98 at discharge. Zolpidem was weaned 3 weeks after discharge. Her WeeFIM score at the conclusion of physical therapy was 123 at the 2-month follow-up (Figure, Table). Six months after discharge, she demonstrated near complete recovery.

Discussion

NMDA receptor antibody encephalitis has been shown to be mechanistically caused by antibody-mediated internalization of NMDA receptor and subsequent alteration of synaptic plasticity. Disorders of consciousness are a common manifestation of anti-NMDA receptor antibody encephalitis. In a recently published article on treatment and prognostic factors in anti-NMDA receptor encephalitis, eight symptom groups were categorized, including loss of consciousness and disorders of consciousness.[4]

Zolpidem is a highly selective nonbenzodiazepine GABA agonist acting on the ω-1 site on $GABA_A$ receptor. Zolpidem has been studied previously in patients with disorders of consciousness ranging from minimally conscious state to vegetative state and coma.[5-9] In a double-blind, placebo-controlled crossover study involving 15 adult patients severe traumatic brain injury, one patient in a vegetative showed clinically significant improvement in the JFK Coma Recovery Scale Revised score after administration of 10 mg of zolpidem.[10] Similarly, in a small study of three pediatric

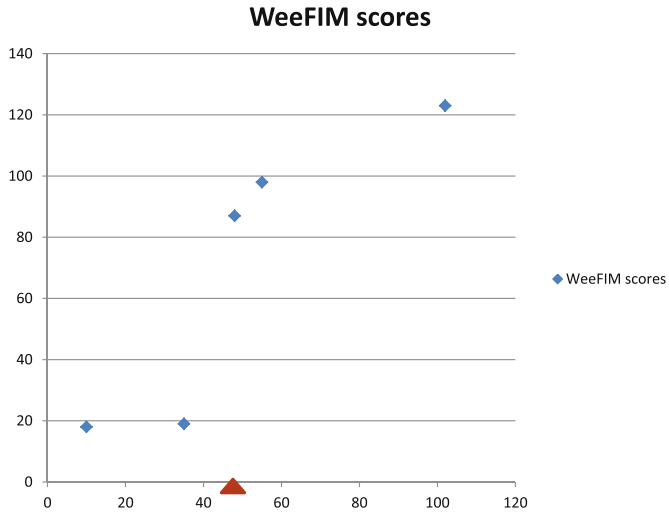

FIGURE.
Graphical representation of functional independence as measured by Functional Independence Measurement for Children (WeeFIM) scores during various stages of clinical recovery following immunotherapy and tumor removal. Minimum possible score is 18 (complete dependence on all activities) and maximum possible score is 126 (complete independence). Closed arrowhead represents daytime initiation of zolpidem on day of hospitalization 45. (The color version of this figure is available in the online edition.)

TABLE.
Shows the timeline of important events during hospitalization

Day of Hospitalization	Events
5	Transfer to intensive care unit
8	Tumor removal, plasma exchange, high-dose steroids
23	Intravenous immunoglobulin
27	Transfer to neurology floor
42	Zolpidem 10 mg at bedtime
45	Zolpidem 10 mg in morning
55	Discharge home

patients in persistent vegetative state resulting from hypoxic ischemic injury and motor vehicle accident, zolpidem treatment resulted in transient improvement in arousal and in the Rancho Levels of Cognitive Functioning Scale.[11]

There are no previous reports of clinically significant beneficial effect of zolpidem in a case of NMDA receptor antibody encephalitis. The exact mechanism of action of zolpidem in NMDA receptor antibody encephalitis is largely unknown.[11-14] A putative mechanism of $GABA_A$ subunit-mediated transient desynchronization of elevated low-frequency oscillations on magnetoencephalography scan was proposed in a single patient with stroke who showed transient cognitive recovery after administration of zolpidem.[15]

NMDA receptor encephalitis is a syndrome that typically requires months of hospitalization during the acute phase, followed by an equally long time devoted to physical, cognitive, and behavioral rehabilitation, often in an inpatient setting or an outpatient day treatment setting.[4] Given the potential reduction in the length of hospital stay during the recovery phase of this syndrome among responders to zolpidem, a trial of zolpidem would be reasonable to consider as an adjunct treatment in similar patients.

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