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A Rare Case of Anti-N-methyl-D-aspartate Receptor Encephalitis in an Adolescent

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Chief Complaint and Presenting Problem

M. is a 16-year-old adolescent girl in the eleventh grade referred to the psychiatric emergency department (ED) for increased agitation and bizarre behavior. The patient reported being ''stressed and having panic attacks.''

M. carries diagnoses of attention deficit/hyperactivity disorder (ADHD), primarily inattentive type, learning disorder not otherwise specified, and anxiety disorder not otherwise specified.

History of Present Illness

M. had been in stable weekly psychotherapy and treated for her ADHD with dexmethylphenidate extended release 10 mg in the morning, dexmethylphenidate immediate release 5 mg in the evening, and atomoxetine 60 mg daily. She had been doing reasonably well. One month prior to her referral to the ED she complained of headaches and occasional dizziness without other symptoms. Review of systems at that time revealed no additional medical or psychiatric symptoms. It was suggested that she discontinue the dexmethylphenidate to assess whether this may have been a contributing factor.

According to mother, M. had experienced episodes of confusion and agitation for one week prior to referral to the ED with onset when the family was in Europe on a vacation. M. first complained of pain and ringing in her ear, and these complaints evolved into symptoms of a panic attack later that day. During this episode, M. screamed for help and experienced perceptual disturbances, reportedly feeling like her facial features had been moved to different parts of her face. She also complained of significant anxiety and that noises seemed louder than normal. M. appeared quite fearful, and mother gave her diazepam 2.5 mg with good effect at that time. She seemed to recover the following day. She was able to recall the episode, saying that she ''freaked out'' and was able to return to the United States by plane without incident.

One day after her returning, M. experienced another episode, which included screaming and irrational thoughts. For example, M. felt that she could not leave her home because the keys would not work and worried that if she did leave, she would not be able to get back inside. M. also exhibited elated mood, excessive energy, and grandiose thoughts. Her mother found her dancing without music and making statements such as ''life is great.'' The episode lasted for several hours, and then abated with a return to near baseline functioning.

M.'s mother grew increasingly concerned about the recent and drastic change in her daughter's mental status and brought her to see her psychiatrist the following day. On exam, M. was noted to be calm, cooperative, organized in her thought content, and linear in her thought process. She described significant anxiety occurring in the context of multiple psychosocial stressors, including her upcoming college entrance exams and college applications. She also described sleep disturbance (jet lag), headaches, and some derealization phenomena, in addition to physical discomfort in her ear and a feeling of being underwater when she spoke. At the time, she was taking atomoxetine 60 mg daily. She had discontinued dexmethylphenidate over the vacation. Her psychiatrist prescribed lorazepam 0.5 mg as needed for what was presumed to be anxiety and panic attacks. Atomoxetine was discontinued to ensure that it was not exacerbating her anxiety or contributing to her mood dysregulation. Lorazepam produced minimal effect on her anxiety, and M. reported feeling groggy after taking it. According to her mother's report, M. continued to experience panic attacks and fearful thoughts, including the belief that the end of the world was near and that she might die.

M. was re-evaluated by her psychiatrist the following day, and lorazepam was replaced by a standing dose of clonazepam 0.5 mg twice a day with the recommendation for continued monitoring and the hope that once her sleep schedule adjusted, her anxiety would improve. Shortly after taking her first dose of clonazepam, however, M. started screaming, stating that her leg looked distorted and that one of her arms felt bigger than the other. Panic episodes and agitation continued intermittently.

The following day M. continued to experience acute and intermittent changes in behavior and thoughts. Symptoms of mania appeared, including racing thoughts, pressured speech, and grandiosity, in addition to panic attacks and perceptual disturbances. It was also noted that at times her speech was altered and her words slurred; family members, including her mother and uncle, described her speech as sounding like ''her mouth was full of cotton.'' Episodes lasted between one and two hours and occurred approximately twice daily without clear precipitants. In between episodes, M. appeared lucid but anxious. She was evaluated again by her psychiatrist the same day, soon after an episode had occurred at home.

Upon psychiatric interview, M. again appeared lucid, and her mood was stable, but she was visibly anxious. She was able to describe some

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of her experiences during the episodes, and the symptoms appeared consistent with panic, depersonalization, and derealization. Initiation of an antipsychotic was discussed, as was hospitalization, but because she remained calm, cooperative, and in minimal distress at the time, M. returned home with instructions to discontinue the clonazepam out of concern that it was causing behavioral disinhibition. She was also instructed to sleep and to monitor symptoms. Of note, M. was evaluated by her pediatrician on the same day and was found to have an ear infection treated with topical antibiotics.

M. awoke the following morning with an episode of screaming that lasted for approximately 90 minutes and was characterized by persistent fears of dying and depersonalization. Her mother described her as disorganized in her thought and reporting bizarre ideas, which included being able to travel in time. Aripiprazole 2 mg was started, and lorazepam 1 mg was restarted as needed. The remainder of the day was relatively uneventful. The plan was to continue monitoring and to titrate aripiprazole as tolerated.

One week after the initial episode in Europe, M. again awoke agitated but insisted on going to school, as it was the first day back from vacation. When her mother tried to convince her to stay home and recover, M. attempted to force her way out of the house. Emergency medical services were called, and M. was brought to the psychiatric emergency department.

On arrival at the emergency department, M. was noted to be tachycardic (heart rate in 130s), extremely anxious, agitated and screaming, and internally preoccupied. She received diphenhydramine 50 mg intramuscular for agitation in the emergency department. Initial routine blood work, toxicology screen, and magnetic resonance imaging [(MRI); non-contrast)] performed in the emergency department were found to be within normal limits. M. was admitted to the inpatient adolescent psychiatry unit for observation and further testing.

Past Psychiatric History

M.'s first psychiatric contact occurred at age twelve when she presented with complaints of inattention and distractibility. She was struggling to keep up with schoolwork and reported feeling bored often. At that time, she was in weekly psychotherapy focused on adjusting to the sudden death of her father from a cerebrovascular accident two years prior.

Previous neuropsychological testing suggested strong overall cognitive abilities and academic achievement, with relative deficits in organization and planning. Parent rating scales and self-report supported a diagnosis of ADHD, and treatment with atomoxetine was initiated.

M. had had no previous hospitalizations, and no history of substance abuse or risk of self-harm.

Developmental History

M. was the product of an uncomplicated pregnancy and delivery. There were no delays in achieving motor, language, or cognitive milestones, although there was some early concern about attentional difficulties, and reading was initially a significant challenge.

Neuropsychological testing performed in 2012 confirmed the presence of a learning disorder not otherwise specified, mostly due to reading fluency and comprehension difficulties.

Educational History

M. has attended regular education private schools. She does not receive special education but does receive testing accommodations, including 50 percent extra time and a separate testing room free from distraction. She works with tutors after school to augment her studies.

Social History

M. was born in a northeastern metropolitan area and raised by her biological parents until her father died suddenly from a cerebral vascular accident when she was 10 years old. She has an older sister, currently in college, who is healthy and typically developing.

Medical History

M. has no chronic medical problems other than a history of exercise-induced asthma. She has no allergies to medication or the environment.

Medication History

Atomoxetine had been titrated slowly to 80 mg with fair effect, and eventually, the dose was divided to 60 mg in the morning and 25 mg in the afternoon due to tolerability issues. Later dexmethylphenidate extended release was added in the morning due to incomplete effect of atomoxetine alone. Dexmethylphenidate extended release 5 mg was added and titrated to 15 mg in the morning and 5 mg immediate release in the afternoon. This regimen was effective for several years and was maintained until the onset of the present illness.

Mental Status Exam

Mental status examination on initial presentation revealed a Caucasian adolescent female who appeared slightly disheveled and in obvious distress. Her affect alternated rapidly between periods of calm and cooperation and periods of irritability and agitation. Her mood was highly labile, and she intermittently began screaming and required significant redirection. At various points throughout the initial interviews, M. appeared alert and maintained good eye contact with no evidence of abnormal psychomotor activity. At other times, she demonstrated fluctuating orientation to time, day, place, and people. Often, M. was aware of her confusion and described significant fears about her experiences. Her speech was loud and rapid at times; at other times she spoke with significant articulation problems and slurring. Her thought process was pressured and disorganized; she responded to some questions with delayed echolalia or stereotyped phrases irrelevant to the question. Her thought content was notable for bizarre delusions, including a fear that she had killed people, and she experienced intermittent perceptual disturbances of her body parts changing shape or position. Her insight was intermittently intact, as was her judgment. At times, she was impossible to engage and seemed unaware of her surroundings.

Hospital Course

On initial evaluation in the inpatient unit, M. appeared sedated and stated that she felt ''out of place.'' She described perceptual disturbances, including feeling as though her mouth was on the side of her face and one ear was higher than the other. She further described a sensation that her hands were shrinking when she washed them and reported that all of these symptoms were contributing to increased anxiety and fear of death.

Throughout her first day of admission, M. experienced a waxing and waning of symptom severity, extreme mood lability ranging

from irritability and fear to elation, and changing levels of cognitive lucidity and thought disorganization. Pediatric neurology was consulted, and M. was found to have intermittent right frontotemporal slowing on a 40 minute routine electroencephalographic (EEG) recording. Given the abnormal finding on the initial EEG, M. was transferred to the neurology service for continuous EEG monitoring. A work-up for encephalitis was initiated, with a working diagnosis of limbic encephalitis. Infectious, autoimmune, rheumatologic, and paraneoplastic etiologies were all explored using tests for Lyme disease, human immunodeficiency virus (HIV), John Cummingham (JC) virus, hepatitis, ANA, antiphospholipid antibodies, double-stranded DNA antibodies, anti smith antibodies, complement C3 and C4, and anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis. Lorazepam and chlorpromazine were used as needed for continued agitation, and oxcarbamazepine was initiated for seizure prophylaxis. Empiric treatment with IV acyclovir was also initiated, but had to be discontinued after one day due to acute renal injury.

A lumbar puncture was performed, and CSF revealed a mild lymphocytic pleocytosis and oligoclonal bands. As anti-NMDA receptor encephalitis moved higher in the differential when other tests were found to be negative, M. had another MRI to look for evidence of intrathoracic, abdominal, or pelvic malignancy such as ovarian teratoma, which could generate anti-NMDA antibodies. Imaging results were all within normal limits.

M. was given a course of solumedrol followed by empiric intravenous immunoglobulin (IVIG) treatment for five days with little impact. At this point, all tests were within normal limits except for the anti-NMDA receptor antibodies, which were positive in serum (1:10 titer and a 1:20 titer) and CSF (1:5 titer), confirming the diagnosis of anti-NMDA receptor encephalitis. M. was switched from treatment with IVIG to weekly infusions of rituximab, a monoclonal antibody against the protein CD20.

M. began treatment with rituximab via a single infusion 17 days after her admission to the hospital. Over the week prior to this infusion, she had had intermittent cognitive impairment and neurological symptoms, including unusual arm movements, paucity of speech, headaches, left facial droop, inability to follow complex commands, and poor performance on the clock face task. Four days after the infusion, noticeable improvements were evident; M. appeared more lucid, oriented, and cognitively intact. Specifically, M. was oriented to person and place, was able to follow some commands, and displayed minimal dyskinetic movements. Her speech was more coherent despite being slow or slurred at times. Symptoms of agitation and psychosis were resolved by her second rituximab dose approximately one week later. At this time, M. continued to exhibit some visual spatial apraxia and was only occasionally able to correctly draw hands on a clock. Her speech was noted to be increasingly fluent, and her left facial droop improved significantly.

M. received her third dose of rituximab after another week and was discharged the next day, psychiatrically stable with minimal residual cognitive impairment. At this time, M. had intact ability to write, draw a perfect clock face, and follow complex commands. She had continued difficulty performing serial 6's, and her mild left facial droop persisted. She received her fourth dose of rituximab the following week and had fully recovered by that time.

Over the following month, M. received close neuropsychiatric follow-up and remained euthymic, sleeping well with only occasional nightmares and without any evidence of panic attacks or perceptual disturbances. She did report concerns about reduced cognitive stamina and concentration, for which she was continuing to seek neuropsychiatric treatment. M. was receiving cognitive remediation treatment with excellent results.

Summary/Case Formulation

In summary, M. is a 16-year-old adolescent girl with a history of ADHD, learning disability, and anxiety treated with atomoxetine, who presented with acute and significant changes in mental status. M. exhibited fluctuations in mental status including extremes of mood, emotional lability and bizarre thoughts. She also experienced waxing and waning of cognitive lucidity and thought disorganization. In addition, M. had intermittent neurological symptoms, including unusual arm movements, paucity of speech, headaches, left facial droop, inability to follow complex commands, and poor performance on the clock face task. Given the acute and fluctuating nature of her symptoms, an organic cause of these symptoms was strongly suspected, which led to a comprehensive medical and neurological work up. The workup confirmed that M.'s symptoms were secondary to anti-NMDA receptor encephalitis.

Anti-NMDA receptor encephalitis is an autoimmune disease, and while autoimmune diseases can be genetically linked, there is no known history of autoimmune disease in M.'s family. Although M. had a history of ADHD and anxiety, it is unlikely that her psychiatric history contributed to this presentation because the current presentation of psychiatric symptoms was secondary to anti-NMDA receptor encephalitis. Patients with anti-NMDA receptor encephalitis have been found to exhibit symptoms similar to that experienced by M, including agitated aggression, generalized anxiety, phobias, depression, psychosis, sleep disruption, and dysregulated mood with lability and disinhibition.

Given that a majority of patients with anti-NMDA receptor encephalitis exhibit psychiatric symptoms, they often present first for a psychiatric evaluation. It is therefore of importance to identify these patients early in the course of the disease so that they are treated in a timely manner.

Multi-Axial Diagnosis

Axis I:	Delirium due to anti-NMDA receptor encephalitis ADHD, predominantly inattentive presentation Specific learning disorder, with impairment with reading
Axis II:	Deferred
Axis III:	Anti NMDA receptor encephalitis Asthma
Axis IV:	Severe; hospitalization
Axis V:	Current Global Assessment of Function score: 30

Discussion

This is a compelling case example of an infrequent but increasingly recognized neuropsychiatric syndrome that cannot be overlooked in child and adolescent clinical practice. Originally reported as paraneoplastic limbic encephalitis in 2005 in four young women with ovarian teratomas, antibodies were expressed in the hippocampus (Titulaer et al. 2013; Vitaliani et al. 2005). Two years later, the anti-NMDA receptor was identified as the target antigen (Dalmau et al. 2007) and it was named anti-NMDA receptor encephalitis. It can occur with or without tumors, is thought to be the second most common cause of autoimmune encephalitis, and acts by altering synaptic plasticity.

Anti-NMDA receptor encephalitis has been reported in all ages but may be more common in youth. The typical course is

characterized by a non-specific prodromal period, followed by subacute or acute behavioral and cognitive changes, anxiety, confusion, and/or psychotic symptoms (Lebon et al. 2012). The course may progress to include neurological symptoms such as seizures, movement disorders, memory deficits, and speech and autonomic dysregulation. Behavioral and neurological symptoms may predominate in younger children, and adolescents may not show neurological signs or symptoms at the beginning (Lebon et al. 2012). Thus, it is very important for child and adolescents to consider this etiology in the acute presentation of major psychiatric symptoms in young patients.

In retrospect, it is possible that M.'s nonspecific prodrome could have been initially manifest by her headaches and dizziness one month before her acute presentation. Chapman et al. (2011) describe a prodrome in which a flu-like syndrome occurs including malaise and headache. As would be the case with most adolescents returning from a vacation in the context of junior year, common stressors and psychosocial issues such as jet lag and college entrance exams and applications were initially reasonable to consider. As her anxiety increased, given the past history, it was also reasonable to try to initially manage her symptoms with anxiolytic medication, which was helpful at first. However, M.'s rapid and intense evolution of her episodic perceptual distortions, manic symptoms, and slurred speech suggested that a wide differential diagnosis needed to be considered, and hospitalization was clearly indicated.

Differential diagnosis includes viral and autoimmune causes; herpes simplex and human herpes-virus 6 are reported to be the most common viral causes. Varicella zoster and cytomegalovirus are reported to be rarely associated, but arboviral encephalitis and rabies virus should also be included (Chapman et al. 2011). Autoimmune disorders such as systemic lupus erythematosus cerebritis, anti-phospholipid syndrome, Sjogren's syndrome, and Hashimoto's thyroiditis may also be associated with limbic encephalitis.

Primary psychotic and/or mood disorders, such as schizophreniform disorder, and mania, are of course, ''top of the list'' considerations for child and adolescent psychiatrists (Chapman et al. 2011). Neuroleptic syndrome would be a consideration in youth on anti-psychotics, particularly if muscle rigidity and autonomic dysfunction are manifest.

The NMDA receptor plays a role in neuroplasticity and neurotransmission; antibodies decrease the number of cell-surface receptors in postsynaptic dendrites. This phenomenon can be reversed by removal of the antibodies (Chapman et al. 2011). Since the syndrome is often associated with tumors, such as ovarian teratomas, removal of the malignancy as well as suppression of the immune response is essential for treatment.

Fortunately for M., neurology was consulted immediately and a comprehensive encephalitis workup ensued; agitation and anxiety was managed symptomatically with lorazepam and chlorpromazine. While initial empiric treatment with steroids followed by intravenous immune globulin for five days had little benefit; once the anti-NMDA receptor antibody titers were positive, diagnosis was confirmed and secondary treatment with a monoclonal antibody, rituximab, was begun. By the end of her course of 4 weekly treatments, M. had fully recovered.

Chapman et al. (2011) noted that there is very little literature on targeted treatment of psychiatric symptoms in the context of limbic encephalitis. Notably, resolution of M.'s psychiatric symptoms followed suppression of immune response. She was worked up to exclude a tumor, which, if present would have been treated.

Most literature indicates that patients improve after hospitalization, immunotherapy, and multidisciplinary care. Titulaer et al. (2013) reported an observational study of 577 patients with anti-NMDA receptor encephalitis, ages 8 months to 85 years (mean age 21 years), with 211 children. Treatment outcome was reported in 501 with median follow-up 24 months. Of the 221 patients who did not improve with first line treatment, 57% received second line immunotherapy which resulted in better outcome compared to those who had not received it. At 24 months, 81% of 252 patients were reported to have good outcome; interestingly but not surprisingly, outcomes continued to improve over 18 months after onset. Predictors of good outcome in this study were early treatment and lack of admission to an intensive care unit.

Titulaer et al. (2013) reported that the time between onset of symptoms and treatment initiation was shorter in children than in adults. Forty-six percent failed first line treatment, but the magnitude of response to second line treatment was similar to the entire cohort. In the 177 children, predictors of good outcome and effect of second line immunotherapy were similar to the findings of the whole cohort.

As M. received early treatment and did not need ICU care, she fits the profile of the good outcome described in this study. One month follow up revealed that M. had stable mood and no evidence of anxiety or perceptual disturbances. Residual symptoms included reduced stamina and concentration; cognitive remediation was beneficial. Given her pre-existing inattentive ADHD, some difficulties with concentration and attention might be expected to persist.

In summary, this case is a dramatic example of the florid presentation of alimbic encephalitis, illustrating the importance of early recognition and comprehensive and exhaustive medical workup, leading to timely diagnosis and early, aggressive treatment. Since these patients can present in many treatment settings, from outpatient practice to emergency departments, as illustrated here, all practitioners should have an awareness of the disorder. Key characteristics in youth appear to be onset of behavioral and psychiatric symptoms, followed rapidly by neurocognitive and neurological symptoms, such as abnormal movements, speech abnormalities, change and fluctuations in consciousness, and autonomic dysfunction and seizures (Luca et al. 2012). Early recognition is essential.

Disclosures

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