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Neuroleptic Malignant Syndrome in a Boy with NMDA Receptor Encephalitis

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Chief Complaint and Presenting Problem

M. is an 11-year-old African American boy who was referred to the psychiatry consult liaison service eight days after admission to an epilepsy monitoring unit for behavioral disruption and inability to sleep.

History of Present Illness

Parents reported that M. had been a normally developing fifth grader who did well in school. M. developed the sudden onset of seizures six weeks prior to admission; his family found him curled in a fetal position with irregular jerking movements. Parents transported him to the emergency department, and an EEG demonstrated absence seizures. M. was hospitalized for several days, treated with valproic acid, and then discharged to outpatient follow-up. During this admission, M. was evaluated by the psychiatry team for anxiety, as he had expressed fear that he was going to die as a result of his illness. He also endorsed auditory hallucinations of hearing voices, at one point telling him to have more seizures. Outpatient psychotherapy was recommended.

In the following six weeks, M. had no identified seizures but experienced many new symptoms. M.'s attention, concentration, and academic performance declined dramatically, according to his teachers. He had multiple crying fits and mood swings each day. M. became increasingly somnolent, but had difficulty sleeping each night and began to slur his speech. Teachers recommended an Individualized Education Plan one month prior to referral due to his significant academic decline.

One day prior to admission, M. presented to the emergency department with four absence seizures, and was loaded with valproic acid and discharged. On the day of admission, M. again presented to the emergency department with two brief absence seizures culminating in a generalized tonic-clonic seizure that lasted 30 minutes and required intravenous midazolam. M.'s serum valproic acid level was 126 (therapeutic range 50–100 ug/mL) and ammonia was 102 (normal range 11–35 uM/L). His presumptive diagnosis was hyperammonemia due to valproic acid toxicity, and he was admitted.

Following admission, M. experienced episodes of dystonic posturing and nystagmus, only some of which were associated with epileptiform activity on long-term electroencephalogram (EEG) monitoring. His EEG consistently showed diffuse delta wave slowing. At the time of psychiatry consultation, M. was in full upper-extremity restraints due to agitation, and his verbal capacity had regressed to repeating the same word or phrase, often speaking in unintelligible sounds entirely. He followed commands inconsistently, and had not slept more than three hours a night in over a week. M. was given 0.3 mg of risperidone for agitation the night before psychiatry consultation. Psychiatry consultation was requested to further advise on medication management.

After extensive assessment, psychiatry concluded that M. had suffered a grand mal seizure of unknown etiology and had recent cognitive decline consistent with delirium. In addition to continuing the extensive workup already underway, the recommendation was made to increase risperidone to 0.5 mg twice daily and institute behavioral interventions for delirium. These included using light and windows to provide day/night cues, minimizing distractions at night, and regularly orienting the patient to his location and situation.

Past Psychiatric History

Several months prior to referral, M. was evaluated by an outpatient psychiatrist for the development of vocal tics. He was started on a medication (that his parents could not remember the name of), but did not tolerate it.

M. had no psychiatric history prior to these events.

Developmental History

M.'s birth history was unremarkable. Mother used no substances during pregnancy. He was born full term via Caesarean section without complications during delivery. Birth weight was 7 pounds, 6 ounces. He met all developmental milestones on time.

Educational History

M. performed well in school until six weeks prior to admission. Teachers had recommended an Individualized Education Plan over the past month due to significant decline in grades.

Social History

M. lived with his mother. Father, who was never married to mother, had recently moved to another state for work. M. had supportive family and friends and did well socially. There was no known history of physical abuse, sexual abuse, or other trauma.

Family History

There was a history of depression in maternal grandmother, but no other known family history of psychiatric illness.

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Medical History

M. had no significant medical problems, hospitalizations, or surgeries prior to his first seizure.

Mental Status Exam

Mental status examination performed eight days after admission at the time of psychiatry consultation revealed an 11-year-old boy wearing only a diaper with head wrapped in gauze securing his EEG leads. He was sitting in bed with both arms in restraints, alternating between staring off into space and looking around the room. He only registered that the interviewer was there when he looked briefly at her, but did not respond to verbal commands. He repeated the word ''purr'' over and over, and did not respond reasonably to any questions. M. was able to identify his mother at times, but not consistently. He could not provide a mood state; affect was anxious and agitated. M.'s thought process was perseverative. He appeared to respond to internal stimuli at times, and to misinterprete stimuli in the room as frightening. He was alert but was not oriented to person, place, or time. Formal cognitive testing was not possible due to delirium, but memory appeared grossly impaired.

Hospital Course

Risperidone did not improve sleep or agitation. Three days later, risperidone was increased to 1 mg at bedtime and 0.5 mg in the morning, which improved sleep to 4–5 hrs the first night, but had no benefit the second night. Two days after beginning ripseridone, M. developed elevated blood pressure in the 140s-150s/90s, but had no fever or appreciable rigidity. He was often flexing his limbs in agitation but, when distracted, his tone was normal. On the third day, M. developed involuntary mouth and tongue movements and rigidity in his extremities, especially the upper extremities. His temperature spiked to 100.9°F.

Given the possibility of neuroleptic malignant syndrome (NMS) M.'s creatine kinase (CK) was checked and found to be highly elevated at 10,823. Risperidone was stopped, and M. was transferred to the intensive care unit for NMS and aggressively hydrated. He never developed a persistent fever; his highest subsequent temp was 100.4°F. Lumbar puncture was repeated, which showed elevated opening pressure. Repeat magnetic resonance imaging (MRI) of the brain showed a small area of hyperintensity in the left cerebellum suggestive of encephalitis.

Over the next two weeks M.'s condition did not improve, and his workup was still largely negative. He continued to be agitated, have very poor sleep, and his language remained grossly impaired. He stopped eating and swallowing, and eventually required gastric tube placement for nutrition. Due to NMS preclusion of antipsychotic medication, lorazepam was administered for agitation. Initially, this improved his mental status; however, the effects of lorazepam were inconsistent.

Repeat MRI two weeks later showed persistence of the area of hyperintensity in the left cerebellum. As a result, the team considered extracellular antibody-mediated encephalitidies such as anti-potassium channel and anti NMDA receptor encephalitis. Though the testing results took several weeks to confirm, M. was eventually found to have anti NMDA antibodies in his cerebral spinal fluid.

M. was started on intravenous immunoglobulin (IVIG) 2 g over two days and IV solumedrol 1 g daily for five days. His agitation and insomnia worsened during and immediately following his treatments. He then received a rituximab infusion. Eventually, agitation and sleep began slowly improving. Clonazepam was initiated and found to be helpful for sleep onset and maintenance. Lorazepam was continued on an as-needed basis for agitation.

Other psychiatric medication trials included gabapentin, methylphenidate, quetiapine, trazodone, and clonidine. Each of these were minimally helpful. At discharge, M. underwent neuropsychological testing, which indicated current cognitive functioning equivalent to a five-year old. Following discharge, clonazepam was tapered without incident. He received outpatient rituximab infusions for prevention of relapse. His mental status and cognition continued to improve following discharge. At one-year follow-up, he had returned to baseline academic and behavioral functioning.

Brief Formulation:

In summary, M. is an 11-year-old African American boy with no prior psychiatric or medical history who developed sub-acute mental status changes over several weeks with new onset seizures. He was treated with risperidone for agitated delirium and developed NMS. He eventually was diagnosed with cerebral spinal fluid-positive anti-NMDA receptor encephalitis. From a biopsychosocial perspective, although his acute neurological illness predominated, there appeared to be no prior other major medical contributing factors. Maternal family history was notable for affective illness. From a psychosocial perspective, M. appeared to be developing on a generally healthy developmental trajectory; parental separation and family history may have rendered him vulnerable to affective symptoms.

Mult-Axial Diagnoses

Axis I:	Delirium NMS Provisional tic disorder
Axis II:	None
Axis III:	Anti-NMDA receptor encephalitis
Axis IV:	Level of psychosocial stressors: Moderate; father's recent move out of state
Axis V:	Global Assessment of Functioning score at time of assessment: 10

Discussion

Anti-NMDA receptor encephalitis has become increasingly reported in medical literature since it was first characterized by Dalmau et al. in 2007 (Dalmau et al. 2007). Anti-NMDA receptor encephalitis is an autoimmune-mediated disease involving autoantibodies in the central nervous system that attack the cell surface NMDA receptors. (Dalmau et al. 2011; Titulaer 2013). It was first characterized as a paraneoplastic syndrome in young women with ovarian teratomas, but has since been expanded to include children and men with or without tumors (Raha 2012). Between 37% and 65% of cases are now thought to occur in children. (Nijmeijer et al. 2013). In one retrospective analysis of encephalitidies of unknown origin, it was found to be present in 1% of young adult intensive care unit patients (Pruss et al. 2010). While there is growing literature on anti-NMDA receptor encephalitis diagnosis and management, M.'s case is unique with his comorbidity with NMS in a pediatric patient.

The disease begins with a prodromal phase consisting of flu-like illness, malaise, headache, fatigue, nausea, vomiting, diarrhea, and upper respiratory symptoms. Approximately 70% of patients have

prodromal symptoms (Dalmau et al. 2011). Within a few days to usually less than two weeks, the prodromal phase resolves and patients develop psychiatric symptoms. (Dalmau et al. 2011)

The second or psychotic phase consists of symptoms similar to a first psychotic break, which include anxiety, mood dysregulation, hyper-religiosity, delirium, agitation, personality disturbance, delusions, disorganized thinking, paranoid ideation, and hallucinations. This appears to be the phase in which M. was first evaluated by psychiatry. Indeed, it is during this phase that patients usually present to or are referred to a psychiatrist. In a majority of case studies reported, patients either presented directly or were transferred to inpatient psychiatry and treated for psychosis before the true etiology was discovered. In adult patients, 72–83% present with psychotic symptoms (Dalmau et al. 2011; Titulaer 2013; Pruss et al. 2010). One study described 46 presentations of new onset, severe psychosis and found that 6.5% were positive for anti-NMDA receptor antibodies, though this has not yet been replicated in other data. (Zandi et al. 2011; Dalmau et al. 2011)

In young children, characteristic behavioral change can be difficult to detect because they often present with temper tantrums, hyperactivity or irritability, as opposed to psychosis. (Dalmau et al. 2011; Van de Reit et al. 2013). In children, the first recognizable symptom is often non-psychiatric, and may include seizures, status epilepticus, dystonia, verbal reduction, or mutism. This was the case in M. who presented with seizures and functional decline before overt psychiatric symptoms. In some cases, behaviors are violent or hypersexual. (Dalmau et al. 2011; Van de Reit et al. 2013) Because of anxiety and insomnia, some children need intense sedation via scheduled sedative medications, including benzodiazepines or, in severe cases, propofol (Florance et al. 2009).

The third phase of the illness is characterized by hypoventilation, autonomic instability, oro-lingual-facial dyskinesias, eyes open but lack of response to visual stimuli or threats, mutism, unintelligible speech, increased tone, catatonia with dystonia or cataleptic postures, oculogyric crisis, and seizure-like activity not associated with EEG correlates; M demonstrated many of these features. Seventy-six to 82% of patients present with seizures (Dalmau et al. 2011; Titulaer 2013). By this phase, patients often require intensive care unit transfer and intubation for hypoventilation. Hypoventilation requiring respiratory support occurs as the patient becomes comatose, but can occur when the level of consciousness is relatively preserved (Dalmau et al. 2011). Autonomic storms during this phase can fluctuate from tachycardia to bradycardia, and long-lasting cardiac pauses that in some cases have required a temporary pacemaker (Sansing et al. 2007).

It is interesting to note that the natural progression of this disease often mimics the progression of NMS, which may represent a common illness pathway. Symptoms overlapping with NMS include rigidity, mental status changes, sympathetic nervous system lability, tachycardia, and tachypnea that may lead to respiratory failure (Dalmau et al. 2011). Likewise, NMDA receptor antagonists, such as phenylcyclidine and ketamine, typically cause hallucinations, repetitive orofacial and limb movements, and autonomic instability (Dalmau et al. 2011).

In addition to the similar pathology of each disease process, treatments overlap as well. Benzodiazepines are often used in the treatment of NMS, and levels of GABA have been found to be low in patients with NMS (Nisijima and Ishiguro 1995). Clonazepam and lorazepam were found to be helpful in the treatment of M's anti-NMDA receptor encephalitis. These factors point toward a common pathophysiology between anti-NMDA receptor encephalitis and NMS.

The overlap of anti-NMDA receptor encephalitis and NMS also presents clinicians with a diagnostic and treatment dilemma. Given the psychotic phase of illness occurs first, patients may be more likely to encounter neuroleptics in this phase. It is then difficult to discern whether subsequent abnormal movements and autonomic instability are a result of neuroleptic induced extrapyramidal effects, NMS, or are a part of the natural disease progression. Several case reports have described concurrent NMS and anti-NMDA receptor encephalitis in adults (Kiani et al. 2014; Chmayssani et al. 2011). One case report describes malignant catatonia and increased creatine kinase in a 17-year-old girl who was treated with antipsychotics for anti-NMDA receptor encephalitis (Consoli et al. 2011). This case highlights the risk of concurrent anti-NMDA receptor encephalitis and NMS in a child.

Psychiatric symptoms often show gradual improvement with immune-modulating treatment without targeted intervention, though a broad range of psychiatric medications have been tried and shown to be of variable benefit. Given the risk for NMS and the difficulty distinguishing early NMS from symptoms of disease progression, there is an argument to be made for using neuroleptics cautiously in this patient population. There are several documented cases of neuroleptics actually worsening neuropsychiatric symptoms and movement abnormalities, especially at higher doses (Dalmau et al. 2011; Kumar et al. 2013; McKeon 2013; Liba et al. 2013).

Electroconvulsive therapy (ECT) has been used with variable benefit, most often in cases with catatonia. One case report demonstrated complete recovery with ECT without the use of plasma exchange or immunosupresants. (Matsumoto et al. 2012). Another showed only partial improvement with a combination of ECT and immunosupresants (Mann et al. 2012; Dalmau et al. 2011). Valproic acid and lithium have been prescribed for mood dysregulation in this illness, but did not show substantial benefit (Mann et al. 2012; Hung et al. 2011). The use of antidepressants to control anxious and depressed states has not been well described in the literature, but benzodiazepines have been used for behavioral control and agitation during the psychotic phase (Mann et al. 2012).

In summary, this is an intriguing case of anti-NMDA receptor encephalitis that may have been complicated by neuroleptic use designed to target aggression and hyperactive delirium symptoms. There is little evidence of reliable benefit from neuroleptic use in the extant literature. Given the overlap in symptoms with the natural disease progression, subclinical NMS may be difficult to diagnose and treat appropriately without a high index of suspicion. The extant literature suggests that the level of evidence for any type of acute treatment consists of aggregated case report data only. It is therefore important in cases of delirium without an identifiable cause to consider and rule out anti-NMDA receptor encephalitis early to minimize the risk of unnecessary and unhelpful neuroleptic exposure in this vulnerable patient population.

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