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Agitation Management in Pediatric Males with Anti-N-Methyl-D-Aspartate Receptor Encephalitis

Lauren T. Schumacher, MD,[1] Andrea P. Mann, DO, MPhil,[2] and James G. MacKenzie, DO[3]

Abstract

Objectives: Severe agitation is a common symptom in pediatric cases of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis—an autoimmune encephalitis with prominent neuropsychiatric symptoms. Agitation is a major barrier to treatment of the underlying disease process and increases patients' risk of harming themselves and others. Furthermore, male patients often have undetectable tumors and are especially at risk for extended hospitalization, but have been infrequently studied. This report presents a case series of four pediatric male patients with anti-NMDAR encephalitis complicated by agitation, the strategies used to address treatment challenges, and a review of the current literature.

Methods: A chart review of four agitated pediatric male patients with anti-NMDAR encephalitis and a PubMed search of the current literature were conducted.

Results: A number of first-generation and second-generation antipsychotics (SGAs) have been reported for use in child and adult patients; however, treatment with these antipsychotics often has been complicated by movement disorders and autonomic instability caused by the underlying encephalitis that appears similar to and can be exacerbated by adverse effects of antipsychotics, including neuroleptic malignant syndrome (NMS), extrapyramidal symptoms (EPS), and tardive dyskinesia. The literature shows SGAs to be less likely to cause NMS and quetiapine to be one of the least likely SGAs to cause EPS. However, quetiapine has rarely been reported for use in patients with anti-NMDAR encephalitis. In the four pediatric male patients, quetiapine was generally effective, well tolerated, and not associated with NMS or significant EPS.

Conclusion: These cases and review of the literature suggest that quetiapine may be particularly beneficial for treating agitation secondary to anti-NMDAR encephalitis in pediatric patients and have fewer adverse effects.

Keywords: anti-NMDA encephalitis, children, delirium, management

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune encephalitis that often presents with prominent psychiatric and behavioral symptoms that complicate management. It was identified in 2007 in a series of women with ovarian teratomas and neuropsychiatric symptoms who were found to have antibodies to the NMDAR (Dalmau et al. 2007).

Initial presentation typically includes a nonspecific prodrome such as fever, headache, nausea, diarrhea, and/or upper respiratory symptoms, followed by psychiatric and behavioral symptoms, including agitation, bizarre behavior, auditory and visual hallucinations, delusions, temper tantrums, and hyperactivity, which progress to neurologic symptoms such as seizures, dyskinesias, choreoathetoid movements, sleep disturbance, mutism, memory loss, and catatonia, and then ultimately autonomic instability (Dalmau et al. 2011; Mann et al. 2012; Kruse et al. 2014; Maneta and Garcia 2014; Barry et al. 2015).

While most often affecting young women, this syndrome has been diagnosed in both men and women with ages ranging from 8 months to 85 years, both with and without tumors (Titulaer et al. 2013; Mann et al. 2014). It is uncommon in pediatric males; in a study of 81 patients diagnosed with anti-NMDAR encephalitis, only 7% of patients were males aged 18 years old and under (Florance et al. 2009). Males and children are less likely to have a detected tumor or teratoma (Florance et al. 2009; Dalmau et al. 2011; Titulaer et al. 2013; Mann et al. 2014). Detection and removal of an associated tumor are correlated with better prognosis and decrease risk of relapse (Mann et al. 2014; Mangalwedhe et al. 2015). Poorer functional outcomes are reported in children without tumors, with some requiring years to recover (Mann et al. 2014).

Intravenous immunoglobulin (IVIG) and plasmapheresis followed by immunotherapy, if needed, are first-line interventions for treating the underlying autoimmune process. However, psychiatric symptoms, especially agitation, can interfere with the medical team's ability to provide this treatment and place patients at

[1]Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois.
[2]Division of Child and Adolescent Psychiatry, Stanford University School of Medicine, Stanford, California.
[3]Department of Child and Adolescent Psychiatry, Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois.

increased risk of harming themselves and others (Dalmau et al. 2011; Kuppuswamy et al. 2014; Monteiro et al. 2015). Agitation is very common, reported in up to 93% of pediatric cases (Mohammad et al. 2015). Psychiatric consultation plays an important role to help manage agitation while the underlying encephalitis is treated. This is particularly crucial in treating pediatric males, as they are less likely to have an associated tumor, placing them at risk for a more prolonged and complicated course. Although there is growing literature on the management of agitation and other psychiatric symptoms in adults with anti-NMDAR encephalitis, the literature is limited with respect to pediatric populations (Chapman and Vause 2011; Mann et al. 2012; Kruse et al. 2014).

This report presents a case series of four pediatric male patients with anti-NMDAR encephalitis complicated by agitation and the strategies used to address challenges of management, most notably use of the second-generation antipsychotic (SGA) quetiapine, which may offer benefits over more traditional strategies. This case series is unique in its focus on relatively rare pediatric male patients and its promising use of quetiapine.

Case 1

A 10-year-old Asian American male presented to the inpatient psychiatry service with altered mental status and suicidal ideation following a week of poor sleep and headaches. He was found talking to himself in nonsensical speech, acting confused, and unable to answer questions. Neurology was consulted for left arm posturing and balance difficulties. After a normal magnetic resonance imaging (MRI) requiring sedation, the patient displayed increased agitation, fluctuating attention, and disorientation, prompting transfer to the pediatric intensive care unit. He was frequently observed mumbling, jerking his body, and screaming without any stimuli. The patient became combative toward nursing and his agitation failed to improve with lorazepam and diphenhydramine. Sequential treatment with risperidone and later haloperidol led to some improvement in agitation. However, the patient had episodes of fever, tachycardia, hypertension, and elevated creatinine kinase without muscle rigidity. Dopamine antagonists were stopped due to concern for possible neuroleptic malignant syndrome (NMS).

Lorazepam and clonidine were somewhat successful in managing agitation, but the patient continued to have breakthrough agitation when overstimulated. After anti-NMDAR antibodies were detected in his cerebrospinal fluid (CSF), he was treated with high-dose methylprednisolone and IVIG. Testicular ultrasound demonstrated bilateral microlithiasis, but no tumor. The patient gradually improved over the course of his month-long stay, eventually recovering the ability to speak a few words and follow some commands. He was transferred to a rehabilitation facility where lorazepam and clonidine were weaned.

Two weeks after transfer, the patient was readmitted for increased agitation and insomnia. Episodes of agitation included violent outbursts, echolalia, and hallucinations. Even though he was restarted on IVIG, rituximab, clonidine, and lorazepam, fluctuating attention and agitation to the point of requiring restraints continued over the next several weeks. Thus, quetiapine 25 mg was initiated at night (qHS). It appeared to improve delusions and insomnia and was increased to 25 mg twice daily (BID). Melatonin 5 mg was added as an adjunctive sleeping aid. The patient gradually became less agitated and was transferred back to the rehabilitation facility, where quetiapine was titrated up to 250 mg qHS and 25 mg as needed (PRN). Subsequently, as an outpatient, he took quetiapine 50 mg in the morning (qAM) and 250 mg qHS. He continued to improve, achieving his premorbid level of functioning.

Case 2

A previously healthy 3-year-old African American male recently diagnosed with a seizure disorder was admitted for worsening abnormal movements, emesis, and agitation following multiple visits to the emergency department. These were initially interpreted as catatonia and he was given intravenously (IV) lorazepam at an outside hospital, which caused aggressive disinhibition (e.g., kicking). After transfer to our institution, electroencephalogram (EEG) showed epileptiform activity and his CSF had neutrophilic pleocytosis. He received IV methylprednisolone followed by IVIG for presumed autoimmune encephalitis without immediate improvement.

The patient had episodes of agitation characterized by tearing off his leads and aggression (e.g., attempting to hit and bite caregivers), as well as orofacial dystonia. IV lorazepam was used for ongoing agitation. Mental status waxed and waned and his sleep became inverted, so lorazepam was discontinued. Low-dose quetiapine (25 mg qHS and 25 mg PRN), along with melatonin 1 mg, was started and found to help him sleep a few hours at night and gradually led to a 50% improvement in behavior.

After 3 weeks, he was discharged for ongoing outpatient psychiatric management, physical therapy, occupational therapy, speech and language therapy, and neurorehabilitative services. After his CSF was found to be positive for anti-NMDAR antibodies, a scrotal ultrasound was performed but revealed no neoplasm. The patient continued to struggle with behavioral lability, learning and speech difficulties, and complex partial seizures. He was weaned off quetiapine. Over the next few years, the patient experienced multiple relapses requiring IVIG and steroids, but slowly returned to his baseline.

Case 3

An 11-year-old Hispanic male was readmitted for worsening lethargy, motor abnormalities, and cognitive difficulties following two prior admissions for possible Epstein–Barr virus encephalitis complicated by seizures and cerebral edema. During his third admission, he developed expressive aphasia, right hemiparesis, and ataxia. Avolition progressed to catatonia. After he received acetazolamide for increased intracranial pressure, IV lorazepam for catatonia, and high-dose methylprednisolone, he became slightly more responsive and gradually stabilized.

Five weeks after initial hospitalization, he was transferred to a rehabilitation unit. He continued to have intermittent lethargy, aggression, screaming, choreiform movements, and difficulty sleeping. For his agitation and insomnia, the patient was started on quetiapine 25 mg BID with an additional 12.5 mg PRN and lorazepam 1 mg by mouth every 6 hours. Trazodone 150 mg was given at bedtime to help with insomnia. His CSF studies returned positive for anti-NMDAR antibody, prompting IVIG treatment.

With immunosuppressive treatment of his encephalitis and continued treatment with quetiapine and trazodone, his cognitive function recovered. He began to communicate in single words, eventually followed by full sentences. His aggression, insomnia, and avolition improved as well, and quetiapine and trazodone were tapered. He was discharged home 3 months after his initial presentation.

Case 4

A 7-year-old Hispanic male was healthy until 6 weeks before admission when he began having right-sided arm and hip pain and weakness, and then gait difficulties. He developed choreiform-like movements in his extremities. Evaluation at an outside hospital,

Table 1. Relative Binding Affinities and Adverse Effect Profiles of Antipsychotics

	Quetiapine	*Haloperidol*	*Ziprasidone*	*Risperidone*	*Olanzapine*	*Aripiprazole*
D2	+	+++	+++	+++	++	+++PA
5-HT1A	+	o	+++PA	+	o	+++PA
5-HT2A	+	++	++++	++++	+++	+++
5-HT2C	o	o	++++	+++	+++	++
H1	+++	+	++	++	+++	++
Adverse effects						
EPS	o	+++	+++	+	++	+
NMS	+	++	+	+	+	+
Sedation	++	+	++	++	++	++
ECG abnormality	+	+	++	+	+	o

5-HT, serotonin receptors; D2, dopamine type 2 receptors; ECG, electrocardiogram; EPS, extrapyramidal symptoms; H1, histaminergic type 1 receptors; NMS, neuroleptic malignant syndrome; PA, partial agonist.

Source: Schmidt et al. (2001), Timdahl et al. (2007), Correll (2008), Schatzberg and Nemeroff (2009), Seitz and Gill (2009), Cohen et al. (2012), Belvederi Murri et al. (2015), Jensen et al. (2015), Kusumi et al. (2015).

including EEG, MRI, and lumbar puncture, was unremarkable. Sequentially, clonidine, carbamazepine, oxcarbazepine, valproic acid, and then haloperidol and clonazepam were used to try to control the movements. As the movements continued to worsen, he was transferred to a center with a neurology movement specialist.

CSF and serum were positive for anti-NMDAR antibodies. Mental status was notable for fluctuating level of arousal and inability to answer questions or follow commands. The patient was episodically febrile, which was attributed to autonomic instability. EEG showed intermittent, rhythmic delta activity predominantly in the frontal region and diffusely disorganized, slow background, concerning for encephalopathy and possible subclinical seizures, which were treated with phenobarbital. He was diagnosed with anti-NMDAR encephalitis and treated with IV steroids, IVIG, plasmapheresis, cyclophosphamide, and rituximab. MRI and scrotal ultrasound showed no evidence of tumor.

Chorea was treated with haloperidol 1 mg BID, clonazepam, and diphenhydramine without significant improvement. The patient was intermittently agitated, which would worsen the movements, and had difficulty sleeping. Haloperidol was discontinued, and quetiapine 25 mg BID and 25 mg BID PRN were started for agitation and insomnia. Diphenhydramine and clonazepam use was reduced given risk of worsening delirium. Melatonin 5 mg qHS was added to help with sleep. Quetiapine was titrated up based on PRN needs to 150 mg qAM and 200 mg qHS. Chorea, agitation, and sleep gradually improved. After 3 weeks, he was significantly better, following commands and answering questions, with more purposeful than nonpurposeful movements. He was transferred for rehabilitation.

Discussion

These cases demonstrate some of the challenges of and strategies for managing agitation in pediatric patients with anti-NMDAR encephalitis and highlight the promise of the SGA quetiapine for agitation management.

Benzodiazepines and diphenhydramine have been used to treat agitation in anti-NMDAR encephalitis (Chapman and Vause 2011; Mann et al. 2012; Kruse et al. 2014). However, the risk of paradoxical agitation from benzodiazepines limits their utility in treating a pediatric population (Cummings and Miller 2004; Marzullo 2014). While diphenhydramine is often used for agitation in otherwise healthy adolescents, it is a less preferred option in medically ill patients because anticholinergic effects can worsen delirium (Cummings and Miller 2004).

This leaves antipsychotics as the mainstay of treatment for agitation in medically ill pediatric patients (Cummings and Miller 2004). A number of antipsychotics, both first-generation (haloperidol and chlorpromazine) and second-generation (aripiprazole, risperidone, olanzapine, quetiapine, and ziprasidone), have been used and discussed in the literature for agitation secondary to anti-NMDAR encephalitis (Kruse et al. 2014; Kuppuswamy et al. 2014; Mohammad et al. 2014; Monteiro et al. 2015). However, use of antipsychotics in these patients can prove challenging. Patients with anti-NMDAR encephalitis can develop fever, rigidity, and autonomic instability, even in the absence of antipsychotics (Dalmau et al. 2011; Mohammad et al. 2014). As demonstrated in Case 1, development of autonomic dysfunction and elevated muscle enzymes in the presence of antipsychotics causes a dilemma, as the presentation could be caused by the underlying encephalitis or by NMS secondary to the antipsychotic. Given the risks, the antipsychotic is usually discontinued, leaving the agitation undertreated (Mann et al. 2014; Mohammad et al. 2014; Barry et al. 2015). NMS has been associated with all classes of antipsychotics, but it is most often seen with high potency first-generation antipsychotics such as haloperidol (Seitz and Gill 2009). Patients treated with SGAs have a lower incidence of NMS and a less severe and potentially lethal course when NMS does develop (Belvederi Murri et al. 2015). Some authors prefer use of mid- or low-potency SGAs, such as olanzapine or quetiapine, in patients with anti-NMDAR encephalitis, reasoning that it would be less likely to cause NMS (Scharko et al. 2015). Table 1 compares relative binding affinities and adverse effect profiles of these antipsychotics.

In addition, movement disorders are present in over 80% of pediatric patients with anti-NMDAR encephalitis, including orofacial dyskinesias (reported in 55% of cases), choreoathetosis, complex stereotyped movements, and dystonias (Dalmau et al. 2008; Florance-Ryan and Dalmau 2010; Titulaer et al. 2013). Presence of these dyskinesias often leads to discontinuation of antipsychotics because they can appear similar to the extrapyramidal symptoms (EPS) and tardive dyskinesia caused by antipsychotics. Repeated discontinuation of antipsychotics makes controlling agitation difficult. Furthermore, antipsychotics can cause EPS, such as dystonic reactions and akathisia, which can worsen motor symptoms of the underlying disease (Kruse et al. 2014; Kuppuswamy et al. 2014; Mann et al. 2014; Mohammad et al. 2015). Thus, antipsychotics that are less likely to cause EPS are recommended (Kruse et al. 2014; Kuppuswamy et al. 2014; Mann et al. 2014).

In a retrospective chart review of 27 children in Australia with anti-NMDAR encephalitis, Mohammad et al. found that 12 were treated with antipsychotics, primarily haloperidol and risperidone. Three developed a dystonic reaction, one developed dysarthria, three developed NMS-like symptoms, and one developed prolonged QTc, all leading to discontinuation of the medication. They hypothesized that an agent with less dopamine type 2 (D2) receptor blockade such as quetiapine may have fewer adverse effects (Mohammad et al. 2015). A retrospective review by Joyce et al. studied 50 pediatric patients diagnosed with delirium from a variety of underlying illnesses and treated with quetiapine. They found that three patients developed clinically nonsignificant QTc prolongation and no patients developed EPS or NMS and concluded that quetiapine is a safe treatment for delirium in critically ill children (Joyce et al. 2015). Despite this, extensive review of the literature showed only one case report of a pediatric patient with anti-NMDAR encephalitis treated with quetiapine (Mohammad et al. 2014).

Quetiapine is an SGA with a low binding profile for D2 receptors and higher affinity for noradrenergic receptors and histamine type 1 (H1) receptors (Correll 2008; Schatzberg and Nemeroff 2009). The H1 receptor affinity is thought to account for its sedating effects, which can help treat sleep disturbances associated with anti-NMDA encephalitis (Schatzberg and Nemeroff 2009; Cohen et al. 2012). With its low affinity for D2 receptors, it is one of the antipsychotics least likely to cause EPS, with rates of EPS comparable to placebo (Timdahl et al. 2007; Correll 2008; Cohen et al. 2012). Because of these characteristics, quetiapine was chosen for agitated anti-NMDAR encephalitis pediatric patients as being less likely to cause NMS, EPS, or worsening of underlying movement disorders and thus helping to prevent discontinuation and ultimately improve control of agitation compared to other antipsychotics. In this case series, quetiapine was generally well tolerated and not associated with NMS or significant EPS. Although quetiapine provided some benefit in these cases, the effects were confounded by concomitant use of multiple medications for the underlying autoimmune process and for seizures. Further investigation is needed to determine optimal strategies for symptomatic management of anti-NMDAR encephalitis.

Clinical Significance

This report presents a series of four pediatric males with anti-NMDAR receptor encephalitis, a distinct relatively rare population at increased risk for prolonged course. These cases and review of the literature provide evidence that quetiapine may be particularly beneficial for treating agitation secondary to anti-NMDAR encephalitis in pediatric patients by adequately treating agitation with fewer adverse effects. Severe agitation is common in pediatric patients with anti-NMDAR encephalitis, and adequate control of agitation is essential for optimal treatment of the underlying illness and to reduce patients' risk of harming themselves and others.

Disclosures

No competing financial interests exist.

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Address correspondence to:
James G. MacKenzie, DO
Ann & Robert H. Lurie Children's Hospital of Chicago
Department of Child and Adolescent Psychiatry
Department of Psychiatry and Behavioral Sciences
Northwestern University Feinberg School of Medicine
225 E. Chicago Ave, Box 10
Chicago, IL 60611-2605

E-mail: jmackenzie@luriechildrens.org