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Literature Review and Case Report about Pediatric Anti-NMDAR Encephalitis

Rong Xiao*

UNI Downtown Behavioral Health Clinic, University of Utah, USA

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***Corresponding author:** Rong Xiao, Child and Adolescent Psychiatrist, UNI Downtown Behavioral Health Clinic, University of Utah, USA, Tel: 5186450128; E-mail: rong.xiao@hsc.utah.edu

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Abstract

Objective: Literature review about pediatric anti-NMDAR encephalitis after reporting four patients hospitalized at a tertiary children's hospital.

Methods: Four patients (age 9, 16, 4, 2) with neuropsychiatric symptoms at a tertiary children's hospital between Jan 1, 2011 to Dec 31, 2016 were identified though a query of hospital billing data. Diagnosis was confirmed by the detection of IgG anti-GluN1 antibodies in either serum or in Cerebrospinal Fluid (CSF).

Results: Neuropsychiatric symptoms are very common, often interfering with care. Psychiatry were consulted in 3 cases.

Conclusions: Antipsychotics are commonly used to treat aggression, psychosis and delirium. Benzodiazepines could be helpful for catatonia and aggression but could worsen delirium. Clonidine could be helpful for agitation, insomnia, and/or autonomic instability. Electroconvulsive Therapy (ECT) could be helpful for malignant catatonia.

Keywords: Anti-NMDAR encephalitis; Psychosis; Aggression; Antipsychotics; Benzodiazepines; Electroconvulsive Therapy (ECT)

Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis was first mentioned in 2005. Since that time, there has been growing recognition and understanding of the disease process and presentation. About 40% of anti-NMDAR encephalitis present before age 18. Anti-NMDAR encephalitis commonly presents with neuropsychiatric symptoms including delirium, catatonia, agitation, mania, psychosis, disorganized behaviors, anxiety, depression, and insomnia. Recent studies suggest that a majority of patients with Anti-NMDAR encephalitis develop psychiatric symptoms, both at initial onset and during relapse [1-5].

Because of the prominent concomitant psychiatric symptoms and the early onset of the disease, child and adolescent psychiatrists are commonly involved in the care of individuals with Anti-NMDAR encephalitis. Although there is a growing body of literature on the overall treatment of Anti-NMDAR encephalitis, there remains limited evidence to guide a psychiatrist in managing the psychiatric sequalae and even less evidence in regards to the psychiatric care of pediatric patients. Multiple questions remain including how to manage individual neuropsychiatric symptoms in pediatric patients with Anti-NMDAR encephalitis.

In an effort to add to the limited literature of psychiatric management of children and adolescents with anti-NMDAR encephalitis, we present a case report of four children hospitalized at a tertiary children's hospital with anti-NMDAR encephalitis. These cases were identified though a query of hospital billing data. Institutional Review Board (IRB) approval was obtained. Diagnosis was confirmed by the detection of IgG anti-GluN1 antibodies in either serum or in Cerebrospinal Fluid (CSF). We present four patients diagnosed with anti-NMDAR encephalitis who were treated for neuropsychiatric symptoms at a tertiary children's hospital between Jan 1, 2011 to Dec 31, 2016. Please see **Table 1** for additional details of the cases.

Case Reports

Case 1

A 9 year-old previously healthy girl was admitted to the hospital due to altered mental status. Parents described a one-month history of personality change, including becoming much more depressed, withdrawn, paranoid, and emotionally labile. Additionally, she was showing increased confusion and memory difficulties. The psychiatry consult team was involved throughout her hospital stay to assist with symptom management. She demonstrated agitation, irritability, and excessive emotional outbursts in the hospital and was started on risperidone for symptom management at the same time her anti NMDAR encephalitis was confirmed, and she was started on Intravenous Immunoglobin (IVIG) and steroids. Her irritability improved some, as did her overall mental status, although she remained quite emotionally labile and was started on citalopram during an inpatient rehab stay. Shortly after hospitalization, risperidone was weaned, although she remained on citalopram for the next year.

Case 2

A 16 years old previously healthy girl was admitted to the hospital after a three-month history of increased withdrawal, fatigue, and an abrupt break up with her boyfriend of 4 years. One week prior to admission, she had a potential seizure and was started on levetiracetam. She developed visual and auditory hallucinations, disorganized speech and behaviors, and disorientation. She was noted to be wandering out of the house, not eating or taking care of her hygiene, and unable to sleep. Psychiatry was involved in her care throughout her stay. During the first several days of hospitalization, she alternated between being tired and energetic; jumping on the bed, kicking or cursing nurses, walking or running in the hallway, disrobing, dancing, trying to elope the unit, urinating or defecating on her bed and moving furniture. She was started on olanzapine to help manage these symptoms while awaiting lab results, although her agitation, psychosis, and manic-like symptoms continued to escalate. When labs results confirmed anti-NMDAR encephalitis, she was started on IVIG and steroids, but continued to struggle. Her significant autonomic instability resulted in temporary intubation, use of atropine, and sedation with propofol. Due to lack of improvement on steroids and IVIG, she was treated with rituximab. Improvement was gradual with persistence of agitation and impulsive behaviors that did not seem to be responding to olanzapine. She developed catatonic features that were managed with high dose lorazepam. Irritability and mood lability persisted and olanzapine was switched to risperidone. Additionally, melatonin and trazodone were used to treat insomnia. Symptoms improved and she was discharged home after 6 weeks in the hospital. All psychotropic medications were weaned off by 10 weeks after hospitalization.

Case 3

A 4 years and 10 months old previously healthy girl was admitted to the hospital for acute onset of altered mental status including significant language regression (using one-word answers, speaking gibberish and not talking much otherwise). On the day prior to admission, she had been febrile, incontinent and stopped walking. Psychiatry was consulted in the emergency department at an outside hospital and felt that her presentation was neurologic in nature. Upon admission, patient was intermittently responsive. This deteriorated over the course of the next couple days leading to a prolonged period of minimal responsiveness to pain or commands with isolated periods of acute agitation, for which she received as needed doses of lorazepam and haloperidol. She received steroids and IVIG with only minimal response. She subsequently received plasmapheresis, rituximab and cyclophosamide. Additionally, she received clonidine for agitation and autonomic instability, topiramate to address abnormal movements, along with quetiapine and melatonin for insomnia. After 14 weeks in the hospital, patient was discharged home still not talking. Over the next 9 months, she was weaned off of all supportive medications. She continued to receive rituximab for the next year, making gradual improvements in both behaviors and neurologic functioning.

Case 4

A 2 years and 1 month old previously healthy girl was admitted after 2 weeks of worsening choreiform movements. Three day prior to admission, she also began exhibiting disorientation, mood lability, and aggression. Anti-NMDAR antibody in CSF and serum came back positive on hospital day 3. Patient was treated with steroids and IVIG, followed by rituximab which eventually reduced the choreiform movements and increased interactiveness. Topiramate was used to manage her choreiform movements. Her agitation was managed by clonidine initially, which was weaned off secondary to increased sedation, and subsequently managed by behavioral interventions alone. Insomnia was treated with trazodone and melatonin. She was discharged on hospital day 23 with outpatient rehabilitation and neurologic services, receiving at least one more dose of IVIG and rituximab. Trazodone, melatonin, and topiramate were weaned within the next 3 months. Psychiatry was never involved in her care.

Table 1 Characteristics of Four Patients with Anti-NMDAR Encephalitis.

	Case 1	Case 2	Case 3	Case 4
Age (years)	9	16	4	2
CSF and Serum IgG anti-NMDAR Ab	Positive	Positive	Positive	Positive
Brain Imaging	Normal	Normal	Normal	Normal
Pelvic Imaging	Normal	Hemorrhagic ovarian cysts	Normal	Mild cystitis
EEG Results	Abnormal	Abnormal	Normal	Abnormal
Immunotherapy	steroids, IVIG	steroids, IVIG, rituximab	steroids, IVIG, rituximab, cyclophosphamide	steroids, IVIG, rituximab, cyclophosphamide
Antiepileptic Medications	levetiracetam, pheytoin, oxcarbazepine	levetiracetam	none	None

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Antipsychotic Medications	risperidone	olanzapine, risperidone	haloperidol, quetiapine	None
Benzodiazipines	none	lorazepam	lorazepam, diazepam	None
Other CNS Medications	citalopram	propofol, fentanyl, diluadid, melatonin, clonidine, trazodone	melatonin, clonidine, topiramate	melatonin, clonidine, topiramate

Discussion

Neuropsychiatric symptoms, including agitation, aggression, catatonia, and insomnia are common in youth with anti-NMDAR encephalitis as demonstrated in the cases mentioned above. Child and adolescent psychiatrists are often consulted to help treat these symptoms which interfere with hospital care.

Potential role of antipsychotics

All of the cases above presented with agitation, often interfering with care. In two of the cases (case 2 and case 4), the individuals became physically aggressive. Case 2 involved psychosis as well. Antipsychotics are commonly used to treat symptoms of agitation and psychosis in multiple settings, including autism, psychotic disorders, and hyperactive delirium due to multiple etiologies. Three of our cases were managed with antipsychotics including risperidone, olanzapine, and quetiapine. Certainly, there is a growing body of literature regarding the safety and efficacy of antipsychotics in pediatric delirium, including short-term use of haloperidol, risperidone, olanzapine, and quetiapine and case reports discussing use of antipsychotics in pediatric anti-NMDRA encephalitis. Because antagonists of the NMDA glutamate receptor remove Gamma-Aminobutyric Acid (GABA)-ergic inhibition, followed by release of acetylcholine and glutamate, which can cause neurotoxicity and psychosis, the use of antipsychotics is presumed to be helpful in improving these symptoms in anti-NMDAR encephalitis. However, patients with autoimmune encephalitis may be more vulnerable to the side effects of antipsychotics, including neuroleptic malignant syndromes (NMS) (4). It can be quite difficult to determine whether autonomic instability and rigidity are related to NMS or part of the natural disease trajectory of a patient with autoimmune encephalitis. Additionally, worsening of anti-NMDAR symptoms with the use of antipsychotic medication may be a potential feature of autoimmune encephalitis. There is some belief that the use of antipsychotics before the use of immunomodulatory agents may lead to symptom exacerbation, whereas the use of antipsychotics in conjunction with or after immunomodulatory agents may be beneficial. Overall, there is still little evidence to guide specific antipsychotic treatment options at this time [6-14].

Potential role of benzodiazepines

In two of the cases mentioned above, patients received lorazepam for agitation and in case 2, for catatonia as well. Because of the wealth of evidence regarding use of lorazepam to treat catatonia, benzodiazepines are a natural choice for treating catatonic features associated with autoimmune encephalitis. There are also studies suggesting the use of benzodiazepines were helpful for agitation and aggression in pediatric patients, with or without features of catatonia. One case study reviewed the treatment of 27 children with anti-NMDAR encephalitis treated with several different benzodiazepines and proposed that midazolam had the highest benefit because it could be used as intravenous infusion, intravenous bolus, or buccal dose with tolerable side effects. The theoretical pathophysiology for the efficacy of benzodiazepines is not clearly elucidated, but likely involves the modulation of GABA. Unfortunately, the presence of autonomic instability in patients with anti-NMDAR encephalitis can complicate the use of benzodiazepines and benzodiazepines may worsen delirium symptoms, cause inhibition (esp. in younger patients), and cause excessive sedation [1,12,14-16].

Potential role of other psychotropic medications

Clonidine may also be helpful for agitation, insomnia, and/or autonomic instability. Case 2 received clonidine for her agitation; case 3 received clonidine patch for her autonomic instability and severe agitation. A meta-analysis concluded that perhaps there is a role for clonidine as an adjunctive or sedative sparing agent (e.g. by reducing opiate dosage) in delirium, although the overall evidence is still relatively scant. Clonidine is also commonly used to help with insomnia, a common symptom in autoimmune encephalitis [17].

Melatonin which regulates the circadian rhythm, may be a reasonable first-line option for isolated sleep disturbance. Trazodone could also be used as a short-term treatment of insomnia, although there is little literature to guide this practice. One case study has also included the use of chloral hydrate, and zopiclone for insomnia [12].

In the post-inflammatory phase of anti-NMDAR encephalitis patient may have ongoing residual symptoms of anxiety, inattention, impulsivity, psychosis, depression, and panic that may benefit from usual treatment of Selective Serotonin Reupdate Inhibitors (SSRIs) or stimulants. One of cases above was started on citalopram during inpatient rehab which seemed beneficial.

Potential role of electroconvulsive therapy (ECT)

ECT has been found by several case reports to be effective in treating patients (age ranging from 14 to 47 years old) with anti-NMDRA encephalitis. Regarding pediatric patients, one case study reported an 11-year-old girl with NMS and malignant catatonia associated with paraneoplastic limbic encephalitis caused by an ovarian teratoma was successfully treated with 8 ECT sessions before treatment team identifying her ovarian teratoma. The ECT was suspended after her surgery, and her psychosis resolved by the fourth postoperative day. Another 16-year-old girl with anti-NMDAR encephalitis, malignant catatonia and autonomic instability who failed aggressive immunotherapy and high-dose of benzodiazepines, had a robust response to 8 ECT sessions. Therefore, removing the underline etiology is still the most important treatment but ECT could resolve the life-threatening NMS and malignant catatonia as quickly as possible. Although ECT might not be as effective as it is to treat NMS or catatonia associated with a primary psychiatric illness, it is still an effective treatment if patients fail benzodiazepines to treat catatonia, or not respond well to immunotherapy, or the treatment team cannot identify the underlying etiology. The combination of benzodiazepines and ECT may be synergistic in efficacy [13,18-20].

Conclusion

Neuropsychiatric symptoms, including agitation, aggression, catatonia, and insomnia are common in youth with anti-NMDAR encephalitis as demonstrated in the cases mentioned above. Child and adolescent psychiatrists are often consulted to help treat these symptoms which interfere with hospital care and treatment and likely play a key role in the multidisciplinary teams needed. Although there is a growing body of literature available, there is still limited evidence to guide treatment algorithms for the psychiatric care of symptoms associated with anti-NMDAR encephalitis. Ongoing multisite and multispecialty collaborative efforts are needed to create standards of care models and more clearly defined treatment algorithms.

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