JPPT | Case Report

Rituximab for Treatment of Refractory Anti-NMDA Receptor Encephalitis in a Pediatric Patient

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Anti-*N*-methyl D-aspartate receptor (anti-NMDAR) encephalitis is a devastating disease that is increasingly being identified in both children and adults with psychosis, language disturbances, behavioral changes, and motor deficits. Currently no consensus guidelines exist for the optimal management of patients with this disease, although intravenous immune globulin (IVIG) therapy is often considered first-line pharmacotherapy. We present a case of an otherwise healthy 4 year-old-child who presented with seizures, loss of age-appropriate language skills, and behavioral changes, in whom anti-NMDAR was subsequently diagnosed. After marked intolerance to corticosteroid therapy and inadequate clinical response to IVIG, immunotherapy with rituximab was initiated. The patient had rapid return of language skills and complete resolution of dyskinesia after a single rituximab infusion, with no residual deficits at her 6-month follow-up visit. Early intervention in patients with anti-NMDAR encephalitis is of paramount importance for successful outcomes and baseline recovery. Only approximately half of patients respond to first-line immunotherapy, necessitating further evaluation of alternative therapies and the development of a treatment algorithm for practitioners. This case report builds upon previous findings illustrating rapid symptom resolution after rituximab infusion and adds to the available body of evidence for management of pediatric patients with anti-NMDAR.

ABBREVIATIONS anti-NMDAR, anti-N-methyl D-aspartate receptor; CSF, cerebrospinal fluid; EEG, electroencephalogram; IVIG, intravenous immunoglobulin

KEYWORDS anti-NMDAR; anti-*N*-methyl D-aspartate receptor; anti-*N*-methyl D-aspartate receptor encephalitis; case report; pediatric; rituximab

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Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a common but often under-recognized cause of encephalitis associated with psychiatric symptoms, language dysfunction, and motor disturbances. Since it was described in early 2007, anti-NMDAR encephalitis has been found to be the most commonly identified cause of encephalitis in cases referred to the California Encephalitis Project between 2007 and 2011, occurring 4 times more frequently than all types of viral encephalitis (41% of cases versus 9%, respectively).[1] The majority of these cases (65%) occurred in pediatric patients. The disease process can be severe and leave up to a quarter of patients with residual deficits. Early recognition and prompt treatment can improve outcomes in patients affected by anti-NMDAR encephalitis; however, limited reports exists regarding the optimal management of these children and how to proceed when first-line therapies result in an incomplete response. We present the case of a 4-year-old child affected by this disease and her responses to first- and second-line therapies.

Case Report

A 4-year-old previously healthy female was transferred from an outside hospital to our institution with focal seizures and dysarthria. Six days prior to admission to our institution, the patient experienced an episode of vomiting followed by a new-onset seizure. The seizure lasted several hours and consisted of staring off to the right side and a clenched right hand. She was taken to an ambulatory emergency center and given lorazepam, which resolved her seizure activity. Shortly thereafter she became unresponsive and was subsequently transferred to our facility where she was admitted for further work-up. Upon admission, her parents reported that the patient was exhibiting hesitant speech with word searching and mild right-sided weakness. Two days later, she experienced a second seizure, following the same course as the first, an episode of vomiting with subsequent staring off to the right and clenching of the right hand. After her second seizure, she "[spoke] like a 1–2 year old," according to her mother, and displayed poor articulation with single-word responses, most commonly "no." Additionally, she experienced difficulty walking and continued right-sided weakness. Her parents reported that she had no dizziness or confusion, was aware of the events happening, and could follow verbal commands. Various diagnostic tests were ordered, including a lumbar puncture to

Table 1. Results of Diagnostic Tests Performed at an Outside Hospital

Test Performed	Results
Clinical laboratory studies	
Serum NMDA receptor antibodies	Negative
CSF findings	
Fluid analysis	Within normal limits*
Culture results	No growth at 24 hours
Gram stain	No white blood cells or organisms
Lumbar puncture	No elevation in WBC or RBC
Serum acetaminophen concentrations	< 3 mg/L
Urine drug screen	Negative
WBC	16.9 × 1000 cells/mm^3
Serum ammonia level	42 mmol/L
MRSA PCR	Negative
Imaging Studies	
1 hour EEG	Slowed L brain activity
Brain MRI	Within normal limits
Brain MRA	Within normal limits
Brain MR sonography without contrast	Within normal limits
CT	Within normal limits

CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MR, magnetic resonance; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; MRSA, methicillin-resistant Staphylococcus aureus*; NMDA,* N*-methyl* D*-aspartate; PCR, polymerase chain reaction; RBC, red blood cell count; WBC, white blood cell count*

*Clear and colorless, 1 total nucleated cell, 1 red blood cell, 5 segmented neutrophils, 94 lymphocytes, 1 monocyte, no. of cells = 1000

assess her cerebrospinal fluid (CSF). Prior to hospital admission, the patient's developmental history had been normal, and she had been able to speak in full, age-appropriate sentences. Her medical history was significant only for incomplete vaccinations but was otherwise non-contributory.

The patient was ultimately transferred to our institution for additional evaluation and a neurology consultation. She was neurologically stable upon admission but had continued dysarthria. According to her parents, her gait and weakness appeared somewhat improved. She was started on levetiracetam therapy for seizure prophylaxis and began electroencephalogram (EEG) monitoring. A 1-hr EEG examination indicated slowed left-brain activity, and further EEG recording showed left centroparietal focal irritability and structural abnormality in the left hemisphere, with no response to photic stimulation. She was alert and oriented to person, place, time, and situation. Her cranial nerves II through XII and sensations were intact. Subtle right hemiparesis was noted, but she had no pathological reflexes. Although she displayed good comprehension and was consistently able to follow verbal commands, her speech remained limited to 1- or 2-word sentences. She was, however, active, playful, and smiling with good eye contact. While at our institution, the patient exhibited no abnormal behavior or movements or seizure-like activity.

Seven days after her initial seizure, the patient's language skills and ability to follow commands declined. She stopped following verbal instructions, occasionally screamed out "no," and exhibited increased irritability. A magnetic resonance imaging scan was ordered, but the results were non-significant. Similarly, the results of all tests performed were negative (Table 1). Additional diagnostic tests were ordered at our institution and results are provided in Table 2. A 5-day course of intravenous methylprednisolone, 250 mg (12.5 mg/kg/dose) twice daily, was initiated 10 days after her first episode due to concern about possible autoimmune encephalitis. Levetiracetam therapy was continued to prevent additional seizures. Steroid therapy, however, did not result in any significant improvement in her speech; it was instead associated with episodic irritability. Her mother also noted the patient's use of her right arm was continuously diminished. After completing the 5-day steroid course, a 4-day regimen of intravenous immunoglobulin (IVIG), 2 g/kg/day, was then started at the recommendation of the pediatric immunologist. The patient's behavior and receptivity to communication appeared to improve slightly following IVIG administration, but her speech, particularly

Table 2. Results of Diagnostic Tests Performed During Admission to Our Institution

Test Performed	Results (reference, if applicable)
Anti-nuclear antibody	Positive
Anti-nuclear antibody titer	1:40
Anti-nuclear antibody pattern	Finely speckled pattern
Acute hepatitis profile	Non-reactive for hepatitis A, B, or C
Calcium channel antibody	Negative
C-reactive protein	<2.90 (0.00–10.00) mg/L (range)
Cerebrospinal fluid	
Enterovirus PCR	Negative
Herpes simplex virus PCR	Negative
Culture with gram stain	No bacteria seen, no growth at 72 hr
% of cell count with differential	Lymphocytes 100 (40%–80%) (range)
Glucose	76 (40–75) mg/dL (range)
West Nile IgM	Negative
Erythrocyte sedimentation rate	62 (0–15) mm/hr (range)
Glutamic acid decarboxylase antibody	6.1 (0–5.0) IU/mL (range)
IgG serum	699 (460–1200) mg/dL (range)
MaTa autoantibody test	Negative
NMDA autoantibody	1:640 (< 1:10) (range)
Paraneoplastic autoantibody	Insufficient volume
Potassium channel antibody	Negative
Thyroglobulin antibody	< 20 (0–40) IU/mL (range)
Thyroid peroxidase autoantibody	Negative < 10 (0.0–35) IU/mL (range)

IgG/M, immunoglobulin G/M;NMDA, N-*methyl* D-*aspartate receptor; PCR, polymerase chain reaction*

word variety, sentence length, and word-finding ability, remained below baseline, as did her motor function. Her right-sided hemiparesis progressed and became more spastic the day after her initial IVIG treatment. The patient held her right hand in a fist, refused to open it voluntarily, and performed all actions with her left hand. She also experienced continued irritability, predominantly responding to questions with the word "no," had several episodes of hitting and kicking in the air with her left side, and did not want to cooperate with physical or speech therapy. A repeat 1-hour EEG examination showed diffuse and left hemispheric slowing with spikes in the bilateral frontal, left central, and right temporal regions but no seizure activity.

Eighteen days after her initial epis ode, the results of our institution's serum anti-NMDAR antibody test came back as highly elevated (Table 2), supporting a diagnosis of NMDAR encephalitis. Immunosuppression with IVIG or corticosteroids has historically been considered standard of care in the management of this disease, but our patient had already experienced significant irritability on large doses of steroids and incomplete clinical response to multiple doses of IVIG. Following a review of available literature on second line therapies and consultation with our pediatric immunologist, the decision was made to initiate a 2-infusion regimen of rituximab, 375 mg/m^2 per dose. The initial infusion was tolerated well, with no infusion-related reactions or anaphylaxis.

The patient's speech significantly improved 2 days after her first infusion of rituximab, as evident by her ability to sing. Her fine motor movement had not yet returned to baseline at that time, however. The patient was discharged 24 days after her initial seizure on levetiracetam prophylaxis. A second rituximab infusion was scheduled for 2 weeks after the initial infusion, pending outpatient follow-up with the immunologist. Due to an almost complete return to baseline at that time, indicated by hemiparesis resolution and the return of normal speech, the second infusion was withheld at the outpatient clinic.

During the patient's second follow-up visit approximately 1 and one-half months after discharge, both her mother and the neurologist reported that she had nearly complete resolution of symptoms. Her speech had returned to baseline, she had no evidence of hemiparesis, and she was attending kindergarten. It was determined at that time that there was no need

for continued immunosuppression therapy.

Discussion

NMDA receptors are best known for their role in excitotoxicity, caused by excess glutamate release, activation of the receptor, and accumulation of intracellular calcium, and cell death. Anti-NMDAR encephalitis is an autoimmune disease in which antibodies form against the extracellular portion of NR1 subunits of NMDA receptors, resulting in neuropsychiatric symptomology.[2,3] The disease, originally described in 2005 as a paraneoplastic syndrome in a group of women with ovarian teratomas, was linked to the presence of anti-NMDA antibodies and was officially defined in 2007.[3,4] An estimated 60% of patients with anti-NMDAR encephalitis have associated tumors; however, in pediatric patients tumors are seldom present, although frequency increases with age.[2,3,6]

The clinical presentation of anti-NMDAR encephalitis typically begins with a prodromal collection of influenza-like symptoms, including headache, fatigue, and low-grade fever.[3,6] Psychiatric symptoms, such as memory problems, confusion, abnormal behavior, paranoia, and hallucinations may also be present, in addition to neurological symptoms of seizures, dyskinesia, autonomic instability, catatonia, hypoventilation, lethargy, and language deficits.[2,3,6] Hypoventilation and memory problems appear more frequently in adults, whereas children experience more movement deficits, including the atypical symptom of hemiparesis.[7] Furthermore, in comparing children and adults, studies suggest that neurological symptoms, including seizures, reduction in speech, and dystonia, may be more prevalent in children than in psychiatric cases.[2,7,8] Detection of behavioral abnormalities in this population may be made more difficult by the fact that irritability, temper tantrums, and hyperactivity can be associated with age rather than a frank psychiatric change.[2] Although variability exists in the constellation of symptoms with which patients present, all symptoms should receive consideration and evaluation regardless of a patient's age.

A number of diagnostic tests are used in the detection of anti-NMDAR encephalitis. Magnetic resonance imaging results are unremarkable in approximately half of patients, with hyperintensity visible in the other half, and abnormal EEG results are observed in most patients.[2,3,6] Abnormal CSF findings are discovered upon initial evaluation in approximately 80% of cases but can also be found later in the course of the disease.[2] Anti-NMDAR antibodies particularly are usually present in the CSF, although they can be detected in sera.[2] Detection of anti-NMDAR antibodies in any body fluid serves to confirm a diagnosis of anti-NMDAR encephalitis in patients with symptoms consistent with the disease. Both the serum and the CSF should be tested as soon as the disease is suspected, with periodically repeated screenings performed to track disease progression and treatment response.[2,6-8] Differential diagnosis represents a major challenge because the disease symptoms are characteristic of other disorders, and initial laboratory tests may not provide directive findings. The symptoms observed upon presentation may lead to a presumptive diagnosis of psychosis or viral encephalitis.[2,6] Anti-NMDAR encephalitis should be part of the differential diagnosis in young patients with significant behavioral changes, dyskinesia, and seizures, with CSF and EEG evaluations used to support the final diagnosis.[2]

The increase in number of documented cases of this disease since its definition suggests that anti-NMDAR encephalitis is not a rare condition.[6] In particular, it is being described more and more commonly in children.[8,9] The average hospitalization duration of patients with the diagnosis of anti-NMDAR encephalitis is approximately 2 and one-half months, although it can be much longer, and the severity of symptoms is directly associated with prolonged stay in the intensive care unit.[3,6] In patients with detectable anti-NMDAR antibodies, 75% experience only mild long-term deficits or recover completely, but the remaining quarter have severe sequelae or die.[2,6] Prognosis is largely time-dependent, including time to diagnosis, time to tumor removal (when present), and time to initiation of immunosuppressive therapy.[6] Early, efficacious treatment appears to be of paramount importance to optimize patient outcomes.[7] Recovery time of patients with anti-NMDAR encephalitis can be slow and variable, and as patients recover, symptoms usually resolve in the opposite order in which they appeared.[2,8]

Determination of tumor presence or absence is a primary consideration of treatment, as tumor removal should be part of the initial management when a teratoma is present.[2,3] Regardless of tumor presence, patients with diagnosis of anti-NMDAR encephalitis should receive first-line immunotherapy, typically corticosteroids, IVIG, or plasmapheresis.[2] Response to removal and first-line therapy in patients with tumors is approximately 80%, whereas patients without tumors have an initial response rate of 48%.[2] Pediatric patients are less likely to have associated tumors, which may contribute to the fact that first-line immunotherapy fails in up to half of all children treated for anti-NMDAR.[7] Poor response in children may also be related to the difficulty in recognizing the disease in this population, which ultimately results in delays in treatment. Second-line therapy, most commonly rituximab and/or cyclophosphamide, is often needed in patients without tumors and in those with a late diagnosis.[2] Approximately 65% of patients show substantial improvements with second-line immunotherapy, which tends to be well tolerated.[2,7] Another study reported a more favorable outcome, a 78% response versus 55% in patients who received second-line therapy compared with those who did not. Even after appropriate treatment,

patients can relapse, especially those without tumors, although relapse symptoms are typically less severe than the initial presentation.[7] Mycophenolate mofetil, cyclophosphamide, and/or rituximab have been proposed as effective relapse prevention agents.[8] These second-line immunotherapies may also decrease occurrence of relapse when administered as part of the initial treatment course and decrease the frequency of subsequent relapses if administered during the initial relapse.[7]

The findings of previous studies and the present case shed light on a number of points regarding anti-NMDAR encephalitis that warrant further consideration. First, only half of patients without an associated tumor experience symptom resolution with first-line immunotherapy. This represents a potential area for optimization and improvement. Corticosteroid therapy regularly results in only minimal improvement despite being administered in almost all reported cases.[8–10] Furthermore, the ability of corticosteroids to cause marked irritability and mood changes has been well established, especially in pediatric patients such as the patient in our case. The side effects associated with corticosteroids, including mood disturbances, may in fact mimic the patient's ongoing disease symptoms and, thus, make it more difficult to assess symptom resolution and response to therapy.

Second-line immunotherapies have shown a demonstrably higher percentage of successful outcomes and have been associated with decreased relapse occurrence. Of these therapies, more attention is being given to rituximab due to its potential role in hastening patient recovery and improving long-term outcomes. Rituximab is directed against the CD20 antigen on the surface of B-lymphocytes, decreasing maturation of B-cells into antibody-secreting cells. Additionally, it depletes the memory of these antibody-producing B-cells making it a favorable immunotherapy option in an antibody-mediated disease process such as anti-NMDAR encephalitis.

One case report of a 42-year-old female patient with anti-NMDAR encephalitis without a tumor suggested consideration of rituximab in patients who do not respond to initial immunosuppressive therapy because of rituximab's apparent recovery expedition effect and the patient's nearly complete symptom resolution after treatment.[11] A pediatric case report advocated use of rituximab to accelerate recovery and even proposed consideration of rituximab as early immunotherapy in place of IVIG or corticosteroids.[9]

The present case adds to the literature on successful treatment with rituximab and the argument for its consideration earlier on in the treatment of anti-NMDAR encephalitis, especially in patients without an identified tumor. The patient demonstrated marked improvement in her language deficits 2 days after the initial rituximab infusion, had complete symptom resolution at her 6-month follow-up visit, and has experienced no relapse to date. Based on these findings, we believe rituximab represents a potentially attractive immunosuppressive agent in patients who experience adverse reactions to or in whom first-line immunotherapies fail and that it warrants investigation as a first-line treatment strategy itself. Future research could be aimed at comparing rituximab versus IVIG and/or corticosteroids for first-line therapy to determine whether rituximab is as effective, if not more so, than these conventionally used agents in treating anti-NMDAR encephalitis.

Conclusions

Anti-NMDAR encephalitis is increasingly being identified in pediatric patients presenting with seizures, dyskinesia, and neurological or psychological symptoms. The outcomes of this disease range from long-term deficits to complete recovery. Rituximab may be an appealing treatment option, especially in patients who do not tolerate or respond to immunosuppressive therapy with corticosteroids or IVIG. Further research is needed to elucidate the potential benefits of using rituximab sooner in the treatment course to improve symptom resolution and return to baseline in patients with anti-NMDAR encephalitis.

ARTICLE INFORMATION

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