Case Report

Anti-N-methyl-d-aspartate Receptor Encephalitis Presenting as New-onset Refractory Status Epilepticus Responding to Rituximab in an Adolescent Girl

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INTRODUCTION

New-onset refractory status epilepticus (NORSE) is defined as a refractory status epilepticus (SE) in a patient, without a clear acute or active structural, toxic, or metabolic cause, previous active epilepsy, or preexisting relevant neurological disorder. Cryptogenic NORSE cases, often immunotherapy is considered empirically as a favorable response, have been documented in anecdotal case reports. More than half of children with the anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis develop seizures and SE may also occur during the clinical course. But NORSE as a presenting feature of anti-NMDAR encephalitis is extremely rare, as most children present with subacute onset neuropsychiatric and extrapyramidal features. We are describing one such case in an adolescent girl with anti-NMDAR encephalitis, in whom even intravenous anesthetic infusion and first-line immunotherapy including corticosteroid and IVIG were insufficient to achieve seizure control. Super refractory left focal SE in this child resolved after 96 h of injection rituximab, following which intravenous anesthetics could be tapered and child survived with only mild functional limitation on follow-up at 6 months. In children with cryptogenic NORSE, the clinicians need to rule out the cerebrospinal fluid anti-NMDAR antibody. Rituximab is one of the most promising second-line immunotherapy options in children with anti-NMDAR encephalitis for achieving seizure control and inducing long-term remission.

KEYWORDS: Anti-NMDAR, autoimmune encephalitis, immunotherapy, NORSE, refractory seizures

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20–30% of children with NORSE do not survive the initial illness and, in survivors also, epilepsy and long-term neurocognitive impairment are fairly common. However, in a proportion of cases, etiology of NORSE can be detected and subsequent treatment depends on underlying etiology.[4] Although more than half of children with the anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis develop seizures and SE may also occur during the clinical course, only a few anecdotal case reports available in the literature describing children with NORSE caused by anti-NMDAR encephalitis.[5] We are describing one such case in an adolescent girl, in whom even intravenous anesthetic infusion and first-line immunotherapy were insufficient to achieve seizure control and required rituximab for controlling the seizures.

**Case Summary**

A 13-year-old premorbid completely healthy girl presented with sudden onset left focal clonic seizures for the last few hours, which did not respond to intravenous levetiracetam, valproate, and phenytoin administered in a local hospital. There was no history of prodromal febrile illness or any other systemic complaints. She did not have any abnormal movements, behavioral disturbances, or speech abnormalities along with the seizures. At presentation, the child was having active focal seizure and encephalopathy, with the Glasgow coma scale (GCS) of 9/15. Magnetic resonance imaging of the brain showed signal changes in frontal and temporal lobes (right > left) with contrast enhancement [Figure 1]. An electroencephalogram (EEG) showed frequent epileptiform discharges originating from the right frontal and temporal electrodes. Cerebrospinal fluid (CSF) examination revealed 10 lymphocytes, mildly elevated protein (69 mg/dL), normal sugar, and no growth on culture. Work up for neurotropic viruses in CSF, inborn error of metabolism, and tuberculosis was negative. Her CSF anti-NMDA receptor antibody was strongly positive by cell-based assay. Her pelvic ultrasonography and fundus examination were normal. By the time the anti-NMDAR positivity report was obtained, the child was already on midazolam infusion (18 µg/kg/min) and phenobarbitone infusion (2 mg/kg/h), on which still the child continued to have an intermittent recurrence of breakthrough seizures. Even after administering first-line immunotherapy (intravenous methylprednisolone pulse therapy for 5 days and intravenous immunoglobulins [IVIG]), intravenous anesthetics could not be tapered due to the persistence of seizures. Hence, she was started on intravenous rituximab (375 mg/m²) infusion. Complete

![Figure 1: Magnetic resonance imaging of the brain. T2-weighted (B, C, F) (coronal) and fluid-attenuated inversion recovery sequences (D, E) axial sequences showed asymmetric hyperintense signal changes in bilateral temporal, basi-frontal and opercular area ((right > left). These areas were hypointense on T1-weighted (A) and showed contrast enhancement on post gadolinium images (G, H)](image-url)
seizure control was achieved after 96 h of rituximab infusion, and midazolam and phenobarbitone infusion were tapered off subsequently. A repeat dose of rituximab was given after 1 week and subsequently at 3 monthly intervals. However, the sensorium took a longer period (around 2 weeks more) to become better. The child required 10 more days of mechanical ventilation after injection rituximab was administered. Thereafter, the child demonstrated slow but steady clinical improvement. On follow-up at 3 months, she required minimal assistance for ambulation (pediatric cerebral performance category scale 3) and, at 6 months, she was ambulatory, with a mild functional deficit (pediatric cerebral performance category scale 2). On Malin's Intelligence Scale for Indian Children, the child had a full-scale IQ of 82 (suggesting subaverage intelligence, but not amounting to intellectual disability, defined as IQ <70).

**DISCUSSION**

About 40% of SE cases ultimately become refractory to benzodiazepine and first-line antiepileptic drugs (AEDs). Management of NORSE is more challenging than refractory SE with known causes. Recent data suggest viral encephalitis rarely contributes to NORSE and no definite monogenic abnormality is detected in such children, while autoimmune causes are being increasingly recognized in these cases.[4] Noteworthy to mention certain viral encephalitis like Herpes simplex (HSV) encephalitis can subsequently trigger autoimmune phenomena including anti-NMDAR encephalitis.[8] But these cases usually do not satisfy the clinical criteria for NORSE.[7] Although in our case anti-NMDA receptor antibody was detected, there are multiple reports of children responding to immunotherapy even without any antibody positivity (seronegative autoimmune encephalitis). As a significant proportion of children with refractory SE develop into super refractory SE, i.e. have recurrence/uncontrolled seizures despite intravenous anesthetics, in such cases, a trial of immunotherapy may prove beneficial. In these cases, often corticosteroid and/or IVIG are tried as initial immunotherapy. But recently plasmapheresis and rituximab have been proven to have favorable results in few case reports and case series.[8] Moreover, the most plausible etiology for FIRES, a subcategory of NORSE remains autoimmune origin and often responds to immunotherapy.[9]

Anti-NMDAR encephalitis, described for the first time by Dalmau et al. in 2007, is a form of autoimmune encephalitis (AIE), where antibodies are targeted against the NR1 subunit of the NMDA receptor can be detected in CSF or serum. It is the most predominant AIE in children and more common in young adults, often associated with tumors like teratoma of ovaries. Unlike in young adults, in whom as much as 81% cases occur in females, in children a substantial proportion of cases occur in males and without any underlying malignancy.[9] Often many affected children had a history of prodromal febrile illness with headaches or upper respiratory symptoms, a few days to weeks before disease onset, but in our case no such symptoms were present. Characteristic clinical features include subacute onset (sometimes acute onset in children) psychosis, memory deficits, reduced consciousness, focal seizures, dyskinesias/other extrapyramidal movements, mutism, sleep disturbance, and autonomic dysfunction.[10] Apart from definite anti-NMDAR encephalitis with detectable autoantibody, a significant proportion have also probable/possible anti-NMDAR encephalitis, with these clinical features, evidence of neuroinflammation detected in CSF or neuroimaging and exclusion of other etiology. Apart from the removal of underlying malignancy, the cornerstone of treatment involves immunotherapy. While first-line immunotherapy includes corticosteroids with/without IVIG and sometimes plasmapheresis, a proportion of refractory cases/cases with relapse require rituximab or cyclophosphamide, as in our case. More than half of the cases achieve remission with first-line immunotherapy within 4 weeks, although a proportion of them are likely to relapse in the future.[9]

Atypical presentation of anti-NMDAR encephalitis is more common in children and seldom clinicians come across underlying ovarian teratoma in pediatric anti-NMDAR encephalitis. Psychiatric symptoms, memory deficit, central hypoventilation, and autonomic instability are less frequent in children, while seizures, mutism, dystonia, and other movement disorders are far more common. Rarely it may even present with hemiparesis, hemiataxia, and even clinical picture resembling meningitis. The delta brush pattern specific for anti-NMDAR encephalitis is also rare in children.[10] Less time to diagnosis and time to initiation of immunotherapy have been shown to have a favorable future prognosis, with only mild long-term deficit in children. Hence, early and efficacious immunotherapy is of paramount importance to ensure the optimum patient outcome. Those with severe symptoms like our case often require second-line immunotherapies, and have shown slower and less satisfactory recovery of symptoms. In pediatric anti-NMDAR encephalitis, response to first-line immunotherapy occurs only in around half of the cases, as tumor removal option is
not available in most, and delay in treatment is often common due to difficulty in recognizing nonspecific/ atypical symptoms.\[9\]

Rituximab is the most commonly used second-line immunotherapy, with cyclophosphamide and mycophenolate mofetil being less commonly used. After second-line immunotherapy, 65–78% of patients recover, as compared to only 55% if these therapies were not administered. Moreover, rituximab has been shown to reduce the risk of occurrence of relapses if administered during initial treatment and risk of subsequent relapses if administered during the first relapse.\[11\]

Often corticosteroid on long-term administration may cause mood disturbances and other psychiatric symptoms and makes it difficult to assess response to therapy and symptom resolution. Rituximab, a monoclonal antibody against CD-20 antigen on the surface of B-lymphocytes, decreases the maturation of B-cells into antibody-secreting cells and depletes memory of antibody-producing B-cells. Hence, it is a favorable immunotherapy option in anti-NMDAR encephalitis, which is an antibody-mediated disease process.\[12\]

Recently, a 50-year-old male had been reported to have NORSE as a presentation of anti-NMDA receptor encephalitis and he also had concomitant SARS-CoV-2 infection. He required IVIG, plasma exchange, and corticosteroids apart from multiple antiepileptic drugs and intravenous anesthetics.\[13\] Kaplan et al. have also described NORSE in a 29-year-old female with anti-NMDAR encephalitis, who required rituximab like our case. However, unlike our case, she had prodromal febrile illness and weakness on the right side of the body previously. She also had left temporoparietal epileptiform activity like our case apart from intermittent high-voltage α–β activity.\[14\] Kurukumbi et al. described three adult patients with serospective autoimmune encephalitis (antibodies against NMDAR, LGI1, and N-type VGCC in one each) and recalcitrant SE who achieved improvement in symptoms and long-term, complete epilepsy control with rituximab.\[12\]

Rituximab has also been found to be clinically highly useful in Rasmussen encephalitis, which has also the probable autoimmune origin.\[15\] However, pediatric cases with such an atypical fulminant presentation, responding to rituximab, are extremely rare in the existing literature.

**Conclusion**

In children with cryptogenic NORSE, the clinicians need to rule out the CSF anti-NMDA receptor antibody. Rituximab is one of the most promising second-line immunotherapy options in children with anti-NMDAR encephalitis for achieving seizure control and inducing long-term remission.

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**Conflicts of interest**

There are no conflicts of interest.

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