Case Series

SEVERE PEDIATRIC ANTI-NMDA RECEPTOR ENCEPHALITIS: FROM INFECTIOUS MIMICRY TO SECOND-LINE IMMUNOTHERAPY – A TWO-CASE SERIES

Fam Haw Yuan[1], Hii King Ching[1], Chin Kar Pui[1]

Author's Affiliation:
1- Paediatric Department Hospital Miri

Correspondence:
Fam Haw Yuan, Email: famkelvin@gmail.com

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ABSTRACT

Background: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is one of the most common forms of autoimmune encephalitis in children. Early diagnosis remains challenging because the initial clinical manifestations frequently resemble infectious meningoencephalitis, resulting in delayed recognition and treatment. Early initiation of immunotherapy has been shown to improve neurological recovery and reduce long-term morbidity. However, a subset of patients with severe disease requires escalation beyond first-line immunotherapy.

Aim: To describe the clinical presentation, diagnostic challenges, treatment strategies, and outcomes of two children with severe anti-NMDAR encephalitis requiring second-line immunotherapy.

Case Description: We report two previously healthy girls aged 9 and 10 years who presented with new-onset seizures, encephalopathy, and progressive neuropsychiatric manifestations. Initial cerebrospinal fluid (CSF) analyses demonstrated lymphocytic pleocytosis, leading to a provisional diagnosis of infectious encephalitis. Persistent neurological deterioration despite empirical antimicrobial therapy prompted further evaluation, and anti-NMDAR antibodies were subsequently detected in both patients. The first patient developed selective mutism, dystonia, and autonomic instability despite treatment with intravenous methylprednisolone and intravenous immunoglobulin (IVIG), requiring escalation to rituximab. The second patient experienced fulminant encephalopathy complicated by cerebral edema requiring mechanical ventilation, plasma exchange, and cyclophosphamide following inadequate response to first-line immunotherapy. An ovarian dermoid cyst was identified during evaluation of the second patient.

Keywords: Anti-NMDAR encephalitis, autoimmune encephalitis, pediatric neurology, rituximab, cyclophosphamide, immunotherapy

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an antibody-mediated autoimmune disorder affecting the central nervous system and is increasingly recognized as one of the leading causes of autoimmune encephalitis in children. Since its initial description by Dalmau and colleagues in 2007, improved clinical awareness and wider availability of antibody testing have led to increased recognition of this potentially reversible neurological disorder. Nevertheless, diagnosis remains challenging because the early clinical presentation

frequently mimics infectious meningoencephalitis, resulting in delays in diagnosis and initiation of appropriate immunotherapy.

The disease is caused by immunoglobulin G antibodies directed against the NR1 subunit of the NMDA receptor, resulting in receptor internalization and disruption of glutamatergic neurotransmission. This reversible synaptic dysfunction gives rise to a broad spectrum of neurological and psychiatric manifestations, including seizures, behavioral changes, movement disorders, speech dysfunction, cognitive impairment, altered consciousness, and autonomic instability. In children, seizures, encephalopathy, abnormal movements, and language dysfunction are often more prominent than the psychiatric manifestations commonly observed in adults, making diagnosis particularly challenging during the early stages of illness.

The diagnostic evaluation of anti-NMDAR encephalitis is further complicated by nonspecific laboratory and neuroimaging findings. Cerebrospinal fluid frequently demonstrates lymphocytic pleocytosis, while brain magnetic resonance imaging (MRI) may be normal or reveal only subtle abnormalities. Consequently, many children are initially treated for presumed viral or bacterial encephalitis before autoimmune encephalitis is considered. Recognition of characteristic clinical features and early antibody testing are therefore essential, particularly in patients who fail to improve despite appropriate antimicrobial therapy.

Current treatment recommendations advocate early initiation of first-line immunotherapy, including high-dose corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange when clinically indicated. Patients with persistent neurological deficits or rapidly progressive disease may require escalation to second-line immunotherapy with rituximab or cyclophosphamide. Early escalation has been associated with improved functional recovery and lower relapse rates in patients with refractory disease.

We report two children with severe anti-NMDAR encephalitis whose initial presentations closely resembled infectious encephalitis. Both patients experienced significant neurological deterioration despite first-line immunotherapy and ultimately required second-line immunomodulatory treatment. These cases highlight the diagnostic challenges posed by infectious mimicry and emphasize the importance of early recognition, prompt

initiation of immunotherapy, and timely escalation to second-line treatment in severe pediatric anti-NMDAR encephalitis.

Case 1

A previously healthy 9-year-old girl presented with a five-day history of fever and upper respiratory tract symptoms, followed by new-onset focal seizures involving the left upper limb. Shortly after seizure onset, she developed progressive behavioral changes characterized by irritability, emotional lability, social withdrawal, and selective mutism. Her neurological condition continued to deteriorate despite initial supportive management, raising concern for an underlying encephalitic process.

Initial laboratory investigations demonstrated cerebrospinal fluid (CSF) lymphocytic pleocytosis, consistent with an inflammatory process involving the central nervous system. Brain magnetic resonance imaging (MRI) revealed leptomeningeal enhancement without focal parenchymal abnormalities. Given the combination of fever, seizures, and CSF pleocytosis, infectious meningoencephalitis was initially suspected, and empirical antimicrobial therapy was commenced while microbiological investigations were pending.

Despite appropriate treatment, the patient exhibited progressive neurological deterioration. Her speech impairment worsened, evolving into complete selective mutism, and she developed generalized dystonia accompanied by autonomic instability, including fluctuations in heart rate and blood pressure. The lack of clinical improvement despite antimicrobial therapy prompted further evaluation for autoimmune encephalitis.

Testing for neuronal autoantibodies subsequently confirmed the presence of anti-NMDAR antibodies in the CSF, establishing the diagnosis of anti-NMDAR encephalitis. High-dose intravenous methylprednisolone followed by intravenous immunoglobulin (IVIG) was initiated as first-line immunotherapy. Although partial clinical stabilization was achieved, persistent dystonia, mutism, and autonomic dysfunction suggested an inadequate response to treatment.

Given the severity of her neurological manifestations and failure to demonstrate meaningful improvement after first-line immunotherapy, rituximab was administered as second-line treatment. Rituximab was selected because of its B-cell-depleting effects and its established role in refractory anti-NMDAR encephalitis. Following treatment,

the patient demonstrated gradual neurological recovery, with progressive improvement in speech, resolution of dystonic movements, and stabilization of autonomic function. Intensive multidisciplinary rehabilitation, including physiotherapy, occupational therapy, and speech therapy, further contributed to recovery. At follow-up, she continued to demonstrate gradual functional improvement and increasing independence in activities of daily living.

Case 2

A previously healthy 10-year-old girl presented with generalized seizures followed by rapidly progressive encephalopathy and declining consciousness. Initial brain MRI was unremarkable, while CSF analysis demonstrated lymphocytic pleocytosis without microbiological evidence of bacterial infection. Based on the initial presentation, infectious encephalitis remained the leading differential diagnosis, and empirical antimicrobial therapy was initiated.

Despite treatment, her neurological condition deteriorated rapidly. She developed severe encephalopathy associated with cerebral edema requiring endotracheal intubation, mechanical ventilation, and admission to the pediatric intensive care unit for comprehensive neurocritical care. The severity of her clinical course and failure to respond to conventional antimicrobial therapy raised increasing suspicion for autoimmune encephalitis.

Subsequent CSF analysis confirmed the presence of anti-NMDAR antibodies, establishing the diagnosis of anti-NMDAR encephalitis. High-dose intravenous methylprednisolone and IVIG were administered as first-line immunotherapy. However, the patient demonstrated minimal neurological improvement, prompting escalation to plasma exchange to facilitate removal of circulating pathogenic antibodies.

Because significant neurological impairment persisted following plasma exchange, cyclophosphamide was initiated as second-line immunotherapy. Cyclophosphamide was selected because of the fulminant nature of her disease and the inadequate response to conventional first-line therapy. During further evaluation, imaging identified an ovarian dermoid cyst. Although tumor-associated anti-NMDAR encephalitis is less common in pediatric patients than in adults, identification of an ovarian dermoid supported the autoimmune etiology and highlighted the importance of routine tumor screening in female patients with confirmed disease.

Following aggressive immunotherapy, intensive care management, and multidisciplinary rehabilitation, the patient demonstrated gradual neurological recovery. Improvements were observed in cognitive function, motor performance, communication, and overall functional status. Although recovery was prolonged, her clinical course illustrates that meaningful neurological improvement is achievable even in children with severe anti-NMDAR encephalitis complicated by cerebral edema when prompt diagnosis and timely escalation to second-line immunotherapy are undertaken.

Summary of two cases

These two cases illustrate the broad clinical spectrum of pediatric anti-NMDAR encephalitis and the diagnostic challenges encountered during the early stages of illness. Both children initially presented with clinical and laboratory findings suggestive of infectious encephalitis, resulting in empirical antimicrobial treatment. However, progressive neurological deterioration despite appropriate therapy prompted further investigation, ultimately confirming anti-NMDAR encephalitis. While both patients required escalation beyond first-line immunotherapy, they demonstrated favorable neurological recovery following individualized second-line treatment and comprehensive multidisciplinary rehabilitation.

Discussion

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is now recognized as one of the leading causes of autoimmune encephalitis in children and should be considered in any child presenting with acute or subacute encephalopathy, seizures, behavioral changes, movement disorders, or unexplained neuropsychiatric symptoms. Although awareness of this condition has increased substantially over the past decade, diagnosis remains challenging because its early manifestations frequently overlap with those of infectious encephalitis. Consequently, many patients receive empirical antimicrobial therapy before autoimmune encephalitis is considered. Our two cases illustrate this diagnostic challenge, as both children initially presented with fever, seizures, encephalopathy, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, findings that strongly suggested infectious encephalitis.

The clinical evolution of both patients, however, emphasized several features that should raise suspicion for autoimmune encephalitis. Progressive neurological deterioration despite appropriate antimicrobial therapy, development of characteristic neuropsychiatric manifestations, movement disorders, speech dysfunction, and autonomic instability are all recognized hallmarks of anti-NMDAR encephalitis. In the first patient, selective mutism, dystonia, and autonomic instability became increasingly prominent despite treatment for presumed infection. In contrast, the second patient experienced rapidly progressive encephalopathy complicated by cerebral edema requiring intensive care support. These differing presentations demonstrate the broad clinical spectrum of pediatric anti-NMDAR encephalitis and reinforce the importance of maintaining a high index of suspicion when the clinical course is inconsistent with an infectious etiology.

The pathophysiology of anti-NMDAR encephalitis is well characterized. Autoantibodies directed against the extracellular NR1 subunit of the NMDA receptor result in receptor cross-linking and internalization, leading to a reduction in functional NMDA receptors on the neuronal surface. This process disrupts glutamatergic neurotransmission and produces the characteristic neurological and psychiatric manifestations of the disease. Importantly, because neuronal destruction is limited, neurological dysfunction is potentially reversible if appropriate immunotherapy is initiated before irreversible secondary brain injury occurs. This mechanism explains why many patients, including those with severe neurological impairment, can achieve substantial functional recovery following timely immunomodulatory treatment.

Diagnosis relies on integrating clinical findings with laboratory investigations. CSF abnormalities, particularly lymphocytic pleocytosis and mildly elevated protein levels, are common but are not specific for autoimmune encephalitis. Likewise, brain MRI findings are frequently normal or demonstrate only nonspecific abnormalities. In our series, one patient demonstrated leptomeningeal enhancement, whereas the second patient had an initially normal MRI despite severe neurological disease. These findings are consistent with previous pediatric studies reporting normal MRI findings in up to half of affected patients. Therefore, a normal MRI should not exclude the diagnosis when clinical suspicion remains high. Detection of anti-NMDAR antibodies in CSF remains the diagnostic gold standard and is generally more sensitive and specific than serum testing.

Early recognition is essential because treatment delay has consistently been associated with poorer neurological outcomes. Current consensus recommendations advocate initiation of immunotherapy as soon as autoimmune encephalitis is strongly suspected, even before antibody confirmation when clinical suspicion is high and infectious causes have been reasonably excluded. First-line therapy generally consists of high-dose intravenous corticosteroids, intravenous immunoglobulin (IVIG), plasma exchange, or a combination of these modalities. These therapies aim to reduce inflammation and remove circulating pathogenic antibodies, thereby limiting ongoing neuronal dysfunction.

Although many patients respond favorably to first-line immunotherapy, approximately 20–40% require escalation to second-line treatment because of persistent neurological deficits or progressive disease. Both patients described in our report required second-line immunotherapy owing to inadequate clinical response after receiving corticosteroids and IVIG. The first patient demonstrated persistent mutism, dystonia, and autonomic instability despite first-line treatment and subsequently improved following rituximab administration. Rituximab is a monoclonal antibody directed against the CD20 antigen expressed on B lymphocytes, resulting in B-cell depletion and reduced production of pathogenic autoantibodies. Increasing evidence suggests that early administration of rituximab in refractory anti-NMDAR encephalitis is associated with improved functional outcomes, reduced relapse rates, and shorter recovery times.

The second patient presented with fulminant disease requiring pediatric intensive care support because of severe encephalopathy complicated by cerebral edema. Following limited improvement with corticosteroids, IVIG, and plasma exchange, cyclophosphamide was selected as second-line immunotherapy. Cyclophosphamide exerts broad immunosuppressive effects by inhibiting rapidly proliferating lymphocytes and remains an important therapeutic option in patients with severe or refractory disease. Although its use must be balanced against potential adverse effects, including gonadal toxicity and increased infection risk, cyclophosphamide remains an effective option when rapid disease control is required or when response to other immunomodulatory therapies is inadequate. Our patient's favorable neurological recovery highlights the importance of individualized treatment strategies based on disease severity and response to therapy.

Another important aspect of management is screening for underlying neoplasms. Ovarian teratomas are well recognized in adult women with anti-NMDAR encephalitis but occur less frequently in children. Nevertheless, pelvic imaging should be considered in all female patients, particularly adolescents, because tumor removal contributes significantly to disease control and reduces the likelihood of relapse. The identification of an ovarian dermoid cyst in our second patient underscores the importance of comprehensive evaluation even in pediatric populations, as associated tumors may influence both treatment decisions and long-term outcomes.

Comprehensive supportive care and multidisciplinary rehabilitation are equally important components of management. Children with severe anti-NMDAR encephalitis often require prolonged hospitalization, intensive care support, nutritional management, speech therapy, occupational therapy, physiotherapy, and neuropsychological rehabilitation. Recovery is frequently prolonged and may continue for several months after resolution of the acute inflammatory phase. Both patients in our series demonstrated gradual neurological improvement following aggressive immunotherapy combined with multidisciplinary rehabilitation, emphasizing that meaningful recovery remains achievable even in severe disease.

Our report has several limitations. As a two-case series, the findings cannot be generalized to all pediatric patients with anti-NMDAR encephalitis. Furthermore, long-term neurocognitive outcomes and relapse rates were not evaluated. Nevertheless, these cases provide valuable insights into the diverse clinical manifestations of pediatric anti-NMDAR encephalitis and highlight the importance of recognizing treatment-refractory disease requiring escalation to second-line immunotherapy. The contrasting clinical courses also illustrate that management should be individualized according to disease severity while maintaining a multidisciplinary approach throughout the patient's recovery.

Conclusion

Anti-NMDAR encephalitis should be considered in children presenting with persistent encephalopathy, seizures, behavioral changes, or movement disorders, particularly when the clinical course is inconsistent with infectious encephalitis. Early diagnosis, prompt initiation of immunotherapy, and timely escalation to second-line agents in refractory disease are essential to optimize neurological outcomes.

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Conflict of Interest

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Ethical Approval

Ethical approval and informed consent were obtained in accordance with institutional requirements.

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