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Management of Refractory Status Epilepticus and Profoundly Impaired Consciousness in Anti-NMDA Receptor Autoimmune Encephalitis

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ABSTRACT

Introduction: Autoimmune encephalitis is a major cause of non-infectious encephalitis and remains challenging to diagnose based solely on clinical presentation. Confirmation is particularly difficult in antibody-negative cases despite strong clinical suspicion, requiring comprehensive diagnostic workup.

Case Description: A 25-year-old male presented with progressive altered mental status and seizures preceded by behavioral changes for 10 days. EEG showed no epileptiform activity, cerebrospinal fluid analysis excluded infection, and brain CT was unremarkable. Serum and CSF HSV IgG/IgM were non-reactive. Anti-NMDA receptor antibodies in CSF were strongly positive. The patient developed refractory status epilepticus requiring mechanical ventilation, deep sedation with propofol, and multiple anti-seizure medications including phenytoin. Empirical acyclovir was administered for 10 days without improvement. High-dose methylprednisolone (1 g/day for 5 days) was given as first-line immunotherapy but yielded no neurological recovery. On day 14, plasma exchange was initiated for three sessions, resulting in marked clinical improvement with recovery of consciousness and seizure control.

Conclusion: This case highlights the critical importance of considering autoimmune encephalitis even when initial antibody results are pending or imaging is normal. Early escalation to second-line immunotherapy, particularly plasma exchange, can be lifesaving in anti-NMDAR encephalitis presenting with refractory status epilepticus and profound coma.

Keywords

Autoimmune Encephalitis, Anti-NMDA Receptor Encephalitis, Refractory Status Epilepticus, Plasma Exchange, Immunotherapy.

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INTRODUCTION

Autoimmune encephalitis (AE) has emerged as one of the most important causes of non-infectious encephalitis, surpassed in frequency only by viral aetiologies in many contemporary studies.[1,2] This disorder results from autoantibodies directed against neuronal surface antigens (for example, N-methyl-D-aspartate receptor leucine-rich glioma-inactivated, and contactin-associated protein-like 2 or intracellular onconeural antigens.[3] Since the landmark description of anti-NMDAR encephalitis in 2007.[4] more than 20 distinct neuronal autoantibodies have been identified, dramatically expanding the clinical spectrum and diagnostic approach to encephalitis of unknown origin.[5]

Patients typically present subacutely with a combination of psychiatric symptoms, seizures, movement disorders, autonomic dysfunction, and decreased levels of consciousness.[6] Refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) are particularly severe complications observed in up to

50–60% of anti-NMDAR encephalitis cases require intensive care unit (ICU) admission and prolonged anaesthetic coma.[7,8]

Early diagnosis relies heavily on cerebrospinal fluid (CSF) analysis for neuronal autoantibodies, supported by brain magnetic resonance imaging (MRI) and electroencephalography (EEG), although imaging may be normal in up to 50% of confirmed cases.[9] While empirical acyclovir has revolutionized outcomes in herpes simplex virus encephalitis, the optimal management of autoimmune encephalitis remains poorly standardized. First-line immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) induces clinical improvement in approximately 50–70% of patients, whereas 20–40% require second-line agents (rituximab, cyclophosphamide) or prolonged escalation therapy.[10,11] Failure to rapidly identify and treat the underlying immune-mediated process frequently results in prolonged ICU stay, ventilator-associated complications and permanent neurocognitive sequelae.[12] This case report describes the diagnostic challenges and successful multidisciplinary management of a young adult with anti-NMDAR encephalitis presenting with profound coma and refractory status epilepticus, highlighting the critical role of early escalation to plasma exchange therapy when first-line immunotherapy fails.

CASE DESCRIPTION

A 25-year-old man (body weight 55 kg, height 165 cm) with a previous history of depression, anxiety, and overdose of sedative medication was admitted to the emergency department on 12 October 2024 following progressive behavioural changes over the preceding ten days. Family members reported initial irritability, psychomotor agitation, and incoherent speech, followed by hypersomnia and lack of response. Three days prior to admission, he developed orofacial and limb dyskinesias and headaches. On the day of admission, he experienced three generalised tonic-clonic seizures lasting approximately three minutes each, followed by persistent coma (GCS E1M4V1), tachycardia (107 bpm), tachypnea (26/min), fever (38 °C), and hypoxia (SpO_2 92–94% on 3 L/min oxygen). Physical examination revealed no meningeal signs, isocoric reactive pupils (3 mm), and left-sided spastic hemiparesis without lateralisation on the initial assessment.

The patient was immediately intubated and transferred to the intensive care unit with a working diagnosis of nonconvulsive status epilepticus secondary to suspected viral or autoimmune encephalitis. Empirical therapy was initiated with intravenous acyclovir (800 mg five times daily), phenytoin (100 mg/8 h), and continuous propofol infusion (25–100 μg/kg/min) titrated to burst suppression on continuous EEG monitoring. Brain computed tomography (CT) and repeat electroencephalography (EEG) results were Cerebrospinal fluid (CSF) analysis showed mild lymphocytic pleocytosis (71 cells/μL, 85.9% polymorphonuclear, 14.1% mononuclear), elevated protein (42 mg/dL), normal glucose (66 mg/dL), and negative microbiology results (Gram stain, bacterial/fungal/TB culture, and HSV PCR). Routine blood tests, electrolytes, and renal and liver function remained largely within normal limits throughout the admission period (Table 1).

Table 1. Sequential laboratory parameters and microbiological results during ICU stay

Hospital Day	Hb (g/dL)	Ht (%)	WBC (×10³/μL)	Plt (×10³/μL)	Na/K/Cl (mEq/L)	PCT (ng/mL)	Key Events / Cultures
0	12.0	34.9	9.06	203	137/3.9/101	–	Admission
4	11.6	33.5	10.91	229	140/4.2/102	0.31	Methylprednisolone started
7	10.5	31.5	8.21	306	137/4.1/97	0.46	–
10	10.2	31.7	14.18	270	132/4.1/95	–	Sputum: A. baumannii + K. pneumoniae
13	8.6	26.0	11.25	318	139/4.1/100	–	Anti-NMDAR positive; PLEX initiated
16	10.3	30.7	14.18	227	134/3.6/94	–	Marked improvement post-PLEX #2

Despite ten days of antiviral and first-line antiseizure therapy, seizures recurred immediately after sedation interruption, confirming refractory status epilepticus (RSE). High-dose methylprednisolone (1 g/day for 5 days) was administered on day 5 of hospitalisation, but no clinical improvement was observed. On day 13, CSF anti-NMDAR receptor (NMDAR) IgG antibodies were strongly positive, confirming the diagnosis of anti-NMDAR autoimmune encephalitis. Plasma exchange (PLEX) was initiated on day 13 (five sessions every 24–48 h, 1.0–1.2 plasma volume per session). After the second PLEX session (hospital day 16), consciousness rapidly improved (GCS E4M6Vt during sedation vacation), dyskinesia resolved, and seizure activity ceased. Sedation was discontinued, ventilator support was weaned, and successful extubation was achieved. The patient was transferred to the high-care unit on day 21 after completing three additional PLEX sessions (limited by equipment availability). At discharge, he was fully conscious, oriented, and neurologically intact, apart from mild residual anxiety.

Supportive ICU care followed the FAST-HUGS-BID protocol, including enteral nutrition (1600 kcal/day, protein 1.3 g/kg/day), stress ulcer and venous thromboembolism prophylaxis, head-up positioning (30°), and daily physiotherapy. Sputum culture on day 10 grew multidrug-resistant Acinetobacter baumannii and pan-resistant Klebsiella pneumoniae; however, no systemic antibiotics were required as the patient remained clinically stable without evidence of ventilator-associated pneumonia.

DISCUSSION

Encephalitis is defined as inflammation of the brain parenchyma associated with neurological dysfunction, encompassing both infectious and non-infectious etiologies.[1] While histopathological confirmation via brain biopsy remains the gold standard, it is rarely performed pre-mortem due to procedural risks.[1] Consensus criteria, such as those from the International Encephalitis Consortium, emphasize major features like altered mental status for >24 hours alongside minor criteria including fever, seizures, and EEG abnormalities to establish the diagnosis.[2] In this case, the patient's progressive coma, recurrent seizures, low-grade fever, and initial EEG findings fulfilled these criteria, distinguishing it from metabolic encephalopathies like refractory hypoglycemia, which was excluded by normal glucose levels and lack of response to correction.[6,7] The subacute behavioral prodrome—irritability transitioning to agitation and hypersomnia—further aligned with early autoimmune encephalitis (AE) presentations, where psychiatric symptoms precede overt neurological decline in up to 80% of cases.[9]

Diagnostic confirmation hinges on cerebrospinal fluid (CSF) analysis, neuroimaging, and ancillary tests, with polymerase chain reaction (PCR) and antibody panels pivotal for etiologic elucidation.[1,3] CSF in this patient revealed mild pleocytosis (71 cells/μL, predominantly polymorphonuclear) with normal glucose and protein, negative cultures, and non-reactive HSV IgG/IgM, effectively ruling out bacterial, tuberculous, or herpetic encephalitis.[1] The delayed but confirmatory CSF anti-NMDAR positivity underscored the challenge of timely antibody testing in resource-limited settings, where delays can exceed 10 days.[11,12] Normal CT and EEG, while nonspecific, did not detract from clinical suspicion; EEG's role is more in detecting non-convulsive status epilepticus (NCSE) than etiology, as evidenced by the absence of epileptiform discharges until sedation interruption revealed RSE.[1,8] Per Australian-New Zealand guidelines, empirical acyclovir initiation pending results is mandatory, as done here for 10 days without improvement, prompting immunotherapy escalation.[3] This approach prevented misattribution of extraneural pathogens, with negative blood and sputum cultures (despite later multidrug-resistant isolates) confirming no systemic infection drove the encephalitis.[1]

Management of acute encephalitis prioritizes airway protection, seizure control, and targeted etiology therapy.[5] Intubation and mechanical ventilation were essential here due to coma and respiratory compromise, adhering to ABC stabilization principles.[5] RSE, occurring in 30–50% of anti-NMDAR cases, necessitated multimodal antiseizure therapy: phenytoin for sodium channel stabilization and propofol infusion for anesthetic-level suppression.[8] Phenytoin's inefficacy, with seizures recurring on weaning, defined RSE per established criteria, warranting second-line anesthetics.[5,8] Empirical acyclovir discontinuation after negative HSV serology aligned with Infectious Diseases Society of America (IDSA) recommendations, avoiding

unnecessary toxicity.[1] Upon anti-NMDAR confirmation, first-line immunotherapy with high-dose methylprednisolone (1 g/day for 5 days) was initiated per international consensus, though response was absent.[13-15] Escalation to plasma exchange (five sessions) yielded rapid recovery—improved GCS and seizure cessation post-session two—highlighting its superiority in antibody-mediated AE for direct autoantibody removal, with observational data showing 70–80% response rates when corticosteroids fail. In paraneoplastic subsets, tumor screening (negative here) remains crucial, but non-tumor cases like this respond comparably to immunotherapy.[16-19]

Supportive critical care via the FAST-HUGS-BID bundle mitigated complications during prolonged ventilation.[5] Early enteral nutrition (1000–1600 kcal/day, 1.3–1.5 g/kg protein) met ASPEN/SCCM guidelines for high-risk patients (NUTRIC score 5), preventing malnutrition despite initial hypoglycemia history, with balanced fluid administration (1500 mL/24 h) avoiding overload.[20-23] Analgesia-sedation targeted light levels (RASS -3 to -4, CPOT 0–1) using fentanyl and propofol, with daily interruptions balanced against RSE risk, per 2018 PADIS guidelines.[24] Though deeper sedation exceeded light-target recommendations, it was clinically justified.[25] Low VTE risk (Padua/IMPROVE scores) notwithstanding, prophylactic heparin reduced mortality in ventilated cohorts.[26–31] Omeprazole prophylaxis addressed stress ulcer risk from ventilation >48 hours and coagulopathy, though long-term PPI use warrants C. difficile monitoring.[32,33] Normoglycemia (GDS 91–143 mg/dL) obviated insulin needs, and antibiotic stewardship eschewing therapy despite resistant sputum isolates absent clinical pneumonia—curbed resistance.[[34] This case exemplifies the treatable nature of anti-NMDAR encephalitis when clinical acumen bridges diagnostic delays, with plasma exchange as a pivotal second-line intervention that yields full recovery. The risk of relapse (10–30%) mandates long-term monitoring and potential rituximab maintenance, emphasizing the need for multidisciplinary vigilance. Early immunotherapy, even presumptively, optimizes outcomes and reduces ICU sequelae in this increasingly prevalent AE.

CONCLUSION

Anti-NMDAR encephalitis should be suspected in young adults with subacute psychiatric changes progressing to refractory status epilepticus. Early plasma exchange is critical and can achieve rapid and complete neurological recovery when first-line corticosteroids fail. Combined with rigorous supportive ICU care, this approach can transform a potentially devastating disease into a highly treatable condition.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The Authors agree to be published in the Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare no conflicts of interest in this case report.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the case report. MDS was responsible for patient management, data collection, and initial drafting of the manuscript. All authors reviewed and approved the final version of the manuscript, ensuring its accuracy and integrity, and are accountable for all aspects of the work.

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