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Anti-NMDA-Receptor Encephalitis: Clinical Case Study and Implications for Nurse Practitioners

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Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a treatable autoimmune encephalitis that often presents with acute behavioral change or psychosis and rapidly evolves to dysautonomia, movement disorder, seizures, and decreased level of consciousness. We report a 26-year-old woman who presented to an Emergency Department (ED) with first-episode psychosis, autonomic instability, and orofacial dyskinesias. After an initial medical evaluation, the patient was referred to the ED Psychiatric Nurse Practitioner (NP), whose prompt application of a structured autoimmune-encephalitis diagnostic approach enabled expedited neurology consultation, cerebrospinal fluid (CSF) confirmation of anti-GluN1 antibodies, and early immunotherapy (steroids, plasma exchange, rituximab). At the three-month follow-up, she had resumed full-time work without psychotropic medication. This case underscores the value of structured diagnostic reasoning and early referral pathways in the emergency department.

Keywords

Anti-NMDAR Encephalitis, Autoimmune Encephalitis, Acute Psychosis, Nurse Practitioner, Diagnostic Criteria

1. Introduction

Since its first description in 2007-2008, anti-NMDAR encephalitis has transformed the evaluation of acute psychosis in young people. Characteristic early features include subacute psychiatric and cognitive changes, speech disturbance, seizures, abnormal movements, autonomic instability, and reduced level of consciousness [1]-[3]. These psychiatric and cognitive changes often dominate the prodrome, followed by orofacial-lingual dyskinesias, seizures, autonomic instability, and fluctuating consciousness. Brain MRI is frequently normal or shows nonspecific T2/FLAIR changes, while EEG commonly demonstrates diffuse slowing and may

reveal the distinctive "extreme delta brush" pattern [3]-[5].

The 2016 Graus framework operationalized early syndromic diagnosis, often before antibody results, supporting timely immunotherapy and better outcomes [1]. Anti-NMDAR encephalitis is mediated by IgG antibodies targeting the GluN1 subunit of the NMDA receptor. Antibody binding results in receptor cross-linking and internalization, leading to hypofunction of NMDA-mediated synaptic transmission in hippocampal and cortical circuits [3]. This receptor hypofunction causes widespread network dysfunction, which underlies clinical presentation. Recovery correlates with declining antibody titers and restoration of receptor density, typically achieved through immunotherapy and tumor removal when present [2] [4] [6].

Though once considered rare, the disorder now has an estimated incidence of approximately 1 per million per year [3] [5]. It predominantly affects young women, with nearly half of cases linked to ovarian teratomas [3] [7]. However, geographic variation exists up to 40% of cases may be male, and tumor associations can be as low as 10% [2] [5] [8]. Late-onset presentations account for about 20% of cases and often involve fewer symptoms, non-ovarian tumors, and worse outcomes [5] [8]. In tumor-associated cases, immune activation is thought to result from molecular mimicry involving NMDAR expression on teratoma cells [3] [7]. While in non-tumor cases, prior viral infections particularly herpes simplex virus may trigger autoimmunity via neuronal injury and antigen exposure [1] [9].

Against this clinical and immunological backdrop, we present a case of anti-NMDAR encephalitis in a young woman whose initial presentation of acute psychosis was rapidly escalated using a structured diagnostic algorithm.

2. Case Presentation

2.1. Patient Profile

A 26-year-old woman presented to the Emergency Department (ED) with an abrupt onset of paranoia, hallucinations, and disorganized behavior over the course of a few days. She had experienced flu-like symptoms approximately one week prior to her psychiatric presentation. After ED medical clearance, she was referred to the ED Psychiatric Nurse Practitioner (NP) for further evaluation. The NP documented that she had no personal or family psychiatric history, an important red flag in a young adult that increased suspicion for an organic or secondary cause.

2.2. Initial Examination

On examination, her blood pressure was 160/95 mm Hg and heart rate 118 beats/min. She exhibited pressured speech, disorganized thought, and intermittent orofacial dyskinesias, further supporting the need for a neurological evaluation. Urine toxicology was negative.

2.3. Decision to Escalate

Given the subacute psychiatric onset in a previously healthy young adult, a recent

viral prodrome, autonomic instability, and orofacial dyskinesias, the ED Psychiatric NP explicitly applied the Graus autoimmune encephalitis algorithm to justify urgent neurology consultation and expedited testing. The patient was assessed against the three qualifying criteria for possible autoimmune encephalitis: 1) subacute onset (≤3 months) of altered mental status/psychiatric symptoms met by her abrupt paranoia, hallucinations, and disorganization; 2) at least one supportive finding to be established with urgent studies (MRI/EEG/CSF); and 3) reasonable exclusion of alternative causes supported by a negative urine toxicology, normal basic labs, and lack of prior psychiatric history [1]. In parallel, within the algorithm's anti-NMDAR encephalitis branch, she already exhibited abnormal behavior/cognitive dysfunction, movement disorder (orofacial dyskinesias), and autonomic dysfunction (tachycardia/hypertension) syndromic features that strengthened pre-test probability and triggered immediate escalation of care while antibody testing was pending.

The ED Psychiatric NP's advanced training included structured psychiatric assessment and neurologic screening techniques designed to detect organic causes of acute behavioral change. This training enabled the NP to recognize key clinical signs such as orofacial dyskinesias, autonomic instability, and fluctuating attention as potential indicators of autoimmune encephalitis rather than a primary psychiatric disorder. By applying this framework, the NP gathered targeted collateral history, ruled out common toxic and psychiatric causes, and escalated care for urgent neurologic evaluation and testing.

3. Diagnostic Process

The patient's head CT/MRI were unremarkable. Her cerebral spinal fluid (CSF) revealed lymphocytic pleocytosis (24 cells/μL) and was positive for anti-GluN1 antibodies, confirming definite anti-NMDAR encephalitis. The pelvic MRI showed no ovarian teratoma. These objective data fulfilled criterion (2) (supportive testing) of the Graus framework and, together with the clinical syndrome and exclusion of mimics, advanced the working diagnosis from possible autoimmune encephalitis to probable anti-NMDAR encephalitis pending serology, which was ultimately confirmed as definite by CSF anti-GluN1 antibody positivity and lymphocytic pleocytosis (24 cells/μL).

The Graus approach enables a probable diagnosis based on subacute onset of key symptom groups plus supportive tests, justifying early therapy while antibody testing is pending [1]. Cerebral spinal fluid NMDAR antibody testing is preferred over serum for sensitivity and correlation with disease activity, and higher antibody titers at diagnosis have been associated with worse outcomes or the presence of a teratoma [3] [4].

4. Differential Diagnosis

Key differentials for subacute psychosis with neurologic features include: infectious encephalitis (notably herpes simplex virus), primary psychiatric disorders,

other autoimmune encephalitides (e.g., LGI1, CASPR2, GABA-B), toxic-metabolic encephalopathy, and drug-induced states [1] [9] [10].

Red flags favoring autoimmune encephalitis over primary psychosis include rapid progression (<3 months), fluctuating consciousness, new seizures, movement disorder, dysautonomia, speech disturbance, and CSF pleocytosis or EEG abnormalities [1] [3].

5. Treatment Approach

The patient received high-dose IV methylprednisolone 1 g daily for 5 days, plasma exchange or plasmapheresis (5 sessions), and rituximab (375 mg/m^2). Early initiation of immunotherapy is associated with higher odds of good functional recovery and lower relapse risk [2] [8].

For incomplete response, second-line therapy commonly involves rituximab, with cyclophosphamide as an alternative, which should be considered within about two weeks [2] [6]. Refractory cases may warrant escalation in consultation with specialty centers. Tumor screening, especially for ovarian teratoma in adult women, should be performed at baseline and repeated if clinical suspicion persists [2] [3].

6. Patient Outcomes

Hospital length of stay was 21 days. At 3 months, her Montreal Cognitive Assessment improved from 19/30 to 28/30; she had resumed full-time work without antipsychotic medication. The patient provided written informed consent for publication.

Population-level data show that most patients achieve good functional outcomes with timely treatment. However, a minority experience relapse often within the first two years, especially when treatment is delayed or second-line therapy is not used [11]. Cognitive recovery often continues for up to three years, yet residual deficits (notably memory/language) and reduced participation can persist, underscoring the need for structured neuropsychological follow-up and rehabilitation planning [12].

7. Discussion

This case highlights how early recognition, structured diagnostic reasoning, and prompt initiation of immunotherapy can result in favorable functional outcomes in anti-NMDAR encephalitis. Cohort studies have shown that timely therapy is associated with improved prognosis and reduced relapse rates [8] [11].

The patient's rapid recovery marked by a short hospital stay and return to baseline functioning without antipsychotics parallels findings in the literature, where approximately 50% of patients achieve complete recovery within months. However, relapse occurs in 12% - 25% of cases, underscoring the need for early diagnosis and escalation to second-line therapies such as rituximab when warranted [11].

Systematic reviews have identified prognostic modifiers, including autonomic instability and need for ICU support, which correlate with worse outcomes [13]. In contrast, early combination therapy, typically high-dose corticosteroids with IVIG or plasma exchange, has been linked to better functional recovery [14].

From an advanced practice perspective, the case illustrates how the Psychiatric NP's training in recognizing "red flags" such as movement disorders, dysautonomia, and absence of psychiatric history can help differentiate organic from primary psychiatric etiologies in the ED. This role is central to reducing diagnostic delays and initiating appropriate care pathways.

This case reinforces findings from larger studies emphasizing early diagnosis as critical to reducing long-term morbidity. The patient's rapid, near-complete recovery illustrates the prognostic value of the Graus diagnostic framework in real-world emergency settings. Furthermore, it underscores the growing recognition of autoimmune encephalitis as a key differential diagnosis in acute psychosis an area of increasing clinical and research attention [15].

8. Advanced Practice Recommendations

1) Screen for autoimmune encephalitis in first-episode psychosis with neurological "red flags," using the Graus algorithm to justify urgent neurology referral and expedited CSF/serum antibody testing.

2) Order targeted studies early: MRI brain, EEG (with attention to extreme delta brush), comprehensive CSF analysis including anti-GluN1 testing, infectious PCR panel, and pelvic imaging for tumor search in adult women.

3) Treat promptly and escalate on a timeline: start first-line immunotherapy once probable criteria are met; if response is incomplete, add rituximab within ~2 weeks.

4) Partner with ICU, psychiatry, and rehabilitation to manage hypoventilation risk, agitation, and functional recovery while immunotherapy takes effect.

5) Plan surveillance: reassess cognition and function over 6 - 12 months and remain vigilant for relapse, which most commonly occurs within 24 months.

9. Conclusions

For young adults with acute psychosis plus neurological red flags, anti-NMDAR encephalitis is a time-sensitive, treatable diagnosis. Nurse practitioners can meaningfully alter outcomes by recognizing the syndrome, initiating the Graus diagnostic pathway, and catalyzing early immunotherapy and multidisciplinary care.

While this case offers valuable clinical insights, its single-patient design inherently limits generalizability. Larger-scale studies are needed to quantify the impact of advanced practice interventions on diagnostic timeliness and patient outcomes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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