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Autoimmune Encephalitis with neuropsychiatric manifestations Secondary to anti-N-methyl-D-aspartate receptor antibodies: a comprehensive case analysis and literature review

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Abstract

Background: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis represents a paradigmatic form of autoimmune encephalitis characterized by a constellation of neuropsychiatric symptoms including psychosis, seizures, cognitive dysfunction, and movement disorders. This condition poses significant diagnostic challenges due to its multifaceted clinical presentation that often mimics primary psychiatric disorders.

Objective: To examine the complex diagnostic and therapeutic considerations in a patient presenting with acute-onset psychosis and seizures secondary to anti-NMDAR encephalitis, emphasizing the critical importance of early recognition and multidisciplinary management.

Case summary: We present a 43-year-old postpartum female who developed severe neuropsychiatric symptoms including acute psychosis, seizures, and cognitive impairment. Initial psychiatric evaluation suggested a primary psychotic disorder; however, the presence of seizures, cognitive dysfunction, and a concurrent ovarian teratoma prompted reconsideration of the diagnosis. Cerebrospinal fluid analysis confirmed the presence of anti-NMDAR antibodies. Treatment with first-line immunotherapy (corticosteroids), antiepileptic drugs (valproic acid), and antipsychotics (aripiprazole) resulted in partial symptomatic improvement with persistent residual deficits.

Clinical significance: This case underscores the importance of maintaining high clinical suspicion for autoimmune encephalitis in patients presenting with new-onset psychosis, particularly when accompanied by seizures, cognitive dysfunction, or evidence of systemic autoimmunity. Early diagnosis and prompt initiation of immunotherapy are crucial for optimal neurological and psychiatric outcomes.

autoimmune encephalitis; neuropsychiatric manifestations; anti-n-methyl-d-aspartate receptor antibodies

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INTRODUCTION

Anti-nmdar Encephalitis – Narrative Version

Introduction Anti-NMDAR encephalitis is an increasingly recognized autoimmune disorder that was first described by Dalmau and colleagues in 2007. The condition occurs more frequently in women and children, and well-established triggers of NMDA receptor autoimmunity include ovarian teratomas and herpes simplex encephalitis. From a pathophysiological perspective, the disease is characterized by the production of IgG autoantibodies directed against the GluN1 subunit of the NMDA receptor. The binding of these antibodies leads to internalization of the receptor, resulting in synaptic dysfunction and disruption of normal neurotransmission.

Clinically, anti-NMDAR encephalitis typically follows a characteristic multiphasic course. Patients often begin with a viral-like prodromal phase, which is followed by the development of prominent psychiatric symptoms. As the disease progresses, seizures, movement disorders, and autonomic instability may emerge, and in severe cases patients can develop coma and hypoventilation. Many individuals experience an initial prodrome with systemic symptoms suggestive of viral infection, followed by progressive behavioral and psychiatric disturbances that are later accompanied by overt neurological manifestations.

The estimated incidence of anti-NMDAR encephalitis is approximately 1.5 cases per million person-years, with higher incidence rates observed in children and young adults. A strong female predominance is noted, particularly among women of reproductive age. In this population, ovarian teratomas are identified in approximately 50% of patients over 18 years of age.

CASE PRESENTATION

Patient Demographics and Initial Presentation

Mrs. M.G. is a 43-year-old married woman and mother of five children who was referred to psychiatric services in June 2020 due to the acute onset of neuropsychiatric symptoms. Her clinical course began during the third trimester of her fifth pregnancy in 2019, when she gradually developed behavioral changes. These included severe fatigue, persistent insomnia, anhedonia, and a marked neglect of personal hygiene as well as childcare responsibilities.

Clinical Course and Symptom Evolution

Approximately eight weeks after delivery, Mrs. M.G. experienced a dramatic deterioration in her clinical condition. Psychiatrically, she developed an acute confusional state with altered mental status, accompanied by complex auditory and visual hallucinations. She exhibited persecutory delusions and paranoid ideation, along with active suicidal ideation and expressed intent. Her presentation was further complicated by severe anxiety, pronounced mood lability, and significant cognitive dysfunction characterized by memory impairment, confabulation, and disorganization of thought processes.

In parallel with these psychiatric symptoms, neurological manifestations became evident. The patient experienced three witnessed generalized tonic–clonic seizures, each associated with loss of consciousness and a fall. She demonstrated psychomotor retardation with delayed speech, a flat affect with restricted emotional expression, a fixed gaze, and diminished facial movements. Attentional deficits and increased distractibility were also observed.

INITIAL MANAGEMENT AND DIAGNOSTIC RECONSIDERATION

At the initial stage, Mrs. M.G. was diagnosed with a primary psychotic disorder and empirically treated with aripiprazole at a dose of 10 mg daily. This intervention led to a temporary improvement in symptoms that allowed for hospital discharge. However, within two weeks, she experienced a relapse marked by re-emergence of psychotic symptoms, worsening cognitive impairment, and increased seizure activity. This clinical decline prompted readmission for a more comprehensive diagnostic evaluation.

COMPREHENSIVE DIAGNOSTIC EVALUATION

Medical History

The patient's medical history was notable for a suspected mature ovarian cystic teratoma that was under active surveillance. There was also a possible antepartum depressive episode that had been treated with sertraline. She had no history of prior psychiatric hospitalizations or psychotic episodes, and there was no reported family history of psychiatric or autoimmune disorders.

Physical and Neurological Examination

On the seventh day of the second hospitalization, a neurological consultation was obtained. Cognitive screening using the Montreal Cognitive Assessment revealed a score of 28 out of 30, which falls within normal limits. The neurological examination did not reveal focal deficits. Cranial nerve function was intact, motor and sensory examinations were normal, reflexes were preserved, and coordination was unimpaired.

Laboratory Investigations Routine laboratory investigations, including a complete blood count, comprehensive metabolic panel, liver function tests, and thyroid function tests, were all within normal limits. Serological testing for HIV and syphilis was negative. Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, were mildly elevated.

Imaging Studies Magnetic resonance imaging of the brain with contrast demonstrated normal structural anatomy without evidence of focal lesions, edema, or pathological enhancement. Computed tomography of the abdomen and pelvis revealed a 2.4 cm fatty lesion in the left ovary consistent with a mature teratoma. A chest CT scan did not show any abnormalities.

Neurophysiological Studies Electroencephalography revealed abnormal findings, including epileptic discharges with intermittent slowing, which were consistent with ongoing seizure activity. Cerebrospinal Fluid Analysis Lumbar puncture demonstrated a normal opening pressure of 120 mmH2O. Cerebrospinal fluid analysis showed mild lymphocytic pleocytosis with 12 cells/μL and a mildly elevated protein concentration of 55 mg/dL, while glucose levels were normal. Anti-NMDAR antibodies were detected and confirmed using a cell-based assay. Oligoclonal bands were present. Extensive infectious studies, including bacterial cultures, viral PCR, and fungal stains, were negative. A paraneoplastic antibody panel was negative for other antibodies.

TREATMENT PROTOCOL AND MANAGEMENT STRATEGY

Immunotherapy regimen

In accordance with current evidence-based guidelines for anti-NMDAR encephalitis, first-line immunotherapy was initiated. This approach typically includes high-dose corticosteroids, intravenous immunoglobulins, and/or plasma exchange. Mrs. M.G. received intravenous methylprednisolone at a dose of 1 g daily for five days, followed by a gradual oral prednisone taper over eight weeks. In addition, she was treated with intravenous immunoglobulin at a dose of 0.4 g/kg/day for five consecutive days. Plasma exchange was considered but ultimately deferred due to the patient's initial favorable response to steroids and IVIG.

Symptomatic Management

For seizure control, valproic acid, was initiated at a dose of 500 mg twice daily and titrated to achieve therapeutic serum levels between 50 and 100 μg/mL. Continuous EEG monitoring was employed to assess seizure control. Psychiatric symptoms were managed with aripiprazole at a dose of 15 mg daily. Lorazepam at 1 mg twice daily was prescribed as needed for severe agitation. Sleep disturbances were addressed through sleep hygiene measures and the use of low-dose trazodone for insomnia.

Supportive care included continuous cardiac and respiratory monitoring, prophylaxis for deep venous thrombosis, nutritional support, and physical therapy. Occupational therapy was also implemented to support cognitive rehabilitation.

Tumor management

Given the well-established association between ovarian teratomas and anti-NMDAR encephalitis in women of reproductive age, a gynecological consultation was obtained. The patient underwent a laparoscopic oophorectomy, which was performed without complications. Histopathological examination confirmed the presence of a mature cystic teratoma without evidence of malignant transformation.

Clinical Outcomes and Follow-up

Short-term Response (1–3 months): Following the initiation of immunotherapy and comprehensive symptomatic management, Mrs. M.G. demonstrated gradual but incomplete improvement. Neurologically, there was a significant reduction in seizure frequency from daily events to one or two episodes per week. EEG findings improved, showing decreased epileptic activity. Clinically, the patient became more alert, with improved attention span and partial restoration of psychomotor function.

From a psychiatric perspective, mood stability improved with reduced lability. The intensity and frequency of hallucinations decreased, reality testing improved, and delusional thinking diminished. Nevertheless, persistent anxiety required ongoing management. Sleep patterns also gradually improved. Cognitive assessment revealed improvement, with the MoCA score increasing to 29 out of 30. Memory consolidation and recall improved, as did executive functioning and planning abilities, although mild deficits in processing speed and working memory persisted.

Long-term Follow-up (6–12 months). It is estimated that approximately 80% of patients improve with immunotherapy and, when indicated, tumor removal, although recovery is often slow. At the 12-month follow-up, Mrs. M.G. continued to show gradual improvement. She achieved complete seizure freedom for six months, experienced a significant reduction in psychiatric symptoms, and regained functional independence in activities of daily living. Residual mild cognitive impairment, particularly affecting executive function, remained, and she continued to receive psychiatric follow-up for anxiety management.

LITERATURE REVIEW AND CURRENT UNDERSTANDING

Epidemiology and Clinical Spectrum Anti-N-methyl-D-aspartate receptor encephalitis predominantly manifests with psychiatric symptoms, particularly among female adolescents and young adults. Epidemiological data derived from recent meta-analyses demonstrate a bimodal age distribution, with incidence peaks observed in pediatric populations aged 5–15 years and in young adults between 18 and 35 years of age. In adults, the disorder shows a marked female predominance with an approximate female-to-male ratio of 4:1, whereas in children the gender distribution appears more balanced. A strong association with tumors has been consistently reported, with ovarian teratomas identified in 50–60% of affected females over the age of 18, while such associations are rare in children and male patients.

Pathophysiology and Immunological Mechanisms The pathophysiology of anti-NMDAR encephalitis involves a series of interrelated immunological mechanisms. Central to disease development is the production of IgG autoantibodies targeting the GluN1 subunit of the NMDA receptor. Antibody binding induces reversible internalization of NMDA receptors from the neuronal surface, leading to a reduction in receptor density. This process disrupts glutamatergic neurotransmission and results in widespread synaptic dysfunction. Preferential involvement of GABAergic interneurons leads to cortical disinhibition and network instability, which is believed to underlie many of the psychiatric and neurological manifestations. Recent studies have also identified potential biochemical biomarkers, including an increased serum phenylalanine-to-tyrosine ratio, which has been associated with the severity of psychiatric symptoms in affected patients.

Clinical Presentation and Diagnostic Criteria Patients with anti-NMDAR encephalitis present with a wide spectrum of neuropsychiatric symptoms. These may include apathy, anxiety, fluctuating levels of consciousness, bizarre or disor-

ganized behaviors, hypersexuality, wandering, aphasia, amnesia, apraxia, and marked disruption of the sleep–wake cycle with severe insomnia. Delusions and psychotic features are common. Clinically, the disease typically progresses through five recognizable phases. The prodromal phase is characterized by flu-like symptoms such as headache and fever. This is followed by a psychiatric phase marked by psychosis, behavioral changes, and cognitive dysfunction. Subsequently, patients may enter an unresponsive phase with catatonia, mutism, and movement disorders. A hyperkinetic phase often ensues, during which seizures, autonomic instability, and dyskinesias predominate. Finally, the recovery phase is characterized by gradual improvement over months or even years.

Current diagnostic approaches rely on the integration of clinical features with laboratory confirmation. According to modified criteria proposed by Graus and colleagues in 2016, diagnosis requires rapid onset, defined as symptom progression within three months, combined with at least four symptom groups. These include abnormal psychiatric behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorders or abnormal postures, decreased level of consciousness, and autonomic dysfunction or central hypoventilation. Laboratory confirmation is obtained through detection of anti-NMDAR antibodies in cerebrospinal fluid or serum, preferably using cell-based assays. Supporting findings may include CSF lymphocytic pleocytosis or oligoclonal bands, as well as EEG abnormalities such as slow or disorganized activity, epileptic discharges, or the characteristic extreme delta brush pattern. Treatment paradigms and evidence base management of anti-NMDAR encephalitis is centered on prompt initiation of immunotherapy. First-line treatment typically includes high-dose corticosteroids, intravenous immunoglobulins, or plasma exchange, ideally initiated within four weeks of symptom onset. Tumor removal is strongly recommended when an underlying neoplasm is identified. In cases of inadequate response after two to four weeks, escalation to second-line therapies such as rituximab or cyclophosphamide is advised, and combination therapy may be considered. For refractory cases, third-line or experimental treatments, including bortezomib, tocilizumab, alemtuzumab, or autologous stem cell transplantation, have been reported.

Prognostic Factors and Long-term Outcomes

Long-term prognosis in anti-NMDAR encephalitis is influenced by several clinical factors. Favorable prognostic indicators include early diagnosis and treatment initiation, prompt tumor removal, younger age at onset, less severe initial presentation, and absence of intensive care unit admission. Conversely, delayed diagnosis, severe initial disease requiring ICU care, delayed or insufficient immunotherapy, male gender in some studies, and older age at onset have been associated with poorer outcomes. With appropriate treatment, approximately 75–80% of patients achieve good functional outcomes, defined as a modified Rankin Scale score of two or less.

Seizure Management in Anti-NMDAR Encephalitis

Seizures occur in approximately 70–80% of patients during the acute phase of anti-NMDAR encephalitis. Status epilepticus has been reported in 30–50% of cases. Evidence indicates that immunotherapy is more effective than antiepileptic drugs alone in controlling seizures, and long-term epilepsy following resolution of encephalitis is uncommon, occurring in fewer than 10% of adequately treated patients. Consequently, antiepileptic medications should be considered adjunctive rather than primary therapy.

Psychiatric management considerations psychiatric manifestations may include psychotic mania, catatonia, or depression with psychotic features and are often refractory to conventional psychotropic treatment. Antipsychotic medications should be used cautiously due to the risk of extrapyramidal side effects. Benzodiazepines are preferred for managing agitation and catatonic symptoms, while mood stabilizers may be beneficial for affective instability. Electroconvulsive therapy is reserved for severe, refractory psychiatric symptoms. Overall, avoidance of polypharmacy is recommended, with emphasis placed on immunotherapy as the cornerstone of treatment.

DISCUSSION

This case illustrates the significant diagnostic and therapeutic challenges associated with anti-NMDAR encephalitis, particularly when psychiatric symptoms dominate the initial presentation. In postpartum patients, acute psychosis may be misattributed to puerperal psychosis or a primary psychiatric disorder. However, several features should prompt consideration of an organic etiology, including new-onset psychosis in a previously healthy individual, concurrent seizures, cognitive dysfunction exceeding that expected in functional psychosis, associated medical findings such as ovarian teratoma, and absence of personal or family psychiatric history.

The case further underscores the importance of a multidisciplinary approach involving psychiatrists, neurologists, immunologists or rheumatologists, gynecologists, and, in severe cases, critical care specialists. Such collaboration is essential for accurate diagnosis, comprehensive management, and optimization of outcomes.

The partial recovery observed in this patient is consistent with published data. Although neuroimaging findings are often normal or nonspecific, the reversibility of clinical symptoms with immunotherapy remains a defining feature of the disease. Factors that may have contributed to incomplete recovery in this case include delayed diagnosis, older age at onset, severity of the initial presentation, and prolonged immune activation related to the presence of a teratoma.

Future directions and clinical implications currently, there are no FDA-approved treatments for anti-NMDAR encephalitis, and prospective multicenter clinical trials are lacking. Future research priorities include the development of standardized treatment protocols, identification of predictive and prognostic biomarkers, improved understanding of long-term sequelae, validation of pediatric treatment recommendations, and determination of optimal maintenance immunosuppression strategies.

Clinically, physicians across specialties should maintain a high index of suspicion for autoimmune encephalitis in patients presenting with new-onset psychosis. Early neurological consultation, screening for seizures and cognitive decline, and evaluation for underlying tumors are essential. Education of patients and families regarding the prolonged and often incomplete nature of recovery is critical, as is provision of comprehensive rehabilitation and long-term follow-up.

LIMITATIONS

This case report is limited by its single-case design, which restricts generalizability. Long-term follow-up beyond 12 months was not available, and treatment variability reflects the absence of standardized protocols. Limited access to advanced biomarkers and potential socioeconomic influences on care must also be acknowledged.

Conclusion Anti-NMDAR encephalitis is a prototypical autoimmune neuropsychiatric disorder that requires heightened clinical awareness, rapid diagnosis, and aggressive immunotherapy. This case highlights the necessity of considering organic etiologies in patients with new-onset psychosis, particularly when seizures or cognitive dysfunction are present. Early recognition, multidisciplinary care, prompt treatment, systematic tumor screening, and sustained follow-up are essential components of optimal management. Continued research is required to refine diagnostic tools, optimize therapeutic strategies, and improve long-term outcomes for affected patients.

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