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Case Report

Paraneoplastic Anti-NMDA Receptor Encephalitis in a Nigerian Female Teenager: A Case Report.

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Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is characterized by neuropsychiatric symptoms, seizures, dysautonomia, and movement disorders. Initially identified as a paraneoplastic syndrome predominantly in young women with ovarian teratomas, it has become clear that not all affected individuals have tumors, and symptoms can occur across genders. With the availability of the NMDAR antibody assay, cases have also been identified in patients presenting with early psychosis, epilepsy, and classic limbic encephalitis. This emerging understanding enables earlier diagnosis, even in resource-limited settings, facilitating a multidisciplinary management approach that combines immunotherapies and tumor removal when indicated. This case highlights the importance of recognizing anti-NMDAR encephalitis in an 18-year-old female, emphasizing the need for prompt intervention to improve recovery outcomes.

Keywords: Encephalitis; Autoimmune; anti-NMDA Receptor Antibody; Seizure; Movement Disorder.

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Introduction

Following the discovery of the paraneoplastic anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, a rare autoimmune disorder first identified in 2007, its recognition has increased globally probably attributable to improved diagnostic accuracy. [1] This disorder occurs when antibodies are produced in response to an underlying neoplasm or infection, abnormally targeting NMDA receptors in the brain. These receptors are known to play important roles in synaptic plasticity, learning and memory. Functional impairment in the activities of these receptors results in a wide spectrum of neurological presentations, including leads cognitive symptoms, autonomic instability and seizures.[1]

Although paraneoplastic syndromes are more commonly associated with older adults and specific tumor types, anti-NMDA receptor encephalitis predominantly affects younger individuals, particularly women in their childbearing years. However, this condition has been reported across a wide demographic, including children.[2]

Anti-NMDA receptor encephalitis is a subacute rapidly progressive autoimmune encephalitis caused by intrathecal autoantibodies directed against the GluN1 portion of the NMDA receptor which typically affects young individuals, with a female predominance of 4:1; however, individuals of all ages can also be affected.[3]

Anti-NMDAR encephalitis typically manifests as a multi-phase clinical disorder resulting from progressive decline in NMDAR function due to its loss from the neuronal cell surface. This disorder usually manifests with neuropsychiatry symptoms with affected individuals eventually experiencing movement disorders, seizures and autonomic dysfunction, with antibodies identifiable in the serum or CSF.[4] Anti-NMDAR encephalitis can be a paraneoplastic manifestation of ovarian teratoma. However, herpes simplex encephalitis has also been shown to trigger NMDA autoimmunity.[3] Approximately half of the patients with this condition are younger than 18 years and are mostly females. About 30% of the females affected, mainly those between 18 and 35 years old, have ovarian teratomas.[5] Early diagnosis with the help of electroencephalogram, neuroimaging imaging and auto-antibody testing in both the serum and cerebrospinal fluid followed by immunosuppressive therapy is crucial in the management of this condition, For the paraneoplastic anti-NMDA encephalitis, surgical resection of the tumor followed by appropriate immunotherapy has proven to confer good prognosis is crucial as treatment with immunosuppressive therapy, and when indicated tumor resection confers good prognosis.[6] Thus, a high index of suspicion for autoimmune encephalitis, such as anti-NMDAR encephalitis, is required when a young female patient presents with subacute onset neuropsychiatric symptoms, seizures and movement disorders.

Diagnosis and management of anti-NMDA receptor encephalitis constitute a huge challenge in Africa, including Nigeria, due to limited awareness, diagnostic challenges, and paucity of specialized care services. Timely diagnosis and intervention are necessary for favorable outcomes, as delayed treatment may lead to increased morbidity and mortality.[7] This case report emphasizes the challenges encountered in managing this complex disorder, particularly in resource-limited environments like Nigeria, and discusses the implications for future healthcare strategies in the region.

The aim of this study is to report an 18-year-old female Nigerian teenager who presented to our facility with clinical features highly suggestive of this rare and complex disorder and to discuss the details of her management particularly in resource constrained setting such as Nigeria

Case Report

An 18- year-old lady presented to the Neurology unit on account of subacute onset involuntary movements, irrational behavior, seizures and recurrent vomiting of less than ten (10) days duration. She had complained of a febrile illness, intermittent colicky lower abdominal pain, and non-projectile vomiting a few weeks earlier. Further to this, she developed gradually progressive and dyskinetic movements, mostly affecting her limbs, trunk and craniofacial regions. At this stage, her movement symptoms had begun to affect her gait, swaying side to side, warranting ambulation with support. During this period, she insidiously developed irrational behavior such as unwarranted exclamations and weeping episodes as well as pressured speech. She also started convulsing and experienced multiple episodes within a few days. Seizures were mostly genderized tonic-clonic with associated interictal loss of consciousness and were mostly aborted using intravenous diazepam. Apart from this index admission, she was previously known to be in apparent stable health with no significant past medical history or neuropsychiatric illness. She did not have a background history of substance use. She did not have a family history of mental illness. Her menstrual cycle was regular.

Her physical examination findings were remarkable for a healthy-looking teenager, slightly agitated talking irrationally. She had significant mixed amplitude dyskinetic movements affecting her trunk and both upper and lower limbs, including the head. Movements were jerky, non-patterned and associated with associated broad-based gait. Her speech was slurred and scanning in nature. Ocular movements were normal in saccades, no gaze evoked or square jerk nystagmus.

Her abdominal examination showed asymmetric pelvic mass, more towards the left, estimated to be about 20-week size uterus. Other systems were essentially normal.

A provisional diagnosis of autoimmune encephalitis with a co-existing pelvic mass was made. She was requested to carry out some investigations, including brain imaging, abdominopelvic ultrasound pregnancy test, full blood count, serum electrolyte, urea and creatinine, cerebrospinal fluid biochemistry, liver function test, retroviral and hepatitis serology. Their results are shown in Table 1 below.

Abdominopelvic ultrasound revealed an asymmetric pelvic mass, more on the right but was not specific regarding the nature of the mass. Consequently, abdominal computerized tomography scan (contrast) was ordered and the result showed bilateral ovarian teratoma, measuring 18.8cm by 19.50cm, in the right, and 7.02cm by 4.01cm by 4.62cm, in the left (see Figure 1)

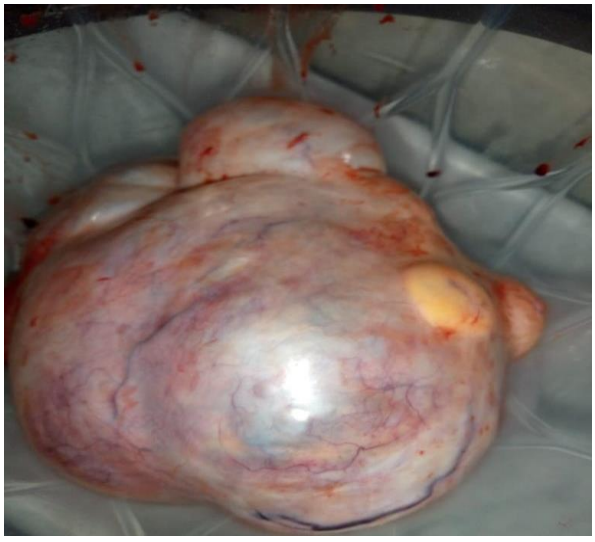

Figure 1 showing the gross appearance of the right ovarian mass

Following this development, the O&G team was invited for further review. Additional investigations, such as serum Ca-125 and anti-NMDA antibody were requested, and their results were also shown below (Table 1)

Table 1: Available investigation results

Investigations	**Results**	**Reference values**
Full Blood Count, ESR		
Hb	10.4	10-14g/dl
WBC	6,600	4-11,000cells/L
Platelet	374000	150-450000 cells/L
Neutrophil	64%	45-75%
Lymphocyte	43%	25-45%
Eosinophil	02%	1-6%
Erythrocyte Sedimentation Rate (ESR)	12	1-15mm/hour (Westergren)
Serum electrolyte, urea and creatinine		
Urea	12	7-20mg/dl
Creatinine	1.2	0.5-1.5mg/dl
Potassium	3.1	3.5-5mmol/L
Sodium	136	135-145mmol/L
Chloride	105	96-106mmol/L
Liver Function Test		
Total Bilirubin	0.8	0 – 1mg/dl
Conjugated Bilirubin	0.3	0 – 3mg/dl
Aspartate transferase (AST)	7	3 – 12IU/L
Alanine transferase (ALT)	8	3 – 12IU/L
Alkaline Phosphatase (ALP)	38	25 – 92IU/L

CSF Biochemistry		
Protein	0.16	0.15 - 0.45 g/dl
Glucose	3.2	2.2 - 4.4 mmol/l
Chloride	126	119 - 129 mmol/l
Cell count	0	0-5/µl
Serum CA125 assay	123.4(**high**)	(0.0 - 35.0 Unit/ml)
Hepatitis C Virus Hepatitis B surface antigen Retroviral screening Pregnancy test	Non-reactive Non-reactive Non-reactive Negative	
CSF NMDA Receptor Ab	1:4	1:<1 titer
Serum NMDA receptor IgG Ab	1:100	1:<10 titer

With the consent of the family members, right and left subtotal ovarian cystectomy was advised which she had few days later.

Intraoperative findings:
Bilateral ovarian masses with polycystic appearance. The right ovary appeared disproportionately larger than the left. The aspirates from the cyst contained yellowish and creamy exudates. Bilateral hydrosalpinx was also noted. However, the uterus looked normal.

Histological findings:
Mature teratoma composed of a cyst lined stratified keratinizing squamous epithelium. The wall of the cyst contains mature skin adnexal structures, bone spicules, lobules of mature fat cells and brain tissue.
A subsequent review of her clinical features, investigation results and histological findings strongly suggested paraneoplastic anti-NMDA receptor limbic encephalitis.

She was then given intravenous methyl prednisolone at 1g daily for 5 days which was followed by mycophenolate tablets 500mg twice daily. Other medications she received for her other various symptoms were Clonazepam tablets 0.5mg BD; Levetiracetam tablets 500mg BD; Risperidone tablets 0.5mg nocte. Figure 1. Gross appearance of the right ovarian teratoma

Focused neurorehabilitation with auto assisted shoulder mobilization exercises focusing on hand grip, sitting and standing re-education, coordination/stability was recommended.

She remained on admission for about 6 weeks during which time she was closely monitored. During this period, she experienced a remarkable improvement evidenced by a significant reduction in her seizure frequency and improvement in her sensorium, but her movement symptoms persisted. After discharge, she continued to follow up at the Neurology Outpatient Clinic, and by the third month post hospitalization, her gait had remarkably improved. Subsequent reviews noted reduction in her involuntary movements, behavioral symptoms and seizure frequency. She still attends clinic till date and no longer needs assistance to ambulate.

Discussion

Anti-NMDA receptor encephalitis is still rare in sub-Saharan Africa, and the first case that was reported in Nigeria more than a decade ago was in a 4-year-old boy who was hospitalized for fever, recurrent seizures and loss of consciousness. [8] Our patient might just be the first established case of this disorder with laboratory confirmed raised serum anti-NMDA receptor antibody and serum Ca-125 levels, the latter most likely due to her underlying ovarian teratoma. Etiology of anti-NMDAR encephalitis is variable and broadly classified as paraneoplastic and non-paraneoplastic. Autoimmune response against NMDA receptors can be induced by viral, tumor-related, or idiopathic causes, which can all potentially result in anti-NMDAR encephalitis and evidence for this can be supported by the observation of clonal plasma cells producing anti-NMDAR in the cerebrospinal fluid (CSF), the presence of plasma cells, IgG deposits, and decreased NMDAR levels in brain biopsies and autopsies.[9] As is typical in the majority of cases of anti-NMDAR encephalitis, the etiology of this disorder in our patient was paraneoplastic from bilateral ovarian teratoma.

Patients develop complex neuropsychiatry symptoms which manifest as prominent psychiatric and behavioral symptoms, rapid memory loss, seizures, abnormal movements (dyskinesias), hypoventilation, and autonomic instability because of disruption in cellular mechanisms. Our patient experienced most of these symptoms in the course of her illness, making her initial diagnosis difficult. As is well noted in the literature, diagnosis of this disorder can sometimes pose a serious challenge considering its atypical presentations.[10] Our patient had florid neuropsychiatric symptoms early in her illness, and was to be taken to a neuropsychiatrist on the suspicion of a primary psychiatric illness but was later brought to our facility. Rakiro et al described an indigenous Kenyan teenage patient, in a case report, who was confirmed to have anti-NMDA receptor encephalitis after presenting with subacute onset florid behavioral symptoms, insomnia and orofacial dyskinesia following a febrile illness.[11] In some cases, patients might present with agitation, aggression, disinhibition and hallucinations, making it difficult for an inexperienced clinician to suspect an organic disorder. This is to demonstrate that etiologies of anti-NMDA receptor encephalitis are diverse and not limited to the common causes.

In terms of the mechanism of this illness, antibodies are produced against the NMDA receptors in the hippocampal neurons, and this has been demonstrated both in vitro and in vivo, supporting the likely direct pathogenicity of the NMDAR antibodies, with disease severity correlating with serum antibody level. [8,12] In anti-NMDA encephalitis, the extracellular domain of the NR1 subunit of the NMDAR is directly targeted by autoantibodies, resulting in reduction in the surface and synaptic density of this NMDA receptors which leads to alteration and dysfunction in the synaptic localization and trafficking of the excitatory glutamate NMDA receptors which is central to the neurological symptoms manifested by the affected individuals. [9,13]

Our patient was a young female which is consistent with the median age of presentation as shown in the literature. Female gender predominance is well noted in the literature with most of the reported cases being females.[14] Notably, for most of the young onset illness, majority of the affected individuals appear to have a tumor that expresses the NMDAR autoantibody, most commonly an ovarian teratoma. [15, 16] According to studies, more than 90% of cases of tumor-associated anti-NMDAR encephalitis are

related to ovarian teratomas; over 2% of these cases were seen in the setting of extra ovarian teratomas; the remaining cases included individuals with lung cancer, breast cancer, testicular tumors, ovarian carcinoma, thymic carcinoma, and pancreatic cancer.[2] While prepubertal girls and male patients exhibit a low rate of associated neoplasm, affected females over the age of eighteen frequently present with ovarian teratomas. Clinical features, however, are typically similar in most patients and are thought to be multiphasic in most cases comprising of an initial prodrome, psychotic and/or seizure phase, unresponsive and/or catatonic phase, hyperkinetic phase and occasionally a gradual recovery phase. Our patient had a prominent pelvic mass in addition to her encephalopathic presentation, which gave away her diagnosis. In resource constrained settings such as ours with limited diagnostic resources and access to autoimmune antibody panel testing, a high index of suspicion is needed to guide a more specific antibody testing.

Apart from clinical features, antibody testing is important in establishing the diagnosis of anti-NMDAR encephalitis. The presence of autoantibodies in patient's serum and CSF, with the latter denoting intrathecal synthesis and high antibody concentration, is crucial for the definitive diagnosis of this condition. Other supportive diagnostic features include CSF pleocytosis, abnormal EEG findings which, on some occasions, can reveal a delta brush pattern, and MRI evidence of medial temporal lobe increased signal change.

Paraneoplastic anti-NMDA Receptor encephalitis is a complex, time-sensitive condition that frequently calls for a multidisciplinary approach to treatment.[17] Thus, early and definitive diagnosis and targeted therapy are crucial due to the nonspecific results of CSF analysis, EEG (electroencephalography), and neuroimaging, and the overlap of symptoms with several other infectious, neuroimmune, and psychiatric disease. In our case this was established by involving neuropsychiatry, obstetrics and gynecology and the neurorehabilitation team in patient management. As a result, our patient had a targeted ovarian tumor resection, and the patient tailored neurorehabilitation/medication in addition to immunosuppressive medicine, which was demonstrated to alleviate the neuropsychiatric symptoms. Studies have shown that despite the severity of the symptoms, 75% of patients recover after receiving immunotherapy and targeted tumor resection when appropriate as shown by symptom alleviation. However, it is not uncommon to see some individuals still left with cognitive, neuropsychiatry and motor deficits, or, rarely, even death. [18]

Steroids, intravenous immunoglobulins, and plasmapheresis are the optimal first-line immunotherapeutic options. Second-line immunotherapy (cyclophosphamide, rituximab, or both) can be tried on patients who do not respond to first-line treatments. The best results are achieved when this strategy is paired with the removal of the tumor, which significantly lowers the levels of NMDAR antibodies as was shown in our patient.[19]

The case report highlights the significance of utilizing a multidisciplinary approach in the identification and management of NMDAR encephalitis, especially in cases where it is associated with an underlying tumor.

Limitations of the study

We acknowledge a few limitations in this study. Firstly, our patient could not do brain MRI (magnetic resonance imaging) and electroencephalography during hospitalization because of her prominent behavioral symptoms at the initial stage of her illness. Instead, they opted for a contrast computerized tomography scan due to cost considerations, short acquisition time and the need to avoid moving patient out of the hospital facility in search of a facility with an MRI. Although brain MRI in autoimmune encephalopathies may be normal, it might also demonstrate signal abnormalities in suspicious areas of the brain in some affected individuals. For the anti-NMDAR encephalitis, MRI abnormalities are usually

noted in the hippocampal area of mesial temporal lobe.[20] Extreme delta brush is an EEG feature that can be seen in anti-NMDA receptor encephalitis. It occurs in about 30 % of the cases.[21] The above investigations are relevant in work up of patients with ant-NMDAR encephalitis and would have further strengthened our diagnosis. However, the availability of histological diagnosis as well as significantly elevated serum level anti-NMDAR antibody provided strong credibility to our diagnosis.

Conclusion

We have described a case of anti-NMDA receptor encephalitis in a female Nigerian patient. This is a heterogenous disorder with diverse clinical presentations. Although it is rare and may not have been encountered by many clinicians, there is need for a high index of suspicion especially in a young female with a subacute onset encephalopathy, seizures and movement disorders in the absence of a prior neuropsychiatric illness. Further search for an underlying ovarian teratoma in such a patient may be warranted, especially in the presence of a suspicious pelvic mass as we saw in our patient. Paraneoplastic anti-NMDAR encephalitis is notably a potentially fatal syndrome especially in younger females and so prompt diagnosis followed by institution of appropriate immunotherapy and surgical excision of the tumor may be live saving.

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