Anti–N-Methyl-D-Aspartate Receptor Encephalitis: Seizures and Psychosis – A Case Report

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Abstract. Anti–N-methyl-D-aspartate (NMDA) receptor encephalitis is a neurologic disease first identified by Dr Josep Dalmau and colleagues at the University of Pennsylvania in 2007. The first confirmed case of anti-NMDA receptor encephalitis reported in the Philippines was published in the *Philippine Journal of Neurology* last August 2012; it was entitled "A rare disease with a unique feature: Anti-NMDA receptor encephalitis and mesenteric teratoma". Anti-NMDA receptor encephalitis is an autoimmune disease where the body creates antibodies against the NMDA receptors in the brain, in which antibodies disrupt normal brain signaling, causing brain swelling, or encephalitis; many reports claim that it is often misdiagnosed due to atypical presentation that overlaps neurologic and psychiatric symptoms, in which it is difficult to recognize, and that may delay management.

Case description. An 18-year-old female from Mindoro, Philippines, was previously well. Two months prior to consult, she presented with sudden onset of unusual behavior noticed by her parents and siblings, such as sexual disinhibition, anxiety, and irritability. The patient was reported to have generalized seizure described as stiffening of both upper and lower extremities with upward rolling of eyeballs occurring five to six times per day, lasting for <30 seconds, with 4-hour intervals, associated with loss of consciousness. No other associated symptoms of fever and decrease in sensorium were observed. The family had no history of seizure conditions. They decided to seek consult at their local hospital, where the patient was being treated as a case of viral meningitis, but apparently, little improvement was noted; hence, she was transferred to a tertiary hospital in Metro Manila at Amang Rodriguez Memorial Medical Center. Upon admission patient was referred to our neurologist with a working impression of anti-NMDA receptor encephalitis versus viral meningitis; acute psychosis. However, during her hospital stay, the patient presented with pseudoseizures such as pelvic thrusting and involuntary muscle stiffening. She was given anti-seizure medications but did not improve. Other symptoms were also noted, such as insomnia, catatonia, and auditory hallucinations. Due to psychiatric features, she was then referred to a psychiatrist for further evaluation of the said symptoms. For further investigation, patient was requested for a 6-hour video electroencephalogram (EEG). The psychiatric service's initial impression was major neurocognitive disorder, probably due to encephalitis, to be determined. Additional medications were given, such as aripiprazole, an antipsychotic drug.

The result of video EEG suggested autoimmune anti-NMDA receptor encephalitis. A sample of cerebrospinal fluid was sent to laboratory to confirm, and it showed positive anti-NMDA receptor encephalitis. The patient was then treated as a case of anti-NMDA receptor encephalitis and managed accordingly. Patient was transferred to the ward with improvement noted. The patient was then discharged.

Conclusion. Anti-NMDA receptor encephalitis is one of the common autoimmune encephalitides. There may be increasing cases of anti-NMDA receptor encephalitis worldwide; however, in our country (the Philippines), there are only few reported and documented cases. Further studies must still be done to fully understand the course of the disease and diagnose it accordingly to avoid delays of management, since it is lifesaving, especially as it is more common in young adult females than in males. Anti-NMDA receptor encephalitis must be suspected and be taken into consideration when there is a patient who presents with variations of clinical presentation with psychosis and seizures.

Introduction

In the Philippines, there are only a few cases of anti–N-methyl-D-aspartate (NMDA) receptor encephalitis identified and documented. Aside from it being only recently discovered (in 2007) by Dr Josep Dalmau and colleagues at the University of Pennsylvania, not all clinicians are familiar with the disease entity, and specific tests are required for it to be diagnosed. The purpose of this case study is to present a case of an early-aged woman with psychiatric features that overlap neurologic symptoms with unknown etiology of anti-NMDA receptor encephalitis. There were primary considerations before

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proper diagnosis was made due to the peculiar and unfamiliar features.

Case Presentation

This is a case of an 18-year-old Filipino female from Puerto Galera, Oriental Mindoro, who was apparently well and suddenly manifested behavioral changes 2 months prior to admission. The behavior was described as self-isolation, sexual disinhibition (humping on the pillow), loss of association, impaired cognition, and poor judgment and insight. During the interim, patient had generalized seizure, described as stiffening of extremities and upward rolling of eyeballs, which occurred five to six times per day, lasting for <30 seconds, with 4-hour intervals, associated with loss of consciousness and inability to recall the said events. No associated symptoms of fever and decrease in sensorium were observed.

One month prior to admission, the patient was noted to have worsening of condition; hence, she consulted at a local hospital, where she was admitted for 2 weeks. The patient was awake but disoriented to time, place, and person. During the hospital stay, further work-up was done such as plain cranial computed tomography scan and cerebrospinal fluid (CSF) analysis which showed normal results. Electroencephalogram (EEG) showed mild-to-moderate encephalopathic process. She was treated as a case of viral encephalitis and given medications such as levetiracetam, dexamethasone, and acyclovir. During hospital stay, the patient was noted to have little improvement and was sent home.

At home, the patient had more frequent episodes of seizure followed by more aggressive behavior such as shouting with incomprehensible sounds, visual and auditory hallucinations, and non-purposeful movements. These symptoms prompted the patient's parents to look for a specialty hospital which they thought could handle the case, hence the patient's admission at Amang Rodriguez Memorial Medical Center.

Medical history was not significant to the progression of the disease: No history of any previous hospitalization prior to the said consult; no gynecologic abnormalities in the history were also noted; no history of seizures or epilepsy in the family.

Upon admission at Amang Rodriguez Memorial Medical Center, patient was awake, incoherent, did not follow simple commands, was unable to recall immediate and remote memories. She was noted to have a lack of hygiene. Patient was unable to ambulate, and no atrophy, weakness, stiffening, or fasciculations were noted on extremities. Fever and tonic seizures were noted. She was referred to our neurologist with an initial working impression to consider anti-NMDA receptor encephalitis versus viral meningitis; acute psychosis. Diagnostic work-up was requested, such as magnetic resonance imaging (MRI) with magnetic resonance angiography with magnetic resonance venography (MRA/MRV) with contrast and electroencephalogram. Medications were started such as acyclovir 500 mg intravenous (IV) every 8 hours (q8), dexamethasone 5 mg IV q8, phenytoin 100 mg IV q8, levetiracetam 100 mg/mL 10 mL twice daily, and diazepam for frank seizures. Patient was then admitted at the internal medicine intermediate care unit. During her hospital stay, patient had a distinct feature of pseudoseizures such as pelvic thrusting, abnormal movement of face (chewing, opening mouth and protruding of the tongue), flexing both lower legs with jerky movements without loss of consciousness, which we doubted if it was pseudoseizures or true seizures which occurred daily.

The MRI with MRA/MRV with contrast that was requested was not done due to uncontrolled frequent non-purposeful jerky movements and head turning to sides despite receiving multiple antiseizure medications. Well-distinct abnormal characteristics of psychosis were also noted, such presence of catatonia, hallucinations and delusions, insomnia, and restlessness. With those features, patient was then referred to psychiatry. A compilation of recorded videos of seizure and bizarre movements of the patient was sent to the psychiatrist for further evaluation. The impression was that patient had major neurocognitive disorder probably due to encephalitis, to be determined. They suggested further work-up, such as video EEG to correlate the seizure with bizarre movements. Additional medication given were aripiprazole and valproic acid, but apparently the symptoms did not improve. Multiple antiseizure medications were added and up-titrated, hoping to control the seizures, but apparently the seizures still did not improve. The neurology service requested for a 6-hour video EEG.

After a few days, the patient's video EEG results came out and were classified as technically difficult and limited due to the presence of abundant movements obscuring the background due to the patient's restlessness and bizarre movements. However, on brief portions seen in the background, there were times when the events of interest, especially the head turning with aversive gaze to the left or right, as well as hyperextension, correlated with rhythm changes over the right parieto-occipital regions. Also seen rarely were sharp-like discharges coming from the right occipital area without any clinical correlations. There was also a mild-to-moderate encephalopathic process of non-specified etiology, but likewise – even prior to the dose of diazepam – were the low-voltage beta activities superimposed on the delta activities, which correlate with autoimmune encephalitis such anti-NMDA receptor encephalitis.

A definitive test for anti-NMDA receptor was done where a sample of cerebrospinal fluid was sent to the laboratory to confirm suspicion, which later turned out to be positive. Other work-ups that were done with complete blood count, blood chemistry, and whole abdominal ultrasound were unremarkable. The patient was referred to obstetrics service for further investigation. A transvaginal ultrasound was done, which could help to determine the cause of the anti-NMDA receptor, and it revealed a normal-sized anteverted uterus, with

proliferative phase endometrium with normal ovaries noted. Serum antinuclear antibody test was also done to rule out autoimmune disease, which turned out negative.

Patient was managed with immunosuppressants (dexamethasone and IV immunoglobulin) for 2 weeks, and significant improvements were noted. The seizure episodes were controlled; the visual and auditory hallucinations were lessened. Patient now was able to answer simple questions. Antiseizures were continued and tapered down. Long-term mental or behavioral problems may occur, and this was explained to the relatives. Patient was then discharged after 1.5 months. Discharge instructions were given: to continue her antiseizure medications at home and have outpatient follow-up.

Discussion

Our immune system takes a big role in protecting us from many diseases. But sometimes, our immune system can also be the reason for our illnesses. There are a wide range of diseases where our own immune system destroys our body itself.[1] One of these is anti-NMDA receptor encephalitis. In this disease, there is an immunoglobulin G (IgG) autoantibody directly against the NMDA receptors in the brain; hence, disruption of normal brain signaling and brain swelling (encephalitis) can occur.[1-4] It can affect both males and females, but it is more common in females, primarily children and adults below 50 years old.[2,4]

Since the NMDA receptor is responsible for moods and cognition, disruption of this receptor can mimic the symptoms of schizophrenia and psychosis, like in the case of anti-NMDA receptor encephalitis. Symptoms in anti-NMDA receptor encephalitis typically starts with mild symptoms of headache and viral-like fever, which is a presentation during the prodromal phase.[2] The disease then slowly progresses to illness phase, wherein psychiatric symptoms can be seen, like behavioral change, delusional thought, progressive decline in speech, and the like. Neurologic complications can also be seen in this phase, where abnormal movements and seizure can warrant hospitalization.[3] The course of disease depends on early detection and management, and some patients can have a prolonged illness. Psychiatric functions are noted to be the last to improve.[2]

Diagnosing anti-NMDA receptor encephalitis based on history and physical exam is not easy, because it can mimic other neurologic and psychiatric diseases.[5] Therefore, the following are essential in diagnosing the disease: A CSF analysis with protein elevation and lymphocytic pleocytosis can be significant, but CSF IgG antibodies against the Glun1 subunit of the NMDA receptor is definitive. Serum/blood analysis is also used where antibody detection is definitive and it is preferred over CSF analysis. Imaging studies like cranial MRI can also aid in diagnosis where 50% of patients have fluid-attenuated inversion recovery–signal hyperintensities in the medial temporal lobe and the frontal and cerebellar cortices. Half of the findings can also be normal. EEG, though sometimes not feasible, can also be used in diagnosing because most, if not all, of the patients have abnormal EEG presentation that shows slow and disorganized activity in the delta and theta ranges with superimposed EEG seizures.[2,4]

There are three criteria which can aid in diagnosing probable anti-NMDA receptor encephalitis.[4] The first criterion, which is classified as rapid onset because of less than 3 months duration, includes at least four of the following: abnormal psychiatric behavior or cognitive dysfunction, speech dysfunction, seizures, and decreased levels of consciousness, movement disorder, autonomic dysfunction, or central hypoventilation. The next criterion includes laboratory results of an abnormal EEG and CSF with pleocytosis or hypoventilation. The last criterion is the exclusion of other relevant disorders.

Management can vary because there is no standard treatment modality, but the first line of treatment includes the removal of tumor if present.[2] Immunosuppression through immunoglobulin and corticosteroids shows significant help in the disease process.[1-3] Rituximab or cyclophosphamide is essential, mostly if there is no underlying tumor.[2,4] For the psychosis features, quetiapine can be given while valproate can help in mood stabilizing and seizure prophylaxis.[2,5]

Conclusion

We rarely see patients with anti-NMDA receptor encephalitis, and only a few reported cases were properly documented, especially in the Philippines. Prompt referral to a specialist is highly recommended, for proper diagnosis and management, such as in this case. Cases like this should also be transferred to a specialty hospital capable of providing proper management and care for the patient. Broadening our knowledge through research and differentials enables us to properly end up with the correct diagnosis and appropriate management. It is highly recommended that further studies also be initiated, especially on cases that we rarely see in our institution, which need further testing for confirmation.

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