Anti-NMDA-Receptor Encephalitis in Filipino Adults: Case Series and Outcomes in a Tertiary Government Hospital in the Philippines

Rodelia C. Pascua, MD, MBA[1] and Debbie Co Liquete, MD, FPNA[2]

ABSTRACT

Introduction

We performed a case series of all five (5) confirmed adult Filipino cases of Anti-N-Methyl-D-Aspartate receptor (anti-NMDA-R) encephalitis in a tertiary government hospital in the Philippines admitted in the past three years. Two cases were identified with unique features: (1) a 23-year old female who presented with combined refractory seizures and persistent chorea and orofacial dyskinesias; and (2) a 22-year old male who presented with refractory epilepsia partialis continuua. The rest of the patients were hereby presented.

Background

In the past years, anti-NMDA-R encephalitis has been considered a diagnosis of exclusion in lieu of other infectious causes of encephalitis. It is rare and an emerging disease with an incidence estimated at approximately 2-3 cases per million. Recent literature recorded severe cases of anti-NMDA-R encephalitis that presented as intractable first onset seizures, combined with hyperkinetic movement disorders, acute psychosis without a premorbid condition, and dysautonomia.

Objectives

To present the clinicodemographic profile and to discuss the management and outcomes of patients with anti-NMDAR encephalitis in a tertiary hospital in the Philippines

Results

Here, we report five confirmed cases of anti-NMDA-R encephalitis admitted in 2019-2021. The mean age is 23 years old, with 4:1 female to male ratio with a median length of hospitalization of 58 days. All patients presented with acute psychiatric symptoms without premorbid condition, focal and generalized seizures, decreased consciousness, dyskinesias, and autonomic instability. Four patients needed airway support for central hypoventilation, one had first onset seizure that developed into refractory epilepsia partialis continuua, one had persistent chorea and orofacial dyskinesia. Imaging studies of the brain included contrast-enhanced CT Scan and MRI with unremarkable findings. No female patients had an ovarian teratoma as revealed in the whole abdominal ultrasound. All CSF analysis for anti-NMDA-receptor was done in the same laboratory outside the hospital which revealed positive for NMDA-receptor antibodies, while CSF lymphocytic pleocytosis was only seen in 1/5 and protein elevation in 4/5. All of the patients underwent electroencephalogram (EEG) studies which revealed diffuse delta-theta slowing without epileptiform discharges. The patient who had persistent chorea and orofacial dyskinesias showed extreme delta brush, while one had normal EEG findings. They all received high-dose steroid and intravenous Immunoglobulin (IVIg); three patients were able to undergo Rituximab infusion. Only one female patient had mild deficits, one female was discharged fully functional and ambulatory from being weaned off from the mechanical ventilator, one female had aborted cardiac arrest and was discharged bedridden at GCS 10, and two died due to the other concomitant medical conditions. The Modified Rankin Scale (MRS) and Mini-mental Status Examination (MMSE) were used to assess the neurological and functional outcomes of our patients.

Conclusion

Anti-NMDA-R encephalitis is an emerging neurological disorder that warrants early identification as it impacts timeliness of management and long-term outcomes.

Keywords: Autoimmune, encephalitis, N-methyl-D-aspartate receptor, dysautonomia, refractory status epilepticus, acute psychosis

INTRODUCTION

Anti-NMDA receptor (NMAR) encephalitis has been one of the emerging neurological diseases for the past decade, first described by Dalmau and colleagues in 2007. It was initially regarded as a paraneoplastic syndrome because of its association with ovarian teratoma which are usually found in young females. Later on, cases were identified in patients even without tumor involvement. Using neuronal cultures and immunolabelling, this emerging disease has been regarded as caused by immunoreactivity against the NMDA receptor 1 (NR1) subunit of the NMDA receptor.[1] Severe forms were associated with the antibodies against NR1–NR2 heteromers of the NMDA receptor. [2]

The typical course of the disease includes a prodromal phase of nonspecific symptoms, usually viral-like prodrome in the first week, followed by the psychiatric manifestations such as acute psychosis, agitation, hallucinations, mania, sometimes reduced verbal output, often with seizures which spans around 1-4 weeks. Most of the patients will undergo the third stage or the unresponsive phase that necessitates intensive care because of hypoventilation, autonomic dysregulation, abnormal movements or dyskinesias, catatonia and even coma. And finally, the recovery phase where deficits are observed to be prolonged until their full recovery such as executive dysfunction, impulsivity, disinhibition and even memory deficit.

However, it is imperative to know that anti-NMDAR encephalitis does not completely adhere to this phasic progression as mentioned earlier. Patients who presented with the progression of symptoms despite initial treatment, cerebrospinal fluid (CSF) analysis findings of pleocytosis and/or oligoclonal bands without infection, magnetic resonance imaging (MRI) multifocal hyperintensities, and electroencephalogram (EEG) abnormalities such as diffuse slowing or delta brush activity, and the presence of another systemic autoimmune disorder should raise our suspicion that we are dealing with a neurological autoimmune disorder. Herekena and Pruss described them as yellow and red flag symptoms. [3]

The first line treatments identified include steroids, immunoglobulin (IVIg), and plasma exchange or plasmapharesis. In patients whose symptoms deem to progress or those who do not respond to these first-line agents, it is always prudent to consider second line treatment such as rituximab, a B-cell depleting monoclonal antibody, and/or an alkylating agent such as cyclophosphamide.

Case 1:

A 20-year old female was brought to our institution in April 2019 due to absent verbal output and catatonia after the first onset seizure of one-week duration where she was managed in another hospital. There was no history of viral-like symptoms and MRI findings done in the previous hospital was unremarkable. Due to our high suspicion for an autoimmune disease, we repeated lumbar tap and routine CSF analysis was done, including anti-NMDAR panel done in the outside laboratory. Electroencephalogram (EEG) showed diffuse slowing with no epileptiform activity. We immediately started high dose Methylprednisolone and on the fourth hospital day, the patient was noted to have autonomic dysregulation and persistence of catatonia and orofacial dyskinesias. She was resuscitated after an aborted cardio-pulmonary arrest and was placed in intensive care support.

We immediately started IVIg at 0.4g/kg/day for five days. During this time, second line treatment was not yet available in our institution, hence after completing IVIg, we maintained her on Prednisone at 1 mg/kg/day tapered down until discharge and Lamotrigine 50mg twice daily. The rest of her

[1]Fourth year resident Physician, [2] Consultant, Department of Neurosciences, Baguio General Hospital and Medical Center

hospital stay for one month and six days was unremarkable. She was eventually weaned off from the mechanical ventilator after tracheostomy. She finally went home at GCS 10 and MRS 4 on follow-up after three months.

Case 2:

A 30-year old female was admitted for a two-week history of agitation and anxiety followed by absent verbal output for the last three days prior to admission. At the ED, the patient was seen gritting her teeth, with orofacial movements and jerking of the left leg lasting for a few seconds. We admitted the patient with an impression of Autoimmune encephalitis where CSF analysis was done including Anti-NMDAR panel. She was started on high-dose Methylprednisolone 1g IV via infusion for 2 days. An EEG was done which revealed normal findings with no epileptiform discharges. On the third hospital day, we started the patient on IVIg and completed the session for five days. Due to the worsening of the autonomic dysregulation and the concomitant nosocomial pneumonia, she was eventually intubated and was placed in intensive care. She was observed for any improvement of symptoms after the five-day regimen of IVIg. After four weeks of no sign of improvement with the pneumonia resolving, we decided to give one dose of Rituximab and noted improvement in her neurological condition. After 53 days from admission, she was eventually discharged awake, conversant, ambulatory. Patient was seen at the OPD after four months with an MMSE score of 26/30 fully functional and back to work.

Case 3:

Another 20-year old female presented at the ED due to first onset of generalized tonic-clonic seizure episodes who initially presented with difficulty understanding her training lessons in college four days prior followed by behavioral changes described as incomprehensible speech and echolalia with persistence of sleep disturbances. She was brought to another ED where she was diagnosed with Adjustment Disorder. Upon admission in our institution, a cranial CT scan plain and contrast was requested in lieu of cranial MRI because of logistic constraint which revealed no acute infarcts, hemorrhages, edema or leptomeningeal enhancements. Medications were continued including the previously prescribed Levetiracetam, Escitalopram and Diazepam PRN for frank seizures.

On the third hospital day, EEG was done revealing focal slowing in the left frontotemporal area with no epileptiform activity. Cranial MRI plain and contrast was eventually done and whole abdominal ultrasound which revealed unremarkable results. On the 5th hospital day, the patient was noted to have absent verbal output and catatonia. Due to our high suspicion of an autoimmune disease, lumbar tap was immediately performed, and routine CSF analysis was done, including an autoimmune panel which was also sent to the designated outside laboratory.

She was started on high dose Methylprednisolone 1g once daily for five days. On the third day of steroids, she was noted to have persistence and worsening of agitation, which was not controlled with diazepam hence, she was started on midazolam drip. After five days of Methylprednisolone, the patient was started on IVIg for five days. Due to the persistence of symptoms, we decided to give Rituximab 500mg IV via infusion after she was cleared of Urinary Tract Infection and Nosocomial Pneumonia. After 29 days from admission, she was discharged, improved, ambulatory and conversant and went back to school afterwards.

Case 4:

A 23-year old female was brought to our Emergency Department due to a five-day history of generalized tonic-clonic seizures with associated low-grade fever and behavioral changes described as increased

sleeping time, blank stares and bradyphrenia. She was admitted in a private institution where a cranial MRI plain and contrast was done which revealed normal findings while an EEG which showed delta brush activity. The family opted to transfer the patient to our institution for further management. Lumbar tap was performed and CSF specimen was also for viral panels and anti-NMDAR. She was initially admitted as a case of Viral Encephalitis and was given Acyclovir 600mg IV every 8 hours for 10 days.

On the 7th hospital day, the patient had Nosocomial Pneumonia and was started on antibiotics. Due to the persistence of symptoms and no improvement of the neurological condition of the patient despite being on anti-viral for one week, we now highly suspected of an autoimmune encephalitis, hence we started the patient on high dose Methyprednisolone at 1g IV via infusion for five days. On the following day, the patient presented with orofacial dyskinesias with lability of vital signs and desaturations. She was then hooked to mechanical ventilator and was placed in intensive care. High-dose steroids were continued, while Acyclovir was continued to complete 10 days. Other medications were started to manage autonomic dysregulation. After five days of Methylprednisolone, the patient still had persistence of orofacial dyskinesias hence, IVIg was given at 0.4g/kg/day for another five days. There was still recurrence of seizure episodes alongside with abnormal movements resembling chorea.

On the 50th hospital day, the patient was eventually cleared by other co-managing services for Rituximab infusion and was given at 500mg IV via a strict infusion rate protocol, one dose of Methylprednisolone was given at 100mg IV in between Rituximab infusion. But despite undergoing one session of Rituximab infusion, there was still persistence of orofacial dyskinesias and autonomic instability. The Cardiology service started other rate controllers while the patient was continuously monitored due to the new onset T-wave inversion with negative Troponin I.

On the 56th hospital day, the patient was managed for another infection hence the second Rituximab session was deferred by the Infectious Disease service (IDS). After the antibiotic regimen, the patient underwent a second Rituximab infusion with unremarkable events and noted improvement in the patient's medical condition. The orofacial dyskinesias eventually decreased in frequency and duration. However, due to the persistence of recurrent infections, she was placed on multiple antibiotics and the patient had sudden CP arrest. Despite immediate and adequate resuscitative measures, the patient expired after 119 days of hospitalization.

Case 5:

A 22-year old male was brought to our institution from another local hospital due to uncontrolled seizures described as generalized tonic-clonic seizures where Cranial CT scan done revealed unremarkable results.

We initially treated the patient as Partially treated bacterial meningitis however Autoimmune encephalitis was also considered who presented as epilepsia partialis continuua. The patient was eventually intubated and Midazolam drip was started but the patient still had refractory seizures hence, Propofol drip was given. A cranial CT scan Plain and contrast was done with unremarkable findings. Lumbar tap was performed and CSF was sent for analysis including NMDAR antibody. An EEG was done which revealed abnormal findings due to the diffuse slowing or delta-theta activity with no epileptiform discharges. Alongside with the antibiotics, anti-seizure doses were increased. Eventually, the seizure episodes decreased with improvement in the sensorium of the patient hence, weaning off

Table 1. Clinico-demographic profile

Characteristics and Clinical Features	Patients (n=5)
Women, younger age	4
Male, younger age	1
Median age, range	23 (20-30)
Prodromal symptoms (viral-like)	1
Psychiatric symptoms	4
Seizures	5
Dyskinesias/abnormal movement	5
Autonomic dysregulation	4
Central hypoventilation	4
Outcome	
Discharged, improved	2
Discharged, bed bound	1
Death	2
Average length of hospital stay	58 days

from mechanical ventilator was initiated. However, on the 15th hospital day or 31 days from the onset of illness, the patient was noted to manifest unusual finger tapping on the right, followed by focal myoclonic seizures on the right upper and lower extremities, accompanied by orofacial dyskinesias. Since we highly suspected Autoimmune encephalitis, we started the patient on IVIg at 0.4g/kg/day for five days, Dexamethasone was continued, Gabapentin was added to his medications. Due to the persistence of focal seizures, Midazolam drip was resumed until seizure-free state was achieved. After completing five days of IVIg, we noted some improvement in the patient's condition. He had now spontaneous eye opening, with regard, was able to follow commands, with decreased episodes of orofacial dyskinesias and no recurrence of seizure episodes.

Chest CT scan plain and contrast was done which revealed an infectious process, highly probable of pulmonary tuberculosis, hence, the patient was started on anti-Koch's regimen and other medications for the recurrent nosocomial pneumonia but despite full resuscitative measures with the co-managing services, the patient expired after 47 days of hospital stay.

DISCUSSION

In the Philippines, most of the available epidemiologic data involves only the pediatric population, while data in adults are mostly case reports and/or institution-based. In our case series done in Baguio General Hospital and Medical Center, we were able to show that our local data encompasses this broad clinical phenotype of autoimmune encephalitis, as well as how similar and different we are in the context of this worldwide emerging disorder.

The clinical demographic profile of these five patients was summarized in Table 1. Younger patients with a mean age of 23 were affected, with female predominance of 4:1, consistent with the findings of recent literature.[4] Only one had a viral-like prodrome before the onset of psychiatric symptoms and which was followed by a persistent seizure combined with abnormal movement and orofacial dyskinesias. This patient underwent three sessions of Rituximab infusion, after high dose steroid and IVIg but eventually expired. All of them presented at the ED as first onset seizure, the only male patient presented as epilepsia partialis continuua which eventually progressed into refractory status epilepticus. There was a note of improvement in the neurological status of the patient after IVIg but succumbed to death due to other concomitant medical conditions. The three other young, female patients all presented with seizures, followed by psychiatric manifestations of agitation, decreased to absent verbal output, echolalia and catatonia. Two of them underwent Rituximab infusion and were discharged, improved and were able to go back to their previous work and school. One had aborted CP arrest but was discharged GCS 10, MRS 4.

As mentioned earlier, anti-NMDAR encephalitis tends to have a phasic progression based on the different symptoms and duration. Here, we were able to note that the timeline of clinical manifestations does

not strictly follow through as such, it still depends on each case. Only one patient had viral-like prodrome and all of the first psychiatric manifestations were present in the first week which persisted up to 4-6 weeks. Moreover, during this phase, all of our patients were simultaneously exhibiting autonomic instability and central hypoventilation and only three recovered. As such, the psychiatric phase may overlap with the unresponsive phase which may last for more than 6 weeks to months. The average length of hospital stay (LOS) of our patients is 58 days, but we need to also include the impact of the other concomitant medical problems of each patient that contributed to this outcome.

Only one of the five patients was seen initially by a Psychiatrist before a Neurologist and was managed as Adjustment disorder. The spectrum of Autoimmune encephalitis may present differently at the onset, and it is important to consider it as one of the differential diagnoses especially when the patient is young, female, with no previous psychiatric problems. In anti-NMDAR encephalitis, the psychiatric manifestation is usually the presenting symptom in the Emergency department or clinic consultations, and it consists of acute psychosis, agitation, anxiety, sleep-wake disturbances, decreased verbal output, aphasia, or memory deficit. The latter, together with profound disorientation, confusion and confabulation may relate to the affectation of the limbic structures is also common in LGI1-antibody syndromes and not only in NMDAR-antibody disorders.[5]

Seizures typical of NMDAR-antibodies are broad, from single, repetitive, non-refractory to refractory status epilepticus. In our series, all of our patients presented with seizures from first onset generalized tonic-clonic to refractory status epilepticus. Other autoimmune encephalitis may present primarily with focal seizures with faciobrachial dystonic features such as in LGI1-antibody,[6] seizure as the first event followed by diffuse brainstem or cortical encephalitis as in MOG-antibody [7]; or status epilepticus which is most frequent in patients with antibodies to the GABAAR/GABABR.[8] Abnormal movements are also common in autoimmune encephalitis and the most common would be chorea, dystonia, or in the case of glycine receptor (GlyR) and dipeptidyl peptidase-like protein 6 (DPPX) antibodies hyperekplexia and myoclonus. [9,10] In CASPR2- and IgLON5-antibody syndromes, gait disturbances are frequent.[11,12] Two of our patients demonstrated persistent abnormal movements such as myoclonic jerks and chorea during their seizure episodes. These patients also had the worst prognosis.

Table 2. Ancillary tests/procedures and treatment

	Patients (n=5)
Imaging (CT or MRI)	
Normal	5
Abnormal	0
EEG	
Normal	1
Diffuse slowing	3
Delta brush	1
CSF	
Abnormal overall	4
Lymphocytic pleocytosis	1
Elevated protein	4
(+) NMDAR Ab	5
Other tests	
Whole abdominal ultrasound (presence of tumor)	0
Treatment	
Corticosteroids	5

Table 2 presents the different ancillary procedures or tests and different treatment regimen our patients underwent. Cranial MRI was done in 4 patients, while CT scan was done in the male patient due to logistics constraints. In our series, no patient had abnormal MRI findings diagnostic of autoimmune encephalitis, while the reported abnormal MRI findings in the most recent literature was 20-30% with a typical limbic encephalitis as a minority. [4]

In recent literature, 90% of EEG showed abnormal findings, most are slowing

and 20% have epileptiform discharges. [4] In our series, three out of five or 60% had generalized or diffuse slowing consisting of delta-theta activity, one had an extreme delta brush activity while the remaining one had normal EEG result. The female patient who had this extreme delta brush EEG activity had the worst clinical features of persistent combined seizure and abnormal movements and had the longest hospital stay of 119 days before her demise. This correlation of extreme delta brush and poor prognosis is consistent with the available literature. [13]

All CSF analysis for anti-NMDA-receptor was done in the same laboratory outside the hospital which revealed positive for NMDA-receptor antibodies, while CSF lymphocytic pleocytosis was only seen in one of five or 20% and protein elevation in 80% which is also consistent in the recent literature. [4] The gold standard in the diagnosis of anti-NMDAR encephalitis remains to be the detection of NMDAR antibodies in the CSF. The sensitivity and specificity decreased when testing only serum. In our institution, we send CSF specimens to the outside laboratory and in this case, we are bound to their turn-around time of results. Hence, it is imperative for us to have a high clinical suspicion of Autoimmune encephalitis based on the symptoms and course of the disease alone with the help of the ancillary procedures mentioned above. [14]

Anti-NMDAR encephalitis is rather a reversible, treatable disease but has a slow recovery period. Some of the reasons mentioned in literature are the delay in recognition and diagnosis of an autoimmune process, delay in the initiation of immunotherapy, and the presence of other concomitant medical problems during their course in the hospital. In our cases series, the median number of days from the onset of symptoms to the time they were seen by our department was nine days. For our first case, she was started on immunotherapy on the third hospital day, or 10 days from the onset of symptoms and was discharged as MRS 4. The second and the third cases discharged as MRS 0-1 were started on immunotherapy upon admission and on the 5th hospital day, respectively. For the two patients who had the longest hospital stay and who expired were initially managed as CNS infections and were both on antibiotics and antiviral for 7-10 days before they were started on IVIg.

Balu, Makuch and colleagues showed that in anti-NMDAR encephalitis, early treatment is strongly associated with a good outcome defined as MRS ≤2 while delays in immunotherapy of > 4 weeks was associated with poor functional outcome at 1 year. [15,16] First-line treatment includes corticosteroids, intravenous immunoglobulins (IVIg), and/or plasma exchange. Second-line therapy includes rituximab and cyclophosphamide. In our experience, IVIg is generally effective but there is a limitation to conclude that it is more beneficial than plasma exchange since this is not available in our institution during the time our patients were admitted. This further needs to be elaborated because, while IVIg is the only immunotherapy that underwent a randomized controlled trial among the three first-line agents, some data appears that IVIg is the least effective. [17] With regards to the utilization of Rituximab, in our case series, the limitation of the second line agents was due to the presence of other concomitant medical problems, in particular, nosocomial infections that may delay the initiation or continuation of Rituximab sessions.

CONCLUSION

This case series showed that a high clinical suspicion is needed for the early diagnosis of autoimmune encephalitis because of its broad manifestations, as well as the similarities and differences of our local data compared with our international counterparts. Early recognition is of utmost importance so that early immunotherapy is initiated for better outcomes.

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