Anti-N-methyl-D-Aspartate (NMDA) Receptor Encephalitis: A Case Report

Salman Mansoor[1], Salman Assad[2], Ahmed Shah Bukhari[2], Nabeel Muzaffar Syed[3], Muhammad Amjad[4], Tahir Aziz[5]

[1]*Registrar Neurology, Department of Neurology, Cork University Hospital, Cork, Ireland*
[2]*MBBS, Shifa College of Medicine, Islamabad, Pakistan*
[3]*FCPS Trainee Neurology, Department of Neurology, Shifa International Hospital, Islamabad, Pakistan*
[4]*Consultant Neurology, Shifa International Hospital, Islamabad, Pakistan*
[5]*Consultant Immunologist, Shifa International Hospital, Islamabad, Pakistan*

Conflict of Interest: None declared

This article has been peer reviewed.

Article Submitted on: 16th October 2017

Article Accepted on: 18th June 2020

Funding Sources: None declared

Correspondence to: Dr Salman Mansoor

Address: Department of Neurology, Cork University Hospital, Cork, Ireland

E-mail: salmanmansoor.dr@gmail.com

Cite this Article: Mansoor S, Assad S, Bukhari AS, Syed NM, Amjad M, Aziz T. Anti-N-methyl-D-Aspartate (NMDA) receptor encephalitis: a case report. J Pioneer Med Sci. 2020; 9(1):19-21

ABSTRACT

We report case of a 42 years old female who came with a constellation of behavioral symptoms, delirium, body stiffness, and fever for one week. Past medical history was significant for a prolonged critical care admission at an outside facility for seizures two years ago. Her examination was consistent with the diagnosis of encephalitis. Initially, she was managed as viral encephalitis based on cerebrospinal fluid analysis with a predominant lymphocytic picture. Computed tomography (CT) scan brain was normal. An electroencephalogram (EEG) revealed moderate to severe diffuse encephalopathy. During her stay at our hospital, she developed orofacial rhythmic dyskinetic movements coupled with autonomic dysfunction. Due to her predominant symptoms of encephalitis coupled with psychiatric, autonomic and dyskinetic features, she was investigated for an underlying autoimmune etiology. She was tested positive for N-methyl-D-aspartate receptor (NMDA-R) antibodies. She received four sessions of plasmapheresis and was referred to another facility where she died. NMDA-R encephalitis poses a significant diagnostic challenge to the clinicians. These cases are potentially treatable if diagnosed earlier and started on recommended treatment with plasmapheresis, intravenous immunoglobulins, pulsed steroids, and immunosuppressants. Autoimmune encephalitis is an expanding entity which is evolving with advancements in neuroimmunology.

Keywords: N-methyl-D-Aspartate Receptors; Anti-N-methyl-D-Aspartate Receptor Antibodies; Encephalitis; Autoimmune

INTRODUCTION

The confluence of neurologic, psychiatric and autonomic symptoms, mostly with a viral prodrome is the hallmark of anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis. Psychiatric referrals are common because initially, these patients present with memory loss, psychosis, hallucination, and personality changes. This is usually followed by dyskinesia, especially in the orofacial region. Other features may be ataxia, seizures, and autonomic instability. Drowsiness leading to loss of consciousness may develop. Brain imaging, cerebrospinal fluid (CSF) examination, and electroencephalogram (EEG) are non-specific. Increased CSF protein, lymphocytic pleocytosis, oligoclonal bands, and reduced uptake in hippocampal areas on Magnetic resonance imaging (MRI) are present [1–3].

Although epidemiological studies suggest that NMDA-R encephalitis may be the second most common cause of encephalitis [4], it is still under-recognized, especially in developing countries like Pakistan. This case report describes the classic presentation of anti-NMDA-R encephalitis. Putative pathophysiology, diagnosis and management of this under-recognized syndrome are discussed through literature review. Clinicians should consider anti-NMDA-R encephalitis in the differential diagnosis of a patient with alleged viral encephalitis.

CASE REPORT

A 42 years old female presented with complaints of behavioral changes for seven days, altered sensorium for two days, and generalized body

stiffness and fever for one day. About seven days ago, she developed low mood, poor appetite and became socially withdrawn and quiet. She was taken to a psychiatrist who prescribed atypical antidepressants and antipsychotics. She became delirious and minimally responsive after five days. She also developed generalized body stiffness with difficulty moving her limbs. Past medical history was significant for a prolonged critical care admission at an outside facility for seizures two years ago. Since then she was taking regular antiepileptics with adequate compliance. Her medications included valproic acid 500 mg twice daily and levetiracetam 500 mg twice daily. Her surgical history was significant for hysterectomy. Her examination in emergency room showed generalized dystonia, Glasgow coma scale (GCS) was 9/15, the motor exam found generalized neck stiffness and power to painful stimuli was 3/5 in upper limbs and 2/5 in lower limbs. She was admitted with a suspected differential diagnosis of neuroleptic malignant syndrome and encephalitis. Within an hour of presentation, her GCS dropped to 3/15 without any clinically observed seizures and she was intubated for airway protection. She remained admitted in the medical intensive care unit and received intravenous ceftriaxone, vancomycin, acyclovir, and dexamethasone empirically for suspected meningitis. Her CSF routine examination, culture and sensitivity, herpes simplex virus by polymerase chain reaction (HSV-PCR), and creatinine phosphate kinase (CPK) are reported in Table 1.

Table 1: Laboratory Investigations

Cerebrospinal Fluid	
Glucose	89 mg/dL
Protein	66 mg/dL
LDH*	47mmol/L
Volume	1.5 mL
RBC count**	3000 cells/uL
WBC***	556 cells/uL
Neutrophils	10 %
Lymphocytes	90 %
HSV by PCR ^	Negative
MTB DNA by PCR^^	Negative
Complete Blood Count	
WBC	11900 /mm^3
Hemoglobin	12 g/dL
Hematocrit	36.5 %
Platelet count	286000 /mm^3
CRP	20.07 mg/L
CPK	58 u/L
Serum electrolytes and Thyroid Profile	
Sodium	141 mEq/L
Potassium	3.7mEq/L
Bicarbonate	31mEq/L
BUN*	14 mg/dL
Serum Creatinine	0.68 mg/dL
Serum TSH	1.5 mIU/L
Free T4	1.4 ng/dL

*Lactate dehydrogenase,
**Red blood cell count,
***White blood cell count,
^Mycobacterium Tuberculosis Deoxyribonucleic Acid by Polymerase Chain Reaction (MTB-DNA PCR),
^^Herpes simplex virus (HSV) by polymerase chain reaction

Urine, blood and sputum cultures were negative. CT scan brain with contrast was normal. An EEG showed moderate to severe diffuse encephalopathy (Figure 1). She was weaned off the ventilator and the next day her GCS improved to 9/15. On the 3rd day of admission, she developed orofacial dyskinetic movements, had cardiac dysrhythmia, had a sudden drop in her conscious level and she was intubated for the 2nd time. On day 5 of her hospitalization, her GCS improved to 10/15 and she was extubated. On the 6th day of admission, the patient was still with dystonic movements, was conscious but drowsy and non-communicating. Due to her predominant dyskinetic features, dystonia, and a similar past medical history, she was tested for central nervous system (CNS) vasculitis and autoimmune encephalitis (Table 1). Anti-NMDA-R antibodies were tested positive in the CSF sample (Table 2). A diagnosis of anti-NMDA-R encephalitis was made. She was started on pulsed steroids and plasmapheresis. Total of four sessions of plasma exchange were performed. We had difficulty in weaning her off of mechanical ventilation and a tracheostomy was performed. Her GCS remained stable at 9/15, although her orofacial dyskinesias subsided. Due to family demands, likely secondary to financial constraints, she was transferred to an outside facility for further sessions of plasma exchange. The patient died at the outside facility after four days of her transfer. The immediate cause of her terminal events could not be established.

DISCUSSION

Anti-NMDA-R encephalitis is an autoimmune disease with a multifaceted presentation that involves memory deficits, psychiatric symptoms, and autonomic instability [5]. Anti-NMDA-R encephalitis presents with a combination of motor symptoms, speech disorder, seizures, decreased level of consciousness, behavioral and cognitive problems, and psychiatric manifestations in earlier stages of the disease.

Table 2: Antibodies Detected

Anti ds- DNA Ab*	Negative
Anti Histone Ab**	Negative
Anti NMDA receptor Ab***	Positive

*Anti-double stranded (ds) DNA antibodies,
** Anti-histone Antibodies,
*** Anti-NMDA receptor Encephalitis

Due to these psychiatric symptoms, patients receive psychiatric evaluation first resulting in late diagnosis and institution of immunotherapy [6]. In one study, 4% of patients presented with pure and isolated psychiatric manifestations without neurological involvement [7]. Abnormal EEG, CSF studies, and brain MRI were present in 33%, 90%, and 79% of patients, respectively. In addition, the outcomes of these diagnostic workups in patients with isolated psychiatric symptoms were similar to the cohort population in general. Recent studies propose that 50 percent of patients with NMDA encephalitis respond to first-line immunotherapy like steroids, intravenous immunoglobulin (IVIG), and plasmapheresis (either alone or in combination) within four weeks of presentation. Rituximab and cyclophosphamide are usually given as 2nd line therapies when first-line therapies fail to treat the patient. The significant prognostic factor is early identification and initiation of therapy. Immediate screening for NMDA-R antibodies should be performed with new-onset psychosis, history of encephalitis, neurological symptoms and abnormal, non-specific EEG, CSF, or MRI manifestations[7].

CONCLUSION

The present case demonstrates the significant need for emergency-room physicians, psychiatrist and neurologists to become aware of anti-NMDA-R encephalitis. The typical presentation involves not only a combination of behavioral, cognitive, and motor symptoms but isolated psychiatric episodes may also be present. Immediate screening for NMDA-R antibodies should be performed with new-onset psychosis, history of encephalitis, neurological symptoms, and abnormal, non-specific EEG, CSF or MRI manifestations. Prompt start of immunotherapy can dramatically treat the encephalitis and decrease the mortality.

REFERENCES

1. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091-8
2. Ishiura H, Matsuda S, Higashihara M, Hasegawa M, Hida A, Hanajima R, et al. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. *Neurology*. 2008;71(23):1921-3
3. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis*. 2009;28(12):1421-9
4. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010;10(12):835-44
5. Wandinger KP, Saschenbrecker S, Stoecker W, Dalmau J. Anti-NMDA-receptor encephalitis: a severe, multistage, treatable disorder presenting with psychosis. *J Neuroimmunol*. 2011;231(1-2):86-91
6. Maneta E, Garcia G. Psychiatric manifestations of anti-NMDA receptor encephalitis: neurobiological underpinnings and differential diagnostic implications. *Psychosomatics*. 2014;55(1):37-44
7. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti–N-methyl-d-aspartate receptor encephalitis. *JAMA Neurol*. 2013;70(9):1133-9
8.

Figure 1: Electroencephalogram (EEG) showing moderate to severe diffuse encephalopathy