Neurology Asia 2022; 27(1) : 169 – 173

Anti N-methyl-D-aspartate receptor encephalitis: A case series from Myanmar

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Abstract

Objectives: Since 2007, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been increasingly reported worldwide. Although the diagnostic testing of anti-NMDAR encephalitis was available in Myanmar since 2016, there have been no studies reported so far. This is a report of anti-NMDAR encephalitis admitted to one of the tertiary care hospitals in Myanmar. *Methods:* It is an observational study of anti-NMDAR encephalitis admitted at North Okkalapa General and Teaching Hospital (NOGTH) for three consecutive years. *Results:* In this study, ten patients diagnosed as anti-NMDAR encephalitis were included. Median age of onset was 21 years, ranged from 16 to 85 years. Nine out of ten patients were female (90%). Seven patients (70%) showed four of the six major groups of symptoms. Only one patient (10%) was found to have ovarian teratoma. EEG abnormalities were observed in all patients (100%). Out of six MRIs done, four (66.6%) were normal.
Conclusion: This study showed that demographic profile, clinical characteristics, and ancillary test results were in similarity with other previous studies but mortality rate of 40% was relatively high as compared to previous studies.

Keywords: Anti-NMDAR-encephalitis, teratoma, delta brush, Myanmar, psychotic, hyperkinetic, plasma exchange

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disease characterized by the presence of psychiatric symptoms, seizures, movement disorders and autonomic dysfunction. Anti-NMDAR encephalitis was first reported as a paraneoplastic syndrome by Joseph Dalmau's group in 2005. The first patients identified were young women with ovarian teratoma who presented with psychiatric symptoms, amnesia, seizures, abnormal movements, autonomic dysfunction, hypoventilation, and decreased level of consciousness.[1] Since then, there is a rapidly growing incidence of anti-NMDAR encephalitis cases worldwide. Recently French nationwide study reported an incidence of 0.5/million in its population.[2,3] In Myanmar, diagnostic testing of anti-NMDAR encephalitis was established in 2016. This is a report of ten cases diagnosed with anti-NMDAR encephalitis admitted at North Okkalapa General and Teaching Hospital (NOGTH) which is one of the tertiary care hospitals in Yangon, Myanmar over three years from January 2018 to December 2020.

METHODS

This is an observational study conducted at NOGTH from January 2018 to December 2020. In this study, the diagnosis of anti-NMDAR encephalitis was based on the presence of anti-NMDAR antibody in either serum or cerebrospinal fluid (CSF). The antibody test was performed by using Indirect Immunofluorescence Test (IIFT) kit. The medical records of all patients diagnosed with anti-NMDAR encephalitis were collected. The demographic profile, clinical characteristics, ancillary test results, types of treatment given, and outcome were reviewed and analysed.

RESULTS

Over the study period, ten patients with anti-NMDAR encephalitis were seen. All patients

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Date of Submission: 28 October 2021; Date of Acceptance: 28 December 2021

https://doi.org/10.54029/2022swp

fulfilled the diagnostic criteria proposed by Graus *et al*.[4] All patients had one or more of the six major groups of symptoms of anti-NMDAR encephalitis; seven patients (70%) showed four of the six major groups of symptoms. Four patients (40%) were diagnosed by the presence of antibody in the CSF and six patients (60%) by the presence of antibody in the serum.

Demographic profile

The median age at disease onset was 21 years, ranged from 16 to 85 years. Nine out of ten patients were female (90%) with female to male ratio of 9:1.

Clinical characteristics

Six patients (60%) had fever; among them, three had headache and vomiting as prodrome. One was discharged as encephalitis of undetermined aetiology before the diagnosis of anti-NMDAR encephalitis was made. One female patient (Case 3) presented with intractable vomiting without fever and headache. Time taken from prodromal phase to diagnosis was from two weeks (Case 4) to one year and three months (Case 7). Only one patient (Case 1) was found to have ovarian teratoma. Co-existing herpes simplex virus (HSV) infection was seen in one patient (Case 10) where diagnosis of HSV encephalitis was made based on the presence of IgM antibody in the serum. Co-existing *Pseudomonas putida* infection of the meninges was detected in one patient (Case 8). In one patient (Case 7), it was complicated by cerebral venous sinus thrombosis.

All patients developed psychiatric abnormalities during their illness. Nine patients (90%) had epileptic seizures; either focal or generalized. Five patients (50%) presented with movement disorders; four exhibited orofacial dyskinesia; two had negative myoclonus. One (Case 9) had speech disturbance. Nine patients (90%) were semi or deeply unconscious upon arrival at the hospital. Two patients were found to have central hypoventilation. One patient (Case 1) had autonomic dysfunction. One patient (Case 8) presented with cognitive dysfunction. Two patients exhibited focal neurological deficits; one with left-sided hemiparesis; the other one with right-sided eight cranial nerve palsy and left-sided sixth cranial nerve palsy. (Table 1)

Ancillary tests results

In routine CSF analysis, CSF pleocytosis was seen in four patients (40%) and raised protein in five patients (50%). Overall, normal CSF findings were observed in four patients (40%). All patients showed abnormal EEG. Electrographic status epilepticus was seen in three (30%); diffuse delta slowing in five (50%); focal slowing in one (10%) and focal epileptiform discharges in one patient (10%) on initial EEG examination. Delta brush pattern was found in one patient (10%). Brain magnetic resonance imaging (MRI) could not be performed in four patients (40%) because they were seriously ill and was warded in intensive care unit (ICU) before they expired. Out of six MRIs performed, four (66.6%) were normal; one (16.7%) showed bilateral hippocampal sclerosis and in one patient (Case 7), T2 hyperintensities at right temporal-parietal region and cerebellum with leptomeningeal enhancement was seen. (Table 2)

Treatment and outcome

All patients received first-line immunotherapies (high-dose steroid infusion followed by oral high-dose steroids). Four patients needed plasma exchange (either by traditional process or by plasma filtration) 2 weeks after steroids infusion as there was little or no response. No side effects of first-line therapies occurred in all patients. None of the patients received second-line therapies. Sixty percent of patients needed three to four antiseizure medications to control seizures. Three patients (30%) died while warded in the hospital; one patient left the hospital against medical advice and died on the way home. Among those who expired, two patients (50%) had plasma exchange and two patients (50%) died while receiving high-dose steroids. On three months follow-up, four patients (40%) achieved complete recovery; one patient (20%) had partial recovery and the other remaining patient had substantial recovery.

DISCUSSION

This is the first reported case series of Myanmar adult patients with anti-NMDAR encephalitis. This study described the clinical, radiological and laboratory findings in patients with anti-NMDAR encephalitis diagnosed and treated at a tertiary care hospital in Yangon, Myanmar. The median age at disease onset in the present study was 21 years which was similar with those from previous studies.[5-7] The eldest age in this study was 85 years which was also the eldest age reported to date.[6] Therefore, this highlights that testing of antibodies against NMDAR in serum or CSF should be performed in elderly patients if clinically indicated. The predominance of female

Table 1: Clinical characteristics of patients with anti-NMDAR encephalitis

Case	Age	Gender	Clinical features		Treatment given	Outcome
			Groups	Details		
1	18	F	Psychiatric behaviour; Seizures; Movement disorders; Decreased consciousness; Autonomic dysfunction/Central hypoventilation	Fever; GTCS; Delusion; Disorganized behaviour; Labile hypertension; Orofacial dyskinesia; Decreased consciousness; Central hypoventilation	High dose steroid infusion + Oral steroid	Death
2	17	M	Psychiatric behaviour	Fever; Headache; Vomiting; Disorganized speech and behaviour; Hallucination; Delirium	High dose steroid infusion + Oral steroid	Complete recovery
3	20	F	Psychiatric behaviour; Seizures; Movement disorders; Decreased consciousness	Intractable vomiting; GTCS; Disorganized speech and behaviour; Depressed mood; Delirium; Orofacial dyskinesia; Decreased consciousness	High dose steroid infusion + Oral steroid	Death
4	16	F	Psychiatric behaviour; Seizures; Movement disorders; Decreased consciousness	Fever; Headache; Vomiting; Focal motor seizure; GCTS; Disorganized speech and behaviour; Orofacial dyskinesia; Decreased consciousness	High dose steroid infusion + Oral steroid + PLEX	Complete recovery
5	16	F	Psychiatric behaviour; Seizures; Movement disorders; Decreased consciousness	Focal motor seizure; GCTS; Disorganized speech; Orofacial dyskinesia; Negative myoclonus; Left-sided hemiparesis; Decreased consciousness	High dose steroid infusion + Oral steroid + PLEX	Complete recovery
6	22	F	Psychiatric behaviour; Seizures; Movement disorders; Decreased consciousness	Focal motor seizure; Disorganized speech; Negative myoclonus; Decreased consciousness	High dose steroid infusion + Oral steroid + PLEX	Death
7	45	F	Psychiatric behaviour; Seizures; Decreased level of consciousness; Central hypoventilation	Headache; Vomiting; Earache; Disorganized behaviour; Hallucination; Focal motor seizure; Decreased level of consciousness; Right eight nerve palsy; Left sixth nerve palsy; Central hypoventilation	High dose steroid infusion + Oral steroid	Partial recovery
8	85	F	Psychiatric behaviour; Seizures; Decreased consciousness	Memory loss; Fever; Headache; Focal motor seizure; Disorganized speech and behaviour; Delirium; Decreased consciousness	High dose steroid infusion + Oral steroid	Substantial recovery
9	26	F	Psychiatric behaviour; Speech dysfunction; Seizures; Decreased consciousness	Fever; Headache; Vomiting; GTCS; Verbal reduction; Disorganized behaviour; Hallucination; Delirium; Decreased consciousness	High dose steroid infusion + Oral steroid	Complete recovery
10	50	F	Psychiatric behaviour; Seizures; Decreased consciousness	Fever; GTCS; Disorganized speech and behaviour; Hallucination; Decreased consciousness	High dose steroid infusion + Oral steroid + PLEX	Death

GTCS: generalized tonic clonic seizure; NMDAR: N-Methyl-D-Aspartate-Receptor; EEG: electroencephalogram; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; PLEX: Plasma exchange NMDAR: N-Methyl-D-Aspartate-Receptor; GTCS: generalized tonic clonic seizure; PLEX: Plasma exchange

Table 2: Summary of ancillary tests results, type of treatment given and outcome of patients with anti-NMDAR encephalitis

			Number	Percent
Initial EEG findings		Normal findings	0	0
		Focal slowing	1	10
		Focal epileptiform discharges	1	10
		Electrographic focal status epilepticus	3	30
		Delta brush pattern	1	10
		Diffuse delta slowing	5	50
MRI findings		Normal	4	67
		Bilateral hippocampal sclerosis	1	16.7
		T2 hyperintensities at right temporal-parietal region and cerebellum	1	16.7
		Not done	4	-
CSF findings	Overall	Normal findings	4	40
		Abnormal findings	6	60
	Protein	Raised	5	50
		Normal	5	50
	Sugar	Raised	5	50
		Normal	5	50
	Cells	Pleocytosis	4	40
		Normal	6	60
Number of antiseizure medication needed		0	1	10
		1	0	0
		2	2	20
		3	3	30
		4	3	30
		5	1	10
Type of immunotherapy		High dose steroid infusion followed by Oral methylprednisolone/prednisolone	6	60
		High dose steroid infusion followed by Oral methylprednisolone + PLEX	4	40
Outcome		Complete recovery	4	40
		Substantial recovery	1	10
		Partial recovery	1	10
		Death	4	40

GTCS: generalized tonic clonic seizure; NMDAR: N-Methyl-D-Aspartate-Receptor; EEG: electroencephalogram; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; PLEX: Plasma exchange NMDAR: N-Methyl-D-Aspartate-Receptor; EEG: electroencephalogram; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; PLEX: Plasma exchange

patients with female to male ratio of 9:1 as well as the clinical picture (psychiatric behaviour, seizures, speech dysfunction, movement disorders, decreased consciousness, autonomic dysfunction/ central hypoventilation) in this series was similar to other previous studies.[5-7]

According to Iizuka *et al*., presentation of anti NMDAR encephalitis has been categorized into five distinct phases: prodromal phase, psychotic phase, unresponsive phase, hyperkinetic phase, and recovery phase.[8] In the present study, seven patients (70%) did not have all five phases of anti-NMDAR encephalitis; five patients lacked hyperkinetic phase and in two patients, there was no prodromal phase preceding the illness.

Although many of the early reported patients were associated with an ovarian teratoma, there was variable prevalence of the underlying neoplasm among subsequent studies.[1] In the study done in United States by Titulaer et al., 38% of total patients had a tumour with 94% being ovarian teratomas, 2% extraovarian teratomas and the remaining 4% lung, breast, testicular, thymic, and pancreatic cancer.[6] Xu *et al*. from China reported that 19.5% of total patients, i.e., 43 patients had a tumour; 42 patients had ovarian teratoma and one patient had lung cancer.[5] In the present study, only one patient (10%) was found to have ovarian teratoma, which was similar with previous studies reported from Malaysia.[9,10] In this study, EEG abnormalities were observed in all patients (100%). This is consistent with Malaysian study by Abdullah *et al*.[10] This indicates that patients with psychiatric symptoms should be evaluated with EEG as EEG is useful in early diagnosis of anti-NMDAR encephalitis versus functional diseases manifesting in psychosis.

Among the four mortalities, all patients had received high-dose steroids, and were followed by plasma exchange in two patients (50%). Timing of initiation of immunotherapy from onset of symptoms varied from 1 to 6 months in these patients. Three of them (75%) needed ICU admission and the remaining one died on the way home when she was discharged against medical advice. All patients who completely recovered did not need ICU admission. These findings were consistent with the report from Titulaer *et al*., which mentioned the need for ICU admission, the delayed initiation of immunotherapy and tumour removal as the two independent predictors of worse outcomes.[6]

This small study shows the general similarities in Myanmar patients with anti-NMDAR encephalitis compared with other previous studies; except a high mortality.

ACKNOWLEDGEMENT

The authors would like to thank Professor Moe Moe Zaw, Professor and Head of Department of Neurology for her permission to publish this article and ASNA2021 abstract committee for their acceptance to present e-poster at 14th biennial convention of ASNA2021.

DISCLOSURE

Financial support: None

Conflict of interest: None

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