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Anti- NMDA Receptor Antibody Encephalitis: - A Review of Nine Patients with Clinical Presentation, Investigations, Treatment and Outcome in Singapore

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Abstract

Objective: To report on epidemiology, clinical and laboratory features of patients diagnosed with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis admitted to Singapore general hospital over the period of four years. This is the first study for the local population.

Introduction: Anti –NMDA receptor encephalitis is a severe form of encephalitis that associates with antibodies against NMDA receptors resulting in a neuropsychiatric syndrome. It has been considered as a Paraneoplastic syndrome.

Methods: Nine patients (6 female and 3 male) admitted to neurology unit from March 2010 to Oct 2013 were studied retrospectively. Diagnosis of anti-NMDA receptor antibody encephalitis was based on encephalitis plus positive CSF serology.

Result: Younger age group affected more (range 16 to 65 years). Clinical presentation usually involves the triad of psychotic (100%); seizures (66%) and movement disorder (45%). Autonomic instability observed in two third (66%) of patients. Serum serology is positive only in 55% patients. CSF analysis was variable. MRI brain was largely unremarkable (77%). Tumour occurrence was seen in 66%; 83% in females, 33% in males. The outcome was favourable in two third patients with the best prognosis in female patients when the tumour was found and resected and worst in male patients with tumour unresected.

Conclusion: Results are consistent with the current literature in terms of epidemiology, investigations and outcome. However, it requires the larger number of patients with longer follow-up to prove its association with a tumour in patients who has no evidence of malignancy at diagnosis.

Keywords: Anti- NMDA receptor; Dementia; Immunology

Introduction

Anti –NMDA receptor encephalitis is a severe form of immune-mediated encephalitis that associates with antibodies against NMDA receptors resulting in a neuropsychiatric syndrome [1]. It was first recognised in 2005 and several reports have been published for its occurrence worldwide. NMDA receptors are ligand-gated cation channels with crucial roles in synaptic transmission and plasticity. The receptors are heteromers of NR1 subunits that bind glycine and NR2 (A, B, C, or D) subunits that bind glutamate [2] NR1 and NR2 combine to form receptor subtypes with distinct pharmacological properties, localisation, and ability to interact with intracellular messengers. Over activity of NMDA receptors causing excitotoxicity is a proposed underlying mechanism for epilepsy, dementia, and stroke, whereas low activity produces symptoms of schizophrenia [3-5].

The antibodies are detected in the CSF and serum of patients who typically develop schizophrenia-like psychiatric symptoms, usually preceded by fever, headache, or viral infection-like illness. After reaching the peak of psychosis, most patients developed seizures followed by an unresponsive/catatonic state with decreased level of consciousness, central hypoventilation frequently requiring mechanical ventilation, orofacial-limb dyskinesia, and autonomic symptoms [6]. Anti-NMDA-receptor encephalitis had initially been described in young women with ovarian teratoma, but is also common in women without tumour, in men and in children [7,8]. The median age at onset is 23 years, but it develops between 5 to 76 years [8].

Brain MRI is usually unremarkable but focal enhancement or medial temporal lobe abnormalities can be observed. The CSF reveals nonspecific changes. EEG often reveals diffuse delta slowing without paroxysmal discharges, despite frequent bouts of seizures [6].

Tumour occurrence was initially believed to be 100%, but now it is estimated to comprise 58%; 62% in women and 22% in men [8].

This disorder is usually severe and can be fatal, but it is potentially reversible. Combined therapy including tumour resection and immunotherapy is recommended [6]. Patient care requires an

interdisciplinary approach including neurologists, psychiatrists, paediatricians, oncologists and gynaecologists [7].

Methods

Patients and procedures

We have reviewed nine patients (n=9) with serology confirmed Anti –NMDA receptor encephalitis for their clinical presentation, relevant investigations, treatment and outcome. This is a single centre retrospective study done on the patients presented to inpatient neurology unit of Singapore General hospital, first and largest tertiary care hospital, over a period of four years from March 2010 to October 2013. All patients had brain Magnetic Resonance Imaging (MRI) using 1.5T field strength, radiological screening including computed tomography of the chest, abdomen and pelvis looking for a systemic neoplasm, and serological or CSF studies that ruled out other disorders such as infectious or lupus or paraneoplastic encephalitis. Anti-NMDA antibodies were analysed in Immunology laboratory in Singapore General hospital [9].

Results

Patients included were six females (66%) and three males (33%). The mean age for females was 25 years range 16 to 33 years. Three male patients were 16, 18 and 65 years old at the time of diagnosis.

All the patients (100%) presented with prominent psychiatric symptoms, including agitation (3 patients), anxiety (4 patients), depression (2 patients), psychosis (4 patients), bizarre behaviour (9 patients), visual hallucinations (1 patient) and auditory hallucinations (1 patient). Three patients (33%) complained of a headache. Seizures were seen in 6 patients (66%) with GTC seizure (4 patients), focal seizure (1 patient), absence seizures (1 patient) and status epilepticus (2 patients). Dyskinesia was seen in 4 patients (45%), the most common type was orofacial dyskinesia. Dystonia and chorea athetoid movement were seen in 1 patient.

2 patients had decreased consciousness. 6 patients (66%) had shown autonomic instability featuring dysrhythmia (4 patients), labile BP (3 patients), hypersalivation (1 patient) and hyperpyrexia (2 patients) (Table 1).

Characteristics	No of patients
Female	6
Male	3
Age average, range (years)	25 (16-65)
Symptoms and signs	
Psychiatric	9
Seizures (any type)	6
Dyskinesia	4
Autonomic instability	6
Headache	3

Table 1: Characteristics and clinical features of patients.

Investigations included serum and CSF serology for confirmation of diagnosis, Magnetic Resolution Imaging (MRI) of Brain, CSF analysis and Electroencephalography (EEG). Radiologic imaging studies were done to look for underlying malignancy [10,11].

All nine patients (100%) shows CSF positive for NMDA antibodies, however, only five (55%) showed serum positive NMDA antibodies. CSF studies results were variable with opening pressure average 20.75 cm H20 with range 15 to 28 cm H20. White cell counts 0-5 for 3(33%), 5-50 for 3 (33%) and more than 50 for 3 (33%) patients. Patients with raised WBC were equal in neutrophilic and lymphocytic predominance.

CSF protein mean was 0.33 g/dl with a range 0.14 to 0.62. MRI of the brain revealed no hyperintense lesion, no leptomeningeal enhancement in 7 patients (77%), only 2 patients (22%) had the mild leptomeningeal enhancement in frontal lobe; one patient had Occipital lobe hyperintense lesions.

EEG studies were normal with no epileptogenic foci in 3 patients (33%), PLEDS (unilateral and bilateral) in 2 patients (22%), unilateral slow waves in 1 patient, status epilepticus in 1 patient, severe diffuse encephalopathy with generalised slow waves in 3 patients (33%). EEG studies were repeated during the course of treatment.

Malignancy screen showed ovarian cysts in 5 out of 6 (83%) female patients that proven to be teratomas on biopsy. Only 1 out 3 (33%) male patients showed a high-grade liver neuroendocrine tumour, hence malignancy screen was positive in 6 out 9 (66%) patients (Tables 2 and 3).

Treatment included immunotherapy with Immune-globulins (IvIg), Plasma Exchange and Pulse Methylprednisolone, second line immunosuppressant i.e., Cyclophosphamide, Etoposide, Rituximab and surgery for malignancy. All five female patients underwent cystectomies. 2 out of these 5 patients did not require any immunotherapy after removal of cysts and 2 patients were given all three first line immunotherapies and one patient was given IvIg followed by four cycles of Rituximab followed by four cycles of Etoposide.

Results	No of patients
CSF results	
Raised opening pressure	4
White cells pleocytosis	6
Raised protein	4
Brain MRI	
Total no of abnormal	2
Leptomeningeal enhancement	2
Occipital lobe hyperintensity	1
EEG	
Total abnormal	6
PLEDs*	2
Unilateral slow wave	1
Status epilepticus	1
Generalised slow wave and diffuse encephalopathy	3
*Periodic lateralized epileptiform discharges	

Table 2: Investigation results for the patients with Anti-NMDA receptor antibodies encephalitis.

The female patient with no cysts was given IvIg and pulse methylprednisolone followed by two cycles of Cyclophosphamide. All three male patients were given Pulse methylprednisolone with one patient required IvIg followed by four cycles of Rituximab and one patient required additional 2 cycles of Cyclophosphamide.

Anti-epileptic drugs, antipsychotics and mood stabiliser were prescribed in patients who presented with seizures and psychotic symptoms respectively.

Age, gender	Clinical presentation	Autonomic dysfunction	Lumbar Puncture findings	MRI findings	EEG findings	Tumour screening	Treatment given	Outcome
31-year-old female	Depression Behavioural change Childlike voice Status epilepticus	Tachycardia Hypotension Swinging pyrexia hypersalivation	opening pressure 18.5 WBC 1 RBC 1 protein 0.29g/l	post-ictal temporal lobe hyper intense lesions in T2 images	status epilepticus	bilateral mature ovarian teratoma	tumour resection no immunotherapy	full recovery
16-year-old female	Headache behavioural changes inability to concentrate no seizures	no	opening pressure 22 WBC 220 Lymphocytic RBC 2 protein 0.4 g/l	no T2/ FLAIR hyperintense lesions were seen	No epileptiform activity	mature ovarian teratoma	Tumour resection intravenous immunoglobulin × 2 cycles Pulse methylprednisolone plasma exchange × 2 cycles	fatal outcome

65-year-old male	Psychosis auditory hallucination no seizures	no	opening pressure 12 WBC 1 RBC 5 protein 0.27 g/l	no abnormal T2/ FLAIR hyperintense lesions	no epileptiform activity	high-grade hepatic neuroendocrine tumour	pulse methylprednisolone oral prednisolone	fatal outcome
33-year-old female	behavioural changes uncontrollable cry blank stares absence seizures	tachycardia	opening pressure 17 WBC 25 lymphocytic RBC 1 protein 0.14 g/l	nil abnormal enhancement seen	left temporoparietal regional PLEDS	Dermoid cyst, Mature ovarian teratoma	Tumour resection No immunotherapy	full recovery
23-year-old male	Seizures behavioural changes irritability hallucination	tachycardia	opening pressure 12 WBC 0 RBC 200 Protein 0.54g/l	nil abnormal enhancement	slow waves in the right hemisphere	no tumour	pulse methylprednisolone cyclophosphamide × 2 cycles	substantial recovery lost to follow-up
18-year-old male	focal seizures behavioural changes aggression irritability decreased consciousness	no	opening pressure 15 WBC 15 Lymphocytes RBC 5 protein 0.28 g/l	mild leptomeningeal enhancement	NIL Epileptiform activity	no tumour	intravenous immunoglobulin pulse methylprednisolone rituximab × 4 cycles	full recovery
16-year-old female	behavioural changes screaming agitation hallucination depression GTC seizures Orofacial dyskinesia	tachycardia alternating with bradycardia	opening pressure 28 WBC 16 Lymphocytes RBC 0 Protein 0.14 g/l	T2/FLAIR hyperintensity in subcortical white matter	Generalised slowing, severe diffuse encephalopathy	no tumour	intravenous immunoglobulin × 2 cycles pulse methylprednisolone cyclophosphamide × 2 cycles	full recovery
32-year-old female	headache meningism decreased consciousness orofacial dyskinesia	hypotension hyperthermia	opening pressure 21 WBC 119 Lymphocytes RBC 3 protein 0.62 g/l	hyperintense lesions at temporal lobes leptomeningeal enhancement at frontal lobes cerebral edema	bilateral diffuse PLEDS severe encephalopathy	ovarian mature teratoma	Tumour resection Intravenous immunoglobulin × 2 cycles rituximab × 4 cycles Etoposide × 3 cycles	full recovery
25-year-old female	depression suicidal tendency hallucination GTC seizures Orofacial dyskinesia	Tachycardia labile Blood pressure	opening pressure 17 WBC 85 Neutrophils RBC 3 protein 0.3 g/dl	nil abnormal enhancement	severe diffuse encephalopathy	bilateral ovarian teratoma	Tumour resection pulse methylprednisolone intravenous immunoglobulin × 2 cycles plasma exchange × 1 cycles	fatal outcome

GTC seizures: - Generalised tonic-clonic seizures

Table 3: Clinical presentation, laboratory investigations, treatment and outcome for patients.

The outcome was favourable in six patients (66%) and fatal in three (33%) patients. Case fatality included two female patients who underwent cystectomies and required all three first line immune-suppressants and one male patient with the hepatic neuroendocrine tumour who was treated with Immunosuppressant but did not want resection. Patients who survived and improved were followed up in the outpatient setting. One patient was lost to follow-up and rest five patients had regular visits to Oncology, psychiatry and neurology clinics. Four out of six patients who presented with seizure did not have the recurrence of seizures and anti-epileptic drugs were stopped. Psychotic symptoms resolved after treatment, however, four out of six patients had persistence of low mood requiring the use of antidepressants for average two years.

Interpretation

In our study, we found that Anti-NMDA receptor encephalitis shows a female predominance (66%) and younger age group is affected more often (88%), this is consistent with the literature. Clinical presentation usually involves the triad of psychotic (100%); seizures (66%) and movement disorder (45%). Autonomic instability observed in two third (66%) of patients. CSF analysis showed variable results, however, CSF serology was diagnostic. Serum serology is positive only in 55% patients. MRI brain was largely unremarkable (77%). Tumour occurrence was seen in 66%; 83% in females, 33% in males. The outcome was favourable in two third patients with the best prognosis in female patients when the tumour was found and resected and worst in male patients with the tumour unresected. The above findings are consistent with existing literature and studies.

Discussion

Anti-NMDA-receptor antibody encephalitis has been described as a syndrome of memory deficits, decreased consciousness and hypoventilation [12,13] in female patients with ovarian teratoma. In our cohort of female patients, five out of six patients did have an association of macroscopic teratoma to this neuropsychiatric syndrome presenting with diverse clinical manifestations ranging from agitation, aggression, depression to frank psychosis, focal twitching to generalised tonic-clonic seizures to status epilepticus. Few of the patients did have orofacial dyskinesia and autonomic dysfunction mainly presenting as tachycardia, hypotension or hypersalivation which has been reported in the literature [14,15]. Prodromal symptoms such as fever, headache and decreased consciousness were not very common and were present only in about 30% patients. This is much less as reported by Josep Dalmau and colleagues [14,15]. in their review as about 70%. In male patients, the only association was found with a neuroendocrine tumour which has been reported previously by Josep Dalmau and colleagues [14] in his case series of patients.

Diagnostic tests have the lower yield. In literature [14,15] it has been reported that MRI imaging is unremarkable in about 50% patients and it may show hyperintense signals in hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions. In our cohort of patients, only four out of nine (44%) patients had T2/ Flair hyperintense lesions in the cerebral cortex, subcortical white matter, temporal lobes and occipital lobes. The mild leptomeningeal enhancement was seen in two of our patients (22%). EEG has been reported to be abnormal with nonspecific, slow and disorganised activity [15] however in our patients, it was abnormal only in 66% patients showing mainly PLEDS, slow wave, status epilepticus. It also showed generalised slow waves in patient with decreased consciousness suggesting diffuse encephalopathy. CSF studies showed mainly lymphocytic pleocytosis with normal to mildly increased protein which is consistent with existing literature [15]. All nine patients had CSF Anti-NMDA antibodies detected (100%) however serum antibodies were only detected in five patients. This is possible if patients have delay in diagnosis or have received plasma exchange or Intravenous immunoglobulin before the testing.

In our nine patients, once the diagnosis was made, treatment was initiated according to current evidence. Surgery was offered to all the patients diagnosed to have the tumour (five females and one male patient). First line Immunotherapy including either pulse methylprednisolone, Intravenous immunoglobulin or Plasma exchange was initiated if surgery was not opted for or was delayed because of clinical instability. Two of our female patients who were diagnosed early and had mild neuropsychiatric manifestations, surgery was done first and improvement was seen as fast as 48 hours postoperatively. These patients were closely monitored for recovery or relapse and both these patients had the full recovery without any need for immunotherapy. In other two female patient's immunotherapy was initiated while awaiting for surgery as they were being mechanically ventilated and required inotropic support for blood pressure. Both these patients required all three first-line immunomodulatory treatment with surgery. There was very mild improvement seen and both these patients succumb to infective complication resulting from profound immunosuppression and prolonged ventilation. Last female patient with teratoma had severe manifestations of the disease with decreased consciousness and hypotension from dysautonomia and had severe encephalopathy on EEG, she was treated with intravenous immunoglobulin prior to surgery, and however she required second line therapy with Rituximab followed by Etoposide before she had the substantial neurologic recovery. The only male patient with neuroendocrine tumour did not want to have surgery and was treated with Pulse methylprednisolone followed by tapering doses of oral prednisolone. He died of diabetic gangrenous foot infection six months after diagnosis. The three patients (one female and two male patients) who did not have any associated tumour was treated with first line immunosuppressant that is intravenous immunoglobulin with or without pulse methylprednisolone, however, all three required second line therapy with either Rituximab or Cyclophosphamide or both for the full recovery. The patients who had substantial recovery were followed up in outpatient department for relapses and with tumour surveillance imaging every six months to one year. Only one patient lost to follow-up as he decided to follow up with doctors in his own country. The full recovery process took few months. Clinical improvement was seen first with increased alertness and engagement in communication with stabilisation of autonomic dysfunction. Psychiatric symptoms such as depression and hallucinations required longer treatment for an average of two years post diagnosis. All

patients who had a seizure at presentation were seizure free post treatment and antiepileptic drugs were gradually withdrawn.

Dalmau and colleagues mentioned in their review [15] that 80% patients with tumours (mostly teratoma) had substantial improvement after removal and first line immunotherapy, however only 48% of patients without tumour had a similar degree of improvement after first line immunotherapy and needed second line chemotherapy (a cyclophosphamide, rituximab or both). In our two patients with teratoma, tumour removal was effective without the need of immunotherapy and another patient required second line immunotherapy after surgery. Similarly, in all three patients without tumour required second line immunotherapy. These findings are consistent with existing studies. The recovery or mild sequel is seen in about 75% patients and severe disability or death in rest 25% [15]. In our cohort of patients, full recovery was seen in 66% patients and mortality in 33%. Two patients died from infection resulting from immunosuppression and one from the unrelated cause.

Conclusion

Existing literature review and results of our study were consistent in terms of epidemiology, clinical presentation, treatment and outcome. It is evident that younger population is affected more often; hence any acute onset change in behaviour in young patient combined with seizures should raise suspicion of encephalitis. It is possible that these patients present more often in psychiatric units, hence appropriate diagnosis can be delayed if treated for psychosis alone. Brain imaging with MRI may not aid in diagnosis and blood serology is not highly sensitive. However, CSF examination cannot be recommended for all acute onset psychosis as patient numbers are very small but it is warranted if patient progress to have seizures or dyskinesia.

This is also to be emphasised that these cases should be actively screened for underlying malignancy because treatment of the tumour can improve the clinical picture even without immunotherapy. The optimal duration of tumour surveillance cannot be recommended for patients without evidence of any malignancy on presentation. This will require a longer follow-up and active search for symptoms and signs of malignancy. We do not suggest ordering tumour markers or invasive investigations for the patients unless there is no improvement despite immunotherapy.

We conclude that Anti-NMDA receptor encephalitis is reversible yet potentially fatal encephalitis. Early diagnosis and treatment can lead to complete recovery, however, more studies with a large number of patients and longer follow-up is required to understand its correlation with malignancy.

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References

1. Dalmau J, Tuzun E, Wu HY (2007) Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61: 25–36.
2. Lynch DR, Anegawa NJ, Verdoorn T, Pritchett DB (1994) N-methyl-D-aspartate receptors: different subunit requirements for binding of glutamate antagonists, glycine antagonists, and channel-blocking agents. Mol Pharmacol 45: 540–545.
3. Coyle JT (2006) Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol 26: 365-384.
4. Waxman EA, Lynch DR (2005) N-methyl-D-aspartate receptor subtypes: multiple roles in excitotoxicity and neurological disease. Neuroscientist. 11: 37-49.
5. Lau CG, Zukin RS (2007) NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. Nat Rev Neurosci. 8: 413-426.
6. Iizuka T, Sakai F (2008) Anti-nMDA receptor encephalitis--clinical manifestations and pathophysiology. Brain Nerve 60: 1047-1060.
7. Prüss H, Dalmau J, Arolt V, Wandinger KP (2010) Anti-NMDA-receptor encephalitis. An interdisciplinary clinical picture. Nervenarzt. 81: 396-398.
8. Florence NR, Dalmau J (2009) Anti–N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis in children and adolescents. Ann Neurol 66: 11-18.
9. Dalmau J, Lynch DR (2007) Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 61: 25-36.
10. Seki M, Suzuki S, Iizuka T, Shimizu T, Nihei Y, et al. (2007) Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 79: 324-326.
11. Wandinger KP, Saschenbrecker S, Stoecker W, Dalmau J (2011) Anti-NMDA-receptor encephalitis: A severe, multistage, treatable disorder presenting with psychosis 231: 86-91.
12. Vitaliani R, Mason W, Ances B (2005) Paraneoplastic encephalitis, psychiatric symptoms and hypoventilation in ovarian teratoma. Ann Neurol 58: 594-604
13. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, et al. (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 7: 1091-1098.
14. Dalmau J, Lancaster E, Martinz-Hernandez E (2005) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10: 63-74.
15. Ishiura H, Mastuda S, Higashihara M (2008) Response of anti -NMDA receptor encephalitis without tumour to immunotherapy including rituximab. Neurology 71: 1921-1923.